

Nederlandse Ziekenhuisfarmaciedagen, 10 en 11 mei 2012

Dit artikel bevat de abstracts van de mondelinge presentaties tijdens de Nederlandse Ziekenhuisfarmaciedagen op 10 en 11 mei 2012 te Nunspeet. De digitale versie van dit artikel op pw.nl omvat ook de abstracts van de posterpresentaties.

Monoamine oxidase inhibitors and the occurrence of intraoperative haemodynamic events

I.M.M. van Haelst ^{ab*}, W.A. van Klei ^b, H.J. Doodeman ^a, C.J. Kalkman ^b and A.C.G. Egberts ^b

^a Medical Center Alkmaar, Alkmaar. ^b University Medical Center Utrecht, Utrecht.

* Correspondence: ziekenhuisapotheek@mca.alkmaar.nl.

Background

Although monoamine oxidase inhibitors (MAOIs) have been available for more than 50 years, the perioperative management of patients treated with MAOIs is still under discussion. There are no evidence-based guidelines and experts disagree whether to continue the use of MAOIs before surgery or not. From the point of view of appropriately treating the psychiatric illness, perioperative continuation is recommended. However, potentially fatal drug interactions have been reported in patients where (ir)reversible MAOIs were used concurrently with opioids or sympathicomimetic agents during anaesthesia. The aim of this study was to investigate the occurrence of intraoperative haemodynamic events, such as hypertension and tachycardia, when MAOIs were continued during anaesthesia.

Methods

A retrospective observational cohort study was conducted among patients who were admitted for elective surgery requiring anaesthesia in eight Dutch hospitals (2004-2010). The index group included current users of MAOIs. The reference group included a sample of non-users matched to the index group on hospital, type of surgery and anaesthesia (ratio 1:3). The outcome was the occurrence of the following intraoperative haemodynamic events: hypotension or hypertension and tachy- or bradycardia. In case of the occurrence of a haemodynamic event (or more than one) the total duration of the episode(s) was measured. The incidence of the serotonergic syndrome was also registered.

Results

Approximately 280,000 surgical procedures were performed in the participating hospitals in the observed 33 years. The index group included 51 current users of a MAOI. The reference group included 149 non-users. Intraoperative hypotension occurred less frequently in users of a MAOI (49%) than in non-users (69%) ($P = 0.01$). The occurrence of hypertension, brady- and tachycardia during anaesthesia was not different between users of a MAOI (28%, 57% and 20%, respectively) and those of the reference group (26%, 56% and 26%, respectively). The total duration of the episode(s) of hypotension or hypertension and brady- or tachycardia in users of a MAOI did not differ from the reference group. In none of the study patients the serotonergic syndrome was diagnosed.

Conclusions

Severe adverse haemodynamic events, such as hypertension and tachycardia, did not occur more frequently in users of MAOIs – who continued their use during anaesthesia – compared to non-users. Intraoperative hypotension occurred even less frequently in users of a MAOI than in non-users. These findings suggest that there is no longer much justification to discontinue (ir)reversible MAOIs before surgery, with the attendant considerable risk of compromising their psychiatric status.

Keywords: monoamine oxidase inhibitors – intraoperative – haemodynamic events – side effects – interactions

The effect of a tamoxifen dose increase from 20 mg to 40 mg in patients with at least one inactive CYP2D6 variant allele and/or concomitant use of a CYP2D6 inhibitor

M.E.B. Welzen ^{a*}, V.O. Dezentjé ^b, R.H.N. van Schaik ^c, E.P.H. Colbers ^a, H-J. Guchelaar ^b, J. den Hartigh ^b, D.M. Burger ^a and H.W.M. van Laarhoven ^a

^a Radboud University Nijmegen Medical Centre, Nijmegen. ^b Leiden University Medical Center, Leiden. ^c Erasmus Medical Center, Rotterdam.

* Correspondence: m.welzen@akf.umcn.nl.

Background

Genetic polymorphisms leading to reduced CYP2D6 activity and the use of CYP2D6 inhibitors both influence the formation of endoxifen [active metabolite of tamoxifen (TAM)]. CYP2D6 genotyping is currently not part of the standard clinical management of patients treated with TAM and there are no formal dose recommendations in patients using TAM and a CYP2D6 inhibitor. We hypothesized that in patients who are either a CYP2D6 intermediate or poor metabolizer and/or are treated with a CYP2D6 inhibitor a dose adjustment of TAM compensates for reduced formation of endoxifen.

Methods

Female breast cancer patients treated with TAM 20 mg QD for at least four weeks were included. They were genotyped for CYP2D6 variant alleles (inactive alleles *3, *4, *5, *6 and decreased activity alleles *10, *41). Patients with at least one inactive allele, two decreased CYP2D6 activity alleles, and/or concomitant use of a CYP2D6 inhibitor received a dose increase of TAM to 40 mg QD for four weeks. TAM, 4-OH-TAM, N-desmethylTAM and endoxifen levels were determined with LC-MS in blood samples at screening and after four weeks.

Results

41 patients with median age 55 (range 37-81) years were enrolled of which 22 extensive (EM), 16 intermediate (IM) and 3 poor metabolizers (PM) for CYP2D6. 3 EMs concomitantly used a CYP2D6 inhibitor (paroxetine, escitalopram or citalopram) and were categorized as PM. Mean (SD) endoxifen levels in EMs, IMs, and PMs were 11.4 (5.2), 8.3 (4.8) and 4.1 (1.4) ng/mL, respectively (one-way ANOVA: $P = 0.006$). Three patients were genotyped as $*4/*41$ or $*41/*41$, and by consensus classified as IMs; their endoxifen levels (1.9; 3.4; 3.7 ng/mL, respectively) were not different from those observed in PMs. 14 patients have completed the four week dose increase (11 IMs, 3 PMs). Mean endoxifen level for the IMs increased from 9.5 to 16.9 ng/mL and from 3.2 to 6.3 ng/mL in the PMs. No serious adverse events occurred after the dose increase.

Conclusions

Increasing the dose of TAM from 20 mg to 40 mg QD can compensate for the reduced endoxifen level in CYP2D6 IMs. In contrast, a dose increase to 40 mg QD in PMs does not appear to be sufficient to reach endoxifen levels as seen in EMs.

Keywords: tamoxifen – pharmacokinetics – CYP2D6 – polymorphism

The influence of the HCV protease inhibitor boceprevir on the pharmacokinetics of the HIV integrase inhibitor raltegravir

Clara T.M.M. de Kanter ^{*}, Maren I. Blonk, Angela P.H. Colbers, Quirine Fillekes, Bas J.J.W. Schouwenberg and David M. Burger
Radboud University Nijmegen Medical Centre, Nijmegen.

^{*} Correspondence: k.dekanter@akf.umcn.nl.

Background

HIV/HCV co-infected patients are likely to use both HIV and HCV treatment. HIV guidelines recommend tenofovir and emtricitabine combined with efavirenz, atazanavir + ritonavir, darunavir + ritonavir or raltegravir (RAL) for the initial treatment of HIV infection. Plasma concentrations of the HCV protease inhibitor boceprevir (BOC) were decreased when BOC was coadministered with efavirenz or ritonavir. Because no interaction between BOC and RAL is expected, RAL might be a more suitable antiretroviral agent when combined with a BOC containing HCV treatment. This study was designed to investigate the absence of a drug interaction between BOC and RAL.

Methods

This was an open-label, randomized, two-period, cross-over phase I trial in 24 healthy volunteers. All subjects were randomly assigned to: BOC 800 mg TID for 10 days plus a single dose of RAL 400 mg on day 10 followed by a wash-out period and a single dose of RAL 400 mg on day 38; or the same medication in reverse order. After observed intake of BOC and RAL with a standardized break-

fast, blood samples for pharmacokinetics (PK) were collected during an 8-hour and a 12-hour period respectively. PK parameters were calculated by non-compartmental analysis (WinNonlin version 5.3). Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for RAL AUC_{last} and C_{max} after log-transformation of within-subject ratios. A 90% CI within the 0.80-1.25 range indicates no clinically meaningful effect of BOC on RAL PK.

Results

22 subjects (10 males) completed the trial. One subject was excluded for non-adherence to the study protocol and another subject because of elevated ALT before receiving BOC. Mean age (range) and BMI were 38 (20-55) years and 23 (18-27) kg/m², respectively. No serious adverse events were reported. The geometric mean (CI95) of RAL AUC_{last} and C_{max} for RAL + BOC vs. RAL alone were 4.27 (3.22-5.66) vs. 4.22 (3.19-5.59) mg·h/L and 1.06 (0.76-1.49) vs. 0.98 (0.73-1.31) mg/L, respectively. GMR (90% CI) of RAL AUC_{last} and C_{max} for RAL + BOC vs. RAL alone were 1.01 (0.85-1.20) and 1.09 (0.89-1.33).

Conclusions

BOC did not affect RAL exposure. Due to the absence of a clinically significant drug interaction, RAL can be recommended for combined HIV + HCV treatment including BOC.

Keywords: hepatitis C – HCV – HIV – boceprevir – raltegravir – interaction

Topical diltiazem cream versus botulinum toxin A for the treatment of chronic anal fissure: a double-blind randomized clinical trial

M. Samim, B. Twigt, L. Stoker ^{*} and A. Pronk

Department of Surgery and Department of Clinical Pharmacy, Diaconessenhuis Hospital, Utrecht.

^{*} Correspondence: l.stoker@altrecht.nl.

Objective

A double-blind randomized clinical trial to compare topical diltiazem with botulinum toxin A (BTA) in the treatment of chronic anal fissure.

Background

Chronic anal fissures remain a challenging condition. Topical diltiazem and BTA are promising agents in the treatment of anal fissure. As to date diltiazem and BTA were never compared in a solid randomized trial, which is the purpose of this study.

Methods

134 patients were randomized to receive either diltiazem cream and placebo injection or BTA injection and placebo cream. The primary end point was fissure healing after three months.

Results

After three months healing of the fissure was noted in 32 of 74 (43%) patients in the diltiazem group and 26 of 60 (43%) patients in the BTA group. Reduction > 50% in mean pain score was noted in 58 of 74 (78%) patients in the diltiazem group and 49 of 60 (82%) patients in the BTA group. Perianal itching was the only side effect reported and was noted in 15% of patients in the diltiazem group, and this difference was statistically significant ($P = 0.012$).

Conclusions

BTA yields higher healing rates in the short term, though after three months diltiazem and BTA resulted in equal healing rates. Also no significant difference in pain reduction was observed for both treatments. This study shows no significant advantage of one treatment compared to the other.

Keywords: diltiazem – botulinum toxin – chronic anal fissure

Ann Surg. 2012 Jan;255(1):18-22.

Dutch Trial Register NTR1012

Sulfonylurea receptor polymorphisms in *ABCC8* affect the response to sulfonylurea treatment in patients with type 2 diabetes mellitus

J.A. Wessels^a, J.J. Swen^{a*}, T. van der Straaten^a, T. El Hajoui^a, W.J. Assendelft^b and H-J. Guchelaar^a

^a Department of Clinical Pharmacy & Toxicology, Leiden University Medical Center, Leiden. ^b Department of Public Health and Primary Care, Leiden University Medical Center, Leiden.

* Correspondence: j.j.swen@lumc.nl

Background

There is significant interpatient variability in response to sulfonylurea derivatives (SUs) in patients with type 2 diabetes mellitus (T2DM). We hypothesize that polymorphisms in the *ABCC8* gene encoding the sulfonylurea receptor 1 influence the response to SUs.

Methods

207 incident SU users (tolbutamide, glibenclamide, glimepiride, gliclazide) with T2DM were recruited from four primary care centers. Retrospective medical and prescription data were retrieved from the electronic patient record. Haplotype analysis of the *ABCC8* gene was performed by means of 15 most informative polymorphisms, resulting in 14 haplotypes defined in 4 blocks. The association of these *ABCC8* haplotypes with the achievement of stable SU dose, prescribed stable SU dose, and time to stable SU dose was explored. Stable SU dose was defined as the first period of ≥ 270 consecutive days without dose adjustment, initiation of other SUs, insulin or metformin.

Results

Carriers of the GTGGC haplotype had a 2.2-fold increased likelihood to achieve stable SU dose ($P = 0.024$), while no significant effect of the number of copies of this *ABCC8* haplotype on prescribed dose was found. Of the patients with two copies of the GTGGC haplotype, 86% achieved stable SU dose, whereas of the patients with one copy and no copy of the GTGGC haplotype 81% and 66% achieved stable SU dose, respectively. Additionally, carriers of the GTGGC haplotype also showed a significantly decreased time to stable dose (hazard ratio: 0.70; 95% confidence interval, 0.54-0.91, $P = 0.006$). No associations with any of the other haplotypes were found.

Conclusion

The sulfonylurea receptor GTGGC haplotype is associated with improved response to SUs in primary care T2DM patients. This suggests that individualization of T2DM treatment according to genetic profile may be an opportunity to improve clinical outcome.

Keywords: pharmacogenetics – type 2 diabetes mellitus – sulfonylureas

Amoxicillin concentrations in sputum in relation to beta-lactamase activity in COPD patients

R.W.M.A. van der Zanden^{a*}, P.D.L.P.M. van der Valk^b, M.G.R. Hendrix^c, J. van der Palen^d, K.L.L. Movig^e and M.G.J. Brusse-Keizer^b

^a Department of Clinical Pharmacy & Toxicology, Maastricht University Medical Centre+, Maastricht. ^b Department of Pulmonary Medicine, Medisch Spectrum Twente, Enschede. ^c Regional Laboratory of Public Health, Enschede. ^d Department of Research Methodology, Measurement, and Data Analysis, University of Twente, Enschede. ^e Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede.

* Correspondence: r.vander.zanden@mumc.nl

Background

COPD exacerbations are often treated with antibiotics, although their use is controversial. A previous study showed that patients with a sputum concentration of amoxicillin lower than the minimum inhibitory concentration (MIC₉₀, value 2 mg/L) were hospitalized 4 days longer than patients with a concentration \geq MIC₉₀. This study investigated if beta-lactamase activity was higher in patients who had a sputum amoxicillin concentration < 2 mg/L than in patients with a concentration \geq 2 mg/L.

Methods

We included 23 hospitalized COPD patients who were treated with amoxicillin + clavulanic acid for an acute exacerbation. Sputum and serum samples were collected at the third day of treatment with amoxicillin + clavulanic acid to determine beta-lactamase activity in sputum and amoxicillin concentrations in both sputum and serum.

Results

We found no difference in beta-lactamase activity between patients with a sputum amoxicillin concentration $< \text{MIC}_{90}$ and $\geq \text{MIC}_{90}$ ($P = 0.79$). Multivariate logistic regression analysis showed no significant relation between beta-lactamase activity and sputum amoxicillin concentrations $< \text{MIC}_{90}$ or $\geq \text{MIC}_{90}$ ($\text{OR} = 0.53$; $\text{CI}_{95} 0.23-1.2$; $P = 0.13$). Amoxicillin concentrations were $< \text{MIC}_{90}$ in 18 out of 23 sputum samples (78%). Serum concentrations amoxicillin were $< \text{MIC}_{90}$ in 7 patients (30%).

Conclusions

Beta-lactamase activity did not differ between patients with sputum amoxicillin concentrations $< \text{MIC}_{90}$ or $\geq \text{MIC}_{90}$ in patients treated with amoxicillin + clavulanic acid for an exacerbation of COPD. The finding that a majority of patients had a sputum amoxicillin concentration below the MIC_{90} is remarkable. This suggests that these patients are being undertreated. Further research could focus on inhalation of amoxicillin to obtain higher concentrations in sputum.

Keywords: COPD – exacerbation – amoxicillin – sputum – beta-lactamase antibiotics

De digitale versie van dit artikel op pw.nl omvat ook de abstracts van de volgende posterpresentaties

Risk factors of medication non-adherence in depression and anxiety, preliminary results
 Development and validation of a paediatric oral formulation of clonidine hydrochloride
 New tracers and methodology for determination of atherosclerotic plaque vulnerability
 Indometacin population pharmacokinetics during prophylactic treatment of patent ductus arteriosus of premature infants
 A practical thrice weekly ertapenem dosing regime for chronic haemodialysis patients
 Metformin elimination by haemodialysis versus continuous venovenous haemofiltration in renal failure patients with metformin associated lactic acidosis
 Evaluation of algorithms for prediction of vancomycin clearance
 Effect of hospital pharmacist participation in intensive care rounds: analysis of medication errors and hospital costs
 Semi-quantitative analysis of GHB while simultaneously using GC-FID for alcohol analysis in serum samples
 Risk of venous thromboembolism in patients with total hip / knee replacements and matched controls: a population-based cohort study in Denmark
 Use of glitazones and risk of bladder cancer: disease or drugs?
 Retrospective cross sectional study to determine the prevalence and incidence of severe hypo- and hypercalcaemia in hospitalized patients
 Cost effective patient medication review in a large geographically wide spread mental health institution
 Resolving the problem of particles in asparaginase (Erwinase) infusion bags
 The effect of pharmacist intervention on medication reconciliation in the emergency department
 Amoxicillin time above MIC in hospitalized patients
 Genetic variation in CYP19A1 is related to response to exemestane: survival in early breast cancer in the Dutch TEAM trial
 Effectiveness of discharge medication related interventions. A systematic review

The effect of a pharmaceutical transitional care program on unplanned rehospitalisations in internal medicine patients
 Development of a clinical prediction model for supratherapeutic INR in hospitalized patients on vitamin K antagonist therapy
 COX-1 affinity determines the NSAID-aspirin interaction with respect to thrombocyte function
 Rhabdomyolysis after auto-intoxication with MDPV, a new designer drug
 Association between CYP2D6 genotype, serum endoxifen concentration and CYP2D6 phenotype determined by a dextromethorphan breath test in breast cancer patients using tamoxifen
 Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy
 Risk of fracture in patients with Parkinson's disease
 Thin layer chromatography to support therapeutic drug monitoring of moxifloxacin in patients with tuberculosis in rural areas and resource limited settings
 Evaluation of the vancomycin dosage guideline in paediatric oncology patients
 Intelligent electronic trigger tool to optimise intravenous to oral antibiotic switch
 Point prevalence study for local antibiotic prescription and usage trends used in a large non-academic teaching hospital in the Netherlands
 Liquid chromatography-spectrophotometric assay for treosulfan in human serum
 Clinical relevance of and risk factors associated with medication administration time errors
 Analysis of medication reconciliation at discharge from a Dutch hospital
 Quetiapine and breastfeeding
 Consequences of a single dose of 2,000,000 IU vitamin D3 in two nursing home patients
 Prevalence of and risk factors for prescription errors in older individuals with an intellectual disability
 Association of risk analysis with user satisfaction after implementation of computerized physician order entry (CPOE) in Dutch hospitals
 Barriers and drivers of medication reconciliation at discharge
 Continuous infusion of vancomycin: a validated dosing schedule
 Does the circadian rhythm affect the pharmacokinetics of aminoglycosides in cystic fibrosis patients?
 Nephrotoxicity of once daily dosed aminoglycosides: tobramycin versus gentamicin
 Nonlinear mixed effects modeling of the diurnal blood pressure profile in a multiracial population
 Anidulafungin pharmacokinetics in critically ill patients
 Voriconazole concentrations are significantly influenced by inflammatory reactions
 The use of a real-time medication monitoring system (RTMM) for the improvement of adherence to inhaled corticosteroids in children with asthma, a study protocol
 Dual absorption in intranasal administration: a new pharmacokinetic model
 Patients' satisfaction with intranasal midazolam versus rectal diazepam as fast-working rescue medication in epilepsy
 Vitamin D deficiency among elderly psychiatric inpatients
 Metformin dose related to renal function in outpatients
 Influence of bariatric surgery on the use of some major drug classes
 Monitoring of methotrexate levels following glucarpidase rescue treatment requires detection by mass spectrometry since immunoassay is not applicable

Nederlandse Ziekenhuisfarmaciedagen, 10 en 11 mei 2012.

PW Wetenschappelijk Platform. 2012;6:a1230.

Risk factors of medication non-adherence in depression and anxiety, preliminary results

Pierre M. Bet^{abx}, Stag D. van Laer^a, Jacqueline G. Hugtenburg^{ac}, Brenda W.J.H. Penninx^{bdef} and Witte J.G. Hoogendijk^{bdg}

^a Department of Clinical Pharmacology and Pharmacy, VU University Medical Center, Amsterdam. ^b Neuroscience Campus Amsterdam, VU University, Amsterdam. ^c EMGO Institute, VU University Medical Center, Amsterdam.

^d Department of Psychiatry, VU University Medical Center, Amsterdam.

^e Department of Psychiatry, University Medical Center Groningen. ^f Department of Psychiatry, Leiden University Medical Center, Leiden. ^g Department of Psychiatry, Erasmus University Medical Center, Rotterdam.

* Correspondence: p.m.bet@vumc.nl.

Background

Depression and anxiety are conditions where chronic medication use is indicated, and are often accompanied by other chronic conditions like asthma, hypertension and diabetes. Previous literature has pointed out a large role for depression as a risk factor for non-adherence to medication regimens. Non-adherence undermines optimal treatment of depression, anxiety and co-morbid conditions. Most studies of non-adherence focus on clinical trials, but their results can be biased due to the attention study patients receive, the announced pill count and drug-accountability. Because non-adherence is difficult to identify in clinical practice, insight in risk factors of non-adherence is important to reveal non-adherence and optimise therapy. The aim of this study was to assess the rate of medication non-adherence, and risk factors for non-adherence in the Netherlands Study on Depression and Anxiety (NESDA), a large cohort study sample in a naturalistic setting.

Methods

The rate of medication non-adherence was assessed using the Medication Adherence Rating Scale (MARS), a five item questionnaire which measures a range of adherence behaviours. Non-adherence in this context is operationalised by both the tendency to avoid, forget, or stop taking medication, and the tendency to adjust or alter the dose from that recommended by the physician, providing a 5 to 25 score. MARS scores of 24 and 25 were classified as adherent and MARS scores of 23 or lower were classified as non-adherent.

We have selected all participants who used medication (n = 1899) at the four year follow-up of the NESDA cohort of 2,402 participants (age 22-69 yr). Potential risk factors included patient-, disease-, and treatment-related factors, and were selected on the basis of previous literature regarding this subject. These factors were tested in univariate and multivariate analyses to assess their relation to non-adherence.

Results

MARS scores ranged from 5 to 25. 44% was classified as being non-adherent. In univariate analysis, risk factors for non-adherence were lower age (OR = 1.16; P < 0.001), low social support (OR = 1.23; P = 0.03), higher IDS score (OR = 1.12; P = 0.003), higher

neuroticism scores (OR = 1.11; P = 0.023), being employed (OR = 1.25; P = 0.03) and having a depression diagnosis (OR = 1.25; P = 0.03). In multivariate analysis, risk factors for non-adherence were lower age (OR = 1.19; P < 0.001), low social support (OR = 1.11; P = 0.01), higher IDS score (OR = 1.18; P = 0.005) and male gender (OR = 1.24; P = 0.049).

Conclusion

In this large study sample in a naturalistic setting, lower age, less social support, higher depression severity and male gender, are all risk factors for non-adherence. Clinicians should recognise these risk factors and apply adherence-improving strategies to improve patient outcome.

Keywords: medication non-adherence – risk factors – depression – anxiety – MARS

Development and validation of a paediatric oral formulation of clonidine hydrochloride

R.R. Boedhram^{*}, A.L. de Goede, M. Eckhardt, L.M. Hanff, B.C.P. Koch, C.H. Vermaat and A. Vermes

Department of Hospital Pharmacy, Erasmus MC, Rotterdam.

* Correspondence: r.boedhram@erasmusmc.nl.

Background

In the Sophia Children's Hospital, clonidine hydrochloride (clonidine HCl) is commonly used for intravenous or oral sedation. However, a suitable formulation for oral paediatric treatment is lacking. The recommended dose is based upon body weight. Commercially available tablets cannot be used, because of inflexibility of dosage and the inappropriate solid dosage form for young children. The oral use of the injectable form of clonidine HCl is limited by its acidity, its inadequate taste and smell, and most importantly, its high concentration. We describe the development and validation of a stable paediatric oral formulation of clonidine HCl 50 µg/mL, allowing individualised paediatric dosing and easy administration.

Methods

Clonidine HCl is soluble in water (pK_a 8.05), enabling development of an aqueous solution of the drug. The 50 µg/mL clonidine HCl oral solution was manufactured (using BUFA materials) by dissolving 10.2 g of citric acid monohydrate and 18.3 g of disodium hydrogen phosphate in 500 mL of distilled water. Once the buffer components were dissolved, 50.0 mg of clonidine HCl was added and dissolved by continuous stirring. Afterwards, 200 mL of saccharose syrup ('sirupus simplex' containing 630 mg of saccharose and 1 mg of methylparaben per g) was added and the solution was homogenised. Subsequently, 10.6 g of methylparaben solution 15% (w/v) was added under continuous stirring, 500 mg of raspberry essence was added and the volume was made up to 1000 mL using

distilled water, resulting in the final acidic solution (pH 5.0). The solution was filled into 100 mL brown PET bottles to the mark. A 12-month long term stability testing program for clonidine concentration and pH (time points 0, 1, 3, 6, 9 and 12 months) was performed, using a validated HPLC method, which was validated for linearity, specificity, precision and accuracy. All twofold sample analyses were preceded by a system suitability test.

Results

As the stability testing program is currently on-going, data have been collected up to 6 months. At 0, 1, 3, and 6 months after manufacture, the clonidine HCl concentration was 101.6%, 96.6%, 102.3%, 98.0% and 99.0%, respectively, and pH was 5.1, 5.1, 5.0, 5.0 and 5.1, respectively. No marked degradation at room temperature occurred.

Conclusion

The described oral aqueous solution of 50 µg/mL clonidine HCl is chemically stable for up to 6 months when stored in brown 100 mL PET bottles at room temperature, enabling adequate oral treatment in paediatric patients.

Keywords: clonidine hydrochloride – paediatric dosage form – formulation – compounding – stability – high-performance liquid chromatography (HPLC)

New tracers and methodology for determination of atherosclerotic plaque vulnerability

Hendrikus H. Boersma^{abc}, Reza Golestani^b, Nynke A. Jager^d, Hans J. de Haas^{be}, Anton G.T. Terwisscha van Scheltinga^a, Marjolijn N. Lub-de Hooge^{ab}, Leila Mirfeizi^b, Philip H. Elsinga^b, Gert Luurtsema^b, Phil A. Low^f, Jagat Narula^e, René A. Tio^{eg}, Johanna Westra^d, Marc Bijl^d, Gooitzen M. van Dam^h, Clark J. Zebregs^{ci} and Riemer H.J.A. Slart^{ac}

^a Department of Clinical and Hospital Pharmacy, ^b Department of Nuclear Medicine and Molecular Imaging, ^c Cardiovascular Imaging Group Groningen,

^d Department of Rheumatology and Clinical Immunology, ^e Department of Cardiology, ^h Division of Surgical Oncology, ⁱ Division of Vascular Surgery, Department of Surgery; University Medical Center Groningen (UMCG).

^e Department of Cardiology, Mount Sinai Medical Center, New York, NY, USA.

^f Department of Chemistry, Purdue University, West Lafayette, Indiana, USA.

Background

PET, SPECT and fluorescence tracers can be used to identify vulnerable plaque formation in atherosclerotic disease. Clinical PET/SPECT camera systems are restricted in terms of resolution for the visualization of detailed inflammation patterns in smaller vascular structures. The aim of this study was to evaluate the possible added value of a high-resolution molecular imaging in excised human carotid artery plaques using several tracers representing the pathogenesis of vulnerable plaques, such as folate (substrate

for activated macrophages; folate receptor beta imaging by ^{99m}Tc- or FITC-folate), bevacizumab (imaging of neovascularization by targeting VEGF-A using ⁸⁹Zr- or 800CW-bevacizumab), Na[¹⁸F]F (microcalcification), and [¹⁸F]RGD-K5 (targeting avb3-integrins).

Methods

In this study 50 patients with a planned carotid endarterectomy were included. Excised plaques were incubated in one of the tracer solutions and subsequently imaged with either microPET, micro-SPECT or a fluorescence camera. Macrophage presence in plaques was evaluated semi-quantitatively by immunohistochemistry. Plaque calcification was assessed additionally with microCT and correlated to tracer uptake.

Results

Tracer uptake from ^{99m}Tc- or FITC-folate, bevacizumab (⁸⁹Zr- or 800CW-bevacizumab), Na[¹⁸F]F, and [¹⁸F]RGD-K5 indicative for plaque vulnerability and macrophage infiltration were compared with patient symptomatology. Heterogeneous distributions and variable intensities of uptake were found within the plaques with good resolution. A positive correlation between the distribution of macrophages and uptake of the tracers was demonstrated for fluorescent folate and ⁸⁹Zr-bevacizumab.

Conclusion

This *ex vivo* study demonstrates that excised human carotid artery plaques can be visualized in detail using nuclear and optical micro-imaging systems. Enhancement of the resolution in clinical imaging of these tracers, either nuclear or optical, is needed for translation into the clinical setting. Subsequently, the most optimal tracer to be used in the clinic is to be determined. Novel developments like opto-acoustic or intra-arterial fiber-based tomographic optical imaging instruments may provide the bridge to the clinic.

Keywords: atherosclerosis – carotid artery – molecular imaging – microPET/SPECT/fluorescence – vulnerable plaque

Indometacin population pharmacokinetics during prophylactic treatment of patent ductus arteriosus of premature infants

N. Boone^{ax}, L. Stolk^a, P. Degraeuwe^b and C. Neef^a

^a Maastricht University Medical Centre+, Department of Clinical Pharmacy & Toxicology, Maastricht. ^b Maastricht University Medical Centre, Department of Pediatrics, Maastricht.

* Correspondence: n.boone@mumc.nl.

Background

The incidence of patent ductus arteriosus (PDA) in pretermes with a gestational age smaller than 28 weeks is > 31% [1]. In the neonatal intensive care unit of the MUMC PDA is treated with

three gifts of 0.1 mg/kg indometacin in pretermatures with a birth weight smaller than 1250 g or a gestational age smaller than 30 weeks. We studied indometacin pharmacokinetics, because information about this treatment modality is not available.

Methods

Surplus plasma samples collected for routine analysis of 34 pretermatures were available. The indometacin concentrations were measured with a validated HPLC-RP system with UV detection. *A priori* a one compartment indometacin PK model was programmed in MW\Pharm 3.60 (Mediware, Groningen) based on literature kinetic parameters [2-4]. $K_{elim} = 0.03 \pm 0.02$ L/h, $V = 0.3 \pm 0.2$ L/kg. Individual kinetic parameters were calculated with MW\Pharm with a maximum *a posteriori* Bayesian estimation. Gentamicin pharmacokinetic parameters during indometacin treatment were also calculated with MW\Pharm as an indicator of glomerular filtration rate. Covariate analysis was performed with SPSS. The ductus arteriosus status was determined after three days with echocardiography.

Results and discussion

In this study 34 premature infants with a median birthweight of 880 g were included. Indometacin pharmacokinetics in the first three days after birth were determined after iterative Bayesian fitting. The elimination rate constants (K_{elim}) and apparent volumes of distribution (V) were graphically analysed in SPSS. A general population of 29 premature infants with a K_{elim} 0.0222 ± 0.0048 L/h ($t_{1/2}$ 31.2 h) and a V 0.3789 ± 0.0477 L/kg was established. A subgroup of 5 patients with a significant difference in K_{elim} 0.0424 ± 0.0040 L/h ($t_{1/2}$ 16.3 h) and $V = 0.1715 \pm 0.0353$ L/kg was determined. No significant relations between indometacin elimination rate constants and gentamicin clearances, GA, PNA and weight could be detected. After three days in 32 of the 34 patients ductus closure was observed. Of 18 patients also indometacin plasma concentrations after three days were available. Those plasma concentrations were more than 1.5 fold higher than predicted in the model based on first three days kinetics. This can probably be explained by ductus closure as suggested by Gal et al. [5].

Conclusions

In both populations no large intraindividual and interindividual differences in kinetics were observed during the first three days. Based on the observations in this study indometacin prophylaxis seems safe and effective.

REFERENCES

- 1 van Overmeire B, Smets K, Lecoutere D, et al. A comparison of ibuprofen and indomethacin for closure of patent ductus arteriosus. *N Engl J Med.* 2000;343:647-681.
- 2 Smyth JW, Collier PS, et al. Intravenous indomethacin in preterm infants with symptomatic patent ductus arteriosus. A population pharmacokinetic study. *Br J Clin Pharmacol.* 2004;58:249-258.
- 3 Al Za'abi M, Donovan T, et al. Orogastric and intravenous indomethacin administration to very premature neonates with patent ductus arteriosus: population pharmacokinetics, absolute bioavailability, and treatment outcome. *Ther Drug Monit.* 2007;29:807-814.

- 4 Wiest D, et al. Population pharmacokinetics of intravenous indomethacin in neonates with symptomatic patent ductus arteriosus. *Clin Pharm Ther.* 1991;49:550-556.
- 5 Gal P, et al. Indometacin pharmacokinetics in neonates: the value of volume of distribution as a marker of permanent patent ductus arteriosus closure. *Ther Drug Monit.* 1991;13:42-45.

Keywords: indometacin – prophylaxis – neonatal pharmacokinetics – patent ductus arteriosus

A practical thrice weekly ertapenem dosing regime for chronic haemodialysis patients

M.S. Bosma ^{a,x}, A.P. Rietveld ^b, P. de Man ^c, D.J. Touw ^d and C.J.C. Geerlings ^a

^a Department of pharmacy, Sint Franciscus Gasthuis, Rotterdam. ^b Department of internal medicine, Sint Franciscus Gasthuis, Rotterdam. ^c Department of microbiology, Sint Franciscus Gasthuis, Rotterdam. ^d Department of pharmacy, Apotheek Haagse Ziekenhuizen, The Hague.

* Correspondence: margriet.bosma@cze.nl.

Background

Infections are the second leading cause of death among patients undergoing chronic renal replacement therapy. The treatment of Gram-negative infections is complicated by the increasing rate of antibiotic resistance, mainly due to the spread of strains producing extended-spectrum β -lactamases. The choice of agents to treat these infections is limiting and the use of broad spectrum agents such as carbapenems has increased.

Ertapenem is a once daily carbapenem antibiotic which is administered intravenously. In patients undergoing intermittent haemodialysis a dosage reduction of 50% is recommended. Hospital admission or home care is needed to administer these doses, while these patients are normally visiting the hospital three times a week to undergo dialysis. In this study we investigate the use of a practical thrice weekly dosage regime, making use of an increased dosage interval rather than a dosage reduction.

Methods

In a single-centre, prospective study 10 chronic haemodialysis patients having an acute infection due to ertapenem-susceptible bacteria were enrolled. The minimal inhibitory concentration (MIC) was determined for all micro-organisms. Patients received 1 gram ertapenem thrice weekly administered immediately after haemodialysis. Blood samples were collected after a dosage, before haemodialysis and after haemodialysis. Ertapenem concentrations were determined with a validated liquid chromatography with a mass spectrometry detection method. The pharmacokinetic data was analysed using MW\Pharm.

Results

Pharmacokinetic parameters of ertapenem in our population were

different when compared to those reported in the literature for non-infectious haemodialysis patients. The volume of distribution was enhanced (V_d 0.16 L/kg vs 0.11 L/kg) and the half-life was prolonged ($t_{1/2}$ 19.9 h vs 14.1 h). The calculated ertapenem trough level at 68 hours was 3.7 mg/L (range 0.5-9.6 mg/L) and exceeded the individual MIC values (range 0.006-0.250 mg/L) during the 68 hour dosing interval.

The overall clinical success rate was 8 out of 10. In one patient treatment was discontinued due to an additional infection with a micro-organism not susceptible to ertapenem. Treatment failure was observed once and could be explained by an occlusion of the supragenaal femoropopliteal bypass right causing a decreased blood flow at the right foot and a low ertapenem concentration at the infection site.

Conclusion

Ertapenem administered in chronic haemodialysis patient as a thrice weekly dosage gives adequate serum levels for the dosing interval of 68 hours. This suggested thrice weekly dosage schedule is a practical and patient-friendly alternative.

Keywords: ertapenem – pharmacokinetics – haemodialysis

Metformin elimination by haemodialysis versus continuous venovenous haemofiltration in renal failure patients with metformin associated lactic acidosis

A. (Arjan) Bulsink ^{a*}, C.G. (Cornelis) Vermeij ^b, C.J. (Cornelius) Doorenbos ^b and I.R.F. (Inge) van Berlo-van de Laar ^a

Departments of ^a Clinical Pharmacy and ^b Nephrology; Deventer Hospital, Deventer.

* Correspondence: a.bulsink@conceptsnl.nl

Background

Patients with renal failure using metformin have an increased risk of developing metformin associated lactic acidosis (MALA). Both haemodialysis (HD) and continuous venovenous haemofiltration (CVVH) can remove metformin and correct uraemia and acidosis. The comparative efficacy of HD and CVVH in the treatment of renal failure patients with MALA is unknown.

Methods

In a retrospective study in patients with renal failure and MALA (pH < 7.35, lactate > 5.0 mmol/L), who required renal replacement therapy; metformin elimination half-life ($t_{1/2,ME}$) and lactic acidosis correction by HD and CVVH were compared.

Results

8 patients with renal failure and MALA were included, 4 patients received initial HD treatment and 4 CVVH. In HD and CVVH sessions with metformin concentrations measured at the start

and end of treatment, the $t_{1/2,ME}$ was calculated. In 7 HD sessions in 5 patients $t_{1/2,ME}$ was 3.9 ± 0.7 h, compared with 19.6 ± 6.9 h in 8 CVVH sessions in 4 patients ($P < 0.001$). Correction of arterial pH and lactate were faster by HD than by CVVH.

Conclusion

In renal failure patients with MALA, metformin elimination was achieved faster by HD than CVVH. Acidosis was corrected more rapidly by HD than by CVVH, but at 24 hours after admission, HD and CVVH were equally effective. In haemodynamically stable patients with MALA and renal failure, HD may be the preferred treatment, because of rapid metformin elimination and acidosis correction. In haemodynamically unstable patients, CVVH also effectively corrects lactic acidosis, but requires longer treatment time than HD.

Keywords: continuous venovenous haemofiltration – haemodialysis – lactic acidosis – metformin

Evaluation of algorithms for prediction of vancomycin clearance

S. Croes ^{a*}, L. Stolk ^a, M. Haeseker ^b and C. Neef ^a

^a Maastricht University Medical Center, Department of Clinical Pharmacy & Toxicology, Maastricht. ^b Maastricht University Medical Center, Department of Medical Microbiology, Maastricht.

* Correspondence: s.croes@mumc.nl

Background

Not any of seven investigated methods for estimating vancomycin pharmacokinetic parameters investigated in 2006 by Murphy et al. was found sufficiently reliable to replace therapeutic drug monitoring (TDM) of vancomycin [1]. During the last years again methods have been proposed to predict vancomycin pharmacokinetic parameters, when vancomycin serum concentrations are unavailable [2-4]. Recently we reported about erroneous results with an algorithm for calculation of AUC, which had been used for investigation of new vancomycin dosing guidelines [5]. We aimed to evaluate three of the recently proposed surrogate methods.

Methods

60 hospitalized adult patients from our institute were included. There were 6.6 ± 4.3 (mean \pm sd) peak and trough routinely measured plasma concentrations of vancomycin per patient available. Individual pharmacokinetic parameters were determined with maximum *a posteriori* Bayesian estimation. Also vancomycin clearance of each patient was calculated with the three prediction methods and compared with Bayesian estimation. The prediction methods are as follows. First creatinine clearance (CrCl) is calculated with the Cockcroft and Gault formula. Then the following algorithms are applied to estimate vancomycin clearance (mL/min). Moise-Broder method (1): $0.79 \times CrCl + 15.4$ [2]; DeRyke

method (2): $\text{CrCl} \times 0.75$ [3]; Pea method (3): $0.48 \times \text{CrCl} + 15.67$ [4]. Prediction bias and precision were calculated as percentage of prediction error and as percentage of absolute prediction error respectively. Linear regression was calculated with PASW Statistics 18.

Results

There exists a correlation between vancomycin clearance calculated both with Bayesian estimation and the prediction methods, as the correlation coefficient (R^2) was found to be 0.67. However, all three methods for estimating vancomycin clearance varied widely in predicting vancomycin clearance in comparison with Bayesian estimation. Prediction bias was measured as a percentage of the prediction error. These are displayed as mean \pm sd, for method 1 (Moise-Broder), 2 (DeRyke) and 3 (Pea) and were found to be large, *i.e.* $64.9 \pm 58.5\%$, $19.4 \pm 40.5\%$ and $16.8 \pm 43.9\%$, respectively. The absolute prediction errors (reflecting precision) were $65.9 \pm 57.4\%$, $32.5 \pm 33.7\%$ and $30.2 \pm 33.0\%$, respectively.

Conclusions

The three methods examined for estimating vancomycin clearance varied enormously in their prediction compared with the results obtained by Bayesian estimation. These methods are therefore not suitable for routine use in patient care and can not be considered as an alternative for TDM and Bayesian estimation.

REFERENCES

- Murphy J, Gillespie D, Batemann C. *Am J Health Syst Pharm.* 2006;63:2365-70.
- Moise-Broder PA, Forrest A, Birmingham MC, et al. *Clin Pharmacokinet.* 2004;43:925-42.
- DeRyke C, Alexander D. *Hosp Pharm.* 2009;44:751-65.
- Pea F, Furlanut M, Negri C, et al. *Antimicrob Agents Chemother.* 2009;53:1863-1867.
- Croes S, Neef C, Stolk L. *Ann Pharmacother.* 2011;45:1313-4.

Keywords: vancomycin (clearance) – Bayesian estimation – prediction methods

Effect of hospital pharmacist participation in intensive care rounds: analysis of medication errors and hospital costs

A.L. de Goede ^{a*}, N.G.M. Hunfeld ^a, M.L. Becker ^a,
J. van Bommel ^b and P.M.L.A. van den Bemt ^a

^a Department of Hospital Pharmacy, Erasmus MC, Rotterdam. ^b Department of Intensive Care, Erasmus MC, Rotterdam.

* Correspondence: a.l.degoede@erasmusmc.nl.

Background

Medication errors may result in patient harm. Especially in intensive care patients, adverse drug events caused by medication errors are common. Interventions by hospital pharmacists have been shown to reduce adverse drug events and costs in intensive care units (ICUs).

During a three-month pilot study, we evaluated the effect of active participation of a hospital pharmacist in the ICU on medication errors and hospital costs.

Methods

The pilot study was performed at the adult 32-bed ICU of the academic hospital Erasmus MC. Four (resident) hospital pharmacists were trained at the electronic IC patient data management system (PDMS) and at specific aspects of intensive care, protocols and guidelines. During July until September 2011, each patient's medication profile was reviewed weekly and a pharmacist of the team was present on rounds once weekly. The medication order review was performed using a standardized written form. If the review revealed any potential medication error requiring intervention, this was documented on the form and discussed during the round. In addition, amount of time spent performing clinical activities at the ICU was recorded.

Results

267 medication reviews were performed for a total of 169 patients in 51 rounds. During the study period 288 interventions were made of which 10% were questions for the ICU physician and 90% were interventions for potential medication errors. About 60% of the medication reviews resulted in at least one intervention. The acceptance rate of the interventions was 56%. In 14% of the interventions it was unknown if they were accepted by the physician. The major cause of non-acceptance was a lack of information at the time the medication review was performed. Interventions, for a total of 120 drugs, were classified into categories with 30% relating to unnecessary drug use, 24% to drug omission and 17% to a wrong dose. Time spent on medication reviews and visiting rounds was 7.3 hour per week.

Based on the results of the pilot study and on literature data, we developed a business case for structural participation of a hospital pharmacist at the ICU.

Conclusions

Participation of a hospital pharmacist in ICU rounds improves medication safety and can be cost-effective. The pilot study and business case have resulted in the appointment of 0.5 FTE hospital pharmacist in the ICU.

Keywords: intensive care – intensive care units – drug safety – adverse drug events – drug costs

Semi-quantitative analysis of GHB while simultaneously using GC-FID for alcohol analysis in serum samples

H.P. de Jong and J.P. Yska *

Department of Clinical Pharmacy and Clinical Pharmacology, Medisch Centrum Leeuwarden.

* Correspondence: j.p.yska@znb.nl.

Background

Gamma-hydroxybutyric acid (GHB) is an endogenous substance, also used as a recreational drug. Clinical effects of GHB and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (BD) are euphoria, amnesia, bradycardia, hypotension, hypothermia, respiratory depression and coma. Long term abuse of GHB may lead to severe addiction. Because GHB toxicity has clinical similarities to ethanol intoxication and simultaneous poisoning is common, a serum ethanol level may be of use in differentiating the two [1]. Many laboratories for clinical toxicology are using GC-FID for determination of ethanol and other alcohols in serum samples. For quantitative determination of GHB a different, more time consuming GC-FID analysis is available [2]. Using the GC analysis for alcohols with a simultaneous semi-quantitative determination of GHB may be very helpful in rapidly diagnosing comatose patients. GHB serum levels > 150-250 mg/L are associated with coma [1].

Objective

To set up a simple, rapid semi-quantitative analysis of GHB in serum from intoxicated patients while using GC-FID for analysis of alcohols.

Materials and methods

Equipment: CP-3800 Varian GC with CP-8410 Varian auto-injector, FID and Empower software; CP-Wax 57 CB column for alcohols and glycols WCOT fused silica 25 m × 0.53 mm × 0.50 µm.

Materials: An internal standard solution of 100 mg/L 1-propanol in water was used. GHB calibration solutions (concentrations of 25, 50, 100, 200 and 500 mg/L in water) were prepared from a stock solution of 1211 mg Na-4-hydroxybutyrate in 100 mL of water. Calf serum, positive alcohol and GHB controls were also used.

Methods: Carrier gas: helium; volume of injection: 1 µL; FID: 220°C; oven: 45°C (0.75 min) → 180°C (20°C/min); run time: 7.5 min. Analysis of serum samples: 200 µL + 1000 µL internal standard solution.

Limited validation: linearity of calibration curve (tested with ANOVA), specificity, selectivity, limit of detection (LOD), limit of quantitation (LOQ), comparison of results of 6 serum samples of patients with specific quantitative GC-FID method.

Results

Linearity was established between 25 and 500 mg/L, with LOD 25 mg/L and LOQ 50 mg/L. The retention times of ethanol, the internal standard 1-propanol and GHB were 1.2, 1.7 and 5.3 min respectively. Recoveries for GHB in patient serum samples in

comparison with results obtained with specific GC-FID method ranged from 98 to 114%.

Conclusion

A simple and rapid GC-FID analysis for screening and semi-quantitative analysis of GHB was developed while using an existing GC-analysis for alcohol and glycols. This method can be very useful for diagnosing overdose of both alcohol and GHB in intoxicated comatose patients.

REFERENCES

- 1 Grouls RJE, Bindels AJGH, Roos A, Keizer K. Gamma-hydroxy-boterzuur (GHB). <http://www.toxicologie.org/monografieen/frametox.asp?ID=32> [accessed 2012 Jan 27].
- 2 Van 't Veer NE, Lameijer W. Gammahydroxyboterzuur. Bepaling in serum. *Pharm Weekbl.* 2001;136:104-5.

Keywords: GHB – alcohol – toxicology – analysis – GC

Risk of venous thromboembolism in patients with total hip / knee replacements and matched controls: a population-based cohort study in Denmark

F. de Vries ^{ab*}, A. Lalmohamed ^b, P. Vestergaard ^c, C. Klop ^b, M. Bazelier ^b and A. de Boer ^b

^a Maastricht University Medical Centre+, Department of Clinical Pharmacy & Toxicology, Maastricht. ^b Utrecht Institute for Pharmaceutical Sciences, Utrecht.

^c Aarhus University Hospital, Department of Endocrinology and Internal Medicine, Aarhus, Denmark.

* Correspondence: frank.de.vries@mumc.nl.

Background

Venous thromboembolism (VTE) is the most common cause for emergency hospital readmission following total hip and knee replacements (THR/TKR). Guidelines recommend thromboprophylaxis for 10-35 days. However VTE risk beyond this period against matched controls has not been studied extensively. Consequently, the objective was to evaluate long-term VTE risk following THR/TKR against matched controls.

Methods

A Danish nationwide cohort study was conducted (1998-2007). Patients with a primary THR/TKR (n = 95,255) were included, and three controls without any evidence for THR/TKR were matched by age, sex, and region. Time-dependent adjusted hazard ratios (HR) for VTE were calculated. Outpatient use of anticoagulants was assessed in the previous six months.

Results

Within six weeks following THR, a 13-fold increased risk of VTE (HR_{adj} 12.88; CI95 11.25-14.76) was observed, as compared to matched controls. Risk remained substantially increased for at

least six months following THR (HR_{adj} 2.23; CI95 1.83-2.70 within 3-6 months postoperatively). In outpatients who were prescribed warfarin, a substantially lower six weeks risk was found (HR_{adj} 7.56; CI95 4.51-12.68), compared to aspirin (10-fold increase), no use (14-fold increase), or other/mixed use (19-fold increase). All findings were similar for TKR patients.

Conclusion

This study shows that VTE risk remains substantially elevated for at least six months following THR/TKR, which is well beyond the recommended duration of anticoagulant use. Furthermore, outpatient use of warfarin appeared to lower VTE risk. It may be worth investigating extended anticoagulant use (for up to six months) in clinical trials.

Keywords: total joint replacement – deep venous thrombosis – pulmonary embolism

Use of glitazones and risk of bladder cancer: disease or drugs?

F. de Vries^{ab*}, M.T. Bazelier^b, P. Vestergaard^c, H.G.M. Leufkens^b and M.L. de Bruin^b

^a Maastricht University Medical Centre+, Department of Clinical Pharmacy & Toxicology, Maastricht. ^b Utrecht Institute for Pharmaceutical Sciences, Utrecht.

^c Aarhus University Hospital, Department of Endocrinology and Internal Medicine, Aarhus, Denmark.

* Correspondence: frank.de.vries@mumc.nl.

Background

Pioglitazone, a thiazolidinedione (TZD), has recently been associated with a small, but increased risk of bladder cancer. However, similar risks for bladder cancer were found in patients with diabetes mellitus. Objective was to evaluate the risk of bladder cancer in diabetic patients according to TZD treatment, in relation the underlying disease.

Methods

We conducted a population-based cohort study (1996-2007) utilizing the Danish National Health Registers. Oral antidiabetic users (n = 179,056) were matched 1:3 by year of birth and sex to non-users. Cox proportional hazards models were used to estimate hazard ratios (HRs) of bladder cancer. Time-dependent adjustments were made for age, co-morbidity, and drug use. Four different treatment stages were defined: the first stage was defined as current use of either a biguanide or a sulfonylurea, the second stage as current use of a biguanide and a sulfonylurea at the same time, the third stage was assigned to patients using TZDs and the fourth stage to patients using insulin.

Results

Compared with non-diabetic controls, patients using antidiabetic

medication experienced a 1.3-fold increased risk of bladder cancer (adjusted HR 1.3; CI95 1.2-1.4). No major differences were observed between the different treatment stages. The risk of bladder cancer varied between 1.2 (CI95 1.0-1.4) in stage 4 and 1.4 (CI95 1.3-1.6) in stage 1. The risk of bladder cancer with TZD use (stage 3) was similar to the other groups (adjusted HR 1.3; CI95 0.6-2.7).

Conclusions

The association between TZD use and bladder cancer is probably confounded by the underlying disease.

Keywords: thiazolidinediones – diabetes mellitus – bladder cancer

Retrospective cross sectional study to determine the prevalence and incidence of severe hypo- and hypercalcaemia in hospitalized patients

J. de Vries^a, M. Kokkelink^a, A.T.M. Wasylewicz^a, A.M.J.W. Scheepers-Hoeks^{a*}, A.M. Harmsze^a, B. Bravenboer^b and R.J.E. Grouls^a

Departments of ^a Clinical Pharmacy and ^b Internal Medicine; Catharina Hospital, Eindhoven.

* Correspondence: anne-marie.scheepers@catharina-ziekenhuis.nl.

Background

Severe hypo- and hypercalcaemia can have serious effects. Few data exist on the prevalence of hypo- and hypercalcaemia in a general hospital setting. Next to certain specific diseases, several drugs are known to influence plasma calcium levels. Clinical rules incorporated in a clinical decision support system (CDSS) are increasingly used as third generation medication safety systems, but can also provide useful epidemiological data [1].

Aim

To identify the prevalence, incidence and causes of severe hypo- and hypercalcaemia and to quantify the percentage of these patients using calcium concentration influencing drugs in a general hospital setting. The secondary objective was to investigate whether clinical rules/CDSS can be used to facilitate epidemiological studies.

Methods

A clinical rule selecting patients with (corrected) critical calcium levels (< 1.8 and > 2.8 mmol/L) and drugs influencing plasma calcium levels was developed and validated according to the method described by Scheepers et al. [2]. Cut-off values and drugs influencing plasma calcium levels were in consensus with the Department of Internal Medicine of the Catharina Hospital Eindhoven (CZE) and based on the guidelines of the Netherlands Association of Internal Medicine (NIV) [3]. Data of all patients admitted to the CZE in 2011 (n = 17,814) were retrospectively analyzed using a CDSS (Gaston, Medecs BV). The electronic medical records (EMR) of

these selected patients were studied to determine the incidence and cause of hypo- and hypercalcaemia.

Results

The validated clinical rule automatically generated a reliable patient database containing all relevant data to calculate prevalence, incidence and drug use. The prevalence of severe hypo- and hypercalcaemia is 0.25% (n = 44) and 0.44% (n = 79) respectively. The incidence proportion for developing a hypo- and hypercalcaemia during admission is 0.16% and 0.07% respectively. In case of severe hypercalcaemia 19.0% of patients used calcium concentration increasing drugs (predominantly thiazide diuretics and/or calcium suppletion). Patients presenting with severe hypocalcaemia used calcium concentration lowering drugs (loop diuretics and/or bisphosphonates) in 18.2% of the cases. The major identifiable causes of hypocalcaemia were saline hydration (20.5%), renal impairment (18.2%), hypoparathyroidism (9.1%) or multiple causes (20.5%). For hypercalcaemia these were malignancy (15.2%), hyperparathyroidism (8.9%), renal impairment (6.3%) or multiple causes (25.3%).

Conclusion

Results of this retrospective study show that the prevalence and incidence proportion of severe calcium disturbances in a general hospital setting are low. Approximately a fifth of the identified patients use calcium influencing drugs. The results also show the potential of CDSS to facilitate the conduct of epidemiological studies.

REFERENCES

- 1 Grouls RJE. Clinical rules and decision support systems for medication safety: the future is now. *Eur J Hosp Pharm.* 2011;17(5):30.
- 2 Scheepers-Hoeks AM, Grouls RJ, Neef C, Korsten HH. Strategy for implementation and first results of advanced clinical decision support in hospital pharmacy practice. *Stud Health Technol Inform.* 2009;148:142-148.
- 3 Agtmael MA, Alleman MA, Balkom B, et al. Acute boekje – richtlijnen voor de diagnostiek en behandeling van aandoeningen op het gebied van inwendige specialismen – vierde editie. Alphen aan den Rijn: Van Zuiden Communications; 2009. p. 177-181.

Keywords: prevalence – incidence – CDSS – clinical rule – hypocalcaemia – hypercalcaemia

Cost effective patient medication review in a large geographically wide spread mental health institution

P.J. de Wolf^{ab*}, E. Knijnenburg^c and M.S.S. Sjak Shie^{ab}

^a GGZ Foundation for Mental Health Care Rivierduinen. ^b Central Hospital Pharmacy The Hague. ^c Numerando.

* Correspondence: p.dewolf@rivierduinen.nl.

Background

In order to optimize patient safety for long stay inpatients in a mental health institution with seven geographical locations, the treatment team (psychiatrist, pharmacist, nurse) has to evaluate the medication records annually. To optimize and standardize this process we wanted to develop a method where pharmacy technicians prepare the medication review.

Objective

The aim of this pilot study is to develop an effective and efficient method for medication review. Effective was defined as a reduction of potential medication related problems with at least 40% and efficient was defined as a first systematic check by a pharmacy technician using a standard evaluation form resulting in lower costs compared to the classical method by a hospital pharmacist with the prescriber on the ward.

Methods

Based on the literature, the HARM-Wrestling report and the Pharmaceutical Care Network Europe classification for medication related problems (MRPs) a pharmacy medication evaluation form was designed for the screening of medication records for possible MRPs specific for chronic psychiatric inpatients. Two wards with in total 55 patients living in our institution for at least one year were selected for medication review. The medication record was screened by the pharmacy technician with the use of the checklist. When the encountered potential MRPs were not documented in the electronic patient record, the pharmacist addressed a proposal for intervention to the prescriber by e-mail. The MRPs and results were collected and categorised.

Results

A checklist with 13 items was designed. 43 medication reviews were conducted and in total 83 MRPs were presented to the prescribers. In the category 'stop medication/no indication (any more)' the response rate was 74%. In the category 'stop medication/also another drug prescribed for this indication' the response rate was 20%. In the categories 'add a drug, reduce the dose or elevate the dose' the response rate was 0%. In the category 'extra monitoring' the response rate was 73%. MRPs were reduced with 46%. The costs of a review were € 35 for the pharmacy.

Conclusions

The results shows that medication review with a standard checklist and prepared by a pharmacy technician is possible. This method reduces the preparation time by the pharmacist and stan-

standardises the process. Standard medication review prepared by a pharmacy technician is an effective way to periodically review the medication and reduce medication related problems with at least 40% in our chronic inpatient population in an institution with seven geographic locations.

Keywords: medication review – psychiatric inpatients – mental health institution – medication related problems

Resolving the problem of particles in asparaginase (Erwinase) infusion bags

F.K. Engels ^{*}, C. Vermaat and L.M. Hanff

Department of Hospital Pharmacy, Erasmus University Medical Center, Rotterdam.

* Correspondence: f.engels@erasmusmc.nl.

Background

Paediatric patients diagnosed with acute lymphoblastic leukemia (ALL) are treated with asparaginase (Erwinase) as part of their chemotherapeutic treatment. The SPC prescribes reconstitution of asparaginase lyophilized powder (10,000 IE) with water for injections and administration as a bolus injection, *i.e.* without further dilution [1]. However, asparaginase, an enzyme derived from *Erwinia chrysanthemi*, often leads to allergic reactions, ranging from mild symptoms to anaphylactic shock (administration is then immediately stopped). Administration as a one hour infusion minimises the risk of a severe anaphylactic reaction and is therefore the preferred route of administration in our clinic. However we often observe visible particles in the 50 mL NaCl 0.9% infusion bags, upon which the infusion is discarded. This results in a longer waiting time for the patient and considerable increase in costs.

Aim

1. Qualification and quantification of particles in the infusion bags. 2. Evaluation of alternative reconstitution/dilution and filtration options to eliminate visible particles in the infusion bags. 3. Assessment and comparison of asparaginase activity.

Methods

Samples containing particles were examined by light microscopy, photographed and analysed by Fourier transform infrared spectroscopy. Particles were sized and counted using a particle counter (PSS Accusizer 780). Given the fact that asparaginase is dissolved in a NaCl/glucose solution prior to lyophilisation dilution in glucose 5% 50 mL was evaluated. Filtration was evaluated using a 5 µm filter (PALL PharmAssure syringe filter HP1050). Quantification of asparaginase activity was performed as reported by Lanvers et al. [2].

Results

The particles were attributed to agglomeration of protein, presum-

ably stemming from precipitated asparaginase. In the reference sample (dilution in NaCl 0.9%) the number of particles sized > 10 µm and > 25 µm was 8 respectively 10 times above the limits of the *Ph Eur*. Filtration of the reconstituted solution through a 5 µm filter before addition to the infusion bag with NaCl 0.9% did not eliminate the visible particles, suggesting that protein agglomeration continues to occur upon dilution with NaCl 0.9%. Number and size of particles in the dilution with glucose 5% (with or without in-line filtration) were according to *Ph Eur* guidelines. Asparaginase activity of the dilution in glucose 5% (mean ± sd) did not differ significantly from the reference dilution in NaCl 0.9%.

Conclusions

Dilution of asparaginase (Erwinase) in glucose 5%, 50 mL after reconstitution virtually eliminates protein agglomeration. Asparaginase activity did not differ significantly from the reference samples diluted with NaCl 0.9%.

REFERENCES

- 1 SPC Erwinase: <http://db.cbg-meb.nl/IB-teksten/h16986.pdf>.
- 2 Lanvers C, Vieira Pinheiro JP, Hempel G, Wuerthwein G, Boos J. Analytical validation of a micro-plate reader-based method for the therapeutic drug monitoring of L-asparaginase in human serum. *Anal Biochem.* 2002;309(1):17-26.

Keywords: asparaginase – Erwinase – protein agglomeration – particles

The effect of pharmacist intervention on medication reconciliation in the emergency department

M. Gam ^{ab}, S. Coenradie ^a, M. van Geest ^a, M.R. de Vries ^c and P.N.J. Langendijk ^{ax}

Departments of ^a Hospital Pharmacy and ^c Surgery; Reinier de Graaf Group Hospitals, Delft. ^b Pharmacy student, University of Groningen.

* Correspondence: p.langendijk@rdgg.nl.

Background

Many efforts have been put into the organisation of good quality and safe pharmaceutical care. In general, the involvement of the hospital pharmacist in the process of medication reconciliation results in a reduction of the number of medication discrepancies. However, in case of emergency admissions this topic is still insufficiently studied. The introduction of medication reconciliation on the emergency department (ER) requires logistical, organisational and financial efforts. We investigated the effects of pharmacists intervention on drug reconciliation in emergency admissions in order to identify discrepancies between medication lists taken by ER physicians and pharmacy technicians.

Methods

In this observational, comparative, non-randomised intervention study we calculated a population size of 65 patients being suf-

ficient to perform reliable measurements. Inclusion criteria: all patients presented at the ER and admitted to a hospital ward < 24 h after presentation, usage of one or more prescription drugs. Exclusion criteria: age < 18 years, residency outside the region Delfland, inability to undergo an oral interview, absence of a medication list of the public pharmacy (OZIS list), decease of the patient during ER stay and patients undergoing surgical procedures.

During the intervention measurement we analysed the reconciled medication by comparing the ER's physician's list with the list of the pharmacy technician after a medication verification interview. Discrepancies between both medication lists were classified in four categories of increasing severity (1 = no discrepancy to 4 = clinical relevant discrepancy) using the index of the National Coordinating Council for Medication Error Reporting and Prevention (www.nccmerp.org). Discrepancies were categorised by a panel of a pharmacy technician, a hospital pharmacist and a 5th year pharmacy student. Statistical analysis was carried out with a statistical software package (SPSS 18) using the Mann-Whitney U test and chi-squares test.

Results

During the intervention measurement 768 patients were admitted to the ER. 65 patients (8.5%) met the inclusion and not the exclusion criteria. The number of medication discrepancies decreased significantly after intervention of the pharmacy technician by 52%, from 161 to 77 discrepancies. The average number of discrepancies per patient after intervention decreased by 68.0%, from average 2.5 to 0.8 discrepancies per patient.

Conclusions

Medication verification by pharmacy technicians in the ER reduces the number of medication discrepancies by half. Medication lists generated with a standard interview by pharmacy technicians in combination with an OZIS list on admission of patients at the ER is more complete and accurate than the current method.

Keywords: medication reconciliation – emergency admissions – pharmacist involvement

Amoxicillin time above MIC in hospitalized patients

T. Havenith ^{a*}, M. Haeseker ^b, A. Verbon ^c, L. Stolk ^a and C. Neef ^a

^a Maastricht University Medical Center, Department of Clinical Pharmacy & Toxicology, Maastricht. ^b Maastricht University Medical Center, Department of Medical Microbiology, Maastricht. ^c Erasmus Medical Center, Department of Infectious diseases, Rotterdam.

* Correspondence: t.havenith@mumc.nl.

Background

Amoxicillin + clavulanic acid is a widely used broad spectrum

antibiotic. The probability of cure of an infection with amoxicillin has been shown to be dependent on time above minimal inhibitory concentration ($t_{>MIC}$). The pharmacodynamic target is $t_{>MIC} \geq 40\%$. Our aim was to determine what percentage of hospitalized patients treated with intravenous amoxicillin + clavulanic acid reached the target ($t_{>MIC} \geq 40\%$).

Methods

Between January 2010 and October 2010 serum amoxicillin concentrations were determined in hospitalized (not intensive care) patients receiving intravenous amoxicillin + clavulanic acid using surplus serum samples and a validated HPLC method. The standard intravenous dose amoxicillin + clavulanic acid was 1000 + 200 mg every 6 hours. Individual pharmacokinetic parameters were calculated using maximum *a posteriori* Bayesian estimation. $t_{>MIC}$ was calculated using individual pharmacokinetic parameters, dose, dosing interval and MIC. Target attainment was determined for standard dose, computer simulated doses and at different MIC's (range 0.5-32 mg/L).

Results

Serum amoxicillin concentrations were determined in 57 patients (17 female, 40 male). The mean age was 67 years (range 23-93 years) and the mean creatinine clearance (CLcr) was 70 mL/min (range 27-143 mL/min). The mean amoxicillin clearance corrected for body weight was 0.17 L·h⁻¹·kg⁻¹ (range 0.05-0.36 L·h⁻¹·kg⁻¹). Patients older than 70 years had a significant lower amoxicillin clearance ($P = 0.023$). 7% and 35% of the patients did not reach the target ($t_{>MIC} \geq 40\%$) at MIC = 4 mg/L and MIC = 8 mg/L respectively. A computer simulated dose increase with twice daily amoxicillin 1000 mg decreased these percentages to 0% and 5% respectively.

Conclusion

This study shows that the amoxicillin pharmacodynamic target ($t_{>MIC} \geq 40\%$) is not reached in a substantial part of hospitalized patients treated with the standard intravenous dose of amoxicillin + clavulanic acid. Increasing the amoxicillin dose with twice daily 1000 mg amoxicillin gives maximum target attainment at MIC = 4 mg/L.

Keywords: amoxicillin – PK/PD

Genetic variation in CYP19A1 is related to response to exemestane: survival in early breast cancer in the Dutch TEAM trial

D. Houtsma ^{a*}, D.B.Y. Fontein ^a, R.J.H.M. van der Straaten ^a, R. Baak-Pablo ^a, J.A.M. Wessels ^a, E. Meershoek-Klein Kranenborg ^a, C. Seynaeve ^b, C.J.H. van de Velde ^a, J.W.R. Nortier ^a, H-J. Guchelaar ^a and H. Gelderblom ^a

^a Leiden University Medical Center, Leiden. ^b Erasmus MC Daniel Den Hoed, Rotterdam.

* Correspondence: d.houtsma@lumc.nl.

Background

In patients with endocrine sensitive breast cancer treated with adjuvant aromatase inhibitors (AI) it is unclear which patients will develop a recurrence and who will benefit from AIs. Variations in the aromatase gene (*CYP19A1*) are associated with altered estrogen levels and altered aromatase activity. The aim of this study was to examine the effect of SNPs in the *CYP19A1* gene on survival in a prospective cohort of breast cancer patients treated with adjuvant exemestane.

Methods

Patients of whom tissue was available and who were treated with five years of exemestane were selected from the Tamoxifen Exemestane Adjuvant Multinational (TEAM) trial. DNA was isolated from tumour samples and 30 SNPs were identified using a tagging SNP approach, aiming for 80% coverage of *CYP19A1*. Genotypes were determined with Taqman assays.

Primary endpoint of the study was relapse-free survival (RFS) and secondary endpoint was overall survival (OS). A Kaplan-Meier analysis was performed and Cox proportional hazards models assessed survival differences. Analyses were adjusted for age at diagnosis, tumour size, nodal status, histological grade, surgery, adjuvant radiotherapy and chemotherapy.

Results

807 patients were included in the analyses and genotypes were obtained in 722 cases. A significant association with worse RFS was found with two SNPs: rs7176005 and rs16964211, showing hazard ratios (HR) of 3.48 and 5.42 for the homozygous variant

types respectively. These SNPs, as well as a third SNP, rs6493497, were also significantly associated with OS (HR 5.87, 5.3 and 3.36 respectively).

Conclusions

Germline variations in the *CYP19A1* gene are related to a worse outcome in early breast cancer patients treated with exemestane. These findings may contribute to the individualization of hormonal therapy in breast cancer.

Keywords: CYP19A1 – breast cancer – polymorphisms – aromatase inhibitors

Effectiveness of discharge medication related interventions. A systematic review

F. Karapinar-Çarkıt ^{ab*}, S.D. Borgsteede ^c, M.J.A. Janssen ^a, M. Adluni-Sheikh Rashid ^a, F. Attema ^a, A.C.G. Egberts ^{bd} and P.M.L.A. van den Bemt ^{be}

^a Department of clinical pharmacy, Sint Lucas Andreas Hospital, Amsterdam.

^b Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University. ^c Health Base, Houten.

^d Department of clinical pharmacy, University Medical Centre Utrecht.

^e Department of Hospital Pharmacy, Erasmus MC, Rotterdam.

* Correspondence: f.karapinar@slaz.nl.

Background

No systematic review has focused on discharge medication related interventions (DMIs) aimed at improving continuity of care between the hospital and community setting. This study aimed to systematically review the evidence for the effectiveness of DMIs in order to reduce post-discharge medication problems in adult patients.

Methods

Multiple electronic bibliographic databases (until August 2010) were searched supplemented with hand searches of references. Independent assessors evaluated 6984 articles. Studies with a control group were included if the article involved a DMI performed around hospital discharge for adult patients discharged home. The outcomes hospital readmission rates (primary), health services use, mortality, medication knowledge, adherence, and drug-related problems (DRPs) were studied. Studies were categorized based on their characteristics (e.g. intervention components, methodological quality). Data were synthesized by use of narrative methods.

Results

58 original articles met the inclusion criteria. Studies described multi-component and various interventions. Hospital readmission rates (n = 17) and health services use (n = 10) were reduced in 18% and 40% of studies respectively. Mortality was not decreased (n = 5). Medication knowledge (n = 20) and adherence (n = 20) was

	Number of genotype	Univariate HR (CI95)	P	Multivariate HR (CI95)	P
rs7176005			0.015		0.033
• CC	578	1 (ref)		1 (ref)	
• CT	130	1.83 (1.15-2.91)		1.75 (1.05-2.92)	
• TT	8	2.78 (0.68-11.4)		3.48 (0.83-14.6)	
rs16964211			0.021		0.019
• GG	629	1 (ref)		1 (ref)	
• AG	67	1.04 (0.52-2.06)		0.52 (0.23-1.17)	
• AA	4	5.82 (1.43-23.7)		5.42 (1.25-23.4)	

improved in 75% and 70% of studies respectively. 28 studies evaluated DRPs of which 26 were effective (93%). In general, larger sample sizes led more frequently to effective studies. Studies with good methodological quality tended to be more frequently effective for the outcomes readmission and knowledge.

Conclusions

DMIs were reported to be effective for process measures (knowledge, adherence and DRPs). Only a limited number of studies reported effectiveness on morbidity (readmission and health services use).

Keywords: continuity of care – hospital discharge – rehospitalisation – drug-related problems – patient adherence

The effect of a pharmaceutical transitional care program on unplanned rehospitalisations in internal medicine patients

F. Karapinar-Çarkıt^{ab*}, S.D. Borgsteede^c, M.J.A. Janssen^a, M. Mak^a, N. Yildirim^a, C. Siegert^d, P.G.M. Mol^e, A.C.G. Egberts^{bf} and P.M.L.A. van den Bemt^{bg}

^a Department of clinical pharmacy, Sint Lucas Andreas Hospital, Amsterdam.

^b Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University. ^c Health Base, Houten.

^d Department of internal medicine, Sint Lucas Andreas Hospital, Amsterdam.

^e Department of Clinical Pharmacology, University Medical Centre Groningen.

^f Department of clinical pharmacy, University Medical Centre Utrecht.

^g Department of Hospital Pharmacy, Erasmus MC, Rotterdam.

* Correspondence: f.karapinar@slaz.nl.

Background

Medication errors occur frequently at points of transition of care and have a negative effect on patient safety. The main objective of this study was to determine the effect of a transitional pharmaceutical care program on unplanned rehospitalisations within six months after discharge.

Methods

A before-after study was performed at the internal medicine ward of a general teaching hospital. All patients admitted with at least one prescribed drug intended for chronic use were included. The transitional pharmaceutical care program COACH consisted of medication reconciliation, patient counselling at discharge and communication to primary care healthcare providers. The primary outcome was the frequency of patients with an unplanned rehospitalisation within six months after discharge. Secondary outcomes included number of interventions to prevent drug-related problems (DRPs), adherence, beliefs about medication and patient satisfaction. Interrupted time series analysis was used for the primary outcome. Descriptive statistics were performed for the secondary outcomes.

Results

In the before-period 341 patients were included and in the after-period 365 patients. In the before-period 27.3% of patients had an unplanned rehospitalisation, whereas this became 33.2% in the after-period. The introduction of the COACH program led to a non-significant increase of 12.7% (CI95: -7.3-32.7) of unplanned rehospitalisations. The change in trend between the before- and after-period was non-significant (-0.2%, CI95: -4.9-4.6). For all patients included in the COACH program interventions were performed to prevent DRPs (mean interventions: 10 per patient). No effect was seen on adherence and beliefs about medication. Patients were significantly more satisfied with counselling provided by a pharmacy member compared to the resident (68.9% resident vs 87.1% pharmacy).

Conclusions

The COACH program showed no effect on unplanned rehospitalisations. For all patients interventions were performed to prevent DRPs. The program increased patient satisfaction with counselling. No effect was seen on other secondary outcomes.

Keywords: continuity of care – transitions – rehospitalisation – drug-related problems – hospital discharge
Dutch Trial Register NTR1519

Development of a clinical prediction model for supratherapeutic INR in hospitalized patients on vitamin K antagonist therapy

A.D. Lindemans^{a*}, J.C. van Blijderveen^b, Y. Vergouwe^c, M.J.H.A. Kruip^d, M.C.J.M. Sturkenboom^b, A.G. Vulto^a and P.M.L.A. van den Bemt^a

^a Department of Hospital Pharmacy, ^b Department of Epidemiology,

^c Department of Public Health, medical decision making, ^d Department of Haematology; Erasmus MC Rotterdam.

* Correspondence: a.lindemans@erasmusmc.nl.

Background

Epidemiological research has shown that in 5-10% of hospital admissions, patients are harmed due to a medical error. In approximately 50% of these cases, medication is involved. Other reports have shown that oral anticoagulants are responsible for a large part of preventable medication-related harm to outpatients. There is no reason to assume this is different in hospitalized patients. We aim to develop a clinical prediction model for the risk of supratherapeutic INR with vitamin K antagonist (VKA) use. This enables hospital pharmacists to identify high-risk patients and provide pro-active, specific medication advice.

Methods

The study was designed as a retrospective cohort study. We included adult patients (admitted to Erasmus MC from 2006-2009)

with a prescription for a VKA. An event is defined as having an INR ≥ 4.5 during the treatment period in the hospital. Multiple hospitalisations for patients were included in the analysis, provided there was a prescription for a VKA.

Predefined potential risk factors for having an event were age and sex, clinical laboratory results for hepatic and renal function ALAT, ASAT, gamma-GT, LDH, albumin, e-GFR (MDRD formula), haemoglobin (Hb) levels, known interacting medication at start of VKA treatment and the number of co-medications at start of VKA treatment. The risk factors, extracted from the electronic patient database, were analyzed by logistic regression analysis using the 'enter' method.

Results

In the period 2006-2009, 5388 admissions with one or more VKA prescriptions were registered for 3573 patients. In 1284 (21%) of these admissions a patient had an INR ≥ 4.5 during the treatment period (677 unique patients).

Male sex, a high Hb, higher e-GFR were protective for a supra-therapeutic INR with odds ratios (OR) of resp. 0.82 (CI95 0.71-0.94), 0.875 (0.809-0.946) and 0.992 (0.990-0.994). Increasing age, the use of amiodarone, the number of comedications and having had a previous event increased the risk of suprathreshold INR with ORs of resp. 1.01 per year (CI95 1.003-1.015), OR 1.45 (1.17-1.80), OR 1.035 per added co-medication (0.016-1.056) and OR 1.64 (1.35-1.99).

Conclusions

The baseline risk factors for use of amiodarone and having had a previous event were the strongest. Amiodarone inhibits VKA metabolism, which increases INR. Having had a previous event might indicate having predisposing other characteristics which are not included in this model.

This prediction model consists of baseline parameters. It will be developed more in depth in future research, including time dependent variables.

Keywords: vitamin K antagonist – coumarin – INR – risk factor – prediction model

COX-1 affinity determines the NSAID–aspirin interaction with respect to thrombocyte function

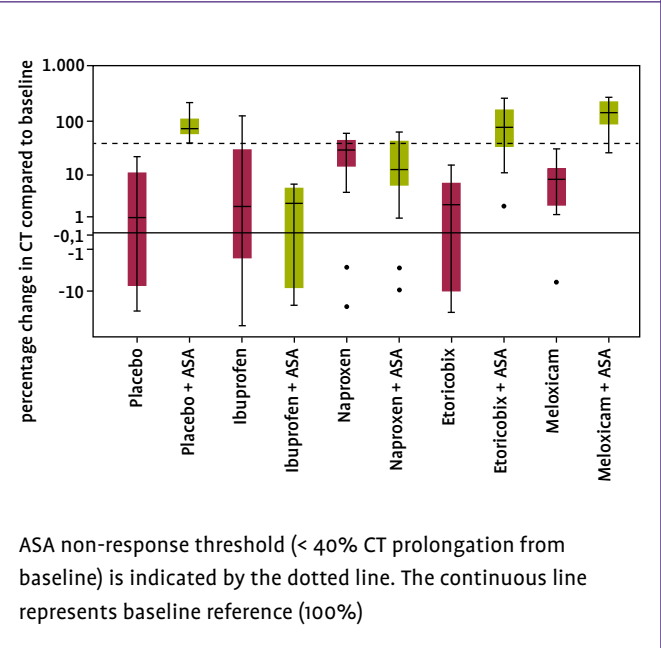
I. Meek, K.L.L. Movig, J. Kasemier, H.E. Vonkeman and M.A. van de Laar

Rheumatology & Clinical Immunology, Rheumatology Centre Twente, Medisch Spectrum Twente & Twente University, Enschede. Department of Clinical Pharmacy, Medisch Spectrum Twente, Enschede.

Background

Non-steroidal anti-inflammatory drugs (NSAIDs) and acetylsalicylic acid (ASA) are often prescribed concurrently in patients with

FIGUUR 1
CT prolongation after use of NSAID or placebo in combination with ASA



rheumatic diseases. Both drugs inhibit the same COX enzymes, and thus may interact. Preceding pharmacodynamic studies confirm significant inhibition of ASA's antiplatelet effect by concurrent use of ibuprofen or indometacin, but show conflicting results for naproxen. ASA's cardioprotective antiplatelet effect is entirely COX-1 dependent, which may explain the limited interaction between ASA and COX-2 selective NSAIDs.

Objective

To examine the interaction between ASA and different selective and non-selective NSAIDs on thrombocyte function.

Methods

Single blind, prospective, placebo controlled, *ex vivo*, serial cross-over trial of three-day cycles separated by washout periods of at least 12 days in healthy volunteers, evaluating interaction on ASA's antiplatelet effect by naproxen, ibuprofen, meloxicam, or etoricoxib taken two hours before ASA. *Ex vivo* platelet function, expressed as closure time (CT) in seconds, was measured using the Platelet Function Analyzer 100 (PFA-100). CT prolongation during a cycle reflects the platelet inhibitory effect. ASA non-response was defined as CT prolongation < 40% in the placebo cycle, ASA non-responders were excluded from the study. The effect of different NSAIDs on CT prolongation was evaluated by Wilcoxon signed-rank test.

Results

Ibuprofen and naproxen show inhibition of ASA's antiplatelet effect below the non-response threshold. Etoricoxib and meloxicam show no relevant change in ASA thrombocyte inhibition.

Conclusion

COX-1 affinity determines the interaction between NSAIDs and ASA on thrombocyte function: aggregation and clotting. Ibuprofen and naproxen, but not etoricoxib or meloxicam, taken two hours before ASA significantly inhibit ASA's antiplatelet effect.

Keywords: NSAID-aspirin interaction – thrombocyte function – rheumatic diseases

Rhabdomyolysis after auto-intoxication with MDPV, a new designer drug

T.T.H. Nguyen ^a, S.C.E. Schuit ^a, B.C.P. Koch ^{b*} and A. Govers ^a

^a Erasmus Medical Centre Rotterdam, Department of Internal Medicine.

^b Erasmus Medical Centre Rotterdam, Department of Hospital Pharmacy.

* Correspondence: b.koch@erasmusmc.nl.

Background

In recent years the use of designer drugs has gained widespread popularity. Designer drugs are new drugs, created to avoid current drug laws, and/or to enhance psychoactive effects of existing drugs, usually by modifying molecular structures. Methylene-dioxypyrovalerone (MDPV) is a new designer drug that has been on the market since 2004 as an alternative to amphetamines with fewer side effects. Although little information can be found in the literature, MDPV can cause severe side effects. Furthermore, standard drug testing does not detect MDPV.

Methods and results

A 21-year old male was admitted to our Emergency Department with an MDPV intoxication. Physical examination revealed a blood pressure of 150/100 mmHg, tachycardia of 132 bpm and significant hyperkinesias and paranoid behaviour. The temperature was 37.0 °C. Laboratory assessment: creatinine 214 µmol/L (65-110 µmol/L), urea 11.6 mmol/L (3-7 mmol/L), creatine kinase 13,508 U/L (< 170 U/L), WBC 39·10⁹/L (4-10·10⁹/L), CRP 12 mg/L (< 10 mg/L). Postrenal causes of renal failure were ruled out by a normal renal ultrasound. Urine drugs of abuse (DOA) screening was negative for amphetamines, cocaine and opiates. Treatment consisted of rehydration according to standard rhabdomyolysis guidelines.

Final diagnosis was rhabdomyolysis with acute renal failure most likely due to MDPV abuse and drug-induced psychosis. The massive leukocytosis was attributed to extreme stress, since there were no clinical signs of infection or haematological disorder. After rehydration and normalization of laboratory parameters and clinical symptoms, the psychiatrist was consulted for the patients' paranoid behavior. Treatment consisted of haloperidol and benzodiazepines and he was later transferred to the psychiatric ward. MDPV is related to methylphenidate and MDMA. It is assumed that it acts as a norepinephrine-dopamine reuptake inhibitor, and to a lesser extent as a serotonin reuptake inhibitor. For oral use

the onset of desired symptoms are expected after 15-30 minutes, primary desired effects last 3-4 hours and coming down effects last 6-8 hours. Side effects can last up to 48 hours. Acute physical effects include hypertension and tachycardia; mental effects are euphoria, increased awareness and arousal, anxiety and agitation. High doses are reported to cause depression, headache, prolonged panic attacks and psychosis. Standard DOA screening does not reveal intoxication with MDPV.

Conclusion

Use of MDPV is not always without consequences and awareness of side effects such as rhabdomyolysis and drug-induced psychosis is necessary. We recommend measuring creatine kinase, as early detection and therefore treatment of rhabdomyolysis can prevent renal failure. MDPV cannot be found in the standard DOA screening in urine.

Keywords: designer drugs – MDPV – toxicology – rhabdomyolysis

Association between *CYP2D6* genotype, serum endoxifen concentration and *CYP2D6* phenotype determined by a dextromethorphan breath test in breast cancer patients using tamoxifen

F.L. Opdam ^{ab*}, V.O. Dezentjé ^{ab}, J. den Hartigh ^b, A.S. Modak ^c, J.W.R. Nortier ^a, H. Gelderblom ^a and H-J. Guchelaar ^b

^a Department of Clinical Oncology, ^b Department of Clinical Pharmacy and Toxicology; Leiden University Medical Center, Leiden. ^c Cambridge Isotope Lab. Inc., Andover, USA.

* Correspondence: f.l.opdam@lumc.nl.

Background

CYP2D6 is one of the main enzymes by which the prodrug tamoxifen is metabolized to its active metabolite endoxifen. Recent literature suggests a minimal concentration threshold of 5.97 ng/mL above which endoxifen is more effective in preventing breast cancer recurrence (Madlensky et al., 2011). The wide inter-individual variation in endoxifen levels is not explained from the *CYP2D6* genotype alone. Other factors like interacting medication might attribute to this variation (Jin et al., 2005). We hypothesized that the actual *CYP2D6* phenotype, determined by the ¹³C-dextromethorphan breath test (DM-BT), predicts serum endoxifen levels better than *CYP2D6* predicted phenotype upon genotyping.

Methods

As part of a prospective multicenter study aimed at relating *CYP2D6* genotype and endoxifen serum levels to tamoxifen efficacy in patients with early breast cancer, in 65 patients *CYP2D6* phenotype was assessed by a ¹³C-dextromethorphan breath test (Cambridge Isotope Laboratories, Inc.). Fifty minutes after administration of 0.5 mg/mL ¹³C-dextromethorphan, a 1.3 L breath sample was collected, from which a ¹³CO₂/¹²CO₂ ratio was determined by

infrared spectrophotometry. Delta-over-baseline after 50 minutes (DOB_{50}) values were calculated from baseline and postdose $^{13}CO_2/^{12}CO_2$ ratios, reflecting CYP2D6 clinical phenotype. CYP2D6 genotype was determined by Amplichip. Genotype was translated into a gene activity and an extensive (EM), heterozygous extensive (hetEM), intermediate (IM) or poor metabolizer (PM) predicted phenotype.

Results

Mean endoxifen levels were 17.16 ng/mL (CI95 14.73-19.60) in EMs (n = 29), which were significantly higher than in hetEMs (n = 25; 10.41 ng/mL; CI95 8.79-12.03), IMs (n = 3; 5.43 ng/mL; CI95 3.60-7.26), and PMs (n = 8; 3.48 ng/mL; CI95 2.33-4.62). CYP2D6 gene activity correlated better ($R^2 = 0.454$, $P < 0.01$) with serum endoxifen levels than did CYP2D6 phenotype determined by DM-BT ($R^2 = 0.267$, $P < 0.01$). Optimal positive predictive values (PPVs; 100%) and negative predictive values (NPVs; 90%) were found for DOB_{50} cut-off values of 0.7-0.9 and gene activity of 1.0.

Conclusion

Despite moderate correlation between CYP2D6 predicted phenotype and serum endoxifen levels, DM-BT reliably predicts serum endoxifen levels and might be of value in selection of individualized endocrine therapy

Keywords: tamoxifen – endoxifen – genotype – phenotype – dextromethorphan – breath test

Association of ABCB1, 5-HT3B receptor and CYP2D6 genetic polymorphisms with ondansetron and metoclopramide antiemetic response in Indonesian cancer patients treated with highly emetogenic chemotherapy

Dyah A. Perwitasari^{abc}, Judith A.M. Wessels^b, Tahar van der Straaten^b, Renee F. Baak-Pablo^b, Mustofa Mustofa^c, Mohammad Hakimi^d, Johann W.R. Nortier^e, Hans Gelderblom^e and Henk-Jan Guchelaar^b

^a Department of Pharmacy, Ahmad Dahlan University, Yogyakarta, Indonesia.

^b Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center (LUMC), Leiden. ^c Department of Pharmacology and Therapy, Universitas Gadjah Mada, Yogyakarta, Indonesia. ^d Department of Obstetrics and Gynaecology, Universitas Gadjah Mada, Yogyakarta, Indonesia. ^e Department of Clinical Oncology, LUMC, Leiden.

Background

Cancer was the fourth leading cause of death in Indonesia in 2005 and it is estimated to become the third in 2030. Chemotherapy, one of the cancer treatment choices, can increase the progression-free survival and overall survival time. However, patients who are treated with cytotoxic agents are also experiencing side effects and they may refuse to continue the next cycles of chemotherapy.

Nausea and vomiting is the most distressing side effect of chemotherapy for cancer patients. Suboptimal treatment of chemotherapy-induced nausea and vomiting (CINV) cause impairment of cancer patient's daily functioning. This study was aimed to investigate the association of selected germline polymorphisms with ondansetron and metoclopramide response in Indonesian cancer patients treated with highly emetogenic chemotherapy.

Methods

We enrolled 202 chemotherapy naive patients treated with cisplatin at a dosage ≥ 50 mg/m² as monotherapy or as combined chemotherapy in a cohort study. Ondansetron 8 mg and dexamethasone 8 mg intravenously were the standard antiemetic therapy for prevention of acute CINV. Metoclopramide 10 mg orally, 3 times/day was given until 5 days after chemotherapy to prevent delayed CINV. We grouped the acute nausea and vomiting into grade 1-2 and grade 3-4 nausea/vomiting according to National Cancer Institute Common Toxicity Criteria v.3 (NCI CTC v.3) as the primary outcome. The secondary outcome was delayed CINV scored dichotomically. Patients without delayed emesis were defined as patients without vomiting and/or had less than a 5 score on the NVAS (Nausea Visual Analog Scale), while patients with delayed emesis were patients with vomiting and/or scored ≥ 5 scale of NVAS. The following single nucleotide polymorphisms were determined in ABCB1: rs1045642, rs2032582, rs1128503; in 5-HT3B receptor: rs45460698, rs4938058, rs7943062 and in CYP2D6: rs16947 (CYP2D6*2), rs3892097 (CYP2D6*4), rs1065852 (CYP2D6*10) using Taqman assays.

Results

During the acute phase, 21.8% and 30.2% patients experienced grade 3 and 4 nausea and vomiting, respectively, whereas 38.6% patients experienced nausea and/or vomiting in the delayed phase. Carriers of the CTG haplotype of the ABCB1 gene experienced grade 3 and 4 CINV more often than other haplotypes in the delayed phase (59.4% vs 40.6%, $P < 0.05$). No associations were found with the 5-HT3B receptor haplotypes and CYP2D6-predicted phenotypes.

Conclusions

Our study shows that in Indonesian cancer patients treated with highly emetogenic chemotherapy carriership, the CTG haplotype of the ABCB1 gene is related to an increased risk of delayed CINV.

Keywords: pharmacogenetics – antiemetics – cancer – Indonesia

Risk of fracture in patients with Parkinson's disease

S. Pouwels^a, A. Lalmohamed^a, A. de Boer^a, C. Neef^b and F. de Vries^{ab*}

^a Utrecht Institute for Pharmaceutical Sciences, Utrecht. ^b Maastricht University Medical Centre+, Department of Clinical Pharmacy & Toxicology, Maastricht.

* Correspondence: frank.de.vries@mumc.nl.

Background

Parkinson's disease (PD) is a movement disorder, which has been associated with fracture risk. However, it is not clear which PD patients are at highest risk. Therefore, the aim is to determine relative fracture risk in incident PD patients stratified by treatment, severity and duration of disease and related co-morbidities.

Methods

We conducted a retrospective cohort study using the UK General Practice Research Database (1987-2011). Each PD patient was matched by age, sex, calendar time, and practice to a control patient without a history of PD and we identified all fractures.

Results

We identified 4,687 incident PD patients. Compared to the control cohort, there was a statistically significant increased risk observed in patients with PD for any fracture [adjusted hazard ratio (AHR) 1.89; 95% confidence interval (CI95) 1.67-2.14], osteoporotic fracture (AHR 1.99; CI95 1.72-2.30) and hip fracture (AHR 3.08; CI95 2.43-3.89). Duration, severity and treatment of PD showed no association with fracture, except for a further increased risk among users of MAO-B inhibitors. Osteoporotic fracture risk further increased among PD patients with use of antidepressants (AHR 1.52; CI95 1.26-1.82), high-dose antipsychotics (AHR 2.98; CI95 1.63-5.47), history of fracture (AHR 1.29; CI95 1.05-1.58), falling (AHR 1.87; CI95 1.48-2.37), low BMI (AHR 1.76; CI95 1.24-2.50) and renal disease (AHR 1.85; CI95 1.19-2.87).

Conclusions

This study showed that PD was associated with a statistically significant 2-fold increased risk for fracture and osteoporotic fracture. Risk for hip fracture was 3-fold increased. Therefore, fracture risk assessment may be indicated among patients with PD, in particular when they have recently used antidepressants or high-dose antipsychotics or have a history of fracture, falling, low BMI or renal disease.

Keywords: Parkinson's disease – bone fracture – antidepressants – antipsychotics

Thin layer chromatography to support therapeutic drug monitoring of moxifloxacin in patients with tuberculosis in rural areas and resource limited settings

A.D. Pranger^a, E.R. van den Heuvel^b, R. van Altena^c, B. Greijdanus^a, W.C.M. de Lange^c, T.S. van der Werf^d, J.G.W. Kosterink^a, D.R.A. Uges^a and J.W.C. Alffenaar^{ab*}

^a Department of Hospital and Clinical Pharmacy, ^b Department of Epidemiology, ^c Tuberculosis Centre Beatrixoord, ^d Department of Internal Medicine and Pulmonary Diseases and Tuberculosis; University Medical Center Groningen.

* Correspondence: j.w.c.alffenaar@umcg.nl.

Background

Its high bactericidal and sterilizing activity against *M. tuberculosis* may nominate moxifloxacin (MFX) as one of the cornerstone agents in treatment of patients infected with drug-resistant isolates. The area under the concentration–time curve (AUC) to minimal inhibitory concentration (MIC) ratio has been accepted as the best parameter to predict *in vivo* efficacy of MFX. Interindividual variability in MFX pharmacokinetics is considerable and AUC may even be lower as a result of rifampicin (RIF) co-medication. Particularly in these patients, therapeutic drug monitoring (TDM) can be recommended to ensure adequate AUC/MIC ratios and to prevent MFX resistant mutants to select in the initial mainly susceptible population. Although TDM requires advanced laboratory facilities, thin layer chromatography (TLC), using non-invasive oral fluid sampling, may be the solution to support TDM in resource limited settings and rural areas. MFX was used as model compound for development and clinical evaluation of this semi-quantitative method of analysis.

Methods

Oral fluid concentrations were determined by applying 10 µL of oral fluid extract on a TLC sheet. At a wavelength of 366 nm, intensity, size and shape of spots with concentrations unknown to the analyst were evaluated and compared with three reference spots (0.5, 1.0 and 2.0 mg/L) by UV detection. The level of agreement between five analysts and between two different batches of TLC plates was calculated to evaluate the robustness of the method. Nine tuberculosis (TB) patients receiving 400 mg MFX once daily for at least five days (steady state) as part of their TB treatment and receiving routine TDM were used for clinical method validation. Blood and oral fluid sampling (t = 0, 1, 2, 3, 4, 8 h) was performed at steady-state. Plasma concentrations were determined by a validated LC-MS/MS method.

Results

An interclass correlation coefficient for the latent variable of 0.969 (95% confidence interval: 0.722-0.997) suggested a moderate to strong agreement among analysts. There were no interfering spots observed by simultaneous determination of commonly used TB agents in oral fluid. The median plasma AUC_{0-24h} was 26.6 (range: 20.6-46.2) mg·h/L. In 5/7 patients a plasma AUC over 25 mg·h/L was observed in case the oral fluid concentration was ≥ 1.0 mg/L one hour post dosage.

Conclusions

Main finding is that MFX AUC_{0-24h} could be predicted accurately semi-quantitatively by TLC using oral fluid. This method can be used to support adequate treatment and to prevent resistance in individual patients in rural areas and resource limited settings.

Keywords: tuberculosis – moxifloxacin – pharmacokinetics – thin layer chromatography

Evaluation of the vancomycin dosage guideline in paediatric oncology patients

S.J.W.J. Sanders ^{*}, Y.A. Bijleveld, E.M. Kemper, L. Lie-A-Huen and R.A.A. Mathôt

Academic Medical Center, Amsterdam.

^{*} Correspondence: stefan.sanders@cze.nl.

Background

In our hospital vancomycin 60 mg·kg⁻¹·d⁻¹ in four doses is used for the treatment of febrile neutropenia in paediatric oncology patients. In the current guideline therapeutic drug monitoring of vancomycin 8-15 mg/L is considered a therapeutic trough concentration. The objective of this study was to determine the percentage subtherapeutic serum trough concentrations (< 8 mg/L) in paediatric oncology patients during the first days of therapy and to identify patient characteristics that are associated with subtherapeutic serum trough concentrations.

Methods

In this retrospective cohort study medical records were screened for vancomycin trough concentrations and patient characteristics age, sex, weight, serum creatinine, C-reactive protein, malignancy, duration of treatment, nephrotoxic co-medication, leukocytes and positive blood cultures. Non-parametric tests were used to identify group differences and Spearman's rho for correlations. The effect of a higher vancomycin dosage on serum trough concentrations was evaluated through simulations, assuming linear pharmacokinetics for vancomycin.

Results

124 paediatric oncology patients were included with ages ranging from 0.3 to 17.3 years. First serum trough concentrations were subtherapeutic in 58% of the patients. Significant correlations with serum trough concentrations were found for age, weight (both $P < 0.05$) and serum creatinine ($P < 0.01$). Patients < 6 years exhibited more subtherapeutic trough concentrations than patients > 6 years ($P = 0.026$) with respective median values of 6.6 and 8.7 mg/L. The trough concentrations for patients < 6 years ($P = 0.003$) and 6-12 years ($P = 0.013$) were significantly lower than for patients > 12 years (median values 6.6, 7.3 and 9.8 mg/L). Simulations with vancomycin 90 mg·kg⁻¹·d⁻¹ in four doses for patients < 6 years and 6-12 years indicated a potential decrease of subthera-

peutic serum trough concentrations to 27% and 19% and increase of supratherapeutic serum trough concentrations to 21 and 25% respectively.

Conclusions

The current guideline for vancomycin dosing is inadequate for paediatric oncology patients < 12 years. A new dosage guideline for paediatric oncology patients < 12 years might be 90 mg·kg⁻¹·d⁻¹ in four doses, but this has to be evaluated in a prospective clinical trial.

Keywords: vancomycin dosage – paediatric oncology – drug monitoring

Intelligent electronic trigger tool to optimise intravenous to oral antibiotic switch

Tom Sprong, Hans Pot, Ton Dofferhoff, Jeroen Schouten, Cees Kramers, Marringje Nabuurs-Franssen, Anne Houterman, Andreas Voss and Hanneke Huntjens-Fleuren ^{*}

Canisius-Wilhelmina Hospital, Nijmegen.

^{*} Correspondence: huntjens@cwz.nl.

Background

Timely switching from intravenous antibiotics to oral is important to improve patient safety and reduce costs associated with intravenous therapy. For this reason, numerous interventions have been devised, and have shown to improve antibiotic switching. However, these interventions are usually time-consuming and therefore expensive and difficult to implement. We have introduced an intervention that relies on a computerized trigger, which intelligently identifies patients who are candidates for antibiotic switching. This was combined with weekly discussing switch therapy during the microbiology/infectious disease multidisciplinary meeting. With this intervention we aimed to improve the rate of intravenous to oral antibiotic switching.

Methods

Intervention was performed on all the internal medicine wards in a large teaching hospital. Daily an automated trigger tool selected patients eligible for switch based on data from the pharmaceutical and patient system. Patients were identified as eligible when parenteral antibiotics were used for 48-72 hours. Patients were ineligible for switch when CRP was rising, neutrophils were < 0.5·10⁹/mL or leukocytes < 1·10⁹/mL, inability to receive oral therapy or when an antibiotic was prescribed for which no oral option was available. Before daily rounds, per candidate for antibiotic switch, a form was generated and given to the resident caring for the patient. Information concerning the ability to switch and reasons which impeded the switch were recorded. Median intravenous days per intravenous prescription and number of intravenous prescriptions > 72 hours in the intervention period were compared to a similar period in the year preceding the intervention.

Results

Of 156 forms generated in 603 intravenous antibiotic prescriptions, 92 (59%) were filled in and returned. In 52% of cases this form led to an intravenous-oral switch. Median number of intravenous days was reduced by 1 (3 vs 2, $P < 0.0001$). Number of intravenous prescriptions longer than 72 hours was reduced by 45% (44% vs 24%). Reasons for not switching antibiotic therapy were inability to receive oral therapy (36%), clinical instability (21%) and stopping antibiotic therapy in 16% of the patients.

Conclusions

We designed an intervention which uses a computerized trigger to identify patients who are candidates for antibiotic switch therapy in combination with frequent but short term education of residents. This was effective in promoting antibiotic switch therapy and reducing number of intravenous days > 72 hours.

Keywords: antibiotic switch – computerized trigger

Point prevalence study for local antibiotic prescription and usage trends used in a large non-academic teaching hospital in the Netherlands

Tom Sprong, Hanneke Huntjens-Fleuren^{*}, Inge Gyssens, Alphons Horrevorts, Jeroen Schouten, Andreas Voss, Jacques F. Meis, Ton Dofferhoff and Marringje Nabuurs-Franssen
Canisius-Wilhelmina Ziekenhuis, Nijmegen.

* Correspondence: huntjens@cwz.nl

Background

In order to optimize in-hospital antibiotic usage, it is essential to gain insight which antibiotics are used and how these choices are made in the local situation. Recently, the European Surveillance of Antibiotic Consumption (ESAC) has developed a point prevalence study for antibiotic surveillance. This is a limited time consuming method to gain insight in local prescribing policies. We adapted this method to see whether, how and when infection specialists (microbiologists and ID physicians) are involved in the decision to start a certain antibiotic.

Methods

The Canisius-Wilhelmina Hospital is a large 653-bed non-academic teaching hospital in the Netherlands with all the major hospital specialities present. Via the electronic prescription system of the hospital pharmacy, all patients that used one or more antibiotics at one day in the fall of 2007 and the spring of 2011 were identified. Patients with surgical prophylaxis were excluded. With a standardised questionnaire, the treating physicians were interviewed to gain insight how the choice for a certain antibiotic prescription was made.

Results

Of all admitted patients, 27% (2007) and 22% (2011) were using antibiotics. Types of antibiotics prescribed and indications were similar between 2007 and 2011. An infection specialist was involved in 28% (2007) and 39% (2011) of prescriptions. Reasons for consultation were a positive culture result in 23%, a direct question about empirical therapy in 23% and a multidisciplinary meeting in 44% of cases. If an infection specialist was consulted, antibiotic therapy was often aimed at a certain pathogen, in contrast to patients that received prolonged (> 72 hours) empirical therapy, for which in a minority of patients consultation was sought (50% vs 8.8% of patients respectively, $P < 0.001$).

Conclusions

A point prevalence study is a fast way to gain insight into local antibiotic prescription and usage trends in a hospital. The PPS can be used to detect reasons for infection consultation. In our hospital we found that multidisciplinary meetings are very important for advice on antibiotic decision making. However, we had poor control on patients that are using prolonged empirical therapy, which is an important group for streamlining antibiotics.

Keywords: point prevalence study – antibiotic surveillance

Liquid chromatography-spectrophotometric assay for treosulfan in human serum

Marloes ten Brink^{*}, Judith Vletter-Bogaartz, Henk-Jan Guchelaar and Jan den Hartigh

Department of Clinical Pharmacy and Toxicology, Leiden University Medical Center.

* Correspondence: m.h.ten_brink@lumc.nl

Background

Treosulfan is a bifunctional alkylating agent and a structural analogue of busulfan. Due to its favourable myeloablative and immunosuppressant activity treosulfan is used in high doses in conditioning regimens prior to haematopoietic stem cell transplantation (HSCT) both in adult and paediatric patients [1, 2]. High-dose treosulfan has been found to be less toxic on non-haematological tissues, compared to high-dose busulfan [1, 3, 4]. Therefore, treosulfan seems to be a candidate to replace busulfan in conditioning regimes prior to HSCT. Busulfan therapy in paediatric patients is often optimized by therapeutic drug monitoring. To date, pharmacokinetic data to optimize treosulfan dosing in paediatric patients are scarce, which can be attributed to the lack of an easy applicable bioanalytical assay. Earlier studies described an analytical method using refractometric detection [5, 6]. Furthermore, sample treatment directly after collection of the blood sample was necessary to prevent *ex vivo* degradation. We developed and validated a RP-HPLC method using ultraviolet (UV) detection for determination of treosulfan in human serum.

Methods

A reversed phase high pressure liquid chromatography (RP-HPLC) method using UV detection to determine treosulfan in human serum samples was developed. Busulfan was used as an internal standard. To make both compounds appropriate for reversed phase chromatographic analysis and UV detection, derivatization with sodium diethyldithiocarbamate (DDTC) was carried out. Gradient elution with a mobile phase consisting of phosphate buffer, methanol and acetonitrile was used. The validation of the analytical assay was based on international guidelines, such as the FDA guidelines [7-9].

Results

The assay was validated in a 15-2000 mg/L concentration range. Accuracies were 96% and 101% for low and high concentrations, respectively. Within day precisions were 0.7% and 2.8%, between day precisions were 10.8 and 5.9%. In earlier studies the need of acidifying patient samples directly after collection was suggested. We studied the stability of treosulfan in serum and whole blood samples thoroughly and showed samples to be stable for up to 5 hours at room temperature, resulting in no need for patient sample treatment directly after collection. Quality control samples showed long term stability when stored at -80°C. To demonstrate the applicability of the assay serum samples of four patients receiving high dose treosulfan were measured.

Conclusions

This report describes the development and validation of a RP-HPLC method to determine treosulfan concentrations in human serum samples. The use of UV-detection and no need for acidifying the patient samples directly after collection makes this treosulfan assay feasible and more commonly applicable.

REFERENCES

- Casper J, Knauf W, Kiefer T, et al. Treosulfan and fludarabine: a new toxicity-reduced conditioning regimen for allogeneic hematopoietic stem cell transplantation. *Blood*. 2004;103:725-731.
- Wachowiak J, Sykora KW, Cornish J, et al. Treosulfan-based preparative regimens for allo-hsct in childhood hematological malignancies: a retrospective study on behalf of the ebmt pediatric diseases working party. *Bone Marrow Transplant*. 2011;46:1510-1518.
- Casper J, Knauf W, Blau I, et al. Treosulfan/fludarabine: a new conditioning regimen in allogeneic transplantation. *Ann Hematol*. 2004;83 Suppl 1:S70-71.
- Greystoke B, Bonanomi S, Carr TF, et al. Treosulfan-containing regimens achieve high rates of engraftment associated with low transplant morbidity and mortality in children with non-malignant disease and significant co-morbidities. *Br J Haematol*. 2008;142:257-262.
- Główka FK, Łada MK, Grund G, et al. Determination of treosulfan in plasma and urine by hplc with refractometric detection; pharmacokinetic studies in children undergoing myeloablative treatment prior to haematopoietic stem cell transplantation. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2007;850:569-574.
- Hilger RA, Harstrick A, Eberhardt W, et al. Clinical pharmacokinetics of intravenous treosulfan in patients with advanced solid tumors. *Cancer Chemother Pharmacol*. 1998;42:99-104.
- Center for Drug Evaluation and Research of the U.S. Department of Health and Human Services Food and Drug Administration, 2001. <http://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/guidances/ucm064964.htm>, accessed 2011 December 20.
- Shah VP, Midha KK, Findlay JW, et al. Bioanalytical method validation – a revisit with a decade of progress. *Pharm Res*. 2000;17:1551-1557.
- Viswanathan CT, Bansal S, Booth B, et al. Quantitative bioanalytical methods validation and implementation: best practices for chromatographic and ligand binding assays. *Pharm Res*. 2007;24:1962-1973.

Keywords: treosulfan – liquid chromatography-spectrophotometric assay – pharmacokinetics – haematopoietic stem cell transplantation

Clinical relevance of and risk factors associated with medication administration time errors

R. Teunissen *, J.M. Bos, H. Pot, M.A.L. Pluim and C. Kramers
Canisius-Wilhelmina Ziekenhuis, Nijmegen.

* Correspondence: rickteunissen@gmail.com.

Background

About sixty percent of medication errors in Dutch hospitals are related to distribution and administration. In literature, time errors are often regarded as less clinically relevant than other errors. However, the relevance of time errors has never been studied. The blister collection method has been developed as a method with high sensitivity to time errors. The objective of this study was to investigate the clinical relevance of time errors. In addition, it aims to identify risk factors for medication administration errors.

Methods

In this cross-sectional explorative study, 66 medication administration rounds were studied on two wards (surgery and neurology) of a 650-bed general teaching hospital. Data on medication errors was collected using the blister collection method. The emptied packaging material of medication was collected one hour after each round and compared to prescriptions. Errors were registered and categorized as time or other errors. Time errors were indicated when medication intake took place more than one hour before or after the prescribed time. In (combinations of) medication in which there were potential drug-drug or drug-food interactions the exact intake was registered. When the time between these administrations was too short or too long according to Dutch guidelines, it was deemed clinically relevant. Generalized estimating equations (GEE) analysis was performed to study relations between medication administration errors and risk factors.

Results

In total, 129 patients were included with a total of 2874 opportunities for error (OFEs, the total number of medications administered or omitted). In 1118 OFEs an actual error or multiple errors occurred (38.9%). There were 774 time errors and 357 other errors (26.9% and 12.4% of all OFEs, respectively). The majority of other errors were omissions (301 errors). There were only 22 administrations with potential drug-drug or drug-food interactions, and in two

OFEs a time error occurred that was clinically relevant (0.07% of all OFEs). GEE analysis showed a statistically significant ($P < 0.05$) decrease of the risk of time errors when medication was administered at 12 noon, at the surgical ward, through injection or infusion or if the prescription worded: 'if necessary'. The risk was higher when medication was administered rectally.

Conclusions

Time errors were the most prevalent medication errors. This study provides the first empirical evidence that time errors do seldom lead to drug–drug or drug–food interactions. This confirms the general consensus in literature. Furthermore, this study provides insight into risk factors associated with time errors.

Keywords: medication administration errors – time errors – blister collection method

Analysis of medication reconciliation at discharge from a Dutch hospital

I.R.F. van Berlo-van de Laar ^{*}, E. Driessen, M.M. Merckx and F.G.A. Jansman

Deventer Hospital.

* Correspondence: laarvdi@dz.nl.

Background

At hospitalisation and discharge the risk of errors in medication information transfer is high. Various studies have shown that unintentional medication discrepancies occur commonly during hospital discharge. The percentage of patients with at least one unintentional discrepancy varies in these studies between 25% and 73%. To prevent medication errors and to increase patient safety, the guideline *Transfer of Medication Information in the Chain of Healthcare* is established and this subject is incorporated in the safety management program for hospitals in the Netherlands. In the Deventer Hospital, the Pharmacy Service Point processes discharge recipes for about 50% of the patients who are discharged. Because the hospital is obliged to follow this national guideline, we performed a study of the routes of medication information transfer at discharge in the Deventer Hospital. The aim of this study was to find ways to improve the transfer of medication information at discharge in this hospital.

Methods

From 6 to 17 December 2010, the following data was recorded across eight hospital wards: the identification number of discharged patients, the date of discharge and the route by which medication information was transferred. The possible route categories recorded were the Pharmacy Service Point, the hospital's public pharmacy, and 'other' routes (which had to be specified). Validation of the data was performed by cross-checking the information collected by the hospital's Admission Office, the

Pharmacy Service Point and the hospital's public pharmacy, in addition to electronic patient files, interviews with ward staff and, where necessary, discussing directly with the discharged patient concerned.

Results

A total of 629 patients were included in the study. The routes of transfer were: Pharmacy Service Point 281 patients (44%), the hospital's public pharmacy 54 patients (9%), and other routes 44 patients (7%). Other routes were most recorded at the children's ward, the short stay and cardiology ward. In 250 patients (40%), there was no transfer of information by the Pharmacy Service Point because they were registered as using no medication or as experiencing no medication changes during hospitalisation.

Conclusions

Medication information was transferred for 53% of the discharged patients, which is close to the maximum achievable result. Further improvement of medication information transfer in the Deventer Hospital can be made by adjusting the current procedure and by educating the ward staff about the importance and the clinical practice of this procedure.

Keywords: hospital pharmacy – hospitalisation – hospital discharge – medication errors – information transfer

Quetiapine and breastfeeding

Anneke A. van Boekholt, Erwin G.T.M. Hartong, Hanneke Huntjens-Fleuren ^{*}, Koen P. Grootens and Ben A. Semmekrot
Canisius-Wilhelmina Hospital, Nijmegen.

* Correspondence: huntjens@cwz.nl.

Background

As breastfeeding is the preferential feeding according to WHO recommendations, a risk/benefit analysis should be made when a breastfeeding mother needs to use medication. Quetiapine is an antipsychotic agent in psychiatric disorders in women of child-bearing age, but literature on the specific neonatal risks is very limited. We describe a single case of quetiapine use in a lactating women measuring infant's serum concentration of quetiapine.

Methods

The mother was on a quetiapine dose of 1299 $\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Her daughter received exclusively breast milk. Infant serum concentration of quetiapine was measured after the intake of breast milk at peak levels twice.

Results

We measured a serum concentration of < 1 and $3 \mu\text{g}/\text{L}$ in the infant with therapeutic concentrations in her mother.

Discussion

According to these preliminary results, there was a minimal transfer of quetiapine from mother to child, and adverse events were absent. Further exploration in a larger patient sample is recommended.

Keywords: lactation – breastfeeding – quetiapine concentrations – infant – blood – breast milk

Consequences of a single dose of 2,000,000 IU vitamin D₃ in two nursing home patients

J.M.W. van den Ouweland^a, M.M.I.J. Drabbe^b,
H.W.H.A. Huntjens-Fleuren^{c*} and E.J. Volvaard^c

^a Department of Clinical Chemistry, Canisius-Wilhelmina Hospital, Nijmegen.

^b Nursing home Waelwick, Ewijk Beuningen. ^c Department of Clinical Pharmacy, Canisius-Wilhelmina Hospital, Nijmegen.

* Correspondence: huntjens@cwz.nl.

Background

Administration of a single high dose of vitamin D₃ is increasingly used as a strategy for rapid normalization of the blood calcidiol concentration in patients with a low vitamin D status. In a nursing home near Nijmegen all residents receive 100,000 IU vitamin D₃ three times a year as a concentrated solution (2 mL Vitamin D₃ aquosum FNA 50,000 IU/mL).

Methods

By mistake two residents (M, 90 yr; F, 95 yr) were administered a whole bottle of 40 mL vitamin D₃ concentrate, thus receiving 2,000,000 IU each. This was reported to the pharmacy immediately, so we had the opportunity to monitor the clinical and biochemical outcome of the overdose soon after intake.

Results

Peak blood calcidiol concentrations were observed 8 days after intake [527 and 422 nmol/L, respectively (ref: 50-200)]. Remarkably, serum calcium levels only slightly increased up to 2.7 mmol/L (ref: 2.20-2.65) between 1 and 14 days after intake. Increases of plasma phosphate and creatinine levels remained within the reference range. No adverse clinical symptoms were noted.

Conclusion

It appears that a single dose (100 times higher than the maximum physiological daily dose of vitamin D₃ from sunlight) does not result in immediate clinical or biochemical toxicity. Nevertheless, we cannot be certain that this dosing error is innocuous because it has recently been shown that intermittent, high-dose vitamin D supplementation may significantly increase the risk of osteoporotic fractures. Therefore the question remains which biochemical data can be used to demonstrate toxicity from a single high dose of vitamin D₃.

Keywords: vitamin D₃ – overdose – toxicity

Prevalence of and risk factors for prescription errors in older individuals with an intellectual disability

Annemieke D.M. van der Kaaij^a, Rianne J. Zaal^{b*},
Heleen M. Evenhuis^c and Patricia M.L.A. van den Bemt^b

^a Pharmacy Student, Utrecht University. ^b Erasmus MC, Department of Hospital Pharmacy, Rotterdam. ^c Erasmus MC, Department Family Medicine, Rotterdam.

* Correspondence: r.zaal@erasmusmc.nl.

Background

Because of an increased risk of chronic conditions, prescription of drugs for older intellectually disabled (ID) persons might be a complex process, possibly leading to a higher risk of prescription errors in this population. Insight into the prevalence of prescription errors is important to estimate the scope of the problem. Besides, knowledge on potential risk factors for prescription errors in this population would enable us to identify high risk patients. Therefore, a study was designed to determine the prevalence of and potential risk factors for prescription errors in older ID individuals.

Methods

A retrospective case-control study was performed. The research population consisted of older (≥ 50 years) ID individuals with one or more medication orders, participating in the Erasmus MC Healthy Ageing and ID study [1]. The medication was independently screened for errors by a hospital pharmacist/clinical pharmacologist and a Master's student pharmacy. Consensus was reached on all discrepancies. The proportion of participants with one or more prescription errors (cases) was the primary outcome. The controls were participants without prescription errors. To identify potential risk factors for prescription errors univariate and multivariate logistic regression analyses were performed. Age, gender, level of ID, situation of living (centralized setting versus in district), body mass index (BMI), frailty index and number of medicines were included in the analysis as potential risk factors.

Results

The medication of 600 included persons was screened for prescription errors. This resulted in 285 cases and 315 controls. The prevalence of older ID persons with one or more prescription errors in their medication was 48%. Independently associated risk factors for prescription errors were age (OR_{adj} 1.0; CI95 1.0-1.1), ID level (moderate: OR_{adj} 0.5; CI95 0.3-0.7; and severe: OR_{adj} 0.6; CI95 0.3-1.0), BMI (OR_{adj} 1.0; CI95 1.0-1.1), frailty index (0.39-0.54: OR_{adj} 2.4; CI95 1.2-4.8; and ≥ 0.55 : OR_{adj} 3.4; CI95 1.0-11.0) and number of medicines (five or more: OR_{adj} 8.1; CI95 5.6-11.6).

Conclusion

The prevalence of prescription errors in the older ID individuals is 48%. The identified risk factors higher age, higher BMI and frailty index, as well as use of five or more medicines and less severe intellectual disability can help to identify high risk patients.

REFERENCES

- 1 Hilgenkamp TI, Bastiaanse LP, Hermans H, Penning C, van Wijck R, Evenhuis HM. Study healthy ageing and intellectual disabilities: recruitment and design. *Res Dev Disabil.* 2011 May-Jun;32(3):1097-106.

Keywords: intellectually disability – elderly – prescription error – risk factor – prevalence – medication order

Association of risk analysis with user satisfaction after implementation of computerized physician order entry (CPOE) in Dutch hospitals

Willem van der Veen ^{a,x}, Katja Taxis ^b, Han (J.J.) de Gier ^c, Tjerk van der Schaaf ^d and Patricia M.L.A. van den Bemt ^e

^a Ziekenhuisapotheek Emmen-Hardenberg, Saxenburgh Groep Röpcke-Zweers ziekenhuis Hardenberg. ^b Research Institute For Health Research SHARE, RUG Groningen. ^c Research Institute of Pharmacy, RUG Groningen. ^d Hasselt University, Hasselt, Belgium. ^e Erasmus MC, Rotterdam.

* Correspondence: w.veen@sxh.nl.

Background

CPOE in hospitals should reduce medication errors and is essential for patient safety, but user satisfaction depends on an adequate implementation process. Risk analysis may influence the implementation process and thus user satisfaction. Therefore, the aim of our study was to determine the association of risk analysis with user satisfaction after implementation of CPOE.

Methods

A cross-sectional study using a questionnaire was performed. All Dutch hospital pharmacies were asked about the extent of implementation of CPOE in the hospitals they served, the performance of (retrospective or prospective) risk analysis and the satisfaction with CPOE of doctors, nurses and pharmacists. Only hospitals that had implemented inpatient CPOE on at least 70 percent of the wards were included in the primary analysis. Primary endpoint was the association of risk analysis with user satisfaction (4 or more on a Likert scale of 5). Statistical analysis of this association was performed by univariate logistic regression using SPSS version 18.

Results

The questionnaire was sent to all 79 Dutch hospital pharmacies. Questionnaires were returned by 70 hospital pharmacies, serving 72 separate hospitals. In 40 hospitals the CPOE was implemented on at least 70% of the wards. The association of risk analysis with the proportion of satisfied users was determined within this group of 40 hospitals. For medical doctors the performance of risk-analysis

was associated with satisfaction (OR 10.0; CI95 1.8-56.0). A non-statistically significant trend towards an association with satisfaction was found for nurses (OR 4.5; CI95 0.8-24.7) and hospital pharmacists (OR 3.3; CI95 0.8-14.1).

Conclusion

The satisfaction of users with implementation of CPOE seems to be associated with the performance of risk analysis. This suggests that the CPOE implementation process can be optimized by performing risk analysis before and/or after implementation.

Keywords: CPOE – implementation – risk analysis – user satisfaction

Barriers and drivers of medication reconciliation at discharge

Anne van Litsenburg ^a, Nelleke van Sluisveld ^a, Stephanie Natsch ^{b,x} and Hub Wollersheim ^a

^a Scientific Institute for Quality of Healthcare (IQ Healthcare), ^b Department of Pharmacy; Radboud University Nijmegen Medical Centre, Nijmegen.

* Correspondence: s.natsch@akf.umcn.nl.

Background

Of all hospitalized patients, 11% experience an adverse drug event after discharge of which 27% are preventable (Foster, 2004). To improve patient safety, the Dutch Government compels hospitals to implement medication reconciliation, *i.e.* obtaining and documenting a complete list of the patient's current medication that is communicated to the next care providers.

Part of the hospital departments indicates that they have problems to implement medication reconciliation at discharge admission, while other departments have implemented it successfully and overcame the implementation problems they faced. The objective of this study is to gain insight into barriers and drivers to implement medication reconciliation at hospital discharge.

Methods

A qualitative study was carried out to identify the barriers and drivers to implement medication reconciliation. 12 clinicians, nurses and pharmacists of the Radboud University Nijmegen Medical Centre were interviewed. The interviews were recorded and transcribed verbatim. The transcripts were systematically analyzed using Atlas.ti 6.2.18, independently by two researchers. The barriers and drivers were classified according to the Innovation Framework of Cabana (1999).

Results

Reported drivers to implement medication reconciliation at hospital discharge are:

- electronic medication record;
- belief that medication reconciliation will lead to better care.

Barriers are:

- no feedback to care givers;
- task reallocation;
- signing the discharge medication implies legal responsibility;
- patient has different needs or priorities.

Conclusions

An important driver of the implementation of medication reconciliation at hospital discharge is an electronic medication record. However, this will not resolve the whole implementation problem. Certain barriers have to be levelled out, like unclear tasks, no feedback about adverse events as a result of the discharge process, legal problems and patients' lack of interest. Strategies should be developed tailored to the drivers and barriers found to improve the implementation of medication reconciliation at hospital discharge. An important strategy could be task reallocation, e.g. more involvement of pharmacists in discharge medication reconciliation. Moreover, feedback given to care givers about effects of incorrect medication reconciliation at discharge, increases awareness of the health problem and therefore would improve the implementation of medication reconciliation and the quality of the discharge process.

Keywords: medication reconciliation – hospital discharge – implementation – electronic medication record – qualitative study

Continuous infusion of vancomycin: a validated dosing schedule

Erik M. van Maarseveen^a, Daan J. Touw^{bc}, Annemien Bouma^d, Cees Neef^e and Arthur R.H. van Zanten^f

^a University Medical Center Utrecht, Clinical Pharmacy, Utrecht. ^b Haga Teaching Hospital, Pulmonary Diseases, The Hague. ^c Central Pharmacy The Hague, Clinical Pharmacy, The Hague. ^d Groene Hart Ziekenhuis, Clinical Pharmacy, Gouda. ^e Maastricht University Medical Center, Clinical Pharmacy, Maastricht. ^f Ziekenhuis Gelderse Vallei, Intensive Care, Ede.

Background

Vancomycin is an antibiotic used in (suspected or proven) bacteraemia, peritonitis or osteomyelitis with Gram-positive microorganisms. Currently in most Dutch hospitals vancomycin is administered as an intermittent infusion. As the killing by vancomycin is dependent of the AUC/MIC ratio and/or time above MIC, a continuous infusion should be at least as effective as an intermittent infusion based on its pharmacodynamics. Studies comparing continuous (CIV) and intermittent (IIV) infusion of vancomycin indicate continuous infusion is as effective and safe as intermittent infusion. In osteomyelitis it might even be superior. However, no loading and maintenance dosages are known for CIV. Here, we tried to establish and validate a dosing schedule for continuous infusion of vancomycin.

Methods

Continuous infusion of vancomycin in patients with a calculated creatinine clearance ranging from 25 to 125 mL/min was simulated in MW\Pharm (version 3.60, MediWare). A population model was used to calculate loading and maintenance dosages within a range of calculated creatinine clearances. The target range for steady state concentration (C_{ss}) at 24-48 h was set at 16-20 mg/L which corresponds with an AUC_{24}/MIC ratio of at least 400 mg-h/L since MICs of most frequently reported pathogens in these patients are usually < 1.0 mg/L. A set of 20 steady state concentrations (C_{ss}) was used to validate the proposed infusion schedule.

Results

An infusion schedule for CIV was established. Samples for validation were drawn 24-48 h after start of infusion. Samples were analysed by immunoassay (TDx, Abbott). Validation showed that 16 out of 20 C_{ss} s (80%) were within the predefined target range (16-20 mg/L). Two patients had a C_{ss} higher than the upper limit (21.9 and 20.5) and C_{ss} s in two patients were low (11.3 and 14.4 mg/L). After dosage correction based on linear pharmacokinetics C_{ss} s at 72 h all patients fell within the target range.

Conclusion

CIV offers clear advantages over IIV for patients with a very high clearance of vancomycin and for outpatients. Furthermore, continuous infusion is less expensive, simplifies TDM and may shorten length of hospital stay in selected patient populations. A simple and validated infusion schedule for continuous infusion is available.

Keywords: vancomycin – continuous infusion – dosing schedule

Does the circadian rhythm affect the pharmacokinetics of aminoglycosides in cystic fibrosis patients?

Erik M. van Maarseveen^a, Renske van der Meer^b, Cees Neef^c, Daniel J. Touw^{bd} and Harry G.M. Heijerman^b

^a University Medical Center Utrecht, Clinical Pharmacy, Utrecht. ^b Haga Teaching Hospital, Pulmonary Diseases, The Hague. ^c Maastricht University Medical Center, Clinical Pharmacy, Maastricht. ^d Central Pharmacy The Hague, Clinical Pharmacy, The Hague.

Background

High cumulative dosages of intravenous aminoglycosides are associated with increased rates of nephro- and ototoxicity. The TOPIC study has shown that once daily dosing of tobramycin (TOB) is at least as effective and may be less toxic compared to multiple daily dosing in patients with cystic fibrosis (CF). With the introduction of once daily dosing the timing of TOB dosing may be relevant, since rapid clearance of aminoglycosides is crucial to prevent renal toxicity. Previously, an effect of the circadian rhythm

on renal clearance of aminoglycosides has been demonstrated in a general ward population and postulated in CF patients. Our aim was to investigate the effect of the circadian rhythm on the pharmacokinetics of TOB in adult CF patients.

Methods

The study was performed in an open randomized design. Patients with cystic fibrosis, treated for a pulmonary exacerbation with intravenous TOB at the Haga Teaching Hospital, were eligible for inclusion. After inclusion patients were randomised, receiving TOB either at 8:00 or at 22:00. After infusion a peak and a second level at 6-10 h after end of infusion of TOB were drawn. Clearance and volume of distribution were calculated using a one-compartment open model with linear pharmacokinetics. Pharmacokinetic parameters and biochemical parameters of renal function (estimated and measured GFR and BUN) were compared between groups using a Student's t-test.

Results

24 patients were included. No significant differences were found in patient characteristics between the two groups. Mean volumes of distribution were 0.28 and 0.29 L/kg ($P = 0.37$) and mean clearances were 5.7 and 5.4 mL/min ($P = 0.43$) for the 8:00 and 22:00 groups, respectively. Biochemical parameters did not differ significantly between the two groups.

Conclusion

Our results show that the time of administration had no influence on the renal clearance and distribution of TOB in CF patients. This could be contributed to absence of a circadian rhythm during a pulmonary exacerbation. Consequently, an effect on treatment outcomes is unlikely.

Keywords: tobramycin – cystic fibrosis – circadian – clearance – pharmacokinetics

Nephrotoxicity of once daily dosed aminoglycosides: tobramycin versus gentamicin

Erik van Maarseveen^a, Marie-Christine van Buul-Gast^{bc},
Wala Abdelhadi^a, Cees Neef^d and Daan Touw^{be}

^a University Medical Center Utrecht, Clinical Pharmacy, Utrecht. ^b Central Pharmacy The Hague, Clinical Pharmacy, The Hague. ^c Medisch Centrum Haaglanden, The Hague. ^d Maastricht University Medical Center, Clinical Pharmacy, Maastricht. ^e Haga Teaching Hospital, The Hague.

Background

Aminoglycosides (AMGs) are frequently used as first line therapy in severe hospital-acquired pneumonia or sepsis with tobramycin (TOB) and gentamicin (GEN) being the most prescribed AMGs for intravenous administration worldwide. Although they are very effective against Gram-negative bacteria, exposure to AMGs can

also cause serious nephrotoxicity. Randomised clinical trials and meta-analyses have shown that when administered as conventional multiple daily dosing TOB is less nephrotoxic than GEN. This has, however, never been demonstrated for the nowadays more common once daily dosing regimens. Therefore, we here investigated the nephrotoxicity of TOB and GEN administered as a once daily dose.

Methods

The study was of retrospective design. Local treatment protocol at the MCH Westeinde, The Hague switched from GEN to TOB in January 2010. 292 out of 2410 adult patients that were treated with a standard dose of 5 mg/kg GEN ($N = 206$) or TOB ($N = 86$) for three days or longer from January 2008 to May 2011 were eligible for inclusion. Two serum levels of GEN and TOB were drawn 1 hour and 6-10 hours after end of infusion. All patients started GEN or TOB once daily and based on the first two serum levels dosing intervals could be adjusted. The rise in serum creatinine (SrCr) at the end of therapy in relation to baseline was compared between GEN and TOB with a paired Student's t-test. The percentage of nephrotoxicity, defined as a rise in SrCr of > 50% from baseline, was compared between GEN and TOB with a Pearson chi-square test. Secondly, determinants predictive of a nephrotoxicity were identified by logistic regression.

Results

The mean rise in serum creatinine (SrCr) at the end of therapy in relation to baseline was 12.3 $\mu\text{mol/L}$ ($P < 0.01$) for GEN and 3.4 $\mu\text{mol/L}$ ($P < 0.46$) for TOB treated patients. There was no statistically significant difference in the mean rise in SrCr between GEN and TOB ($P = 0.16$). 11.7% of GEN and 9.3% of TOB treated patients developed nephrotoxicity ($P = 0.56$). Covariate analysis showed only the area-under-the-curve (AUC) of the first administration was independently predictive of developing nephrotoxicity.

Conclusion

Although the rise in SrCr in relation to baseline tends to be higher for GEN, our results show that when administered once daily there is no difference in the occurrence of nephrotoxicity in hospitalised patients treated with intravenous GEN or TOB 5 mg/kg for three days or longer. Based on the predictive value of the AUC of the first administration we recommend performing TDM shortly after initiation of AMG therapy in patients that may require treatment for longer than three days.

Keywords: tobramycin – gentamicin – nephrotoxicity – once daily dosed

Nonlinear mixed effects modeling of the diurnal blood pressure profile in a multiracial population

P.C. van Rijn-Bikker ^{a*}, N. Snelder ^b, O. Ackaert ^b,
R.M. van Hest ^a, B. Ploeger ^b, G.A. van Montfrans ^a,
R.P. Koopmans ^c and R.A.A. Mathôt ^a

^a Academic Medical Center, Amsterdam. ^b LAP&P Consultants, Leiden. ^c Academic Medical Center Maastricht.

* Correspondence: p.c.bikker@amc.uva.nl.

Background

Specific features of the 24-hour diurnal blood pressure (BP) profile, such as the daytime and nighttime BP, the nocturnal dip (ND) and the morning surge (MS), have been associated with the occurrence of cardiac and cerebrovascular events in hypertensive patients. Simple statistics to more complex smoothing techniques as Fourier modeling have been proposed for the characterization of the diurnal BP profile. These methods are however descriptive and do not produce direct estimates for the clinically relevant parameters as mentioned above. The aim of this study was to develop a nonlinear mixed effect model to describe 24-hour diurnal systolic BP with parameters that correlate with daytime and nighttime BP, ND and MS.

Methods

Ambulatory 24-hour BP measurements of 201 non-treated subjects from three ethnic groups were available. A physiological population model was parameterized in NONMEM to estimate the parameters *baseline BP (BSL)*, *change* (BP difference between day and night) and *nadir* (minimum BP during the night) for adequate description of the 24-hour diurnal BP profile. The clinical relevance of the model parameters was evaluated by testing the correlation between Bayesian estimates of *BSL*, *change* and *nadir* and the parameters obtained by the classical approach (daytime and nighttime BP, ND, MS). The cause of the inter-patient variability was analyzed on the basis of a covariate analysis.

Results

The model adequately characterized the diurnal BP profile. The following typical values (inter-patient variability) were found: *BSL* 139 mmHg (11%), *change* 25 mmHg (52%), *nadir* 122 mmHg (14%) and residual error 12 mmHg. Correlation (R^2) of these parameters with parameters obtained by the classical approach were 0.89 for *BSL* with daytime BP, 0.92 and 0.85 for *nadir* with the average respectively the minimum nighttime BP, 0.79 for the ratio *nadir/BSL* with ND and 0.50 for *change* with MS. The covariate analysis showed that ethnicity was associated with *change*: *change* was 43.3% higher in Dutch caucasian subjects and 29.6% higher in South Asian subjects compared with black patients. This could explain 3.7% of the inter-patient variability in the *change* parameter.

Conclusions

The developed model allows clinically relevant BP parameters (*BSL*, *change*, *nadir*) to be estimated directly in a large population. The

quantification of inter-patient variability in these parameters allows the evaluation of the relationship between individual (Bayesian) estimates of these parameters with the individual risk for cardiovascular events. Furthermore, this model may be used in PK/PD studies of antihypertensive drugs allowing accurate quantification of the effects on the clinically relevant BP parameters.

Keywords: NONMEM – diurnal BP profile – nighttime BP – nocturnal dip – morning surge – ethnicity

Anidulafungin pharmacokinetics in critically ill patients

M.J.P. van Wanrooy ^{*}, M.G.G. Rodgers, D.R.A. Uges,
J.P. Arends, J.G. Zijlstra, T.S. van der Werf, J.G.W. Kosterink
and J.W.C. Alffenaar

University of Groningen, University Medical Center Groningen.

* Correspondence: m.j.p.van.wanrooy@umcg.nl.

Background

Early antifungal treatment with adequate drug exposure reduces mortality in patients with candidaemia. Efficacy of anidulafungin is driven by AUC (area under the curve)/MIC ratio. As anidulafungin clearance is approximately 30% higher in patients with invasive candidiasis than in patients with oesophageal candidiasis patients at the ICU may be at risk for underexposure. Therefore, insight in anidulafungin pharmacokinetics in a 'real-life' population of critically ill patients is important.

Methods

We conducted a prospective open-label study in adult patients admitted to an intensive care unit between June 2010 and November 2011. Patients were eligible for inclusion in case of a positive culture for *Candida* from a sterile site (blood or intra-abdominal fluid). Blood samples were taken just before administering anidulafungin and at 1.5, 2, 3, 4, 6, 8, 12 and 24 hours after start of infusion on day 3 or 4 of treatment. Anidulafungin plasma concentrations were measured with a validated LC-MS/MS method. The AUC was calculated using a non-compartmental method.

Results

20 patients with a median age of 71 (IQR 60-75) were studied; 11 males and 9 females. Cultures for *Candida* were positive in blood for 7 patients and in intra-abdominal fluid for 13 patients. In comparison with previously reported data of critically ill patients, we observed an apparent lower exposure and clearance and longer half-life in our patients (see table). The volume of distribution was similar. MIC values ranged from < 0.002 to 0.02 mg/L, and AUC/MIC ratios from 3,580 to 32,250. Both anidulafungin C_{\max} and C_{\min} showed a significant correlation with the anidulafungin AUC (C_{\max} : $R = 0.854$, $P < 0.001$; C_{\min} : $R = 0.884$, $P < 0.001$; Spearman correlation coefficient).

PK parameter	Our data	De Rosa et al. (ECCMID 2010)	Liu et al. (TIMM 2011)	SPC
C_{max} (mg/L)	ICU (n = 20) \square 4.7 (3.7-5.8)	ICU (n = 8) \square 6.3 (4.7-9.9)	ICU (n = 20) \diamond 7.7 (56)	Patient model \diamond 7.2 (23.3)
C_{min} (mg/L)	2.1 (1.8-3.1)	2.4 (1.3-3.2)		3.3 (41.8)
AUC ₀₋₂₄ (mg·h/L)	65.7 (57.3-85.0)	89.7 (62.2-111.9)	92.7 (41)	110.3 (32.5)
Clearance (L/h)	0.5 (0.3-0.8)	1.1 (0.9-1.6)	1.3 (51)	1.0 (33.5)
Volume of distribution (L)	33.0 (24.5-38.4)	33.5 (27.7-47.4)		
Half-life (h)	33.9 (26.5-57.2)	20.0 (14.5-27.5)		26.5 (28.5)

\square median (IQR), \diamond : mean (CV)

Conclusions

1) Anidulafungin exposure in our critically ill patients seems lower compared to earlier data. Further analysis is required to determine the factors causing the apparent difference. The effect on outcome has to be evaluated in a prospective study.
 2) Trough concentrations correlated very well with total exposure. We propose to use trough concentrations as a surrogate for AUC as this is much easier and practicable in routine practice.

Keywords: anidulafungin – critically ill – pharmacokinetics

Voriconazole concentrations are significantly influenced by inflammatory reactions

M.J.P. van Wanrooy *, L.F.R. Span, M.G.G. Rodgers, D.R.A. Uges, T.S. van der Werf, J.G.W. Kosterink and J.W.C. Alffenaar

University of Groningen, University Medical Center Groningen.

* Correspondence: m.j.p.van.wanrooy@umcg.nl.

Background

Cytochrome P450 (CYP) isoenzyme expression is influenced during inflammation and infection. As voriconazole is extensively metabolized by CYP isoenzymes 2C9, 2C19 and 3A4, inflammation may contribute to the variability of voriconazole (VRZ) pharmacokinetics. In this retrospective study we explore the correlation between inflammation, reflected by CRP levels, and VRZ trough levels.

Methods

A retrospective chart review was performed for all patients aged ≥ 18 years receiving VRZ between January 2006 and December 2010. Patients that had at least one VRZ trough level measured at steady state were included. Patients were divided in three groups: mild inflammation (CRP < 40 mg/L), moderate inflammation (CRP 41-200 mg/L) and severe inflammation (CRP >200 mg/L). 128 patients with a median age of 55 (IQR 42-62) years were included.

Results

A significantly ($P < 0.001$, Kruskal-Wallis test) higher trough level of VRZ was observed in patients with severe inflammation (6.2 mg/L; IQR 3.4-8.7; n = 20) in comparison to patients with no to mild inflammation (1.6 mg/L; IQR 0.8-3.0; n = 48) and moderate inflammation (3.4 mg/L; IQR 1.6-5.4; n = 60). Patients received similar dosages of VRZ ($P = 0.368$, Kruskal-Wallis test). The CRP concentration showed a significant correlation with the VRZ trough level ($R = 0.517$; $P = < 0.001$, Spearman correlation coefficient). Of the 48 patients with a CRP < 40 mg/L, only 1 patient (2%) had a VRZ trough level > 5.0 mg/L (5.8 mg/L). Of the 20 patients with a CRP > 200 mg/L, only 1 patient (5%) had a VRZ level < 2.0 mg/L (1.9 mg/L).

Conclusions

VRZ trough levels showed a positive correlation with CRP levels. Inflammation is likely to contribute to the variability in pharmacokinetics of VRZ by a reduced hepatic metabolism. Changes in inflammatory status, marked by a rapid increase or decline in CRP levels should be taken in consideration in TDM of VRZ for optimal dosing and eventually outcome. Prospective longitudinal studies are needed to determine the predictive value of CRP for VRZ TDM.

Keywords: voriconazole – inflammation – pharmacokinetics

The use of a real-time medication monitoring system (RTMM) for the improvement of adherence to inhaled corticosteroids in children with asthma, a study protocol

e-Monitoring of Asthma Therapy to Improve Compliance in children (e-MATIC)

Erwin Vasbinder ^{ab*}, Hettie Janssens ^c,
Maureen Rutten-van Mölken ^d, Liset van Dijk ^e,
Arnold Vulto ^a and Patricia van den Bemt ^a

^a Erasmus Medical Center, Rotterdam. ^b Groene Hart Hospital, Gouda. ^c Erasmus Medical Center / Sophia Children's Hospital, Rotterdam. ^d Institute for Medical Technology Assessment (iMTA), Rotterdam. ^e NIVEL, Utrecht.

* Correspondence: erwinvasbinder@gmail.com.

Background

Asthma is the most common chronic childhood disease in industrialised countries. Asthma can be well treated with maintenance inhalation therapy, if well taken. However, a great proportion of children do not have sufficient asthma control, leading to increased healthcare cost and productivity loss of parents. In a previous study it has been shown that adherence to asthma treatment is poor. Effective interventions improving medication adherence may improve asthma control and reduce socio-economic costs.

Aim

Primary: To improve adherence to inhaled corticosteroids in children with asthma by using a real-time medication monitoring system (RTMM) with SMS alerts.

Secondary: To study whether improved adherence has an effect on asthma control, quality of life and cost-effectiveness of treatment.

Methods

Design: A multicenter, randomized controlled trial in the St Lucas Andreas Hospital, the Academic Medical Center, the BovenIJ Hospital (all three in Amsterdam), the Erasmus MC (Rotterdam) and the Groene Hart Hospital (Gouda).

Patients: Included will be 220 children (4-11 years) with moderate to severe doctor diagnosed asthma, who have been using inhaled corticosteroids (ICS) with a pressurized metered dose inhaler for asthma for at least three months preceding the intervention.

Intervention: All children receive an RTMM device which registers time and date of administered ICS doses. In the intervention group, parents and if applicable, children will receive SMS alerts to remind when a dose is at risk of omission. The SMS alert is tailored in that warnings are only sent if non-adherence is likely to occur. The study period is one year.

Outcome measures and data collection: The primary outcome measure is the rate of ICS adherence, which is defined as the percentage of prescribed dosages taken by the child within a 6 hour time frame around the expected time of inhalation. Secondary outcome measures include asthma control (defined as Asthma Control Test score > 19 points), asthma exacerbations, healthcare use (collected from hospital records, patient report and drug deliv-

ery data), and disease-specific quality of life (collected through the PAQLQ questionnaire). Online focus groups and patient questionnaires will be used for evaluation of parental and children's acceptance of RTMM. An economic evaluation will be performed adopting a societal perspective, including all relevant healthcare costs and parental productivity loss. Furthermore, a decision-analytic model will be developed. Different levels of adherence and the outcomes, both clinical and costs, associated with these levels will be modelled. Also sensitivity analyses on different price levels for RTMM will be done.

Keywords: adherence – asthma – children – inhaled corticosteroids – real time medication monitoring – text-message reminder

Dual absorption in intranasal administration:
a new pharmacokinetic model

N. Veldhorst-Janssen ^a, N. Punt ^b and C. Neef ^{a*}

^a Department of Clinical Pharmacy & Toxicology, Maastricht University Medical Centre+, Maastricht. ^b Medimatics, Maastricht.

* Correspondence: c.neef@mumc.nl.

Background

The role of pharmacokinetic modelling is important in the development of new formulations. Some of these models are related to a particular dosage form, others are similar to models that have already been developed. An intranasal administration can be an example of a dosage form with a specific pharmacokinetic model. Especially when it is applied to create a systemic effect.

Methods

A strategy for prediction of dual absorption was developed to describe the pharmacokinetics of an intranasal administration (model 1 and model 2). Midazolam nasal spray was used as an example for this model. To validate the final pharmacokinetic model, Monte Carlo simulations were performed.

Results

We had trouble fitting the observations to a single one-compartment dual absorption model. In many cases a flip-flop condition occurred in which the fitted absorption rate was lower than the estimated elimination rate, and the elimination rate showed an unrealistic value. To prevent this flip-flop condition, we used the absorption parameters from the associated observations. We developed the following model: the model superposes two one-compartment absorption models where the dose is split up over the two compartment inputs and the concentration–time curves are separated by using different lag times (t_{0j}). Monte Carlo simulations resulted in a plasma concentration–time profile, indicating the median concentration and the 5th–95th percentile ranges. Biphasic profiles were observed starting at a parameter error of 15%, increasing to 13.6% of biphasic profiles at a parameter error

of 50%. When increasing the difference between a parameter in model 1 and model 2, the contribution of t_0 to create a local minimum exceeded the contribution of k_a . The AUC of the measured and estimated curve was $201.6 \mu\text{g}\cdot\text{L}^{-1}\cdot\text{h}$ and $201.3 \mu\text{g}\cdot\text{L}^{-1}\cdot\text{h}$, respectively.

Conclusions

The model developed is able to fit concentration–time curves showing individual dual absorption curves adequately.

Keywords: dual absorption – midazolam – intranasal – pharmacokinetics

Patients' satisfaction with intranasal midazolam versus rectal diazepam as fast-working rescue medication in epilepsy

N. Veldhorst-Janssen ^a, A.A.A. Fiddlers ^b, P.H.M. van der Kuy ^c, M.H.J.M. Majoie ^d, A.G.H. Kessels ^e, C. Neef ^a and M.A.E. Marcus ^f

^a Department of Clinical Pharmacology & Toxicology, Maastricht University Medical Centre+, Maastricht. ^b Department of Anaesthesiology, Maastricht University Medical Centre+, Maastricht. ^c Department of Clinical Pharmacology, Orbis Medical Centre, Sittard. ^d Epilepsy Center Kempenhaeghe, Heeze. ^e Research School Mental Health & Neurosciences, Maastricht University Medical Center+, Maastricht. ^f Department of Clinical Epidemiology and Medical Technology Assessment, Maastricht University Medical Centre+, Maastricht.

Background

Fast-acting rescue medication is often needed to control persistent or acute epileptic seizures, and rectally administered diazepam is currently used for this purpose in the Netherlands. An alternative rescue medication is intranasal midazolam. In deciding which medication to use, it is important to know patients' preferences and attitudes towards intranasal midazolam and rectal diazepam. The aim of this study is to evaluate patients' satisfaction with intranasally administered midazolam compared with rectally administered diazepam.

Methods

Patients ($n = 25$) who used rectal diazepam or intranasal midazolam were invited to participate in the study by their pharmacist or physician. Patients completed the Treatment Satisfaction Questionnaire for Medication (TSQM), which scores the effectiveness, side effects, and convenience of treatment, and patients' global satisfaction. Baseline patient characteristics were recorded. Student's *t*-test was used to estimate a difference in satisfaction between the two groups.

Results

Satisfaction with the effectiveness and convenience of drug administration and global satisfaction were higher with intranasal midazolam (84.6%, 92.3%, 84.7% respectively) than with rectal

diazepam (58.3%, 63.4% and 58.3% respectively), whereas mean satisfaction with side effects was higher with rectal diazepam (91.7%) than with intranasal midazolam (69.3%). However, none of the differences were statistically significant.

Conclusions

Although not statistically significant, patients who used intranasal midazolam were overall more satisfied than were patients who used rectal diazepam; however, the side effects of rectal diazepam were more tolerable than those of intranasal midazolam.

Vitamin D deficiency among elderly psychiatric inpatients

M. Volkerijk ^{ab}, M.S.S. Sjak Shie ^{acx} and E.J. Giltay ^b

^a GGZ Foundation for Mental Health Care Rivierduinen. ^b Leiden University Medical Center. ^c Central Hospital Pharmacy The Hague.

* Correspondence: m.sjakshie@rivierduinen.nl.

Background

Vitamin D deficiency is a risk factor for osteomalacia, osteoporosis, rickets, falling and fractures. Annually approximately 4500 nursing home residents visit the Emergency Room department because of falling incidents. Mood stabilizers carbamazepine and valproic acid are risk factors for vitamin D [25(OH)D] deficiency. Depression and poor cognition are risk factors for staying indoors and therefore a risk factor for vitamin D deficiency. Vitamin D deficiency has also been pointed out as a risk factor for poor cognition and depression. Strong dopamine antagonist like haloperidol and risperidone are risk factors for hyperprolactinaemia and hyperprolactinaemia is a risk factor for osteoporosis. These risk factors may precipitate in elderly psychiatric inpatients. Data from nursing home residents show that 25(OH)D deficiency is highly prevalent but data from elderly psychiatric inpatients are scarce. In our institution neither screening for 25(OH)D deficiency nor standard 25(OH)D supplementation are common practice.

Objective

The aim of this pilot study is to determine in our elderly psychiatric inpatient population whether 25(OH)D deficiency (< 30 nmol/L) or insufficiency (30–50 nmol/L) is prevalent and associated with the use of carbamazepine or valproic acid, with poorer cognitive functioning or depressive symptoms.

Methods

Subjects (32 patients) were at least 60 years and living in our institution for at least 1 year. Assessment of depression was done using the MADRS and GDS-15 and assessment of cognitive functioning was done using the MMSE and a clock test (Shulman categories). Serum 25(OH)D measurements, MADRS, GDS-15, MMSE and the clock test were done in April 2011. Multivariate logistic regression

analysis was performed with SPSS and covariates included age, sex, education level and BMI.

Results

20 of the 32 patients were vitamin D deficient (28%) or insufficient (34%). 8 patients (25%) had a sufficient vitamin D level (≥ 80 nmol/L) of whom 7 received high dose vitamin D supplementation. 26 patients (81%) used antipsychotics. An association with carbamazepine (1 patient) or valproic acid use (3 patients) could not be determined because of the low sample size. Vitamin D deficiency was not associated with MADRS score (0.07; $P = 0.79$), GDS-15 score (-0.9 ; $P = 0.74$), MMSE score (-0.14 ; $P = 0.76$) or the clock test (-0.53 ; $P = 13$).

Conclusions

Vitamin D deficiency and insufficiency are highly prevalent in our elderly inpatient population. There was no association with depressive symptoms or cognitive impairment. Our population is at risk for osteomalacia, osteoporosis, falling and fractures and high dose vitamin D supplementation is indicated.

Keywords: vitamin D deficiency – psychiatric inpatients – mental health institution

Metformin dose related to renal function in outpatients

The MetClear study

L. Winkelmolen ^{a*}, R.D. Oude Engberink ^b, R. Roelofs ^a, A.G. Vlug ^c, L.J. Vleming ^b, G.A.E. Ponjee ^c, E.B. Wilms ^a and N. Geelhoed-Duijvestijn ^c

^a Apotheek Haagse Ziekenhuizen, The Hague. ^b HagaZiekenhuis, The Hague.

^c Medisch Centrum Haaglanden, The Hague.

* Correspondence: l.winkelmolen@ahz.nl.

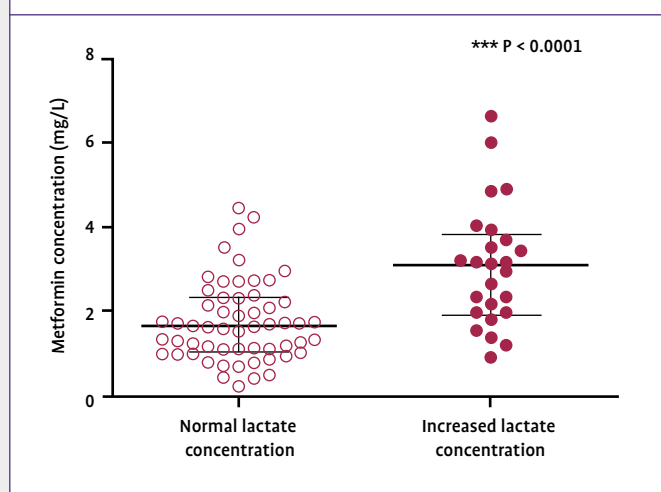
Background

Metformin is the most commonly prescribed drug for diabetes mellitus type 2 (DM2) and is renally excreted. Decreased renal clearance might lead to accumulation of metformin, associated with rare but potentially harmful development of lactate acidosis. For this reason, guidelines advise to adjust the metformin dose according to renal function. A clear correlation between metformin and lactate acidosis could, however, not be found in a recent meta-analysis. The MetClear study was designed to investigate the prescribed doses of metformin in outpatients and the correlation between renal function, metformin blood concentrations and lactate blood concentrations.

Methods

In this prospective pilot study, 86 DM2 outpatients on metformin without further selection criteria were included. The prescribed dose of metformin on the day of routine blood sampling was

Metformin concentrations for normal and increased lactate concentration



registered. The following concentrations were measured in the blood samples: lactate, metformin, creatinine (for calculation of MDRD) and HbA1c. The dataset was divided in 'high' and 'normal' lactate concentrations (normal reference concentration 0.7-2.1 mmol/L) and 'high' and 'therapeutic' metformin concentrations (therapeutic drug concentrations ≤ 2.5 mg/L).

Results

We included 86 patients, average age 67 years (38-89 years). In 14% the MDRD was ≤ 30 ml/min, in 34% the MDRD was between 30 and 50 ml/min and in 52% the MDRD was > 50 ml/min. The daily doses of metformin in these three groups were between 1000 and 2550 mg, 1000 and 3000 mg and 850 and 3000 mg, respectively. In 25 patients an increased lactate concentration was measured. In these patients, metformin concentrations were higher than in the normal lactate concentrations group: 3.11 mg/L and 1.65 mg/L, respectively (see figure; $P < 0.0001$). The mean MDRD was 57 and 53 ml/min, respectively ($P = 0.48$).

In 28 patients high metformin blood concentrations were found. The MDRD in these patients was lower than in the group of patients with therapeutic metformin blood concentrations: 42 and 61 ml/min, respectively ($P < 0.001$).

Conclusions

This study shows that metformin dose in outpatients is often not adjusted to decreased renal function. Daily doses up to 3000 mg were continued even though guidelines advise a reduced dose or discontinuation of metformin below an MDRD of 50 and 30 ml/min. Metformin accumulation seems to be related with an increased lactate level and a decreased renal function. In further analyses the effect of co-morbidities such as heart failure and the parameters metformin dose and HbA1c on lactate levels will be determined.

Our data confirm that we should exercise caution in dosing metformin in patients with decreased renal function.

Keywords: metformin – lactate concentration – TDM – decreased renal function

Influence of bariatric surgery on the use of some major drug classes

J.P. Yska ^{a*}, D. van der Meer ^a, W. Eilander ^a, A.R. Dreijer ^a, J.A. Apers ^b, M. Emous ^b, E. Totté ^b, B. Wilffert ^c and E.N. van Roon ^a

^a Department of Clinical Pharmacy and Clinical Pharmacology, Medical Centre Leeuwarden. ^b Department of Surgery, Medical Centre Leeuwarden. ^c Department of Pharmacotherapy and Pharmaceutical Care, University of Groningen.

* Correspondence: j.p.yska@znb.nl.

Background

Patients undergoing bariatric surgery are severely obese characterized by multidrug use for multiple co-morbidities. Bariatric surgery can influence the prevalence and incidence of co-morbidities, as well as the pharmacokinetics of drugs. This might lead to changes in the use of drugs.

Objective

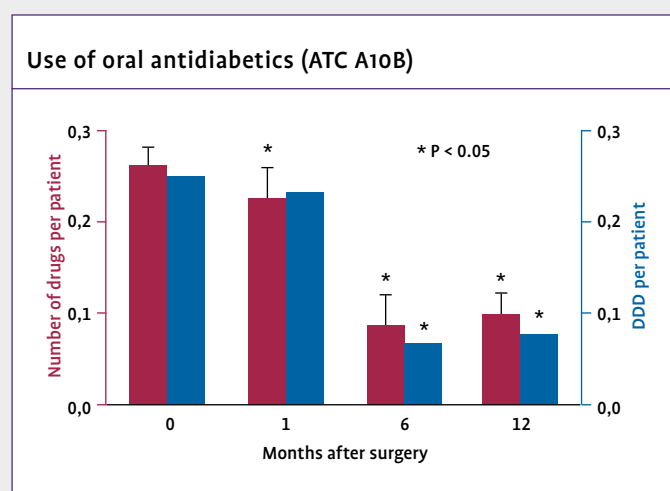
To study the influence of bariatric surgery on the use of some major drug classes twelve months after surgery.

Methods

A retrospective, observational study was carried out in Medical Centre Leeuwarden. After having obtained written informed consent drug dispensing data from pharmacies were collected from patients undergoing their first bariatric surgery between January 2008 and December 2010. Dispensing data from the day of surgery and 1, 6 and 12 months after surgery were analyzed. Drugs were classified according to the WHO-ATC classification system. Dosages of drugs were compared using defined daily dose (DDD).

Results

224 patients were included (19.2% male). Mean age (SD) was 43.4 (10) yr; mean BMI (SD) was 45.0 (7.3) kg/m². Roux-en-Y gastric bypass was performed in 68% of the patients. Mean BMI (SD) twelve months after surgery was 32.8 (9.3) kg/m². The mean number of drugs per patient (CI95) decreased from 3.38 (2.99-3.82) to 2.93 (2.60-3.30) twelve months after surgery.



The mean number of drugs per patient decreased by 64%, 34%, 35%, 39% and 22% for antidiabetics, diuretics, betablockers, agents acting on the renin-angiotensin system and lipid-modifying agents respectively. From those drug classes patients used lower DDD twelve months after surgery. See figure for the use of oral antidiabetics. Drugs for acid related disorders, thyroid drugs, drugs for obstructed airway diseases, antidepressants and psycholeptics showed no significant change in use.

Conclusion

Twelve months after bariatric surgery the use of drugs decreases in terms of mean number of drugs per patient and, for some major drug classes, in dose intensity.

Keywords: bariatric surgery – drug classes – use of drugs – DDD

Monitoring of methotrexate levels following glucarpidase rescue treatment requires detection by mass spectrometry since immunoassay is not applicable

M.L. Zandvliet ^{a*}, B.S. Jacobs ^b, E. den Boer ^c, R.J.W. Meesters ^d, A.L. de Goede ^a, F.K. Engels ^a, R. de Jonge ^c, S. Natsch ^b and B.C.P. Koch ^a

^a Department of Pharmacy, ^c Department of Clinical Chemistry, ^d Department of Neurology, Erasmus University Medical Center, Rotterdam. ^b Department of Clinical Pharmacy, Radboud University Nijmegen Medical Centre, Nijmegen.

* Correspondence: m.zandvliet@erasmusmc.nl.

Background

Patients treated with high dose methotrexate may experience severe toxicity when excretion is delayed, e.g. due to development of acute renal dysfunction. Potentially lethal toxicity may be limited by hydration, alkalinisation, and administration of folinic acid as rescue therapy. In addition, the use of glucarpidase (Voraxaze) may be considered. Glucarpidase is an enzyme capable of metabolizing methotrexate into glutamate and metabolite 2,4-diamino-N10-methylpteroic acid (DAMPA), which has very low cytotoxic activity. Glucarpidase is unlicensed in the EU and US, partly due to concerns regarding pharmaceutical quality, and the interaction with folinic acid. However, recent data support its efficacy in reducing methotrexate-induced toxicity [1]. Yet to date, limited information is available to support optimal dosage of glucarpidase.

Aim

To monitor the effect of glucarpidase administration on methotrexate levels in three children with delayed excretion following high dose methotrexate therapy.

Methods

Plasma concentrations of methotrexate were determined by flu-

orescence polarization immunoassay (FPIA) and matrix-assisted laser desorption ionization mass spectrometry (MALDI-MS) [2] or liquid chromatography electrospray mass spectrometry (LC-ESI-MS).

Results

Using FPIA measurement, methotrexate concentrations appeared to decrease with 78-82% (range) 30 minutes after glucarpidase administration. Residual methotrexate concentrations appeared to decline slowly thereafter. In contrast, MS measurement showed very rapid and nearly complete methotrexate clearance, with a 98-99% (range) reduction within 30 minutes. Subsequently, a minor increase in methotrexate levels was observed, most likely resulting from redistribution.

Conclusions

After glucarpidase administration, FPIA analysis can not be used for follow-up of methotrexate levels, most likely due to cross-reactivity of metabolite DAMPA. Instead, MS detection can provide specific detection of residual methotrexate, and confirms nearly complete methotrexate degradation after glucarpidase administration. Specific MS monitoring may result in prevention of further glucarpidase administration or dialysis, limited folinic acid administration, and more rapid hospital discharge.

REFERENCES

- 1 Widemann BC, Balis FM, Kim A, Boron M, Jayaprakash N, Shalabi A, et al. Glucarpidase, leucovorin, and thymidine for high-dose methotrexate-induced renal dysfunction: clinical and pharmacologic factors affecting outcome. *J Clin Oncol*. 2010;28(25):3979-86.
- 2 Meesters RJ, den Boer E, Mathot RA, de Jonge R, van Klaveren RJ, Lindemans J, et al. Ultrafast selective quantification of methotrexate in human plasma by high-throughput MALDI-isotope dilution mass spectrometry. *Bioanalysis*. 2011;3(12):1369-78.

Keywords: therapeutic drug monitoring – mass spectrometry – methotrexate – glucarpidase