Nederlandse Ziekenhuisfarmaciedagen, 26 en 27 mei 2011

Dit artikel bevat de abstracts van de mondelinge presentaties tijdens de Nederlandse Ziekenhuisfarmaciedagen op 26 en 27 mei 2011 te Amersfoort. De digitale versie van dit artikel op pw.nl omvat ook de abstracts van de posterpresentaties.

Pharmacodynamics of 5700 IU nadroparin subcutaneous in morbidly obese patients using anti-Xa levels

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Background

Morbidly obese patients (BMI > 40 kg/m^2) are at increased risk for thromboembolism, especially after surgery. Low-molecular-weight-heparins have been shown to substantially reduce this risk. However, if and how the dose should be adjusted with large increases in body weight is unknown. In clinical practice a double dose of nadroparin for thrombosis prophylaxis is often used for (morbidly) obese patients with limited clinical evidence. The primary aim of this study was to evaluate the efficacy and safety of a double dose of nadroparin (5700 IU) in morbidly obese patients using anti-Xa levels, ultrasound and occurrence of bleedings. Secondarily, we developed a population pharmacodynamic (PD) model of nadroparin used for thrombotic prophylaxis in morbidly obese patients, thereby studying the influence of covariates.

Methods

At induction of anaesthesia for bariatric surgery, 5700 IU (= 0.6 ml) nadroparin was administered subcutaneously. Chromogenic anti-Xa levels were measured just before and 10, 30, 60, 90, 120, 180, 240, 300 and 420 minutes after nadroparin injection and the next morning within 24 hours after administration. Primarily, it was evaluated whether the recommended prophylactic range of 0.2-0.5 IU/ml was reached four hours after administration (C_{4h}) while the $AUC_{0\text{-}24h}$ and the occurrence of thrombotic events (echo) and bleedings were reported. Secondarily, population PD modelling was performed using NONMEM VI.

Results

Twenty morbidly obese patients were included with a median body weight of 144 kg (range 112-260 kg) and a median BMI of 51 kg/m^2 (range 38-79 kg/m^2). Median C_{4h} was 0.21 IU/ml (SD 0.07), with ten patients showing C_{4h} levels below the therapeutic range. Median $AUC_{0\text{-}24h}$ in morbidly obese patients was 2.80 h·IU/ml (SD 0.97). No clinically reported, ultrasound-measured thrombotic events or bleeding were observed. In a two-compartment pharmacodynamic disposition model with delayed absorption, body weight (BW) proved to be the most predictive covariate for clearance [$CL = 47.6 \text{ mL/min} \cdot (BW/144)^{1.5}$] while lean body weight (LBW) was the most predictive covariate for volume of distribution [$V_{ss} = 12.6 \text{ L} \cdot (LBW/66)^{1.5}$].

Conclusions

Upon a double dose of nadroparin in morbidly obese patients, anti-Xa concentrations four hours after administration were below the therapeutic range in 50% of the patients and $AUC_{0\text{-}24h}$ levels proved comparable to $AUC_{0\text{-}24h}$ levels described for non-obese patients after a single dose of 2850 IU nadroparin. The pharmacodynamics of nadroparin measured using anti-Xa levels, are influenced by excessive body weight and therefore an adjusted dose seems necessary for morbidly obese patients.

Keywords: nadroparin – anti-Xa – morbid obesity

ATTACK-study (interim analysis): Allopurinol TreatmenT And oxipurinol Concentrations in gouty patients: Knowing the therapeutic window

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Objective

Allopurinol is proven effective in treating gout [1]. Nevertheless, only 25% of gouty patients is successful in reaching target urate concentrations [2, 3]. When urate lowering is insufficient allopurinol dosage should be raised until the maximum dosage of 900 mg per day is reached [4]. The active metabolite of allopurinol is oxipurinol. The marketing authorization holder of allopurinol advises to measure the oxipurinol concentration in case of impaired renal function, where the oxipurinol concentration should be beneath 15.2 mg/l to avoid adverse effects [4]. Common practice shows that oxipurinol concentrations are seldom measured. In the past years several authors have made suggestions about measuring oxipurinol concentrations in allopurinol-

treated patients and the therapeutic window that should be pursued [5-7]. The objective of the ATTACK study is to investigate whether there is an association between oxipurinol concentration and the chance of successful lowering of urate concentration in gouty patients (defined as reaching urate concentrations < 0,30 mmol/l).

Methods

An observational, prospective, multicenter study on gouty patients, treated with allopurinol. Inclusion criteria were: gout diagnosed with microscopic urate crystals, first treatment with allopurinol, completed informed consent. Exclusion criteria were: age beneath 18 years and pregnancy, estimated GFR below 20 ml/min, patients using azathioprine, mercaptopurine or cyclophosphamide. Primary outcome measures: association between oxipurinol concentration and the chance of successful treatment of gout (defined as reaching urate concentrations of < 0.30 mmol/l). Patients were seen by the rheumatologist after two and four months. Quantification of serum allopurinol and oxipurinol was performed by a validated HPLC-UV method. Compliance was measured with a validated questionnaire for gouty patients. Statistical analysis for the association of serum oxipurinol concentrations and treatment success was performed by using Receiver Operating Characteristic (ROC) in SPSS (18.0).

Results

94 patients were available for inclusion, of which 60 are evaluable at this moment (80% male). ROC analyses of the results two months after inclusion showed an AUC of 0,67 (P = 0.03). A cut-off value of oxipurinol was found at 12.2 mg/l with a sensitivity of 78%. The average compliance was 74%. Average urate lowering was 0,23 mmol/l (baseline vs. first follow-up visit) and 0,18 mmol/L (baseline vs. second follow-up visit).

Conclusions

Oxipurinol concentration is associated with successful urate lowering in gouty patients (P = 0,03) defined as reaching serum urate < 0.30 mmol/l.

Keywords: therapeutic drug monitoring – gout – allopurinol – oxipurinol

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Identification of drug-related problems by a clinical pharmacist in addition to computerized physician order entry alerts

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Background

Problems associated with pharmacotherapy occur frequently in hospitalized patients and can result in patient harm and increased costs. Active participation of clinical pharmacists on the ward has been shown to reduce drug-related problems (DRPs, i.e. medication errors and adverse drug events) in different settings. Besides, implementation of computerized physician order entry systems together with clinical decision support systems (CPOE/CDSS) has the potential to reduce DRPs, particularly medication errors. However, the added value of clinical pharmacists compared to the identification of DRPs via CPOE/CDSS is unclear. Therefore, this study was performed to determine which DRPs identified by a clinical pharmacist would also be detected by CPOE/CDSS.

Methods

A clinical pharmacist performed weekly medication reviews to identify possible DRPs in patients admitted to two surgical wards and two neurological wards. For each patient, the relevance of identified DRPs and proposed actions to ameliorate them were discussed with the responsible physician. Follow-up of the proposed actions for relevant DRPs as well as the presence of alerts in the CPOE/CDSS (Theriak Medication Management) were assessed by the clinical pharmacist. Primary outcomes were the possible and relevant DRPs identified by the clinical pharmacist and the number of DRPs that generated an alert in the CPOE/CDSS. Secondary outcome was the percentage of follow-up of the proposed action.

Results

During 1206 medication reviews, 445 possible DRPs were identified in 228 patients; 289 DRPs (65%) were considered relevant for the individual patient and 250 (87%) of the proposed actions for these relevant DRPs were completed. In total 35 (8%) of the possible DRPs identified by the clinical pharmacist resulted in a CPOE/CDSS alert, of which 25 (71%) were considered relevant. The proportion of relevant DRPs among DRPs detected by the clinical pharmacists only and DRPs also detected by CPOE/CDSS did not differ (odds ratio 1.38; 95% confidence interval 0.65-2.96). The most common relevant DRPs were unnecessary drug therapy (21%), requirement of additional drug therapy (14%) and discrepancy with pre-admission medication (14%). Drugs frequently involved were those for the nervous system (25%), the cardiovascular tract (14%), the blood system (13%) and the gastro-intestinal tract (13%).

Conclusions

The majority of DRPs identified by a clinical pharmacist was not detected by CPOE/CDSS in daily pharmacy practice. Therefore, a clinical pharmacist in addition to a CPOE/CDSS contributes to the reduction of DRPs. Besides, these results can be used to optimize the sensitivity of CPOE/CDSS to identify DRPs.

Keywords: clinical pharmacist – medication errors – adverse drug events – computerized physician order entry – clinical decision support system

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Medication safety

Electronic monitoring to assess adherence and validate alternative adherence measures in tuberculosis patients on community-based Directly Observed Treatment

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Background

Non-adherence to tuberculosis (TB) treatment is a major obstacle to the control of this infectious disease. WHO's solution of Directly Observed Treatment (facility-based DOT) is causing overburdened healthcare facilities worldwide. Involvement of community members in the provision of DOT is an alternative, but adherence under community-based DOT is unknown and this strategy may need monitoring by adherence measures. The objective of this study was to assess adherence rates of TB patients on community-based DOT by using the Medication Event Monitoring System, a bottle with a chip in the cap (MEMS bottle), and to determine the validity of other locally feasible adherence measures with MEMS as reference standard.

Methods

This was a longitudinal study among 50 adult TB outpatients in Tanzania's Kilimanjaro Region who were monitored by community-based DOT. Adherence to once-daily TB drugs was assessed throughout 6 months of TB treatment by using MEMS, a urine test for isoniazid, urine colour test for rifampicin, the Morisky adherence scale, the Brief Medication Questionnaire (BMQ), an adapted version of the AIDS Clinical Trials Group (ACTG) adherence questionnaire, pill counts and clinic attendance for medication refills. MEMS data were used to calculate adherence rates by dividing the number of days on which bottle opening was registered by the number of monitored days, multiplied by 100%. MEMS adherence rate cut-off values of 100% and 95% were used to differentiate between adherence and non-adherence. The sensitivity and specificity to detect non-adherence as assessed by MEMS was calculated for the other (combination of) adherence measures.

Results

50 patients were enrolled; 37 completed treatment, 6 died, 3 defaulted and 4 dropped out. Adherence rates ranged from 50 to 100% (median 98%) in all patients, and from 89 to 100% (median 98%) in the patients who completed treatment. In the latter group, 70% of patients were less than 100% adherent and 19% less than 95%. The ACTG questionnaire and urine colour test had the highest sensitivity (70-100%) but lowest specificity (20-37%) for detecting non-adherence, and the Morisky scale and clinic attendance the highest specificity (80-100%) but lowest sensitivity (14-35%). The sensitivity of the routinely available combination of pill counts and clinic attendance improved when the ACTG questionnaire was added.

Conclusions

The high adherence rates confirm that community-based DOT can be an effective strategy to prevent non-adherence. The combination of pill counts, refill visits and ACTG questionnaire is a feasible method to monitor adherence when MEMS is not affordable.

Keywords: adherence – tuberculosis – community-based Directly Observed Treatment (DOT) – Medication Event Monitoring System (MEMS)

The role of the pharmacist in geriatric ward rounds

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Introduction

Adverse drug events (ADE) are responsible for a substantial part of the hospital admissions and for prolongation of hospital stays [1, 2]. The hospital pharmacist can help in preventing these ADEs. A large number of studies in several settings confirms this role [3, 4]. In this study, we assessed how many medication-related problems were identified and intervened by a (resident) hospital pharmacist during ward rounds on a geriatric ward in an academic hospital.

Methods

In the period between January 2009 and December 2010, a resident hospital pharmacist participated regularly in the weekly geriatric ward rounds. He screened the medication prior to the ward rounds for medication-related problems. During the geriatric ward rounds all patients and their medication were discussed with the geriatricians, resident geriatricians, nurses and in some cases a psychiatrist, and, if applicable, suggestions were given to change the medication. During the study period all suggestions and the changes in medication were recorded.

Results

During the study period, 49 ward rounds were attended and 302 patients were discussed (average 6.2, range 3-9 patients). 242 of these 302 patients were newly admitted. The average patient was 82 years of age (range 53-102) and used 7.8 drugs (range 0-18). In total, 93 suggestions were given to change the medication. 60 suggestions (65%) resulted in a medication change. More interventions were done in patients using more drugs (P = 0.015), but no association was found with the age of the patients (P = 0.37). 19 suggestions involved switching to another drug, and

18 suggestions were to stop medication, most often to prevent adverse drug reactions. The other 23 suggestions were to start medication (n = 7), to change the dose (n = 6), to change the dose regimen (n = 6), or to use another preparation (n = 4). 33 suggestions were not accepted by the physicians. The type of intervention did not differ between the accepted and the non-accepted suggestions (P = 0.66). Reasons for not changing the medication were that a clinical reason to continue the medication was present (n = 14) or not knowing the indication or the prescriber of the drugs (n = 10).

Discussion

One way to avoid ADEs may be to regularly screen the medication of hospitalized patients by a pharmacist. The ward rounds are a good opportunity to do so. In this study, we found that a pharmacist could intervene in the medication of one in four patients that were hospitalized on a geriatric ward.

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Keywords: medication review – adverse drug events – geriatrics

Development of an outpatient, pharmacist-led group intervention to improve medication adherence

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Background

Almost 50 % of prescribed medication in chronic conditions is not taken as directed. Improving adherence could therefore improve the efficacy of medical treatments. However, interventions to improve adherence are as yet not very effective. An explanation for the limited success of existing interventions is that most interventions attempt to overcome unintentional non-adherence (e.g. by issuing reminders or clear instructions), but fail to target the beliefs about medication that may lead to intentional non-adherence. Therefore, a short patient-centered group intervention was developed targeting individual's beliefs about medication and, if necessary, practical barriers for adherence.

Methods

The development of the group intervention consisted of three steps: (1) choice of a theoretical model on which the intervention will be based, (2) development of the intervention method, and furthermore piloting the intervention in (3) a patient panel, an expert panel and finally as a pilot intervention.

Results

Theoretical model. The intervention is based on a simplified I-Change model, suggesting that individuals will adhere with health regimens if they regard themselves as having been or being susceptible to the condition in question, if the condition has serious current or future consequences, if the action would be beneficial, and if they feel that barriers to action are outweighed by the benefits. Patients consider whether their beliefs about the necessity of medication outweigh their concerns about potential adverse effects of taking them. Thus, besides practical barriers like forgetfulness, clinicians should also be sensitive to personal beliefs that may impact medication adherence. *Intervention method.* In order to target the complex and individual decision making process in medication adherence Motivational Interviewing (MI) will be used as a method to change beliefs and behaviour. MI-based interventions to improve medication adherence have been studied before in patients with chronic diseases and there are some indications that these interventions are effective to improve medication adherence. The intervention only included non-adherent patients [measured with the compliance questionnaire on rheumatology (CQR)]. *Pilot.* After the development phase, the intervention was reviewed by an expert panel consisting of psychologists, an MI expert, rheumatologists, (hospital) pharmacists and patients. Finally, two pilot interventions (12 patients) were executed. The results of the expert review combined with video tapes of the pilot interventions were used as input for the optimization of the adherence intervention.

Conclusion

A short motivational patient-centred intervention addressing the primary causes of non-adherence in non-adherent patients is successfully developed. Currently the effectiveness of this intervention is tested in a randomised clinical trial in 100 non-adherent patients with rheumatoid arthritis.

Keywords: adherence – rheumatoid arthritis – beliefs – intervention

Assessment of the incidence and nature of adverse drug events in surgical patients using a new surgical trigger tool

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Background

Harm caused by medication errors, i.e. preventable adverse drug events (pADEs), are still a problem in hospitals. Several studies reported pADE incidences between 0.6 and 16%. Even in hospitals using computerized physician order entry (CPOE) systems, pADEs still occur. Furthermore, the healthcare process of surgical patients differs greatly from other patients. Until now, the incidence and nature of pADEs in the surgical population has not been determined. The aim of this study was to quantify preventable ADEs in a Dutch surgical population of hospitals, where CPOE with clinical decision support (CDS) is well implemented.

Methods

In this observational cohort study, eight surgical units in three different hospitals participated. Elective surgical patients with a hospital stay longer than 48 hours were included. The units contained mainly gastro-intestinal and vascular surgery patients. To pre-select medical records with potential ADEs, a trigger tool was developed. This tool was based on current literature as well as quality indicators of good healthcare and was adjusted to the surgical population. The final causality, severity and preventability of the detected ADEs, were assessed by an independent expert panel of surgeons and clinical pharmacologists.

Results

The medical records of 567 prospectively included patients were screened using the surgical trigger tool. 340 medical records contained one or more triggers for potential ADEs and were evaluated by the expert panel. This panel found 28.2 ADEs per 100 admissions of which 15.6% was judged as preventable. Thus, the incidence of preventable ADEs was 4.4 per 100 admissions. Of these pADEs, 24% was classified as severe or life-threatening.

Conclusions

In the surgical population of three different Dutch hospitals using CPOE with CDS, a total incidence of 4.4 preventable ADEs per 100 admissions was found, of which a considerable proportion was classified as severe or life-threatening. To improve medication safety, an intervention strategy to reduce this incidence of preventable ADEs is proposed, the so-called ward-based pharmacy care approach. Pharmacy technicians and clinical pharmacists actively participate in the clinical decision-making and executive processes on medical wards. The effect of this approach on pADE incidence is now being carefully scrutinized in a randomised controlled trial (NTR2258).

Keywords: preventable adverse drug events – trigger tool – causality assessment – surgical patient

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Influence of barcode-assisted medication administration on the rate of medication administration errors in a surgical ward

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Background

In recent years information technology has become important in preventing medication errors. For example, computerized physician order entry systems are used to reduce prescription errors. Medication administration errors (MAEs) are another important category of medication errors because they are seldom perceived and they are irreversible. Barcode-assisted medication administration (BCMA) is seen as a promising tool in the prevention of this type of error. Up to now, few studies have investigated the influence of BCMA on the medication administration error rate and therefore we conducted the present study.

Methods

Nurses on a surgical ward were observed during a five-day period one week before and six months after implementation of BCMA, using the disguised observation technique. MAEs were counted as primary outcome. Besides BCMA a new logistic procedure was implemented comprising a thrice daily supply of drugs from the hospital pharmacy to the ward instead of once daily. MAEs were categorized in: wrong patient, wrong drug, unauthorized drug, wrong dose, wrong route, wrong time, omission and omission due to absence of the drug on the ward (logistic omission). Two pharmacists independently classified the severity of the observed errors using the National Coordinating Council for Medication Error Reporting and Prevention taxonomy of medication errors. In case of initial differences in classification consensus was reached. The distribution of MAEs in classes of severity was scored as a secondary outcome. The difference in occurrence of MAEs before and after implementation of BCMA was analysed using univariate and multivariate logistic regression analysis. A chi-square test was used to test differences in MAE classes of severity.

Results

The observed number of medication administrations before implementation of BCMA was 945 and after implementation 1001. Prior to implementation 68 MAEs including time errors (7.2%) were observed and excluding time errors 28 (3.0%). After implementation including and excluding time errors respectively 36 (3.6%) and 4 (0.4%) MAEs were seen. This corresponds to odds ratios (OR) of 0.48 (CI95 0.31-0.73) and 0.13 (CI95 0.05-0.38) including and excluding time errors, respectively. Adjusted ORs were 0.63 (CI95 0.4-0.99) and 0.12 (CI95 0.04-0.35) respectively (age was included in the multivariate model). MAEs prior to implementation of BCMA were categorized in class C 79.4% and D 20.6% and after implementation in class C 88.9% and D 11.1% (OR 0.48; CI95 0.15-1.59).

Conclusion

Medication administration errors are considerably reduced using barcode-assisted medication administration. No severe MAEs occurred during the observation period and no difference in distribution in categories of severity was seen after implementation of BCMA.

Keywords: medication administration errors – barcode-assisted medication administration

Effect of instruction manuals on the documentation of medication changes and clinical information by community pharmacies for discharged patients

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Background

The St Lucas Andreas Hospital (SLAZ) sends discharge medication overviews (containing reasons for medication changes/clinical information) to community pharmacies to improve continuity of care. However, community pharmacies do not always document the new information in their pharmacy records, which may hamper medication surveillance and thus patient safety. The aim of this study was to evaluate whether the documentation of information on the discharge medication overview improved after introducing instruction manuals.

Methods

A before-after study was performed (July 2009-August 2010). Patients who were discharged home from the cardiology/pulmonology ward with a discharge medication overview that contained a change in preadmission medication and/or clinical information were included. The intervention consisted of faxing the discharge medication overview together with the instruction manual. This manual specified how community pharmacies could document the information in their pharmaceutical dossier. Usual care consisted of faxing only the overview. Two weeks after discharge, medication records of the community pharmacies were requested by fax. These records were compared with the original discharge medication overviews regarding the documentation of allergies/contra-indications and medication changes. For medication changes the community pharmacy's documentation should clarify that a dose had increased/decreased (dose change), a medication had been replaced (switch) or that a medication should not be prescribed anymore (discontinued medication). Independent t-tests were used for continuous variables and chi-square tests for proportions.

Results

In the study 218 patients (112 before, 106 after intervention) were included. There were no significant differences between groups (age, sex, number of medication changes/clinical information). Documentation of contra-indication (35% before vs. 29% after intervention, P = 0.678) and correct documentation of switched medication (19% vs. 23%, P = 0.728) was not different after the intervention. Allergy documentation improved non-significantly (54% before vs. 82% after, P = 0.057). Dose changes (1.4% vs. 8.6%, P = 0.006) and discontinued preadmission medication (5.8% vs. 28%, P < 0.001) were documented significantly more frequently in the intervention period.

Conclusion

The instruction manuals led to an increased documentation of the discharge medication overview information. However, the frequency of incorrect/incomplete documentation remains high: more than 90% of the dose changes and more than 80% of the discontinued medication was documented incorrectly by community pharmacies. Faxing an instruction manual is insufficient to improve the quality of information transfer between hospital and community pharmacies.

Keywords: hospital discharge – medication errors – communication and documentation – information transfer – continuity of care

A new clinical rule for identifying hyperkalemia in patients using potassium-influencing drugs

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Background

In clinical practice potassium disorders are a common, and potentially dangerous, electrolyte abnormality. Reported incidence of hyperkalemia in hospitals is 1% to 10%. It is known that patients using a combination of potassium supplements and potassium-sparing diuretics or renin-angiotensin-aldosterone-system (RAAS) inhibitors are especially at risk. Previous studies on the incidence of hyperkalemia in patients with concurrent use of two or more potassium-influencing drugs were either small in sample size or did not investigate the full range of drugs involved. In this study we explored the occurrence of hyperkalemia in a large cohort of patients using potassium-influencing drugs. Also, we studied the role of other potential risk factors for hyperkalemia.

Objective

To measure the incidence of hyperkalemia and to identify risk factors for hyperkalemia in hospitalised patients using potassium supplements, potassium-sparing diuretics and RAAS inhibitors concurrently.

Methods

A retrospective, nested case–control study was executed. Hospitalised patients using a combination of potassium supplements and RAAS inhibitors or potassium-sparing diuretics were included in the study. Cases were defined as patients with serum potassium ≥ 5.5 mmol/L on at least one occasion, controls were patients with normal serum potassium levels. Cases and controls were included in a ratio of 1:2. Known risk factors associated with hyperkalemia (diabetes mellitus, congestive heart failure, renal function, advanced age, gender, the use of heparin, digoxin, NSAIDs, beta-blocker, calcineurin antagonists and trimethoprim) were recorded and statistically analysed.

Results

Of 774 patients included in this study, 52 patients developed hyperkalemia; an incidence of 6.7%. From the studied risk factors, only lowered renal function – expressed as an estimated glomerular filtration rate (eGFR) < 50 ml/min – was significantly associated with hyperkalemia (OR 5.08; CI95 2.46-10.48).

Conclusion

Decreased renal function already starting from an eGFR < 50 ml/min was identified as a statistically significant risk factor for hyperkalemia in patients using potassium-influencing drugs. None of the other risk factors were identified as significant. In previous studies an eGFR < 30 ml/min was considered as threshold below which development of hyperkalemia substantially increases, however, our study observed a threshold of eGFR < 50 ml/min. This result provides a specific clinical rule that will help to predict the risk of developing hyperkalemia in patients using a combination of potassium-influencing drugs.

Keywords: hyperkalemia – potassium – potassium-sparing diuretics – potassium supplements – renin-angiotensin-adosterone system (RAAS) inhibitors – drug-drug interaction

Comparison of antibiotic dosing recommendations for neonates from established textbooks: paving the way for e-prescribing standards

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Background

Incorrect dosing is the most frequently occurring prescribing error in paediatrics and antibiotics are the most frequently prescribed medicines. Computer physician order entry (CPOE) and clinical decision support systems can contribute to the reduction of medication errors. Although evidence-based dosing recommendations should be included in such systems, the necessary evidence is not always available and subsequently dosing recommendations mentioned in guidelines and textbooks are often based on expert opinion. The aim of this study is to compare dosage recommendations for antibiotics in neonates provided by seven commonly used and well-established international textbooks.

Methods

Neonatal daily doses for the 10 most frequently used antibiotics, classified by categories for birth weight and gestational age, were identified from 7 well-respected textbooks in paediatrics/paediatric infectious diseases, and expressed as standardized average daily dosage.

Results

Antibiotics with a wide therapeutic window (e.g. ampicillin, benzylpenicillin, ceftazidime and cefotaxime) showed greater variation in dosage recommendations compared to those with a small therapeutic window (e.g. meropenem, gentamicin and vancomycin). The BNF showed larger variation in dosage recommendations compared to the other textbooks.

Conclusions

Gold standard, expert opinion antibiotic dosage recommendations for neonates can be derived from important textbooks and guidelines for most, but not all antibiotics. Further exploration to

overcome variation in dosage recommendations is necessary to obtain standardized dosage regimens and thus full benefit of CPOE and clinical decision support systems in neonatology.

Keywords: antibiotics – dosing – neonates

Development of a ward-based pharmacy intervention strategy to improve medication safety in surgical patients (part of the SUREPILL study)

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Background

Adverse events caused by medication errors (preventable adverse drug events, pADEs) still constitute an important cause of morbidity and mortality, even in hospitals using computerized medication order entry providing decision support. Many studies have demonstrated that clinical pharmacists and pharmacy technicians can reduce pADEs by participating in the clinical decision-making and executive processes on medical wards. In this study, we describe the development and implementation of a ward-based pharmacy intervention strategy to improve medication safety in surgical patients.

Methods

To develop the intervention strategy of ward-based pharmacy, we used literature and evidence-based guidelines to determine the critical steps in the medication process and to define clinical interventions related to specific types of problems in surgical patients. We recently implemented this strategy and we are currently assessing its effect in a prospective controlled study with randomisation at ward level by measuring the number of pADEs (SUREPILL study).

Results

We developed a structured and uniform method consisting of steps tailored to the clinical process. Firstly, at admission and discharge, medication reconciliation with the patient is performed by pharmacy technicians. During hospital stay, clinical pharmacists daily intervene in the patients' pharmacotherapy in liaison with ward doctors. To execute and record these intervention steps, the acronym TREATRAFID is used. The TREATRAFID worksheet identifies the Type of problem by analyzing the patients medication and clinical status, describing the Reason for intervention, the Evaluation of the problem and the risks incurred by the patient, the Action needed to prevent the adverse event, the Type of intervention, the Reaction to and Acceptance of the intervention by the physician, possible Follow-up actions to monitor the problem and information on the Intervener and the Date and time of intervention. The types of potential problems such as medication-related strategies to prevent infections, thrombo-embolic complications, nausea/vomiting in surgical patients and related clinical interventions were preclassified. The intervention strategy resulted in a uniform working structure for the clinical pharmacists in which clinical pharmacists and pharmacy technicians become well integrated in the daily routine of a multidisciplinary care teams on a surgical ward.

Conclusions

We developed a ward-based pharmacy intervention strategy to improve medication safety in surgical patients and implemented this strategy in daily clinical practice. The effect of this approach on pADE incidence is now being carefully scrutinized in a randomised controlled trial (NTR2258).

Keywords: adverse drug events – ward-based pharmacy – surgical – intervention

The effect of medication verification at hospital admission by pharmacy technicians on medication discrepancies

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Background

Patient transitions in care are a source of discrepancies between pre-admission and admission medication. Some discrepancies are unintended and are the result of errors that are potentially harmful for patients. A medication interview with the patient by a pharmacy technician at admission may reduce the frequency of medication discrepancies. We therefore studied the effect of medication verification by pharmacy technicians at hospital admission on the frequency and nature of intended and unintended medication discrepancies between pre-admission and admission medication.

Methods

An intervention study with pre-test/post-test design was performed at the VU Medical Center in Amsterdam. Patients who were scheduled for elective surgery and were using five or more chronic preadmission medicines were included in the study at admission to a chirurgical ward. In the pre-test period, the drug regimen of patients was verified by an anesthesiologist during the preoperative screening and by a nurse and a physician at admission. The

intervention was the introduction of a medication interview with the patient at admission by a pharmacy technician. The medication prescribed on the first day of admission was compared with the pre-admission medication. Intended and unintended discrepancies were identified after checking the patient documentation. Unintended discrepancies were classified into four categories: omission of medication, addition of medication, change in dosage or change in dosage form. The primary outcome was the effect of the intervention on total, intended and unintended discrepancies. The secondary outcome was the frequency of different types of unintended discrepancies.

Results

67 patients were included in the pre-test period (mean age 65 years, 54% men, mean number of preadmission medicines per patient 8.4) and 68 patients were included in the post-test period (mean age 63 years, 53% men, mean number of preadmission medicines per patient 9.1). The frequencies of medication discrepancies per patient before and after the intervention were respectively 8.1 and 8.4 ($P = 0.57$), divided in 5.6 intended discrepancies before and 8.2 after the intervention ($P < 0.001$) and 2.4 unintended discrepancies before and 0.3 after the intervention ($P < 0.001$). Addition of medication and change in dosage were the main types of unintended medication discrepancies which were identified less frequently in the post-test period.

Conclusion

The introduction of medication verification by pharmacy technicians at hospital admission does not change the frequency of total discrepancies per patient between pre-admission and admission medication. However, the introduced medication interview results in a decrease of unintended and an increase of intended medication discrepancies.

Keywords: medication at admission – medication discrepancies – pharmaceutical care – drug safety

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Alert fatigue absent among HIV specialists, but trust in alert texts low

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Background

Computerized physician order entry (CPOE) with drug safety alerting is an important measure to improve medication safety. However, alert fatigue resulting from unspecific alerts consuming too much time and energy, can cause relevant alerts to be unjustifiably overridden along with clinically irrelevant ones. Physicians treating patients infected with human immunodeficiency virus (HIV) encounter many drug safety alerts, because of numerous drug–drug interactions (DDIs) in highly active antiretroviral therapy (HAART) and have limited time because of treating patients in outpatient clinics. However, resistance due to low drug serum levels caused by DDIs is a serious problem to be prevented. The aim of this study is to investigate how medical HIV specialists handle DDIs in the outpatient clinic.

Methods

All HIV specialists of Erasmus MC were invited for a semi-structured interview with open questions, propositions, and patient cases.

Results

All 9 HIV specialists agreed to participate. They were warned often by the CPOE for DDIs they already knew. They all prepared their consulting hours by looking up potential DDIs in the booklet 'DDIs with antiretroviral drugs' by David Burger, and the websites www.hiv-druginteractions.org and www.uptodate.com. They trust and value these information sources more than the CPOE alerts, based on Burger's booklet, that do not provide severity and evidence levels and lack references and information whether texts are updated regularly. They perceive the alerts as an extra check and always look at the alert texts at least slightly. This is followed by more thorough reading of the text if DDIs are unexpected or unknown, in case of comorbidity (e.g. renal failure), in DDIs that lower HAART serum levels, and in long courses (e.g. tuberculosis treatment). DDI alerts are generally overridden after weighing risks and benefits. Short-term rise of HAART serum levels is often accepted. Toxicity that can be monitored is mentioned as an important override reason and several DDIs are consciously prescribed for cost effectiveness. Serum level lowering combinations perceived clinically relevant are prevented by dose adjustments or alternative drug prescribing. All respondents showed thorough DDI knowledge in the patient cases presented.

Conclusions

HIV specialists do not suffer from alert fatigue and perceive DDI alerts as an extra check after they have prepared their consulting hours with other information sources that they trust and value more. The physicians need a severity and evidence index, literature references, and information on updates to weigh benefits and risks and this information is absent in the alert texts.

Keywords: computerized physician order entry – CPOE – drug safety alerting – drug-drug interactions – human immunodeficiency virus – HIV

The association between hospitalisation and discontinuity of psychotropic drug use

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Background

Patients receive care across different healthcare settings. A hospitalisation is an important event at which patients are at increased risk of discontinuity of medication use. Especially medication unrelated to the reason of hospitalisation may be at increased risk of discontinuation. In this study we test this hypothesis.

Objective

To assess the association between hospitalisation and discontinuity of psychotropic drug use in patients hospitalised for a non-psychiatric disease.

Methods

For this retrospective follow-up study 10,000 hospitalisations between 1 July 1998 and 30 June 2000 were randomly selected (index patients) from the Dutch PHARMO database, as well as 10,000 non-hospitalised controls, matched on region, age and gender. The controls were assigned the same index date as the hospitalisation date in the corresponding index patients. Patients who were admitted for mental disorders (ICD-9-CM code 290-319) were excluded. Three mutually exclusive types of treatment discontinuities were defined: generic/brand/product substitution, therapeutic switch and stop. The primary study outcome was the incidence of one or more medication therapy discontinuities of psychotropic drugs at the index date and at several control moments during a period of 18 months before and 18 months after the index date. The represcription rate for the same pharmacotherapeutic group was estimated in the time window of 4-12 months after the index date.

Results

The study population comprised 8,555 hospitalized patients and an equal number of controls. Of the 497 hospitalised patients using psychotropic drug therapy at the index date 30.6% had a medication therapy discontinuity of psychotropic drugs, predominantly stops (n = 132, 26.6%). Of the 325 controls using psychotropic drug therapy at the index date, 49 (15.1%) had any type of discontinuity (RR 2.03; CI95 1.47-2.80.) The highest risk estimate was found for a stop (RR 2.54; CI95 1.74-3.70), followed by therapeutic switch (RR 1.09) and generic/brand/product substitution (RR 0.73). The represcription rate was 23.5% for the hospitalised group of patients.

Conclusion

Patients admitted to the hospital for a non-psychiatric disease and while using psychotropic medication are at increased risk for stopping these psychotropic medication. This rate of represcription indicates that a part of stopped drug therapies can be unintended stops.

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Keywords: prescription – admission – discharge – discontinuity – psychotropic drugs – represcription

Frequency of laboratory measurement and hyperkalemia in hospitalised patients using serum potassium concentration increasing drugs

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Objective

Although drug–drug interactions (DDIs) between potassium-increasing drugs (PIDs) are known risk factors for developing hyperkalemia, not much is known about their risk and management strategies during hospitalisation. This study describes the frequency of serum potassium measurement and of hyperkalemia for hospitalised patients using one or more PIDs, and determinants thereof.

Methods

Adult patients hospitalised in the University Medical Centre Utrecht in 2006-2008 were included in this cross-sectional study. Frequency of serum potassium measurement and hyperkalemia were compared between patients using only one PID at a time (monotherapy group) and patients using two or more PIDs concomitantly (interaction group). Determinants studied were renal failure, diabetes mellitus, use of diuretics, type of DDI, start of the PIDs within the hospital versus continued home medication, and medical speciality.

Results

Serum potassium was measured more frequently in the interaction group compared to the monotherapy group [67% vs. 56%; RR = 1.19 (1.14-1.24)] but the risk of hyperkalemia was increased [9.9% vs. 5.9%; RR = 1.7 (1.3-2.1)]. The combination of potassium-sparing diuretics plus a potassium supplement, start of the PID within the hospital and hospitalisation at non-internal departments was associated with higher relative risk estimates for hyperkalemia.

Conclusions

Even when physicians receive a direct pop-up to monitor serum potassium levels when prescribing two PIDs concomitantly, serum potassium levels are not measured in 33% of patients and 10% of patients develop hyperkalemia. Improved management strategies and/or clinical decision support systems are needed to decrease the frequency of hyperkalemia following DDIs.

Keywords: potassium – hyperkalemia – drug-drug interactions – monitoring – clinical risk management – clinical decision support

Refill adherence with inhaled corticosteroids in children with asthma and the risk of asthma exacerbations

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Background

Asthma is the most common chronic disease in children. Its prevalence is estimated to be 5-10% [1, 2]. Nevertheless, non-adherence to inhaled corticosteroids (ICS) is still a major problem in asthma treatment [3, 4]. Also, persistence to ICS is very limited: only 59% of preschool children continues ICS use after the first prescription and 10% continues for three years [5]. This may lead to serious deterioration of asthma control [6]. It is not clear whether these results can be extrapolated to older children. Therefore, the aim of this study is to measure adherence to ICS in children with asthmatic symptoms aged 5-12, and to study the association of adherence with the frequency of asthma exacerbations and asthma-related hospital admissions.

Methods

This study was designed as a retrospective cohort study. In the PHARMO database a cohort was selected of children aged 5 to 12 who filled their first prescriptions of ICS in the observation period (1 January 1998 to 31 December 2008). Refill adherence of ICS use was based on drug dispensing records present within the database. The frequency of asthma exacerbations was calculated from dispensing records of high dose therapy with oral corticosteroids and from hospital discharge data on asthma-related hospital admissions. The association of refill adherence > 80% with the occurrence of one or more asthma exacerbations was calculated with multivariate logistic regression analysis.

Results

935 children 5-12 years old matched the inclusion criteria. Mean refill adherence was 73.4% ± 23.5%. 21.3% of children had an adherence rate under 50% and 29.1% of children showed 100% adherence. During follow-up, 29 children had an asthma exacerbation (20 corticosteroid episodes, 7 asthma-related hospital admissions and 2 children with both). Children with a refill adherence > 80% showed a decreased asthma exacerbation rate (OR 0.40, CI95 0.17-0.94, univariate analysis). In the multivariate analysis other risk factors that were univariately associated with exacerbation rate ($P \leq 0.2$), were subsequently added to the multivariate model, including short or long acting beta-agonists as co-medication in the year preceding the cohort entry date, and the type of prescriber of the initial ICS treatment (i.e. paediatrician vs. general practitioner). In the final model refill adherence > 80% was non-significantly associated with a decreased risk of asthma exacerbations (OR 0.48; CI95 0.20-1.14).

Conclusions

In children 5-12 years old adherence to ICS (refill adherence > 80%) is non-significantly associated with a decreased risk of asthma exacerbations. Therefore, optimizing adherence may prevent hospital admissions and high dose corticosteroid use, although these results need confirmation in a larger study cohort.

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Keywords: refill adherence – persistence – inhaled corticosteroids – asthma – hospitalization – database study

Oncology and pharmacogenetics

Simvastatin sensitizes KRAS mutant tumor cells for cetuximab and panitumumab

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Background
The EGFR antibodies cetuximab and panitumumab are registered for the use in KRAS wild-type colorectal cancer (CRC) patients, since retrospective analysis of clinical trials showed lack of effect in KRAS mutated patients. About 40% of the CRC patients have an activating KRAS mutation and therefore do not benefit from EGFR antibody treatment. The G13D KRAS leads to a permanently activated KRAS protein. To exert its biological activity, KRAS requires post-translational activation by prenylation (addition of a carbon15 FPP or carbon17 GGPP group). KRAS modulation has become a promising concept for new therapies, mostly by interference with the mevalonate pathway and subsequently by prenylation of KRAS. The HMG-CoA reductase inhibitor simvastatin also affects the synthesis of the isoprenoids FPP and GGPP and may therefore affect KRAS activation. We hypothesize that simvastatin decreases KRAS activation by inhibiting KRAS prenylation and thereby is able to make KRAS mutant colorectal cancer cell lines sensitive (again) for the EGFR antibodies.

Methods
The human colorectal cell lines A431 (KRAS wild-type), LoVo and HCT116 (both KRAS G13D) were treated with combinations of cetuximab (500 µg/ml), panitumumab (500 µg/ml) and simvastatin (2 µmol/L) for three days. A Sulforhodamine B colorimetric assay was preformed after three days of incubation, to measure the cytotoxicity effects in the cell lines.

Results
The wild-type cells A431 are sensitive for EGFR inhibitors, whereas KRAS mutant cells HCT 116 and LoVo are not. Pre-incubation with simvastatin makes cells sensitive for cetuximab and panitumumab. As a result, after one day of pre-incubation with simvastatin followed by two days of combined treatment (either cetuximab or panitumumab) a decrease in survival was found. Conversely, simvastatin alone inhibits survival in KRAS mutant cell lines; however in the wild-type A431 cell lines this effect is not seen.

Conclusions
Inhibition of the mevalonate pathway by simvastatin sensitizes KRAS mutant colorectal cancer cells for cetuximab and panitumumab. On the basis of these findings we have started two clinical studies on the combination of 80 mg simvastatin and cetuximab or panitumumab in patients with KRAS mutant colorectal cancer (ClinicalTrials.gov Identifier: NCT01190462 and NCT01110785).

Keywords: KRAS – modulation – EGFR antibodies – simvastatine – prenylation

Concordance of predictive markers for EGFR inhibitors in primary tumors and metastases in colorectal cancer

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Background
Currently, only KRAS mutational status is used as a decisional marker for EGFR inhibitor therapy in colorectal cancer (CRC). Indeed, the EGFR inhibitors cetuximab and panitumumab are registered for KRAS wild type colorectal tumors only. Concordance of KRAS status between primary tumors and metastases has always been considered to be close to perfect; however, cases of discordance have been reported. This may potentially lead to undertreatment since KRAS wild type metastases could be sensitive for EGFR inhibitors. Since the actual rate of concordance of KRAS status remains unclear, it is unknown whether it is necessary to perform KRAS analysis on metastases instead of on (or additional to) primary tumors.

Methods
A systematic review of the literature was conducted to collect all studies testing concordance of KRAS in CRC, and also of BRAF, PIK3CA and loss of PTEN.

Results
Twenty investigations have studied concordance of KRAS in primary tumors versus metastases, with an overall concordance rate of 92% (range 76%-100%). Overall concordance rates of studies testing concordance of BRAF status and loss of PTEN were 98% and 68%. Three studies reported concordance of PIK3CA status (range 89%-94%).

Conclusions
Though discordance of KRAS status does occur, it is uncommon. When considering the downsides of testing metastatic tissue in all patients along with the low incidence of discordance, we conclude that testing the primary tumor (or whatever tissue available) is sufficient for clinical decision making on EGFR inhibitor therapy.

Keywords: KRAS – concordance – EGFR inhibitors – primary tumors – metastases

Potential drug interactions in cancer therapy: a prevalence study using an advanced screening method

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Background

In cancer patients, drug interactions may intensify adverse events or reduce antitumour effects. We assessed the prevalence of potential drug interactions (PDIs) among ambulatory cancer patients on i.v. treatment using an advanced screening method.

Methods

Data on drugs used for comorbidities, anticancer agents, over-the-counter (OTC) drugs and comorbidities were collected by means of a structured interview among the patients and review of medical charts. PDIs were identified using electronic (Drug Interaction Facts software, version 4.0) and manual screening methods (peer-reviewed reports).

Results

In this study 278 patients were enrolled. We identified 348 PDIs. Of all patients 161 (58%) had at least one PDI. Of all PDIs, 34% was classified as major and 60% as moderate. Coumarins, quinolones, antiepileptics and hydrochlorothiazide were frequently part of a PDI. Interactions that potentially cause QT interval prolongation, gastro-intestinal toxicity and central nervous system depression were also common. In multivariate analysis, an increasing number of drugs [odds ratio (OR) = 1.4, confidence interval (CI) 1.23-1.52; P < 0.001] and the use of an OTC drug (OR = 0.56, CI 0.32-0.97; P = 0.045) were risk factors.

Conclusion

PDIs are common in patients treated for an (haemato-)oncological disease. Screening for potential interactions should take place routinely before administering chemotherapy.

Keywords: chemotherapy – drug interactions – risk factors

Population pharmacokinetics and pharmacogenetics of everolimus in renal transplant patients on a calcineurin inhibitor free regimen

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Background

Everolimus is a novel macrolide MTOR targeting immunosuppressant with a small therapeutic window. The highly variable pharmacokinetics of everolimus complicates prediction of the individual dose as to assure reaching adequate everolimus exposure in renal transplant patients. Therefore the development of a population pharmacokinetic model is crucial to optimize everolimus therapy in renal transplant patients.

Methods

A total of 779 blood samples obtained from 53 renal transplant patients who had been switched from ciclosporin to a calcineurin inhibitor free regimen of everolimus (3 mg twice daily) and prednisolone were collected over a 1.5 year period. Everolimus blood concentrations were analyzed using liquid chromatography tandem mass spectrometry during routine therapeutic drug monitoring. A population pharmacokinetic model using NONMEM was built and demographic factors and genetic polymorphisms in genes coding for ABCB1, CYP3A5, CYP2C8, Pregnane X receptor were included as covariates. The final model was validated by using a bootstrap and visual predictive check. In addition, a limited sampling model based on the final model was developed.

Results

The pharmacokinetics of everolimus was best described by an open two-compartment disposition model with first order absorption and lag-time. A significant contribution was found for the demographic covariate Ideal Body Weight on everolimus distribution volume of the central compartment which explained 15.4% of the inter-individual variability in distribution volume. None of the selected genetic polymorphisms contributed significantly in explaining the variability in everolimus pharmacokinetics. A posteriori Bayesian estimation allowed accurate prediction of the AUC12 of twice daily everolimus, using three sampling moments (0, 1 and 3 hours post-dose) with a mean bias of –3.63% and good precision (MAPE = 4.47%).

Conclusions

A two-compartment pharmacokinetic model with lag-time describing the concentration–time profile of oral everolimus in renal transplant patients has been developed. Ideal Body Weight significantly influences the apparent volume of distribution of everolimus, whereas polymorphisms in genes coding for ABCB1,

CYP3A5, CYP2C8, Pregnane X receptor do not significantly influence everolimus pharmacokinetics. Everolimus blood concentrations at 0, 1 and 3 hours post-dose can be used to accurately estimate everolimus exposure.

Keywords: everolimus – population pharmacokinetics – NONMEM – limited sampling model

The *PCSK9* E670G variant and reduced statin effectiveness

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Background

Although the efficacy of statins has been well established, genetic variability has been shown to affect statin responsiveness. The aim of this study was to investigate the genetic influence of tagging SNPs within candidate genes involved in the cholesterol lowering pathway of statins on the effectiveness of statins in reducing the risk of the outcome myocardial infarction (MI).

Methods

Participants from the Utrecht Cardiovascular Pharmacogenetics (UCP) studies were enrolled from a population-based registry of pharmacy records linked to hospital discharge records (PHARMO). Patients who received a prescription for an antihypertensive drug, and/or had hypercholesterolemia (prescription for a cholesterol-lowering drug or total cholesterol > 5.0 mmol/L), were selected from the PHARMO database. We designed a nested case-control study in which cases were hospitalized for MI and controls were not. Patients were contacted through their community pharmacies. For this study, only hypercholesterolemic participants were selected. Logistic regression analysis was used to investigate pharmacogenetic interactions. The Heart and Vascular Health Study (HVH) was used to replicate findings from UCP.

Results

The study population included 668 cases and 1217 controls. We selected 231 SNPs of which 209 SNPs in 27 genes involved in the cholesterol-lowering pathway passed quality control and were tested. Ten SNPs in eight genes were found to influence the effectiveness of statins in UCP, of which the most significant interaction was found with *SCARB1* rs4765615. Five out of ten statistically significant SNPs were available in the HVH study for replication. None of the HVH findings reached statistical significance. Carriers of the *PCSK9* rs505151 variant allele had less benefit from statin treatment in UCP, a finding that was replicated in the HVH study, although the formal test for interaction was not statistically significant.

Conclusions

In conclusion, carriers of *PCSK9* 670G variant allele may benefit from more aggressive lipid-lowering treatment. Furthermore, confirmation of interactions reported with other SNPs in *SCARB1*, *PCSK9*, and *LIPC* should be pursued.

Keywords: pharmacogenetics – statins – PCSK9 – SCARB1 – case-control study

Pretargeted immuno-PET imaging and radioimmunotherapy of prostate cancer with an anti-EGP1 × anti-HSG bispecific antibody

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Background

The epithelial glycoprotein 1 (EGP-1 or Trop-2) is a pancarcinoma marker that is expressed at high levels on virtually all prostate carcinomas. The aim of these studies was to develop a pretargeting system for imaging and radioimmunotherapy of hormone-independent prostate cancer based on an anti-EGP-1 antibody in human tumor/nude mouse models.

Methods

In all experiments, a trivalent anti-EGP-1 × anti-HSG bispecific antibody (TF12) produced by the so-called Dock-and-Lock method was used. For immuno-PET-imaging, an orthotopic PC3 mouse model was developed by injecting PC3 cells into the prostate during laparotomy in NMRI nude mice; animals were injected i.v. with 2.5 nmol of TF12 followed 16 hours later with 0.1 nmol of the diHSG peptide ^{68}Ga-IMP-288 (10 MBq). Images were acquired 1 hour p.i. with an Inveon microPET/CT scanner. For radioimmunotherapy, athymic mice with s.c. PC3 tumors were injected i.v. with 2.5 nmol of TF12 followed 16 h later with an i.v. injection of ^{177}Lu-IMP-288 (13 MBq). Two control groups were injected with either PBS or PBS and ^{177}Lu-IMP-288 (13 MBq). Mice were evaluated during 6 months for hematological (thrombocytes, leukocytes, hemoglobin), renal (urea, creatinine) and physical (body weight, tumor size) changes.

Results

Pretargeted immuno-PET images clearly visualized the tumor in the prostate 1 h p.i. with minimal activity in background tissues such as liver and kidneys. Radioimmunotherapy with TF12 and ^{177}Lu-IMP-288 more effectively inhibited the growth of the s.c. PC3 tumors than ^{177}Lu-IMP-288 alone, with median survival times of 88 days vs. 67 days, respectively ($P < 0.05$). Hematological, renal and physical side-effects of ^{177}Lu-IMP-288 therapy were minimal or absent, indicating that further dose escalation is possible.

Conclusion

Pretargeting with TF12 in combination with radiolabeled IMP-288 is a promising system for specific and high contrast imaging of prostate cancer and for pretargeted radioimmunotherapy of hormone-independent prostate cancer. Further improvement may be achieved by increasing the radioactive dose and by repetitive dosing.

Keywords: EGP-1 – pretargeting – radioimmunoimaging – radioimmunotherapy – prostate cancer – antibody

Genetic risk factors for type 2 diabetes mellitus and response to sulfonylurea treatment

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Background

Following the identification of T2DM risk alleles, models have been developed to identify subjects at high risk to develop T2DM [1-13]. We hypothesize that these risk alleles influence treatment response to oral antidiabetic drugs. In this study, we assessed if genetic risk factors for T2DM are associated with response to sulfonylurea (SU) treatment.

Methods

Incident SU users (tolbutamide, glibenclamide, glimepiride, gliclazide) with T2DM were recruited from 4 primary care centers. Data were retrieved from the electronic patient record. Primary endpoint was achieving stable SU dose defined as the 1st period of ≥ 270 consecutive days without dose adjustment, initiation of other SU, insulin or metformin. 20 SNPs consistently associated with T2DM in 19 genes were selected: *TCF7L2*, *KCNJ11*, *HHEX/IDE*, *SLC30A8*, *CDKAL1*, *CDKN2A/CDKN2B*, *IGF2BP2*, *KCNQ1*, *PPARG*, *FTO*, *NOTCH2*, *WFS1*, *JAZF1*, *THADA*, *CDC123/CAMK1D*, *TSPAN8/LGR5*, *ADAMTS9*, *HNF-1β*, *MTNR1B* [1-16]. A genetic risk score per patient was calculated based on the number of risk-alleles. χ^2-test was used to compare the primary endpoint between genetic risk score groups.

Results

The mean genetic risk score was 19.0 (CI95 18.7-19.4) in our T2DM population (n = 207). The risk score was associated with achievement of stable SU dose: 84.7% of the patients in the low risk group (n = 59) achieved stable dose vs. 74.1% and 62.3% of the patients in the intermediate risk (n = 81) and high risk group (n = 62; P = 0.004).

Conclusion

Patients with an increased genetic risk for T2DM are less responsive to SU.

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Keywords: pharmacogenetics – type 2 diabetes mellitus – sulfonylurea

Pharmacogenetics: from bench to byte

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Background

In recent years the field of pharmacogenetics has made substantial progress. However, guidelines that link the result of a pharmacogenetic test to specific dose recommendations are only sparsely available. Therefore the Royal Dutch Association for the Advancement of Pharmacy established a Pharmacogenetics Working Group (PWG). The objective of the PWG is to develop pharmacogenetics-based therapeutic (dose) recommendations based on systematic literature review, and to assist physicians and pharmacists by integrating the recommendations into computerized systems for drug prescription, dispensing, and automated medication surveillance.

Methods

A list of genetic polymorphisms affecting pharmacokinetics and pharmacodynamics, including an overview of drug substrates, was compiled. For each drug, a systematic search of the literature was performed. Gene–drug interactions were scored on two parameters. First, the quality of evidence for the gene–drug interaction was scored on a five point scale ranging from 0 (lowest evidence) to 4 (highest evidence). Secondly, the clinical relevance of the potential gene–drug interaction was scored on a 7 point scale ranging from AA (lowest impact) to F (highest impact). For each gene–drug interaction a risk analysis containing a review of the selected articles, their assigned levels of evidence and clinical relevance, and a therapeutic (dose) recommendation was composed. Recommendations could include a dose adjustment and advice on therapeutic strategy (e.g. TDM, selection of alternative drug, warning for ADE etc.).

Results

Therapeutic (dose) recommendations for 163 genotype/phenotype–drug combinations comprising 53 drugs and 11 genes were composed. The drugs were associated with genes coding for CYP2D6 (n = 25), CYP2C19 (n = 11), CYP2C9 (n = 7), thiopurine-S-methyltransferase (n = 3), dihydropyrimidine-dehydrogenase (n = 3), vitamin-K-epoxide-reductase (n = 2), uridine-diphosphateglucuronosyltransferase-1A1, HLA-B44, HLA-B*5701, CYP3A5, and factor V Leiden (all n = 1). Therapeutic (dose) recommendations were formulated for 39 (74%) of the drugs. For 3 drugs no evidence for a gene–drug interaction was found. For 11 drugs (21%) a gene–drug interaction was present but no therapeutic (dose) recommendation was deemed necessary. The therapeutic (dose) recommendations were included in the G-Standard, an extensive electronic drug database, thereby directly linking them to the electronic prescribing and medication surveillance. The first recommendations were released with the October 2006 edition of the G-Standard.

Conclusions

To the best of our knowledge this is the first initiative to integrate pharmacogenetic test results and therapeutic (dose) recommendations into electronic prescribing and medication surveillance systems to be applied nationwide. Recommendations for 53 drugs were composed. The availability during the process of therapeutic decision making presents an important step in the clinical use of pharmacogenetic information.

Keywords: pharmacogenetics – personalized medicine – algorithms – genotype – translational medicine

Pharmacokinetics and pharmacodynamics

Prevalence and persistence of low infliximab serum trough levels in RA patients with low disease activity in daily clinical practice

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Background

Treatment of RA with infliximab requires optimal dosing to balance maximum effect and minimal dose related side effects and costs. DAS driven dose de-escalation can be used in patients with low disease activity, but costs time and can lead to flaring. Since infliximab serum trough levels and presence of human anti-chimeric antibodies (HACAs) demonstrated a correlation with

TABLE 1

	Infliximab serum trough levels		HACAs		Total
DAS28	low (< 1.0/ml)	high (> 1.0/ml)	yes	no	
≤ 3.2	20 (31%; 19-42)	45 (69%; 58-81)	7 (11%; 3-19)	58 (89%; 81-97)	65
≤ 2.6	14	26	5	35	
2.6-3.2	6	19	2	23	
> 3.2	39 (48%; 37-59)	43 (52%; 41-63)	25 (30%; 59-80)	57 (70%; 20-41)	82
Total	59	88	32	115	147

clinical effect in cross-sectional studies, they could be used as predictors for successful de-escalation. There is however a lack of data on prevalence and persistence of serum trough levels and HACAs in RA patients treated in daily clinical practice. This prospective observational study aims to study prevalence and longitudinal course of serum trough levels and HACAs and their persistence within patients, focussing on patients with low disease activity.

Methods

All RA patients treated with infliximab at the Sint Maartenskliniek, Nijmegen, The Netherlands, for at least 6 months were included and followed in a 1.5 year period. At every visit DAS28, serum trough levels and HACAs were measured. Cross-sectional analysis of the prevalence of low serum trough levels and/or HACAs was done for patients with low and high disease activity and in a subgroup with stable low DAS28 ≤ 3.2 for at least 3 consecutive visits. Persistence at 2 consecutive visits in patients with stable DAS28 and infliximab dosing was analysed by means of a Spearman correlation coefficient and Wilcoxon test for serum trough levels, and with kappa analysis for HACA presence.

Results

147 RA patients were included, 65 and 40 patients had a DAS28 < 3.2 and 2.6 respectively. In 35% of the patients with a DAS28 ≤ 2.6 and in 31% with a DAS28 ≤ 3.2 non-measurable/very low serum trough levels were found. 30% was associated with presence of HACA's (table 1). The longitudinal analysis showed that, in patients with stable low DAS28, 38% had low to non-measurable serum trough levels, with nearly 50% showing HACAs. There was no statistical difference between trough levels at two consecutive visits in patients with stable DAS28 and dosing (P = 0.38). The correlation between serum trough levels between two consecutive visits was very high (r = 0.97, P = 0.00001), as was the agreement for the presence of HACA's between visits (kappa 1.0).

Conclusion

Among patients with low disease activity low to non-measurable serum trough levels are prevalent both in cross-sectional and longitudinal analyses. In patients with stable treatment and DAS28 there is a high persistence between two consecutive measurements of trough levels and HACAs. Therefore, infliximab serum trough levels and HACA are promising candidates to be tested for their predictive value for successful dose de-escalation.

Keywords: infliximab – rheumatoid arthritis – therapeutic drug monitoring – disease activity – human anti-chimeric antibodies

Therapeutic drug monitoring of voriconazole is warranted in pediatric patients and results in target attainment

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Objective

Voriconazole (VRZ) has a wide inter- and intra-individual pharmacokinetic variability. It is unclear if the officially recommended dosages for pediatric patients are sufficient to achieve adequate exposure.

Methods

All pediatric patients (age 0-18) in our hospital with at least one plasma trough concentration of VRZ over a 2 year period were included. Case report forms were used to collect information on patient's characteristics like underlying disease, fungal infection, treatment regimen and outcome. Invasive fungal infections (IFI) and response were classified according to the definitions of the EORTC-MSG. Provisional targets were: pulmonary infection: 1-6 mg/L and sanctuary sites/disseminated infection: 2-6 mg/L.

Results

18 patients (range 3 months–18 years) were included. 16 had hematologic malignancies, 1 cystic fibrosis and 1 patient had a solid tumor. 5 patients had proven, 2 probable and 4 possible IFI, 6 episodes remained unclassified. 7 patients had fungal pneumo-

nia, 5 disseminated disease to ≥ 2 sites and 2 had disseminated blood stream infection. 1 patient had a CNS IFI. In 3 patients there was no clear focus. 39 VRZ samples were collected (1-7 samples per patient). Mean trough concentrations (n = 25) in children < 12 years was 1.3 mg/L (range < 0.1 to 6 mg/L), and 1.7 mg/L (range < 0.1 to 9.6 mg/L) (n = 14) in children > 12 years. Overall, in 8 of 18 patients, the first trough concentration was below the target. 4 of 5 patients with CNS infection or disseminated infection had initial trough concentrations < 2.0 mg/L. In 3 of 4 patients, the trough concentrations was < 1 mg/L. From the patients who did not attain the target concentration, 6 of 12 were 0-12 years and 2 of 6 were 12-18 years. No correlation between the administered dosage and the trough concentrations was detected. In 5 of 8 patients, treatment was adjusted after TDM. In 3 patients this resulted in target attainment. In the remaining 2 patients, multiple interventions had to be done (3 of 5 and 1 of 2 follow-up samples were adequate). In 5 patients adverse events were reported. No relation was observed between plasma concentration and adverse events. After nine weeks of VRZ 8 patients showed a complete response, 3 had a partial response and 2 stable disease. 2 patients showed progressive disease and 1 patient died. From 1 patient outcome is unknown and 1 patient was unclassified. Numbers were too small to draw conclusions on a relation between outcome and VRZ concentrations.

Conclusion

Great variability was seen in plasma concentrations. 44% of measured plasma concentrations were subtherapeutic. TDM is warranted and results in target attainment in pediatric patients.

The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma: a global proficiency testing program

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Background

The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma was initiated in 1999 by Radboud University Nijmegen Medical Center, The Netherlands. After two pilot years, the Program was continued in collaboration with the Dutch Association for Quality Assessment in Therapeutic Drug Monitoring and Clinical Toxicology (www.kkgt.nl). The aim of this analysis was to evaluate the first 10 years of the Program and to determine variables associated with reporting of less accurate results.

Methods

For each year of the Program, two rounds were organized in which blind samples were shipped to participants containing either a low, medium, or high concentration of each antiretroviral drug. The Program started with ritonavir, saquinavir, indinavir and nelfinavir in 1999; amprenavir, lopinavir, nevirapine and efavirenz were added in 2001. Most recent additions to the Program were atazanavir (2005), tipranavir and darunavir (both in 2009). Any result that deviated more than 20% from the spiked concentration was defined as inaccurate. For this analysis, data on darunavir, tipranavir and ritonavir were excluded due to insufficient numbers.

Results

By the end of 2009, the number of laboratories participating in the Program had increased to 56; 44 (79%) laboratories are located in Europe. The remaining 12 laboratories are spread over four continents: North America (n = 8), Asia (2), Africa (1), Australia (1). Within Europe, the Program is dominated by laboratories from The Netherlands (n = 11) and Spain (10). In 2008, a small majority of the labs (52%) was using HPLC as the analytical method, with the remaining 48% using LC-MS. A total of 12,798 test results was available for analysis, of which 2,104 (16.4%) were reported as inaccurate. Performance was best for samples containing nevirapine [mean (± SD) of inadequate scores per round: 11.1% ± 5.5%] and lopinavir (11.9% ± 6.5%), and worst for indinavir (18.7% ± 12.5%), atazanavir (18.9% ± 9.9%), saquinavir (19.6% ± 8.8%) and nelfinavir (21.3% ± 11.7%). Amprenavir and efavirenz scored in between. High and medium concentrations were less frequently reported as inaccurate than low concentrations: 13.5%, 13.0%, and 22.4%, respectively. Although the overall performance of the laboratories varied per year, a trend was visible for improvement over time, with 19.9% of the results being inaccurate in 2002 (n = 20 laboratories) to 15.7% in 2009 (n = 56 laboratories). As an example of this 'learning curve', laboratories that already participated in 2002 tended to have a better performance in analyzing nelfinavir in 2009 (on average 27.8% of the results were inaccurate) than laboratories who joined the program after 2002 (32.9% inaccurate results).

Conclusions

The Program provides a proficiency testing program in which laboratories are alerted to potential analytical errors while performing therapeutic drug monitoring. Laboratories should put more effort in adequately analyzing concentrations of antiretroviral drugs with low minimum effective concentrations.

Keywords: therapeutic drug monitoring – pharmacokinetics – HIV – proficiency testing

A comparison of the pharmacokinetics of raltegravir during pregnancy and post-partum

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Background

It is important to achieve effective concentrations of antiretroviral drugs in the blood to prevent treatment failure and the development of resistance. During pregnancy, physiological changes take place, influencing the pharmacokinetics of medicines. In most cases, the net effect will be a decreased exposure during pregnancy. Only very limited data are available about the pharmacokinetic behaviour of raltegravir during pregnancy and whether the drug passes the placenta. In 2008, a European network was established to study the pharmacokinetics of newly developed antiretroviral drugs during pregnancy (PANNA). We present preliminary data on third trimester exposure to raltegravir.

Methods

Patients treated with raltegravir (400 mg BID) during pregnancy were screened and a 12 h pharmacokinetic curve (t = 0, 0.5, 1, 2, 3, 4, 6, 8, 12 h) after supervised intake of 400 mg raltegravir after a standardised breakfast took place in the third trimester and at at least 2 weeks post-partum. Where possible a cord blood sample and matching maternal blood sample were taken at delivery. Safety and antiviral efficacy were evaluated. Raltegravir plasma concentrations were determined with a validated HPLC method with fluorescence detection and an LLOQ of 0.014 mg/L. Pharmacokinetic parameters were calculated with WinNonlin 5.2.

Results

Raltegravir plasma concentrations are available from 5 patients. The results are presented as medians (range). $AUC_{0\text{-}12h}$ (mg·h/L) was 10.3 (1.9-28.3) in the third trimester and 7.4 (3.3-16.0) post-partum. C_{max} (mg/L) was 1.13 (0.38-9.67) in the third trimester and 1.78 (0.78-4.03) post-partum. C_{12h} (mg/L) was 0.10 (0.02-0.33) in the third trimester and 0.10 (0.05-0.23) post-partum. Ratios of PK parameters third trimester/post-partum [median (range)] were: 1.50 (0.66-1.77) for $AUC_{0\text{-}12h}$; 1.53 (0.44-2.40) for C_{max}; 1.76 (1.46-2.33) for C_{12h}. The ratio of cord blood/maternal plasma raltegravir concentrations, determined in two patients, was 1.02 and 1.16 respectively. All children were HIV uninfected, no birth defects were reported.

Conclusions

In this small population (n = 5) exposure to raltegravir was no lower during pregnancy (third trimester) than post-partum. This is in contrast to a number of other antiretroviral agents, especially protease inhibitors. Raltegravir efficiently crosses the placenta. These results need to be confirmed in a larger group of patients.

Keywords: raltegravir – pharmacokinetics – pregnancy – cord blood

Therapeutic drug monitoring to improve safety and efficacy of posaconazole in hematology patients

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Background

Posaconazole is indicated for therapy and prophylaxis of invasive fungal infections (IFIs). During the time frame of our study, minimum serum concentrations per indication were: primary prophylaxis 0.5 mg/L; secondary prophylaxis 0.7 mg/L and primary therapy 1.0 mg/L. Several drugs and co-morbidities have been identified to hinder reaching target concentrations. It was postulated that patients with interacting drugs or co-morbidities should be monitored.

Methods

Of the 17 patients included, we analyzed 42 serum concentrations using a validated LC-MS/MS analysis method. Patient characteristics, co-medication, co-morbidities and therapeutic drug monitoring interventions were retrospectively evaluated based on (electronic) medical records.

Results

In total 8 patients did not reach therapeutic posaconazole serum concentrations. 57% of patients using a PPI did not reach target concentration with a corresponding median concentration of 0.48 mg/L. PPI usage was shown to significantly increase the risk of attaining a subtherapeutic serum posaconazole concentration (P = 0.032 for first measured and 0.002 for all measured analyses, respectively). Neutropenia and diarrhea only occurred in patients with subtherapeutic concentrations, with an occurrence of 25% and 63%, respectively. One patient developed a breakthrough pulmonary aspergillosis at low serum concentration (0.37 mg/L). Two patients had extremely high concentrations (> 3 mg/L), both

not taking PPI's. After TDM intervention 3 out of 4 patients (75%) reached target concentration by spreading dose administration.

Conclusions

Subtherapeutic posaconazole concentrations were significantly more frequent in PPI users, and more frequent in patients with neutropenia or diarrhea. TDM appeared to be a helpful tool in identifying low concentrations and individually optimize posaconazole therapy.

Key words: posaconazole – hematology – proton pump inhibitor (PPI) – therapeutic drug monitoring (TDM) - dosage optimization

Mitotane has a strong and a durable inducing effect on CYP3A4 activity

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Background

Effects of mitotane on the pharmacokinetics (PK) of co-administered drugs are mostly unknown. The aim of the present study was to describe the effects of mitotane on the PK of the phenotypic probe midazolam and of the tyrosine kinase inhibitor sunitinib. A serendipitous observation was made in 2 of 9 patients who volunteered in a sunitinib pharmacokinetic study. Both patients were diagnosed with adrenocortical carcinoma (ACC) and were exposed to mitotane. The sunitinib PK study was designed to determine the relationship between CYP3A4 activity and sunitinib exposure using 7.5 mg midazolam orally as a phenotypic probe.

Methods

Serial blood samples for PK analysis of midazolam, 1-hydroxymidazolam and sunitinib were collected at steady-state sunitinib PK (between days 14-20). To confirm this observation in the mitotane exposed patients midazolam PK was evaluated in 2 additional patients with ACC and mitotane treatment.

Results

The 4 mitotane treated patients showed highly induced CYP3A4 activity, even after interrupting mitotane therapy months before study entry, reflected by decreased midazolam exposure compared to the other 7 patients [mean $AUC_{0\text{-}12h}$ (CI95): 7.6 (5.5-9.7) vs. 139.0 (95.1-182.9) µg·h/L, respectively; P = 0.001], increased 1-hydroxymidazolam exposure [mean $AUC_{0\text{-}12h}$ (CI95): 409.6 (290.5-528.7) vs. 35.0 (26.4 43.6) µg·h/L; P = 0.008]. Sunitinib exposure was decreased in the 2 patients who were co-treated with mitotane: 267 and 268 µg·h/L vs. [mean (CI95)] 1344 (1079-1609) µg·h/L.

Conclusion

Mitotane has a strong and long-lasting inducing effect on CYP3A4 activity which will result in clinically relevant interactions with multiple drugs since many drugs are metabolized by this enzyme.

Pharmacokinetics of efavirenz dosed according to the WHO weight-bands in children in Uganda

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Background

Efavirenz (EFV) is commonly used in children over 3 years worldwide, but there is only limited pharmacokinetic (PK) information available in African children.

Methods

41 HIV-infected Ugandan children aged 3-12 years on generic EFV plus 3TC+ABC were enrolled in a cross-over PK study of twice to once-daily 3TC+ABC 36 weeks after ART initiation in the ARROW trial. Once-daily EFV doses following WHO weight-bands were 200/250/300*/350* mg for children weighing 10-15/15-20/20-25/25-30 kg respectively, using EFV capsules or *halved 600 mg tablets. Intensive plasma PK sampling (t = 0, 1, 2, 4, 6, 8, 12 h post observed ingestion) was performed on twice-daily ART at steady state (PK1) and repeated 4 weeks later (PK2, including a further 24 h sample). EFV daily area under the curve ($AUC_{0\text{-}24}$) and clearance (CL/kg) were estimated using WinNonlin. Predictors of $\log_{10}$AUC and CL were assessed using multivariate mixed models, fitting random effects for each child.

Results

39 and 37 children had evaluable EFV profiles at PK1 and PK2 respectively. 16/39 (41%) children were boys, 18 were aged 3-6 years and 21 7-12 years. 5/16/15/3 were in the 10-15/15-20/20-25/25-30 kg weight-bands. The geometric mean (%CV) $AUC_{0\text{-}24}$ was 50.4 (91.7%) and 54.0 (80.8%) h·mg/L at PK1 and PK2 respectively, with no significant variation across weight-bands (P = 0.51). Between- and within-child %CV were 81% and 28% respectively. 3 sub-populations were identified from normal mixture modeling: 40% children with geometric mean $AUC_{0\text{-}24}$ 27.2 h·mg/L, 32% with 49.9 h·mg/L, and 28% with 137 h·mg/L. 6 children at PK1 and 7 at PK2 had subtherapeutic C_{8h} and/or C_{12h} (< 1.0 mg/L), 7/39 (18%) at

either visit. At PK2, 14/37 (38%) children had C_{24h} < 1.0 mg/L (median/IQR/range 1.1/0.7-2.5/0.3-18.4 mg/L). 9 children at PK1 and 10 at PK2 had C_{8h} and/or C_{12h} and/or C_{24h} > 4.0 mg/L; 11/39 (28%) at either visit. Overall mean (SD) clearance was 6.8 (3.9) and 6.2 (3.7) L/h at PK1 and PK2 respectively (P = 0.04). CL increased by 0.50 L/h for every year older (P = 0.05), but did not depend on weight (P = 0.30), weight-for-age (P = 0.56) or height-for-age (P = 0.82).

Conclusion

African children aged 3-12 years, on daily EFV using WHO weight-bands, had lower and highly variable EFV PK parameters compared to data from adults. There were no differences across weight-bands, suggesting no major effect of some using half tablets. Increased EFV doses for children should be investigated, but risk increasing the proportion of children with toxic levels further.

Keywords: efavirenz – pharmacokinetics – HIV-1 – children – Uganda

Ribavirin plasma concentrations in chronic hepatitis C infected patients with or without HIV co-infection: is there a difference?

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Background

A human immunodeficiency virus (HIV) co-infection in patients with chronic hepatitis C virus (HCV) infection lowers the response to antiviral HCV treatment. Several trials show an association between ribavirin plasma concentrations and virologic response. Our hypothesis is that inferior response to HCV therapy in HCV/HIV co-infected patients may be explained by lower ribavirin plasma concentrations in HCV/HIV co-infected patients than in patients with an HCV mono-infection.

Methods

A retrospective cohort study was performed in chronic HCV mono- or HIV co-infected patients who received pegylated interferon in combination with weight-based ribavirin dosing. Plasma ribavirin concentrations at week 4 and 12 were determined by a validated high-performance liquid chromatography (HPLC) assay. In addition to absolute ribavirin plasma concentrations we also normalized the concentrations to a dose of 1000 mg to correct for differences in dosing practices between the two subpopulations. The proportion of patients with a subtherapeutic ribavirin plasma concentration, defined as < 2.0 mg/L, was also calculated.

Results

A total of 55 HCV-infected patients (36 male, 19 female) was included of which 23 patients (42%) were HIV co-infected. Median (range) age was 49 (22-68) years. 38 (78%) were infected with HCV genotype 1 or 4, 11 (20%) with genotype 2 or 3, and for 6 patients the genotype was unknown. Median (range) ribavirin plasma concentrations for HCV mono-infected patients and HCV/HIV co-infected patients at week 4 were 1.92 (0.66-3.97) mg/L and 1.82 (0.79-3.24) mg/L, respectively. At week 12 median (range) concentrations were 2.41 (0.65-9.80) mg/L and 2.17 (1.10-12.1) mg/L, respectively. The median (range) ribavirin plasma concentration normalized to a 1000 mg dose at week 4 were 1.78 mg/L (0.83-3.90) and 1.70 mg/L (0.99-3.16) for HCV mono-infected patients and HCV/HIV co-infected patients, respectively. At week 12 these values were 2.40 (0.81-9.80) mg/L and 1.74 (1.23-12.1) mg/L. None of the differences in ribavirin concentrations between HCV mono- or HCV/HIV co-infected patients reached statistical significance (0.21 < P < 0.51; Mann-Whitney U tests). Interestingly, a statistically non-significant trend was observed of a higher proportion of patients with a subtherapeutic plasma ribavirin concentration (defined as < 2.0 mg/L) in HCV/HIV co-infected vs. HCV mono-infected patients: week 4: 60 vs. 54% (P = 0.66; chi-square tests); week 12: 47 vs. 23% (P = 0.10).

Conclusion

Plasma ribavirin concentrations show no statistically significant difference between HCV-infected patients with or without an HIV co-infection. We did find a trend of a higher proportion of patients having a subtherapeutic plasma concentration of ribavirin in the HCV/HIV co-infected population suggesting that therapeutic drug monitoring in this subgroup might be indicated.

Keywords: hepatitis C – HIV – concentration – ribavirin

The effect of ritonavir on pharmacokinetics of tacrolimus in pretransplant kidney failure patients with HIV: the need for new trough levels?

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Background

The introduction of highly active antiretroviral therapy (HAART) has improved life expectancy of HIV patients and therefore chronic complications such as kidney failure are seen more frequently. An increasing number of HIV patients is accepted for kidney transplantation. Ritonavir-boosted protease inhibitors are frequently

used in HAART. Ritonavir inhibits the cytochrome P450 (CYP) 3A enzyme and transporting protein P-glycoprotein (P-gp). In kidney transplantation the calcineurin inhibitor tacrolimus, which is a substrate for both CYP3A and P-gp, is predominantly used for transplant rejection prophylaxis. Here we present data on the influence of ritonavir on tacrolimus pharmacokinetics in pretransplant kidney failure patients with HIV.

Methods

Six HIV patients accepted for kidney transplantation and treated with a ritonavir-containing regimen were included. At least 12 blood samples were drawn in each patient after an oral test dose of tacrolimus (Prograft). Pharmacokinetic curves of tacrolimus in all patients were analyzed. A population model was created using Monte Carlo simulation in MW\Pharm (PK Software edition 3.60, Medi\Ware).

Results

In ritonavir users the area under the curve (AUC) after a 5 mg dose of tacrolimus was 50-fold higher than in non-ritonavir users (8680 vs. 174 ng·h/mL). The mean oral clearance (CL/*F*) in ritonavir users was 25-fold lower than in non-ritonavir users (0.98 vs. 24.2 L/h). The pharmacokinetic curve of tacrolimus in ritonavir users did not show the usual peak and trough pattern, but rather resembled a flat line with a half-life up to 20 days. This resulted in a 40% lower estimated AUC when conventional target trough levels were applied. In four patients who were monitored longer than 24 hours, tacrolimus concentrations were above 3 ng/mL for at least one week after administration of a single oral dose.

Conclusions

Ritonavir changes pharmacokinetics of tacrolimus in pretransplant kidney failure patients with HIV dramatically, requiring lower dosing and close pharmacokinetic monitoring in these patients. As a result of 'flat line' pharmacokinetic curves due to extremely prolonged half-lives, target tacrolimus trough levels should be higher (17.5 ng/mL one month and 10 ng/mL one year after transplantation) in these patients compared to non-ritonavir users in order to achieve an equal exposure in terms of AUC.

Keywords: tacrolimus – ritonavir – interaction

Population pharmacokinetic-pharmacodynamic analysis of the antihypertensive effect of eprosartan

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Background

Heterogeneity in pharmacokinetics (PK) and pharmacodynamics (PD) determines the inter-patient variability in antihypertensive drug response. This study aimed to develop a PK-PD model to determine the relationship between the exposure and the drug response and to describe the time course of the diastolic blood pressure (DBP) following oral administration of the angiotensin receptor blocker eprosartan. Using this model, the inter-patient variability is estimated for the different PK and PD parameters and the influence of ethnicity on the inter-patient variability is investigated.

Methods

Eprosartan plasma concentrations (349 observations) and DBP were determined in 87 mildly hypertensive patients aged 47.8 ± 7.6 years with different ethnic backgrounds (33 Dutch Caucasians, 41 Creole Surinamese, 13 Hindustani Surinamese). All patients participated in the ROTATE study (Am J Hypertens. 2009;22:1295-302). Baseline DBP was recorded and drug efficacy was assessed after 3- and 6-week single-drug treatment with eprosartan dosed 600 or 800 mg/day. Data were analysed using nonlinear mixed effect modelling (NONMEM).

Results

Time profiles of eprosartan concentrations were adequately described with a 2-compartment PK model with 0 order absorption. The population parameter of clearance was estimated at 111 ml/min; the estimated inter-patient variability of clearance was 35%. Fourier analysis showed that 2 cosine functions with different amplitude (AMP_{24h} and AMP_{12h}) adequately describe the circadian 24-hour DBP-pattern, with a nocturnal dip and a morning surge [DBP = baseline DBP +AMP_{24h}·cos(2π·time/24) + AMP_{12h}·cos(2π·time/12)]. The delay between the increase in eprosartan plasma concentration and the antihypertensive drug effect was modelled using a hypothetical effect compartment. A log-linear relationship was used to describe the relationship between concentration in the effect compartment (C_{eff}) and the reduction in DBP (ΔDBP = slope·log[C_{eff}]). Estimated population parameters of baseline DBP, AMP_{24h} and AMP_{12h} were 92 mmHg, 10.7 mmHg and −4.6 mmHg; inter-patient variability was 6% (baseline DBP) and 29% (AMP_{24h}). Inter-patient variability in drug response (i.e. slope) was 51% and decreased to 39%, when ethnicity was included in the model as covariate. It was observed that the Creole Surinamese population exhibited a smaller drug response than Dutch Caucasians and Hindustani Surinamese [slope values were −0.3 mmHg (n = 41) vs. −2.4 mmHg (n = 46); $P < 0.05$].

Conclusions

The developed PK-PD model allows the quantification and explanation of variability in DBP between individuals with ethnicity as a useful determinant of responsiveness to eprosartan. PK-PD models may be used to optimize and individualize dosage regimens. Future research will focus on systolic BP and identification of other patient characteristics that influence response to eprosartan.

Keywords: blood pressure – population pharmacokinetics-pharmacodynamics – eprosartan

Pharmacokinetics of orally administered uracil in healthy volunteers and in DPD-deficient patients, a possible tool for screening for DPD deficiency

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Background

5-Fluorouracil (5-FU) and uracil are metabolized by dihydropyrimidine dehydrogenase (DPD). DPD deficiency can lead to severe toxicity in cancer patients treated with standard doses of 5-FU. Administration of an oral uracil test dose and subsequent measurement of uracil and its metabolite dihydrouracil (DHU) in plasma might be useful to detect patients with DPD deficiency. The purpose of this study was to compare the pharmacokinetics of uracil and its metabolite dihydrouracil after oral uracil administration in adult subjects with normal and deficient DPD status.

Methods

An oral dose of 500 mg/m^2 uracil was administered to 11 adult healthy volunteers with normal DPD status (mean DPD activity: 7.2 ± 1.3 nmol·mg^{-1}·h^{-1} in PBMCs) and to 10 patients with reduced DPD activity (mean DPD activity: 3.6 ± 0.8 nmol·mg^{-1}·h^{-1} in PBMCs). In addition, repeated administration (n = 3) of this dose was performed in 4 volunteers and 1000 mg/m^2 uracil was administered to 4 volunteers to assess intra-individual variation and linearity of pharmacokinetics, respectively. Blood samples were taken just before and during 4 hours after uracil intake and plasma concentrations of uracil and DHU were determined.

Results

Oral administration of 500 mg/m^2 uracil resulted in uracil C_{max} levels of 14.4 ± 4.7 mg/L at t_{max} = 30.0 ± 11.6 min in subjects with normal DPD status and of 20.0 ± 4.5 mg/L at t_{max} = 31.5 ± 1.1 min in DPD-deficient subjects. The uracil $AUC_{0>180}$ was 31.2 ± 5.1 mg·L/h in DPD-deficient subjects which was significantly higher ($P < 0.05$) than in the subjects with normal DPD status (13.8 ± 3.9 mg·L/h). The DHU metabolite $AUC_{0>180}$ values were 4.4 ± 1.7 mg·L/h and 5.9 ± 1.9 mg·L/h in subjects with DPD-deficient status and normal DPD status, respectively ($P < 0.05$). Repeated uracil dosing showed reproducible uracil PK in subjects with normal DPD status and dose elevation of uracil suggested linear pharmacokinetics.

Conclusion

The pharmacokinetics of uracil differs significantly between subjects with a normal DPD activity and those with a deficient DPD status. The AUC and C_{max} of uracil can be useful as a diagnostic tool to differentiate patients with regard to DPD status.

Keywords: dihydropyrimide dehydrogenase – uracil – cancer – 5-fluorouracil – pharmacokinetics

Various

Randomized double-blind controlled trial of intravenous morphine 2.5 mg versus 7.5 mg for procedural pain in postoperative cardiothoracic patients

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Background

As procedural-related pain is the most common condition of healthcare-induced pain, in this study the efficacy of intravenous morphine 2.5 vs. 7.5 mg for procedural pain relief in postoperative cardiothoracic patients is evaluated within the context of a standard pain protocol.

Methods

A prospective, double-blind randomised clinical trial was conducted in a 30-bed surgical/medical intensive care unit (ICU). 117 non-paralysed postoperative adult cardiothoracic patients were treated with continuous morphine infusions, according to a standard pain titration protocol for pain at rest. On the first day after cardiothoracic surgery, patients were randomised to receive either intravenous morphine 2.5 (n = 59) or 7.5 mg (n = 58) at thirty minutes before a painful intervention (turning of the patient and/or chest drain removal). Pain scores using the numeric rating scale (NRS, range 0-10) were rated 5 minutes before, during and 5 minutes after the painful intervention.

Results

Overall incidence of unacceptable pain (NRS ≥ 4) during a painful intervention was 25%, and was comparable between patients receiving 2.5 mg or 7.5 mg morphine (NRS ≥ 4 28% vs. 22%, $P = 0.53$), when administered on top of the standard pain titration

protocol for pain at rest. There was no difference in NRS scores during intervention [2.6 (CI95 2.0-3.2) vs. 2.7 (CI95 2.0-3.4)]. Of the patients with NRS ≥ 4 before intervention (n = 109), 21% experienced NRS ≥ 4 during intervention, whereas of the 8 patients with NRS ≥ 4 before intervention, 88% reported NRS ≥ 4 during intervention.

Conclusions

A low incidence of unacceptable NRS scores during painful intervention (25%) was found, which is partly the result of the strict pain-titration-protocol for basic pain relief and partly the result of a bolus of morphine, although there was no difference between the morphine 2.5 and 7.5 mg group. More research using other analgesics or methods is needed.

Keywords: pain scores – NRS – morphine – ICU – procedural pain

The effect of daily versus weekly folic acid supplementation on the incidence of transaminase elevations in methotrexate-treated patients with rheumatoid arthritis

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Background

Methotrexate (MTX) treatment in rheumatoid arthritis (RA) can be hindered by side effects, including transaminase elevations. These might be a surrogate marker for liver disease. Folic acid (FA) supplementation reduces the incidence of toxicity whilst not compromising efficacy, thereby allowing more patients to continue treatment. Dutch rheumatologists prescribed 1 mg daily, and since 2004 5 mg (twice) weekly, due to changing reimbursement. No evidence is available that directly compares these doses with regards to liver enzyme elevations. Therefore, this non-inferiority comparative study compares the occurrence of transaminase elevations in RA patients on MTX, supplementing folic acid on either a (twice) weekly or daily base.

Methods

All patients participating in the Nijmegen early RA inception cohort, initiating MTX and FA from 1 January 2000 with available charts and follow-up transaminase values were included in this study. Patients were split into two cohorts based on folic acid intake [daily versus (twice) weekly]. The primary endpoint is the proportion of patients with abnormal liver enzyme findings in each group, measured in time to event. 'Persistent abnormal liver enzyme values' were defined as serum values of AST and/or ALT of either > 3× more than the upper limit (UL), or > 2× but < 3× more than the UL, occurring on at least 2 of 4 consecutive evaluations. Secondary outcome parameters include gastro-intestinal (GI) intolerance, MTX dose and DAS28. Data were analyzed using Cox proportional hazard analysis for the specified endpoints. Sensitivity analysis was performed for alternate event definitions.

Results

133 (38%) patients had twice-weekly folic acid supplementation, 61 (18%) weekly and 153 (44%) daily folic acid supplementation. When corrected for location and ESR, an HR of 1.20 (0.46-3.10) was found for the association between folic acid dose and liver enzyme events (table 2). This remained non-significant in sensitivity analysis. For GI complaints, an HR of 4.22 (1.19-14.98) was found corrected for location, DMARD use, and disease duration (table 2).

Conclusion

Changing to a weekly regimen incurs no difference in the occurrence of liver enzyme elevations, but abolishes the preventive effect of folic acid with regards to GI intolerance. Combining this information with a comparatively low cost difference, daily folic acid supplementation should be preferred over weekly supplementation.

Keywords: methotrexate – folic acid – rheumatoid arthritis – adverse effects – liver enzyme elevations

TABLE 2

	Hazard ratio (95% confidence interval) crude	adjusted	adjusted for
Persistent abnormal transaminase elevations > 3× above UL or > 2× above UL on at least 2 of 4 consecutive evaluations	1.47 (0.57-3.79)	1.20 (0.46-3.10)	location, ESR
Single transaminase elevations (> 1× above UL)	1.59 (0.93-2.64)	1.67 (0.97-2.88)	location, baseline AST
Gastro-intestinal events	4.20 (1.25-14.13)	4.22 (1.19-14.98)	location, RA duration, DMARD use

Influence of a Pharmacotherapeutic Consultation on the duration and character of the rheumatologist's outpatient consultation

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Background

Polypharmacy appears to be common and considerable among people with musculoskeletal diseases. Previous research illustrated that an average patient with RA uses 5.4 drugs/day (range: 2-19 drugs/day). In order to facilitate the continuity of pharmaceutical care for patients with rheumatoid arthritis, the department of Pharmacy at the Sint Maartenskliniek developed a Pharmacotherapeutic Consultation (PC) to provide the rheumatologist with structured information about drugs used, side effects, and non-adherence risk prior to the patient's visit to the outpatient ward. Although the PC is primarily designed to improve the quality of patient's pharmacotherapy, it is also thought that the PC facilitates the consultation of the rheumatologist, and probably reduces the average length of the consultation, although this is never measured. This study therefore measures the influence of a PC on the length of the entire consultation and the length of the conversation about different medication related topic areas.

Methods

Consecutive patients attending the outpatient rheumatology ward of the Sint Maartenskliniek from October until November 2011 for a regular consultation were included. Patients were randomly assigned to receive a PC or standard care. All consultations were directly observed by the researcher (YN), who assessed the total time of the consultation and the time spent on the different medication related topics. Physicians and patients were not informed about the purpose of this study.

Results

97 consultations were examined; 37 (38%) consultations with PC and 60 (62%) without PC. The average length of a consult was 14.7 minutes, of which 2.6 minutes were spent on medication related issues. Although there were no significant differences in the length of the total consultation and the time spent on drug-related issues (table 3), the specialist's time spent on both medication reconciliation and prescribing was significantly reduced.

Conclusion

Although the PC shortened the duration of the medication reconciliation and the prescribing, neither the total duration of the consultation nor the time spent on drug related issues was affected. This suggests that the PC did not reduce the consultation time, but changes the medication related topics discussed during the consultation.

Keywords: consultation – rheumatoid arthritis – drug use – medication reconciliation

Purple gastric juice discoloration in an infant receiving omeprazole – inactivation of omeprazole due to premature coating dissolution

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Introduction

Omeprazole can be prescribed for gastro-oesophageal protection. It usually is administered in an oral pharmaceutical formulation preventing pH-dependent release of omeprazole before it reaches the duodenum.

TABLE 3

	With PC (n = 37)	Without PC (n = 60)	P value
Duration			
Total consultation	14.4 (5.3)	14.8 (6.5)	0.72
Medication reconciliation	2.6 (1.8)	2.5 (2.0)	0.88
Time (min) spent on (p25-p75)			
Reconciliation	0.18 (0.10-0.43)	0.70 (0.37-1.28)	< 0.00*
Efficacy	0.50 (0.27-0.71)	0.41 (0.26-0.83)	0.73
Adverse effects	0.58 (0.24-1.33)	0.47 (0.22-0.88)	0.29
Drug use	0.63 (0.39-1.03)	0.39 (0.27-0.67)	0.16
Prescribing	0.33 (0.19-0.65)	0.73 (0.48-0.95)	0.01*
Other aspects	0.61 (0.30-1.35)	0.53 (0.16-0.83)	0.25

Methods
We describe an infant who developed purple-colored gastric juice discoloration after buccal omeprazole administration. The mechanism of omeprazole discoloration is simulated in a laboratory setting.

Results
A three-week old Caucasian boy developed symptoms of gastro-esophageal reflux in combination with poor weight gain. Therefore, he received omeprazole, 10 mg once daily in the evening. After opening the capsules (omeprazole 10 mg, Ratiopharm), the coated particles were inserted in the buccal space, immediately followed by breastfeeding. Five weeks after start of omeprazole therapy the boy's refluxed gastric juice contained purple particles. This occurred almost every day, but only in the morning after sleeping. The omeprazole administration regimen was changed: after administration in the buccal space the child sucked a dummy teat for a few minutes, so that the particles were swallowed adequately. Consequently he was breastfed. The purple particles were then observed only twice in a couple of months. In a laboratory setting addition of the coated particles to a basic solution resulted in degradation of the coating and a visible turbidity of the solution. By adding hydrochloric acid the solution was made acidic, turning the solution and particles yellow. When making the solution basic again, the yellow solution and particles turned violet-red. Addition of coated omeprazole particles to a neutral solution resulted in no visible coating degradation.

Conclusions
Buccal administration of coated omeprazole leads to premature dissolution and inactivation of omeprazole, visible as purple particles. Co-administration of a bit of an acidic (semi-)liquid product will decrease premature coating dissolution and reduce oral retention time because of facilitated swallowing. Grapefruit juice should be avoided because of an interaction with the hepatic cytochrome P450-3A4 enzyme. Furthermore, administration of omeprazole thirty minutes before feeding will optimize effectiveness, because the peak plasma concentration will coincide with mealtime.

Keywords: omeprazole – coating

The effect of a preoperative erythropoietin protocol on allogeneic blood transfusions in daily clinical practice

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Background
Various perioperative blood management strategies have been applied to reduce allogeneic blood transfusions (ABTs) in patients undergoing total hip arthroplasty (THA). In clinical trials, preoperative treatment with recombinant human erythropoietin (rHuEPO) has been shown to reduce the transfusion rate up to 50%. The efficacy of an erythropoietin protocol in daily clinical practice has been insufficiently studied. Therefore, this study evaluated the effect of such a protocol on ABT in THA patients. The protocol was part of an integral blood management strategy.

Methods
This observational study was designed as an interrupted time series over the period from 1999 to 2010. The intervention was the implementation of a preoperative rHuEPO protocol in THA patients in hospital A in 2003. Patients were classified according to baseline Hb: 10-13 g/dL (eligible patients for rHuEPO) and > 13 g/dL. In hospital B patients never received rHuEPO. We therefore additionally compared the outcomes to those in hospital B. Since 2004, local transfusion protocols were based on a national transfusion guideline. The outcome was the percentage of patients receiving an ABT both during surgery and/or postoperative admission. Segmented regression analysis was used to estimate changes in outcomes that occurred after the intervention.

Results
A total of 4,568 and 1,001 elective primary THA patients were included in hospital A and B, respectively. In hospital A approximately 65% of the THA patients with a baseline Hb between 10 and 13 g/dL received rHuEPO. The immediate absolute reductions in transfusion rate after the intervention in hospital A were 16% (CI95 21-10) for the total study population and 26% (CI95 35-6) and 6% (CI95 13-1) for the Hb strata 10-13 g/dL and > 13 g/dL, respectively. In 1999 the transfusion rate was significantly higher in hospital A compared to B. In 2009, transfusion rates in hospital A and B were comparable.

Conclusions
The introduction of a preoperative rHuEPO protocol in the intervention hospital resulted in a significant reduction in transfusion rate in the THA patients with a baseline Hb between 10 and 13 g/dL. In the introduction period a reduction was also seen in the group of patients not eligible for the protocol (baseline Hb > 13 g/dL). The implementation of a rHuEPO protocol seemed to have led to a stricter perioperative transfusion policy in all THA patients in hospital A. At the end of the study period, hospital B had comparable transfusion rates, however without a rHuEPO protocol.

Keywords: perioperative blood management – erythropoietin – allogeneic blood transfusion – total hip arthroplasty – interrupted time series

First EDI (GS1 standard) invoice implemented in Dutch healthcare

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Background

The reason to investigate the possibilities of EDI (electronic data interchange) invoicing is the conviction that the invoice process can be more efficient, of higher quality, with lower costs and with better management information.

Methods

In cooperation between Sint Franciscus Gasthuis (SFG), Chipsoft and Brocacef the software to support EDI invoices is developed according to the standard in Dutch healthcare; GS1 EANCOM. With a test script that is jointly created the software is tested 'end to end'. Due to the shared effort and costs the project is a success.

Results

After implementing the EDI Purchase Order and the EDI Advance Ship Notice, SFG, Chipsoft and Brocacef are the first users of the EDI invoice according to GS1 EANCOM standard in the Netherlands. Since the EDI invoice is recently implemented there are few measurements from the production environment. The process is more transparent and non-value adding activities are eliminated from the process. We have already seen improvement in the speed of the process because only invoices with problems require manual intervention (management by exception). Manual work is only necessary for approximately 1-5% of all invoices. A cost reduction of 70% to 90% per invoice is possible. Alignment of the handling of EDI invoices by the hospital pharmacy with procedures of the Economic Administrative Service of the hospital is necessary.

Conclusions

EDI invoices can be a great tool for improvement of efficiency and effectiveness in healthcare. Successful implementation is a precondition for implementation of new distribution concepts. We proudly can say we are the first businesses in Dutch healthcare to use the EDI invoice.

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Gartner Inc. Top Guidelines for Successfully Leveraging Supplier E-Invoicing Networks. 23 June 2010.

Keywords: EDI – invoice – GS1 – joint effort

Evidence-based choice of opioids in frail elderly patients with chronic pain

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Background

Pharmacotherapy in frail elderly is complicated and driven by multifactorial issues. Age-related changes and increased frailty may lead to less predictable drug response like: increased drug sensitivity and potential harmful drug effects. As a result, physicians are faced with a complex task when prescribing to elderly patients. In this study, the appropriateness of the opioids buprenorphine, fentanyl, hydromorphone, methadone, morphine, nicomorphine and oxycodone is determined for use in elderly patients. Evidence-based recommendations for prescribing opioids in frail elderly are presented.

Methods

A literature search was performed for all individual drugs by use of a validated set of 23 criteria concerning effectiveness, safety, pharmacokinetics and pharmacodynamics, experience and convenience in elderly patients as described earlier [1]. First, information on the criteria was obtained from pharmaceutical reference books. Additionally a PubMed search was performed (1966-2010) to identify papers concerning information on the remaining criteria. The information obtained on the individual drugs in the class of opioids was compared to the reference drug morphine. Evidence-based recommendations were formulated based on the pros and cons for frail elderly.

Results

Of the set of 23 criteria morphine, fentanyl, oxycodone and hydromorphone scored best. In order to improve the convenience for elderly patients, the controlled release oral and transdermal formulations are preferred. Buprenorphine, methadone and nicomorphine have strong negative considerations in the treatment of chronic pain in frail elderly. Buprenorphine is a partial agonist/antagonist and has a high drug–drug interaction potential. Methadone also has a high drug–drug interaction potential and is associated with prolongation of the QT-interval and a potential risk of accumulation due to a long elimination half-life of the parent drug and the main metabolite normethadone. In addition, methadone is difficult to titrate due to its large interindividual variability in pharmacokinetics, particularly in frail elderly. For the use of nicomorphine in the treatment of chronic pain, only a rectal formulation is available. In addition, there is no evidence for the effectiveness of nicomorphine in the treatment of chronic pain.

Conclusions

In the treatment of chronic pain in frail elderly the opioids of first choice are morphine, fentanyl, oxycodone and hydromorphone. In order to improve the convenience for elderly patients, the controlled release oral and transdermal formulations are preferred.

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Keywords: frail elderly – opioids – chronic pain – pharmacotherapy

Long-term effects of melatonin on sleep and quality of life in haemodialysis patients (Melody study)

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Background

Sleep disorders are much more prevalent in haemodialysis patients than in the general population. A disturbance in the biological clock that regulates circadian sleep-wake rhythm is a novel topic of interest in this patient group. The pineal hormone melatonin plays a major role in circadian sleep-wake rhythm. Previously, we reported that the nocturnal endogenous melatonin rise, which is associated with the onset of sleep propensity, is absent in many haemodialysis (HD) patients and that short-term daily use of exogenous melatonin 3 mg improves sleep onset latency (SOL), actual sleep time (AST) and sleep efficiency (SE) in HD patients [1].The aim of the current study was to investigate the long-term effects of exogenous melatonin on sleep parameters and quality of life (QoL) in daytime HD patients.

Methods

We conducted a 1 year randomized double-blind placebo-controlled trial with melatonin 3 mg in 68 HD patients (ClinicalTrials.gov: NCT00388661). Objective sleep measurements were taken at 0, 3, 6, 9 and 12 months by means of actigraphy. QoL parameters were measured by the Medical Outcomes Study Short Form-36 questionnaire (MOS SF-36) at 0, 6 and 12 months. Endogenous melatonin concentration curves were sampled in saliva at 0 and 6 months during 5 consecutive time-points at 9 and 11 PM and 1, 7 and 9 AM. Statistical analysis was performed by generalized estimating equation.

Results

Administration of exogenous melatonin 3 mg resulted in higher endogenous melatonin levels. At 3 months, the previously shown beneficial effect of the short-term use of exogenous melatonin on SOL was confirmed (P = 0.023). A trend in improvement of SE (P = 0.105), AST (P = 0.057) and actual awake time (AAT) (P = 0.150) was observed. In contrast, at 12 months none of the measured sleep parameters differed significantly from placebo. At the end of the study period a positive effect on social functioning (P = 0.032) and a trend in improvement of mentality (P = 0.094) were seen.

Conclusions

In conclusion, in this study the short-term beneficial effects of melatonin 3 mg on sleep parameters were confirmed. However, there is no indication that these beneficial effects persist in long-term usage of this melatonin dosage regimen. A better course of social functioning was seen with melatonin compared to placebo. Follow-up research is warranted to elucidate the reasons why the hypnotic effects of melatonin diminish in time.

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Keywords: haemodialysis – melatonin – sleep – quality of life

Sugammadex compared to neostigmine does not decrease postoperative complications

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Background

Neostigmine and sugammadex are used to reverse nondepolarizing neuromuscular blocking agents (NMBAs) such as rocuronium or vecuronium. Different pharmacological backgrounds of these substances would suggest that suggamadex compared to neostigmine may have a different adverse events profile. The aim of the study was to compare the occurrence of postoperative complications and the duration of hospital admission of patients treated with neostigmine or sugammadex.

TABLE 4

	Neostigmine (n = 252)	Sugammadex (n = 193)	P value
Patients with complications (%)	30 (11.9)	24 (12.4)	0.865 □
Surgical complications†	15	13	0.736 □
Cardial complications†	8	4	0.565 ◇
Pulmonary complications†	5	5	0.669 □
Other complications†	7	5	0.904 □
Mean duration of hospital stay (days)	4.42	5.07	0.308 △

□ Chi-square test.
† Complications don´t add up to `patients with complications´ because some patients had more than one complication.
◇ Fisher's exact test.
△ Independent samples Students T test.

Method

A retrospective cohort study of the incidence of postoperative complications, surgical and non-surgical, and hospital admission in surgical patients. From 2008 tot mid 2010 patients, receiving rocuronium, who were reversed with sugammadex or neostigmine were included. Choice of substance was left to the discretion of the anaesthesiologist. Patient charts were reviewed for postoperative complications, chart viewer was blinded for sugammadex or neostigmine. To determine baseline complication risk, the ASA score was obtained and the IRIS score was calculated. (The Identification of Risk In Surgical patients, IRIS score, accurately predicts mortality after general or trauma surgery.)

Results

Data on 252 patients receiving neostigmine and 193 patients receiving sugammadex were collected (table 4). There was no difference in number of patients with complications, surgical and non-surgical, between sugammadex or neostigmine (11.9% vs. 12.4%; P = 0.865). The occurrence of surgical, cardial, pulmonary or other complications was not different between groups. Adjustment for ASA and IRIS score did not alter the results. There was no significant difference in mean duration of hospital admission between sugammadex or neostigmine (5.07 vs. 4.42 days; P = 0,308).

Conclusion

Duration of hospital stay and the occurrence of postoperative complications is equal for both sugammadex and neostigmine if administered to reverse nondepolarizing neuromuscular blocking agents (NMBAs).

Keywords: sugammadex – neostigmine – complications – rocuronium

Evaluation of caspofungin treatment in daily practice

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Background

Caspofungin is used for the treatment of invasive *Candida* infections in moderately severe to severely ill patients and for patients who were recently exposed to an azole. For adequate treatment of *Candida* infections it is important to start fluconazole as soon as possible and to ensure that adequate fluconazole plasma concentrations are reached [1, 2]. The aim of this study is to assess if these predictors (dose and treatment delay) also have an influence on the outcome of caspofungin treatment.

Methods

A retrospective chart review was performed for patients who received caspofungin for at least 5 days between January 2006 and March 2010. Patients aged 18 years and older with a positive *Candida* culture in blood or intra-abdominal fluid were included. Treatment response was assessed based on culture conversion and/or improvement of CRP concentrations and leukocyte count. Death from any cause was considered an unfavorable response.

Results

Seventy patients with a median age of 61 (IQR: 53-68) years were included. In 6 of the 70 patients no loading dose was administered. Of the 29 patients with a bodyweight of 80 kg or more 24 (83%) received a maintenance dose that was too low (50 mg instead of 70 mg). Table 5 displays the other results. The number of days of caspofungin treatment was significantly lower in patients who did not respond to therapy – obviously because 50% of these patients died during treatment.

TABLE 5: CHARACTERISTICS

	No response (n = 20)	Response (n = 50)	P value
Gender			0.636*
• male	12 (60%)	33 (66%)	
• female	8 (40%)	17 (34%)	
Weight (kg)	85 (74-94)	75 (68-83)	0.018 ◇
Source of *Candida* isolation			0.184 □
• blood	5 (25%)	21 (42%)	
• intra-abdominal fluid	15 (75%)	29 (58%)	
Treatment delay (days)	3 (2-4)	4 (2-6)	0.092 ◇
Dosed according to weight	9 (45%)	37 (74%)	0.021 □
Loading dose	20 (100%)	44 (88%)	0.105 □
Treatment duration (days)	10 (5-15)	16 (12-25)	0.001 ◇

Data presented as n (%) or median (interquartile range)
□ Chi-square test.
◇ Mann-Whitney U test.

Conclusions

Most patients with a bodyweight of 80 kg or more (83%) did not receive the advised higher dose of 70 mg. Despite the limitations of our retrospective study our results demonstrate that treatment is likely to fail in patients that are dosed too low. A possible influence of treatment delay on outcome could not be confirmed. Our results show that a prospective study evaluating the effect of PK/PD parameters on outcome may be helpful in optimizing the outcome of caspofungin treatment.

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Keywords: caspofungin – dose – invasive candida