

Nederlandse Ziekenhuisfarmaciedag, 24 november 2008

Dit artikel bevat de abstracts van de mondelinge presentaties tijdens de Derde Nederlandse Ziekenhuisfarmaciedag op 24 november 2008 te Rotterdam. De digitale versie van dit artikel op pw.nl omvat ook de abstracts van de posterpresentaties.

The influence of computerized prescribing on medication errors and preventable adverse drug events: an interrupted time series study

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Background

Literature generally shows positive effects of computerized prescribing on the incidence of medication errors (MEs) with some indication of a positive effect on preventable adverse drug events (pADEs). These studies are however mainly pre/post analyses that do not control for underlying trends and predominantly originate from the USA. This study evaluates the effect of a computerized physician order entry (CPOE) system on the incidence of MEs and pADEs in two Dutch hospitals using an interrupted time series design.

Methods

Data were prospectively collected for 1,195 patients admitted during twenty weeks before and twenty weeks after the introduction of CPOE. Primary outcome measures were the percentage of medication orders (MOs) with one or more MEs and the percentage of patients with one or more pADEs. The causal relationship between errors and ADEs was assessed by a panel of five pharmacists using a combination of the NCC MERP index [1] and the Yale algorithm [2]. Segmented regression analysis was used to analyze the interrupted time series data.

Results

During the baseline period, the mean percentage of MOs containing at least one ME was 55% whereas in the post-intervention period this was 17%. Introduction of CPOE led to a significant immediate absolute reduction of 40.3% (CI95%: -45.1- -35.5%) of MOs with one or more errors and a change in trend of -0.92% (CI95%: -1.31- -0.52%) per week. In the baseline period, the mean percentage of admitted patients experiencing at least one pADE was 15.5% in contrast to 7.3% in the post-intervention period. However, this decrease could not be attributed to the introduction of CPOE: the immediate change is not significant (-0.4%, CI95%: -15.5-14.7%) because of the observed underlying negative trend during the pre-CPOE period of -4.0% (CI95%: -7.7-0.4%) per month.

Conclusions

This study showed that CPOE reduces the incidence of medication errors and thus indirectly has a positive effect on the potential risk for patient harm. However a direct effect on actual patient harm (pADEs) could not be demonstrated.

REFERENCES

- 1 NCC MERP Index for Categorizing Medication Errors. <http://www.nccmerp.org/>. Accessed August 2008.
- 2 Kramer MS, et al. An algorithm for the Operational Assessment of Adverse Drug Reactions. *JAMA* 1979;242:623-32.

Keywords: computerized prescribing – medication errors – preventable adverse drug events

The CYP2D6*4 polymorphism affects breast cancer survival in tamoxifen users

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Background

Tamoxifen is one of the most widely used drugs for the treatment of estrogen receptor-positive breast cancer in post-menopausal women. Cytochrome P450 2D6 (CYP2D6) plays an important role in the formation of endoxifen, the active metabolite of tamoxifen. Genetic variation in the CYP2D6 gene may lead to a decreased efficacy of tamoxifen therapy. In this study the association between the most prevalent CYP2D6 null-allele in Caucasians (CYP2D6*4) and breast cancer mortality was examined among users of tamoxifen in a population-based cohort study.

Methods

In the Rotterdam Study all incident tamoxifen users with CYP2D6 genotype available (n = 85) were followed until death. The association between CYP2D6 genotype and all-cause mortality, cancer mortality and breast cancer mortality was examined using Cox proportional hazard models with drug use as time-dependent variable.

Results

No increased risk of all-cause mortality or cancer mortality was found in tamoxifen users carrying a CYP2D6*4 allele. In an allele-

effect model there was a significantly increased breast cancer mortality risk with a hazard ratio of 2.0 per additional variant allele (CI95% 1.1-3.4, $p = 0.015$). Breast cancer mortality was significantly increased in patients with the $*4/*4$ genotype (HR = 4.1, CI95% 1.1-15.9, $p = 0.041$) compared to wild type patients. Taking homozygous and heterozygous individuals together in a dominant model, the breast cancer mortality risk was 2.1 (CI95% 1.1-4.2, $p = 0.031$).

Conclusions

The risk of breast cancer mortality is increased in tamoxifen users with decreased CYP2D6 activity.

Keywords: CYP2D6 – breast cancer – tamoxifen – pharmacogenetics

Incidence of contrast-induced nephropathy in a general CT population: a retrospective cohort study

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Background

The definition of contrast-induced nephropathy (CIN) is the rise in serum creatinine of 25% or 44 $\mu\text{mol/L}$ within 3 days after the intravascular administration of a iodinated contrast medium in the absence of an alternative etiology. Although the clinical relevance of this rise can be disputed, these changes can be associated with significant morbidity rates, especially in patients with a marginal renal function. CIN is the third leading cause of hospital-acquired acute renal failure, accounting for up to 12% of all cases. In order to determine the effect of the measures installed to prevent CIN we retrospectively reviewed our patient data. The purpose of the study was to determine the incidence of CIN in patients undergoing contrast enhanced CT, and to determine how many patients with an estimated glomerular filtration rate (eGFR) ≤ 45 (ml/min)/1.73m² experienced CIN.

Methods

All records of patients undergoing CT from December 2006 to February 2007 were retrospectively reviewed. Eligible patients experienced a CT scan for which intravenous iopromide 300 mg/ml (Ultravist 300, Bayer-Schering Healthcare, Mijdrecht, The Netherlands) administration was indicated. Patients were included when serum creatinine was established ≤ 7 days before and within 3 days

after administration. Patients on haemodialysis were excluded. CIN was diagnosed as a rise in serum creatinine after contrast administration of ≥ 44 $\mu\text{mol/L}$ (0.5 mg/dl) or a rise of $\geq 25\%$ from baseline in the absence of an alternative etiology. Renal function (eGFR) was estimated using the 4-point MDRD formula.

Results

In the 3 months period 1,325 patients experienced a iodinated contrast-enhanced CT scan. In 276 patients (20.8%) serum creatinine was established within 7 days before contrast administration and within 3 days afterwards. This was the eligible population. Of the eligible population 33 patients experienced CIN (12.0%). The CIN patient population consisted of 13 males and 20 females. The mean age was 69 years (28-88). The mean GFR before contrast administration was 61.4 (ml/min)/1.73m² (15.1-144.3). The mean GFR decline was 23.8 (ml/min)/1.73m² (4-66). Before contrast administration 19 patients (58%) had a GFR ≤ 60 (ml/min)/1.73m². 13 patients (39%) had a GFR ≤ 45 (ml/min)/1.73m². 6 patients had a eGFR 45-60 (ml/min)/1.73m². The mean injected contrast volume was 115 ml (80-150).

Conclusions

In the eligible population of 276 patients 33 cases of CIN were established. This corresponds with an incidence of 12.0%. The mean GFR decline was 23.8 (ml/min)/1.73m² or 40%. Of the CIN patient population 13 patients (39%) had a GFR ≤ 45 (ml/min)/1.73m² before contrast administration.

Keywords: contrast-induced nephropathy – iodinated contrast – radiology

Economic evaluation of an inpatient medication reconciliation project

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Background

The aim of medication reconciliation (MR) is to correct discrepancies

in medication use between health care settings and to check the quality of pharmacotherapy in order to improve effectiveness and safety of the therapy. However, MR might also reduce costs. The aim of this study is to evaluate medication-related costs vs. hospital pharmacy labour costs when comparing interventions registered due to MR vs. no interventions.

Methods

An observational study was performed at the Sint Lucas Andreas Hospital. All patients discharged with at least one prescribed drug from the department of pulmonology were included. Exclusion criteria were: terminal illness, discharge to a nursing home or out of office hours and unable to be counselled (physically/mentally or language restrictions). A project was developed which consisted of MR at admission and discharge and patient counselling at discharge (covering the reasons for changes in pharmacotherapy and instructions for use of any new drugs started). Four types of interventions were registered: start, stop, change in medication and change in dose/formulation. The medication-related costs were calculated by using the prices listed in the Dutch *Farmacotherapeutisch Kompas* on June 2008 and a fixed prescription fee of € 6.10. The calculations were done for periods of 1, 3, 6, and 12 months after discharge. A pharmaceutical consultant needed approximately one hour per patient for the MR project. The labour costs were calculated with the hour salary and a mean productivity of 70% (due to courses or meetings). The outcome parameter was the medication costs vs. the labour costs. Data were analysed with descriptive statistical analysis.

Results

262 patients were included in the study. Costs were made due to the start of medication. On the other hand substantial savings (Table 1)

Table 1			
Costs and savings after one month; n = 262			
Intervention type	Costs	Savings	Example
Start	€ 209.23	–	undertreatment
Dosage *	€ 56.38	€ 75.62	formulary not appropriate
Switch	€ 50.66	€ 679.16	cheaper alternative possible
Stop	–	€ 5,207.36	indication not present
Total	€ 316.27	€ 5,962.14	
Difference	savings: € 5,645.88 (€ 21.55 per patient)		
* Dosage adjustments are not included as dose decrease and dose increase were not distinguished.			

were made by stopping medication which had no indication at discharge (e.g. hypnotics, laxatives, analgesics and proton pump inhibitors). We also extrapolated the costs as medication is frequently used chronically. After 3, 6 and 12 months respectively € 48.02, € 91.55 and € 178.61 per patient was saved on medication costs. The MR project took approximately one hour per patient. The year salary of a pharmaceutical consultant is € 50.000 (hour salary: € 30). When taking into account a mean productivity of 70% the MR project costs € 40 per patient.

Conclusions

After six months the MR project saved approximately € 90 per discharged patient on medication costs. The labour costs were € 40. In conclusion, there was a net saving of € 50 per patient.

Note: The pulmonary department also spent time on the project. As the hospital pharmacy had taken over their discharge activities, we assumed that these costs would not be substantial.

Keywords: patient education – hospital discharge – pharmaceutical care – economic evaluation

Parenteral drug admixtures on the ICU: “Mind your steps!”

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Background

The preparation of parenteral drug admixtures on the ward is associated with risks of medication errors and microbiological contamination. Methods to limit these risks are the training of nurses and reducing the amount and complexity of the preparations. Recent studies show that medication errors mainly occur in multi-step preparations.

Methods

In this study we have made an analysis of the risks of the most common parenteral drug admixtures on the intensive care units (IC units) in the Zaans Medical Centre and the Maxima Medical Centre. The parenteral drug admixtures are divided in continuously and intermittently administered drugs. The risk score is determined by

three factors: frequency of preparation (per day), number of steps during the preparation and if a drug is a high-alert medication or not (according to the list of high-alert medications of the Institute of Safe Medicines Practices, www.ismp.org). Based on the risk scores hospital pharmacists and medical specialists can assess for a specific parenteral drug admixture whether intervention is necessary.

Results

37 patients were included who, in total, received 1522 parenteral drug admixtures. Most drugs used on the IC units, in both hospitals, are classified as high-alert medication. The analysis showed that the risk score of the preparation of continuously administered drugs is generally higher than those of intermittently administered drugs. Bupivacaine-fentanyl, insulin and enoximon have the highest risk scores in Zaans Medical Centre while insulin, fentanyl and norepinephrine scored the highest risks in Maxima Medical Centre.

Conclusions

By using this analysis a risk score for the preparation of a specific parenteral drug admixture can be calculated. Admixtures with the highest risk score should be of first interest for intervention. Possible interventions are: relocating the preparation of parenteral drug admixtures to the hospital pharmacy and/or replacement by a 'ready to use' product made by a regional or national production unit.

Keywords: parenteral drug admixtures – intensive care unit – risk analysis – complexity – high risk

Optimizing calcineurin inhibitor exposure in kidney transplant recipients early after transplantation

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Background

To prevent acute rejection episodes it is important to reach adequate calcineurin inhibitor (CNI) exposure early after kidney

transplantation. With a better understanding of the factors determining the high variability in pharmacokinetics (PK) of tacrolimus and ciclosporin, the starting dose of these drugs can be individualized and may result in a reduction in dose adjustments upon therapeutic drug monitoring. Therefore, this study aimed at a combined analysis of genetic and non-genetic factors that may explain variability in CNI PK.

Methods

PK data were obtained from kidney transplant patients (n = 64) receiving either once or twice daily ciclosporin or tacrolimus. PK was sampled on multiple occasions (10 per patient) up to one year after transplantation. The population PK analyses were performed with non-linear-mixed-effects-modelling and used to determine the effects of the following covariates: hematocrit, serum albumin concentration, prednisolone dose, once or twice daily dosing, demographic factors and genetic polymorphisms in ABCB1, CYP3A5, CYP3A4 and the nuclear factor pregnane-X-receptor (PXR) on CNI PK.

Results

For ciclosporin bodyweight appeared to be the most important covariate and explained 25% of the observed variability in ciclosporin clearance. A prednisolone dose over 20 mg/day was associated with an increased ciclosporin clearance of 23%. The tacrolimus analysis revealed three significant covariates. CYP3A5 was most important and explained 27% of the variability in tacrolimus clearance. Clearance was 3.7 ± 0.7 L/h vs. 5.9 ± 1.1 L/h for the genotypes CYP3A5*3/*3 and CYP3A5*1/*3 respectively. A polymorphism in PXR A+7635G explained 3.5% of the variability in tacrolimus clearance: clearance was 3.5 ± 0.7 L/h in the A-allele carriers vs. 4.9 ± 1.0 L/h in the GG genotype. Finally, the tacrolimus clearance was increased with 17% in those patients with a concomitant prednisolone dose over 10 mg/day. Tacrolimus exposure in terms of clearance did not correlate with bodyweight.

Conclusions

The results of the present study indicate that the initial ciclosporin exposure depends mainly on bodyweight, whereas the initial tacrolimus exposure in adult kidney transplant recipients should be optimized by using genotype rather than bodyweight.

Keywords: calcineurin inhibitor – transplantation – individualization – exposure – genotype – bodyweight

Non-steroidal anti-inflammatory drugs and gastroprotection: development and validation of a clinical rule

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Background

Gastrointestinal complications are common side effects of non-steroidal anti-inflammatory drugs (NSAIDs). Certain factors can increase the risk on this complication. A regional expert-group guideline defines a high-risk patient if one severe or two or more cumulative risk factors are present. It is recommended to initiate prophylactic gastroprotection in these patients by a proton pump inhibitor. A clinical decision support system (CDSS) can be used to develop a clinical rule to select these patients and provides the opportunity to generate alerts in case the treatment differs from the guideline.

Guideline

- Severe risk factors: age over 70 years, history of (complications of) an ulcer, untreated *H. pylori*-infection.
- Cumulative risk factors: age 60 to 70 years, use of anticoagulants, use of corticosteroids, use of selective serotonin reuptake inhibitors (SSRIs), debilitating rheumatoid arthritis, heart failure, diabetes, high-dose NSAID treatment.

The aim was to develop and validate a clinical rule to guide gastroprotection during the use of NSAIDs, using the CDSS Gaston (Medecs), and to analyse pro- and retrospectively the compliance to the guideline and the potential impact of implementation of this clinical rule in the Catharina Hospital.

Methods

The clinical rule was developed following a Plan-Do-Check-Act cycle. The rule was retrospectively tested on 3047 patients using an NSAID more than one day, admitted in April and May 2008 at the Catharina Hospital. The prospective test includes 694 patients admitted to the Catharina Hospital between the 12th and the 18th of July 2008. A signal was generated for each day of a high-risk patient using a NSAID and not using a gastroprotective drug.

Results

The retrospective test reveals that 535 patients used a NSAID more than one day. 225 of these patients (42.1%) generated one or more signals. The prospective test selected 101 patients that used an

NSAID for one or more days, among them 40 that lacked gastroprotection although recommended by the guideline. In our hospital setting this is an average of 5 to 6 patients per day.

Conclusions

40% of NSAID users is not treated according to the guideline, despite current effort of physician and pharmacy using current medication safety systems. This may lead to severe gastrointestinal complications. The clinical rule for gastroprotection selects high-risk patients, generates a message and draws a physician's attention to compliance to the guideline. Hereby, implementation of this clinical rule can significantly improve medication safety in practice.

Keywords: CDSS – clinical rules – NSAIDs – gastroprotection – guidelines

Unintended consequences of reducing QTc-alert overload

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Background

After complaints of too many low-specificity QTc-alerts, the rules for QTc-alerting in the Dutch national drug database G-Standaard were adjusted in May 2007. The aim of this study was to investigate whether this adjustment would identify patients at risk of developing torsades de pointes better than the old system.

Methods

All inpatients with overridden drug safety alerts on QTc-prolongation in a half year study period could be included if ECGs were available before and within one month after the QTc-alert override. Patients with ventricular pacemakers, or using the low risk combination cotrimoxazole + tacrolimus were excluded. QTc-interval prolongation and the risk of developing torsades de pointes were calculated for all included patients and related to the number of patients for which a QTc-alert would be generated in the new alerting system. Increased risk of torsades de pointes was defined as a QTc-interval >500 ms or an increase of the QTc-interval >60 ms between the two ECGs. Patients were considered to have additional risk factors for QTc-prolongation if they were female and over 65 years of age, had cardiovascular disease, diabetes mellitus, renal failure and/or hypokalemia.

Results

49 patients met the inclusion criteria. The mean number of additional risk factors was 2.7 (SD 1.1) and all patients had at least one additional risk factor (other than drug therapy) for developing torsades de pointes. In this study population, the adjustment of the G-Standaard for QTc-alert generation reduced the number of QTc-alerts with 55%. However, the positive predictive value of QTc-alerts decreased from 31% to 27% and only 40% of the patients at risk of developing torsades de pointes was identified by the new alerting system.

Conclusions

The new system with adjusted QTc-alerting identified patients at risk of developing torsades de pointes worse than the old system. The expected increase in positive predictive value of the alert remained absent. Furthermore, 60% of the patients at risk identified

by the old system were missed in the new system. These unintended consequences were caused by many non-drug-related risk factors for QTc-prolongation not incorporated in alert generation. The partial contribution of all risk factors should be studied and used to make clinical rules for QTc-alerting with an acceptable positive predictive value.

Keywords: computerized physician order entry – patient safety – alert override – drug therapy, computer assisted – error management – QTc-prolongation

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

PPORT: post-operative pain treatment in orthopaedic surgery
The safety, efficacy and pharmacokinetics of saquinavir boosted by ritonavir (1000/100 mg bid) in pregnant HIV-infected women
Prevention of opioid-induced constipation using a clinical rule
Therapeutic drug monitoring of nevirapine in resource-limited settings
International interlaboratory proficiency testing program for measurement of antifungal azole plasma concentrations
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Pharmacokinetics and toxicity of linezolid in MDR-TB patients
Improved analgesia after realization of pain management program in ICU patients after cardiac surgery
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Missense polymorphisms in three oxidative-stress enzymes (GSTP1, SOD2, and GPX1) and dyskinesias in Russian psychiatric inpatients from Siberia
Generation of virus-specific T cell lines for treatment of viral infection after allogeneic stem cell transplantation
Alteration of individual 6-thioguanosine phosphate metabolite levels by co-administration of 5-aminosalicylic acid: prospective pharmacokinetics in IBD patients under steady-state azathioprine therapy
Improved efficiency and sustained accuracy in prescribing glucose intake using a Computerized Physician Order Entry system in the Neonatal Intensive Care Unit.
¹³C-urea is a suitable nonradioactive marker substance for assessment of *in vivo* behaviour of oral colon-targeted dosage forms

PPORT: post-operative pain treatment in orthopaedic surgery

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Background

Effective pain treatment after total hip or knee arthroplasty (THA or TKA) is essential for fast recovery and patient satisfaction. Patient-controlled intravenous analgesia (PCIA) in combination with oral analgesics is one of the treatments recommended by literature but little is known on the outcomes in daily practice. This study aims to evaluate the effectiveness and side effects of this treatment in a general Dutch hospital.

Methods

A total of 264 patients (154 THA and 110 TKA) were recruited within the Joint Care program from March 2006 to August 2007. Primary endpoints were effectiveness of pain treatment and the incidence of side effects. Secondary endpoints were patient satisfaction and PCIA morphine consumption.

Results

On the day of the surgery (day 0) and the first postoperative day (day 1) 65% vs. 81% of the THA patients and 45% vs. 62% of the TKA patients had a mean acceptable pain score in rest (VAS-R ≤ 40 mm). In the following days these percentages rose to 98% and 97% for THA and TKA respectively at discharge. At day 1 43% of the THA and 24% of the TKA patients had a mean acceptable pain score in movement (VAS-M ≤ 40 mm). Mean daily pain scores were lower in the THA group than in the TKA group ($p < 0.0005$). Nausea and vomiting which predominantly occurred on day 0 and 1 were seen more frequently in the TKA group than in the THA group ($p = 0.002$). Mean PCIA morphine consumption was 21.9 vs. 34.7 mg for THA and TKA patients respectively ($p < 0.0005$). After 72 hours satisfactory scores (sufficient to outstanding) were reported by 93% and 85% of the THA and the TKA group respectively ($p < 0.0005$). At discharge these percentages had risen to 95% and 91% ($p = 0.618$).

Conclusions

Despite the high degree of satisfaction, adjustments in the postoperative pain management after THA and TKA may be considered to improve the outcomes on effectiveness and side effects. Especially on day 0 and 1 improvements can be made. The biggest gain seems feasible after TKA.

Keywords. postoperative pain – orthopaedic surgery – outcomes – PCIA

The safety, efficacy and pharmacokinetics of saquinavir boosted by ritonavir (1000/100 mg bid) in pregnant HIV-infected women

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Background

The pharmacokinetics (PK) of several protease inhibitors have shown to be influenced by pregnancy resulting in a lower drug exposure. This may lead to suboptimal antiviral efficacy, and hence mother-to-child transmission. Ritonavir-boosted saquinavir is hardly studied in this setting.

Methods

In this prospective multicentre study, HIV-1 infected pregnant women without previous protease inhibitors failure, started with saquinavir 500 mg tablets + ritonavir, 1000 + 100 mg BID + 2 non-nucleoside reverse transcriptase inhibitors. Patients could enrol either before the second or the third trimester. Safety, efficacy and 12 hour PK curves were recorded in the second trimester (week 20 \pm 2), the third trimester (week 33 \pm 2) and post-partum (PP) (week 4-6; optionally PP). PK parameters were calculated using WinNonlin software version 4.1. Statistical analysis was conducted using SPSS version 14.0.

Results

40 women were included; 8 patients dropped out between baseline and their first PK visit (2 due to the study product related toxicity). At baseline, the mean age was 30.3 years, weight 68.0 kg, 42% of the patients was antiretroviral-naïve and 42% had < 50 copies/ml HIV-RNA. 2 SAEs were reported: one abortion and one diabetes gravidarum. AST/ALT grade 3/4 was reported in 3 patients, lipids remained unchanged. The proportion HIV-RNA below 50 copies/ml was 73%, 91% and 87% at week 20, 33 and 6 weeks PP, respectively. No virological failure was recorded. Mean (SD) value for saquinavir AUC_{0-12h} was 23.5 (11.9) $mg \cdot l^{-1} \cdot h$ on week 20; 23.7 (9.1) $mg \cdot l^{-1} \cdot h$ on week 33, and 25.0 (11.8) $mg \cdot l^{-1} \cdot h$ on week 6 PP. None of the women showed a subtherapeutic C_{min} of saquinavir (< 0.10 mg/L) in any of the 12 hour curves during pregnancy or PP.

Conclusions

Saquinavir is a safe and efficacious drug for use during pregnancy. The plasma concentrations of saquinavir were not influenced by the pregnancy.

Keywords: HIV – pregnancy – pharmacokinetics

Prevention of opioid-induced constipation using a clinical rule

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Background

Because of the high prevalence of opioid-induced constipation, the prophylactic use of a laxative is widely recommended. However, not all patients get a laxative prescribed when opioid treatment is initiated. Clinical decision support systems (CDSS), third-generation patient-based medication safety systems, can identify patients who lack prophylactic treatment. A CDSS uses clinical rules to generate patient-based recommendations. The aim of this research is to develop and validate a clinical rule that identifies patients who have an opioid but no laxative prescribed and to determine the potential impact of this rule.

Methods

A clinical rule is developed using the CDSS Gaston (Medecs). The Plan-Do-Check-Act cycle is followed to create a reliable rule. The content is based on both literature and expert opinion. To determine the potential impact, the clinical rule is tested retrospectively on all patients admitted in January and March 2008 and prospectively for 15 days in July and August 2008 on the patient database of the Catharina Hospital, Eindhoven. For prospective testing, the clinical rule is designed to classify recommendations as high priority or normal priority, depending on the risk of the development of opioid-induced constipation. High priority messages should be delivered directly to the clinician, while normal priority messages should be delivered to the nurses. Reliability is measured by manual validation of the recommendations and expressed as the positive predictive value. The potential impact is measured by counting the number of recommendations that the CDSS generates.

Results

A total of 3313 patients were admitted in January and March 2008. Of these patients, 791 had an opioid prescribed. 536 (68%) of them did not use a prophylactic laxative during one or more days. During prospective testing, a total of 656 recommendations to prescribe a prophylactic laxative are generated, of which 80 are classified as high priority. The most frequently generated high priority recommendations involve patients who have been prescribed morphine ($n = 31$), fentanyl ($n = 27$) or oxycodone ($n = 10$). 99 of 100 validated messages are correct, resulting in a positive predictive value of 99%.

Conclusions

68% of patients using opioids do not get a prophylactic laxative prescribed. This research has shown that a reliable clinical rule can be developed to identify patients who need the prescription of a prophylactic laxative. When this clinical rule is implemented and

used in daily practice, prevalence of opioid-induced constipation can be reduced.

Keywords: CDSS – clinical rules – opioids – laxatives – constipation

Therapeutic drug monitoring of nevirapine in resource-limited settings

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Background

We developed a simple and inexpensive thin layer chromatography (TLC) assay for semi-quantitative detection of nevirapine saliva concentrations in resource-limited settings. The method was validated in an African target population.

Methods

Paired plasma and saliva nevirapine concentrations were assayed by HPLC; saliva concentrations were also assayed by TLC. The false-positive rate was the proportion of subtherapeutic nevirapine saliva and plasma concentrations by HPLC reported as being therapeutic in saliva by TLC. The false-negative rate was the proportion of therapeutic nevirapine saliva and plasma concentrations by HPLC reported as subtherapeutic in saliva by TLC. The extent of agreement in TLC readings between 5 technicians and 2 batches of TLC sheets was evaluated.

Results

25 (9%) of 286 African adults had a subtherapeutic plasma nevirapine concentration. The median saliva/plasma nevirapine concentration ratio was 0.51. The false-positive rate by TLC was 0.00 (none out of 23) compared to HPLC saliva result and 0.08 (2 out of 25) compared to HPLC plasma result. The false-negative rate by TLC was 0.01 (3 out of 263) compared to HPLC saliva result and 0.01 (3 out of 261) compared to HPLC plasma result. The extent of agreement in TLC result was substantial between 5 technicians (Fleiss' kappa 0.77) and 2 batches of sheets (Cohen's kappa 0.80).

Conclusions

The TLC assay was found to be sensitive, specific and robust in detection of subtherapeutic nevirapine concentrations in saliva of African HIV-infected adults. It is an attractive alternative to HPLC for therapeutic drug monitoring of nevirapine in resource-limited settings.

Keywords: nevirapine – TDM – TLC method – saliva – plasma

International interlaboratory proficiency testing program for measurement of antifungal azole plasma concentrations

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Background

An international interlaboratory quality control program for measurement of azole antifungal drugs in plasma was initiated as a means to validate accuracy and specificity of azole antifungal assays.

Methods

Drug-free plasma from selected healthy volunteers was obtained through plasmapheresis and was provided by the Dutch Blood Bank (Sanquin, Nijmegen). The obtained plasma was spiked with fluconazole, itraconazole, hydroxyitraconazole, voriconazole and posaconazole. All antifungal azoles were obtained from pharmaceutical industries and had a very high (>99%) and specified purity. Five samples with variable concentrations of the antifungal agents were shipped to 35 international laboratories in Europe, Australia and Asia. Fluconazole, itraconazole and hydroxyitraconazole were dispatched in one concentration. Voriconazole and posaconazole were dispatched in a low and a high concentration. Participants were requested to analyze the samples within 6 weeks after dispatch and were asked to provide details about their analytical method. All weighed-in concentrations were considered true values and the obtained concentrations were all within a concentration range that is generally achieved after oral or intravenous administration of azole drugs. Concentrations that were found within $\pm 20\%$ of the weighed-in concentration were considered to be correct. Results of the participating laboratories were reported anonymously.

Results

36 laboratories subscribed to the program; 33 laboratories returned results that could be evaluated. Laboratories used HPLC ($n = 24$), LC-MS ($n = 6$) or bioassay ($n = 3$) to measure the azoles. Correct results were: fluconazole 79% ($n = 14$), itraconazole 78% ($n = 23$), hydroxyitraconazole 78% ($n = 18$), voriconazole 82% ($n = 57$), posaconazole 62% ($n = 26$). All results were correctly reported by 18 out of 33 laboratories (55%). A one-way ANOVA analysis yielded no statistically significant differences between the absolute inaccuracies related to the different azole antifungal drugs: $F(4,86) = 0.884$, $p = 0.477$. There was a non-significant trend for less accurate performance for the lowest concentration posaconazole vs. the higher concentration (54% vs. 69%; $p = 0.130$). For voriconazole there was no difference visible between high and low concentration. None of the laboratories reported lower limits of quantitation that

were above the spiked concentrations, indicating the suitability of these methods for use in clinical practice. Laboratories were informed about their performance to enable them to optimize their methods.

Conclusions

A quality control program for TDM of azole antifungals is a useful instrument to monitor and optimize analytical methods. The program will be extended to more laboratories and more antifungal drugs.

Keywords: proficiency testing – antifungal – quality control program – azole – EQA

Different melatonin rhythms and sleep-wake rhythms in patients on peritoneal dialysis, daytime hemodialysis and nocturnal hemodialysis

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Background

End-stage renal disease is associated with an increased prevalence of sleep disturbances. The circadian sleep-wake rhythm may be negatively affected in this patient group due to the pathology of end-stage renal disease and the dialysis process. The pineal hormone melatonin plays an important role in the synchronization of the circadian sleep-wake rhythm. The onset of the evening rise in endogenous melatonin is called the dim light melatonin onset and correlates with the increase in sleep propensity. Renal replacement therapy can be performed by means of hemodialysis and peritoneal dialysis. The latter can be performed overnight with an automated system (automatic peritoneal dialysis, APD). Little comparative data on sleep-wake rhythms in different dialysis groups exist. The aim of this study was to investigate sleep-wake parameters measured with the objective method of actigraphy and the subjective method of sleep questionnaires as well as melatonin rhythms in a group of APD, conventional daytime hemodialysis (CHD) and nocturnal hemodialysis (NHD) patients.

Methods

Patients with end-stage renal disease from our hospital were asked to participate in the study. CHD ($n = 20$), NHD ($n = 13$) and APD patients ($n = 6$) were included in the study. Melatonin in saliva was sampled at 5 time points (21:00-23:00-1:00-7:00-9:00). Furthermore actigraphy measurements and sleep questionnaires for 7 consecutive days were started the day following after melatonin sampling,

as nocturnal melatonin sampling can influence sleep parameters. All parameters were tested by Mann Whitney U test to find significant differences ($p < 0.05$).

Results

Although most sleep parameters were impaired in all 3 groups, actigraphy and sleep questionnaires revealed that CHD patients had less sleep efficiency, more sleep onset latency and more awake time at night compared to APD and NHD patients. Other parameters were not significantly different. The melatonin rhythm was best shown in NHD patients with a normal nocturnal surge. In the CHD and APD patients the normal melatonin rise was absent.

Conclusions

The study showed impaired sleep parameters in APD, NHD and CHD patients. CHD revealed the worse sleep. Melatonin rhythm was absent in APD and CHD patients and recovered in NHD patients. As APD is also performed during night time, the same effect on normalized melatonin was anticipated as was found in NHD. Although melatonin production is impaired in the same way, APD patients seem to have less sleep problems than CHD patients. Melatonin seems to play a subordinate role in the sleep-wake rhythm of PD patients.

Limited sampling strategies for mycophenolic acid in patients with autoimmune disease

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Background

Mycophenolate mofetil (MMF) is increasingly used for the treatment of autoimmune diseases (AID). In renal transplant recipients it has been demonstrated that adjustment of MMF dose according to the area under the plasma concentration vs. time curve (AUC) of mycophenolic acid (MPA), the active moiety of MMF, improves clinical outcome. The aim of this study was to develop a maximum a posteriori Bayesian estimator (MAP-BE) to estimate MPA AUC₀₋₁₂ in AID patients using a limited number of samples. The predictive performance of the MAP-BE was compared with a multilinear regression method.

Methods

Full MPA concentration vs. time curves (13 samples per curve) were available from 38 patients with AID (26 with antineutrophil cytoplasmic antibody-associated vasculitis; 12 with systemic lupus erythematosus) treated with mycophenolate mofetil (MMF). Nonlinear mixed-effect modeling was used to develop a population pharmacokinetic model. Patients were divided in an index and a validation dataset. The population pharmacokinetic model derived from the

index dataset was used to develop several Bayesian estimators. The Bayesian estimators were used to predict AUC₀₋₁₂ on basis of a limited number of blood samples. The bias and precision of these predictions were compared with those of limited sampling strategies developed with multilinear regression.

Results

A two-compartment model with a combination of short and long lag-time, followed by first order absorption, with first-order elimination was used to describe the data. The pharmacokinetic model accounted for the enterohepatic recirculation of MPA as well. Using 1 to 4 samples MPA AUC₀₋₁₂ was adequately estimated by the Bayesian method. Bias (−5.5%) was not significantly different from zero and precision was lower than 27%. The predictive performance of the multilinear regression method was comparable.

Conclusions

MAP Bayesian estimators were developed for the estimation of MPA AUC₀₋₁₂ in AID patients taking MMF. The predictive performance of the MAP Bayesian estimators was good and comparable to those of the multilinear regression method. Due to its flexibility with respect to sample times the MAP Bayesian method may be preferred over the multilinear regression method.

Keywords: mycophenolate mofetil – population pharmacokinetics – limited sampling strategy – autoimmune disease

Population pharmacokinetics of mycophenolic acid: a comparison between enteric-coated mycophenolate sodium and mycophenolate mofetil in renal transplant patients

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Background

Mycophenolic acid (MPA) is an immunosuppressive agent used in renal transplant recipients to prevent graft rejection. The two prodrugs of MPA, mycophenolate mofetil (MMF) and enteric-coated mycophenolate sodium (EC-MPS), exhibit similar efficacy and safety profiles. A therapeutic range for MPA AUC₀₋₁₂ of 30–60 mg·h/L is recommended to improve clinical outcome. In this study the pharmacokinetics of MPA were compared between renal transplant patients receiving either MMF or EC-MPS.

Methods

MPA concentration vs. time profiles were included from EC-MPS- (n = 208) and MMF-treated (n = 184) patients, 4 to 257 months after renal transplantation. Population pharmacokinetic analysis was performed using nonlinear mixed-effects modeling. A two-compartment model with first-order absorption and elimination was used to describe the data.

Results

No differences were detected in MPA clearance, intercompartmental clearance, central or peripheral volume of distribution. Respective values and inter-patient variability (IPV) were: 16 L/h (39%), 22 L/h (78%), 40 L (100%) and 518 L (494%). EC-MPS was absorbed more slowly than MMF with respective values of 3.0 h⁻¹ vs. 4.1 h⁻¹ (p < 0.001) (IPV 136%). A mixture model was used for the change-point parameter lag-time (t_{lag}) in order to describe IPV in this parameter adequately for EC-MPS. Following the morning dose of EC-MPS t_{lag} was 0.95, 1.9 and 4.8 h for 51%, 32% and 17% of the population (IPV 8%). The morning t_{lag} following EC-MPS was significantly different from both the t_{lag} of MMF [0.30 h, p < 0.001 (IPV 11%)] and the t_{lag} following the evening dose of EC-MPS [9.0 h, p < 0.001 (IPV 40%)]. Post-hoc analysis showed that t_{lag} was longer and more variable after EC-MPS administration [morning: median 1.95 h (range 0.95-5.5 h), evening: median 8.87 h (range 5.4-12.3 h)] compared to MMF administration [median 0.30 h (range 0.26-0.34 h), p < 0.001]. Following EC-MPS administration MPA predose levels were higher and more variable than following MMF administration, with respective values of 2.6 mg/L (0.4-24.4 mg/L) and 1.6 mg/L (0.2-7.6 mg/L). The correlation between predose levels and AUC was lower in EC-MPS treated patients ($r^2 = 0.02$) than in MMF treated patients ($r^2 = 0.48$).

Conclusions

Absorption of MPA is delayed and varies more in EC-MPS-treated patients. The increased variability in the absorption profile causes a wider range in predose concentrations and a lower correlation with exposure. This may have major consequences for MPA monitoring.

Keywords: pharmacokinetics – mycophenolate mofetil – enteric-coated mycophenolate sodium – absorption profile

Pharmacokinetics and toxicity of linezolid in MDR-TB patients

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Background

For the treatment of multi- and extensively drug resistant tuberculosis (MDR-TB and XDR-TB) there is a dire need for new potent drugs. Linezolid is a promising compound but its use is limited by toxicity

with prolonged administration. From a preliminary evaluation, it appeared that 3/12 patients developed severe toxicity which led to discontinuation of therapy [1]. A case series of 3 patients being treated with linezolid showed that a 50% dose reduction of linezolid led to reduced toxicity. Although the authors suggested that efficacy was maintained they failed to produce evidence for this claim [2]. As patients with MDR-TB are typically treated with combinations of drugs, and as response to treatment is a multifactorially determined event, only pharmacokinetic/pharmacodynamic data help to decide whether single agents in a drug combination contribute to total effectiveness. We investigated whether linezolid administered with reduced dosage results in drug concentrations in excess of MIC ($AUC_{0-24h}/MIC > 100$ [2]), to maintain efficacy with reduced toxicity. This study (n = 8) is designed as pharmacokinetic study of 300 mg and 600 mg in MDR-TB patients. Primary endpoint is AUC_{0-24h}/MIC ratio. Secondary endpoint is side effects of linezolid.

Methods

8 patients (aged >18 years) with MDR-TB (or XDR-TB) received linezolid as part of their treatment. They received 300 mg of linezolid bid, 3 days later followed by 600 mg bid. Serum samples taken at predefined intervals (t = 0, 1, 2, 4, 8, 12 h post dosage) were processed by a validated LC-MS/MS procedure [3], and 12-h plasma-time concentration curves for linezolid at steady state of each dosage were modelled using MWPharm software (Mediware, The Netherlands). Break-point data for drug sensitivity were obtained from the RIVM. Monitoring for side effects (affecting blood, nervous and GI system) was performed during treatment with linezolid.

Results

The median AUC_{0-12h} was 58.5 mg·h/L (range: 27.8-83.4 mg·h/L) with 300 mg, and 137.2 mg·h/L (range 86.6-181.0 mg·h/L) with 600 mg dosage. The AUC_{0-24h}/MIC ratios were 450 (range: 122-757) with 300 mg, and 1055 (range: 346-2098) with 600 mg dosage. All 8 patients achieved adequate drug concentrations with 300 mg bid. No serious adverse events were observed during treatment.

Conclusions

Assuming that AUC_{0-24h}/MIC ratio is a reliable model to predict efficacy, dose reduction of linezolid to 300 mg was adequate. Larger numbers of patients should be studied to confirm our findings, along with observational data to confirm the efficacy of this approach for MDR-TB or XDR-TB treatment.

This study is financially supported by Stichting Beatrixoord Noord Nederland.

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Keywords: linezolid – MDR-TB – therapeutic drug monitoring

Improved analgesia after realization of pain management program in ICU patients after cardiac surgery

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Background

Adequate pain management in the intensive care unit (ICU) is not yet common practice. Pain in ICU patients is a frequently experienced problem and attributes to significant morbidity. Little is known of the effects of pain training and pain management systems on pain in ICU patients after cardiac surgery. Aim of the study was to evaluate the effect of a pain training program and systematic measurement of pain scores on actual pain levels and the use of analgesics.

Methods

In a two phase prospective controlled study, 190 consecutive ICU patients after cardiac surgery through sternotomy were included. In both the control (n = 60) and intervention phase (n = 130) pain was indicated by the patient himself when possible (54% of total pain scores), or scored by the attending nurses (46% of total pain scores). During the control phase, pain levels were asked by researchers twice a day on weekdays. During the intervention phase, nurses were explained the benefits of adequate analgesia and trained in assessing pain. Meanwhile, a patient data management system was implemented obliging nurses to register pain levels at least three times a day (7 days a week). The numerical rating scale (NRS) was used for pain assessment. A NRS ≥ 4 was considered unacceptable. A generalized linear mixed effects model was used for analysing repeated measurements data.

Results

In the intervention phase unacceptable pain (NRS ≥ 4) occurred 2.54 times less often than in the control group (CI_{95%} = 1.22-5.65; p = 0.01). The percentage of patients who experienced at least one unacceptable pain event (NRS ≥ 4) was unchanged (46% vs. 49%, p = 0.74). In the intervention group a positive relation was found between the morphine dose administered and the NRS (p = 0.01). Patients in the intervention group received significantly more morphine compared with the control group (29.3 mg vs. 22.6 mg a day, p < 0.01) without an increase of adverse events.

Conclusions

The pain training program and the systematic assessments of pain successfully reduced the occurrence of unacceptable pain. Nonethe-

less, further improvement of pain management focussed on the prevention of pain is needed as 46% of the patients in the intervention group still experienced at least one unacceptable pain event during their stay.

Keywords: pain scores – pain training program – ICU – critically ill patients

Effect of self-measurement of blood pressure on adherence to treatment in patients with mild to moderate hypertension

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Background

Poor adherence to treatment is one of the major problems in the treatment of hypertension. Self blood pressure measurement (SBPM) may help patients to improve their adherence to treatment.

Methods

In this prospective, randomized controlled study coordinated by a university hospital a total of 228 mild-to-moderate hypertensive patients were randomized to either a group that performed self-measurements at home in addition to office blood pressure measurements (OPBM): the self pressure group (n = 114) or a group that only underwent OBPM: the office pressure group (n = 114). Patients were followed for one year in which treatment was adjusted, if necessary, at each visit to the physician's office according to the achieved blood pressure. Adherence to treatment was assessed by means of medication event monitoring system TrackCaps.

Results

Defined as the percentage of days with correct dosing, median adherence was slightly greater in patients from the self pressure group than in those from the office pressure group (92.3% vs. 90.9%; p = 0.043). Although identical among both groups, in the week directly after each visit to the physician's office adherence (71.4%; IQR 71-79%) was significantly lower (p < 0.001) than at the last seven days prior to each visit (100%; IQR 90-100%). On the remaining days between the visits patients from the self pressure group displayed a modestly better adherence than patients from the

office pressure group (97.6% vs. 97.0%; $p = 0.024$).

Conclusions

Although SBPM as an adjunct to OBPM led to somewhat better adherence to treatment in this study, the difference was only small and not clinically significant. The time relative to a visit to the doctor seems to be a more important predictor of adherence.

Keywords: adherence – compliance – self-measurement – SBPM – blood pressure – hypertension

Immune reconstitution after haematopoietic stem cell transplantation in children using different stem cell sources

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Background

Haematopoietic stem cell transplantation (HSCT) is complicated by severe infectious complications during the neutropenic period. We investigated the early immune reconstitution after bone marrow derived HSCT and cord blood derived HSCT in children.

Methods

All children transplanted between 2005-2007 were prospectively included in this study. The amount of T and B lymphocytes was determined by direct whole blood fluorescence-activated cell sorting (FACS) every two weeks. In this study we analyzed the maximum CD3+, CD8+ T-cell and CD19+ B-cell numbers during the first 100 days after HSCT.

Results

78 patients were included, median age 5.9 years (0.11-18.1). 52 recipients received bone marrow while 26 patients received cord blood derived stem cells. The number of CD3+ T-cells was significantly higher in bone marrow recipients compared to cord blood; median 401 vs. 193 cells/ μ l, $p = 0.003$. Median time to maximum CD3+ T-cell number within 100 days after HSCT was shorter in bone marrow recipients compared to cord blood; day 60 vs. day 73, $p = 0.05$. The median amount and time to reach the maximum CD3+ CD8+ T-cell numbers after HSCT were significantly increased in bone marrow compared to cord blood recipients (median 257 cells/ μ l after 31 days vs. 40 cells/ μ l after 76 days, $p < 0.001$ and $p = 0.03$). CD4+ T-cell numbers did not significantly differ among these two groups. In contrast, the number of CD19+ B-cells was significantly higher in

cord blood recipients (median 728 vs. 202 cells/ μ l in bone marrow, $p = 0.018$). Median time to maximum CD19+ B-cell number did not significantly differ among the two groups.

Conclusions

CD3+ and mainly the CD3+ CD8+ T-cell reconstitution occurs earlier in patients after bone marrow derived HSCT compared to cord blood derived HSCT, while no difference was found in reconstitution of CD3+ CD4+ cells between the two groups. In contrast, B-cell reconstitution was significantly higher in patients after cord blood transplantation, compared to bone marrow transplantation. The delay in T-cell reconstitution after cord blood transplantation is associated with severe infections. A higher B-cell reconstitution might reflect an increased proliferative activity of cord blood derived stem cells.

Future studies

The supposed two most important covariables that might influence stem cell source-related immunoreconstitution after HSCT: the amount of T-cell numbers in the graft (less in the cord blood grafts), and differences in pharmacokinetic of anti-thymocyte globulin (ATG). Therefore, in future studies we will perform an analysis of the variability in pharmacokinetics of ATG between patients after HSCT in collaboration with the LUMC. Individualisation of the ATG treatment may prevent a prolonged immunosuppressive period and associated serious infectious complications after HSCT in both stem cell sources.

Keywords: immune reconstitution – haematopoietic stem cell transplantation – anti-thymocyte globulin

Pharmacogenetic determinants for discontinuation of non-ergoline dopamine agonists in Parkinson's disease

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Background

Long-term treatment of Parkinson's disease (PD) with levodopa often leads to motor complications such as wearing-off and dyskinesias. Therefore, dopaminergic therapy with dopamine agonists (DA) has gained popularity as initial therapy in younger patients and as add-on in older individuals. It has been demonstrated that within three years non-ergoline DA ropinirole and

pramipexole are discontinued in clinical practice in 51% and 60% respectively. Determinants for discontinuation of non-ergoline DA therapy are largely unknown. Therefore, we aimed to identify genetic determinants for discontinuation of non-ergoline DA treatment in patients with PD. Polymorphisms in DRD2 and DRD3 could be important determinants, because the non-ergoline DA have high binding characteristics for the DRD2 and a preferential affinity to the DRD3 subgroup.

Methods

The setting of this cohort study was the neurology department of Medisch Spectrum Twente in Enschede. Patients included were first time users of the non-ergoline DA ropinirole or pramipexole diagnosed with PD before 2005. Treatment discontinuation was defined as a gap of 180 days or more between two refills of the DA. Genetic determinants for non-ergoline DA treatment discontinuation were the following polymorphisms: DRD2 141C Ins/Del, DRD2 (CA)_n STR, DRD2 TaqIA, DRD3 MscI SNP and DRD3 MspI SNP. Cox proportional hazard analysis was used to estimate the hazard ratios (HR) for discontinuation of non-ergoline DA treatment.

Results

The population consisted of 38 patients. The mean age of the patients was 63.4 years with a mean duration of PD of 52.6 months. The proportion of patients using levodopa at the index date was 50%. The allele frequencies were in accordance with those reported in the literature. Absence of a 15x DRD2 CA repeat allele was significantly related to a decreased discontinuation of DA treatment (HR: 0.23; CI95%: 0.07-0.81). The DRD3 MspI G allele was not significantly related to a two times higher risk of discontinuation (CI95%: 0.61-7.17). Furthermore, there was a G-allele dose effect on discontinuation (A/A: ref; A/G: HR 1.56; CI95% 0.42-5.77; G/G: HR 3.50; CI95% 0.91-13.4).

Conclusions

This study identified the 15x DRD2 CA repeat allele as a genetic determinant for discontinuation of DA treatment in patients with PD. The DRD3 MspI polymorphism needs further study, because of existence of an allele dose effect. The consequences of these polymorphisms on the DRD2 and DRD3 protein function are still not unravelled. More research is needed to replicate these findings and to elucidate the consequences of these polymorphisms.

Keywords: pharmacogenetics – Parkinson's disease – discontinuation – dopamine

Pharmacokinetics of rifampicin, pyrazinamide, ethambutol and moxifloxacin in patients from tuberculosis referral centers in The Netherlands

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Background

The treatment of tuberculosis is complicated by problems of suboptimal response, emergence of resistance and adverse effects. Plasma drug concentrations may be an important determinant of these undesirable effects. Exposure to tuberculosis drugs may be even more critical in complex and vulnerable patients who are referred to tertiary tuberculosis treatment centers. The objective of this study was to describe the pharmacokinetics (PK) of tuberculosis drugs in patients admitted to Dutch tuberculosis referral centers and to evaluate possible determinants of PK parameters in this population.

Methods

Adult patients with pulmonary and extrapulmonary tuberculosis who were admitted to the two Dutch referral centers for tuberculosis treatment were included. Tuberculosis drugs were administered once-daily, were dosed according to American Thoracic Society (ATS) guidelines and were ingested together under direct observation. After at least two weeks of tuberculosis treatment, a full 24 h PK curve was recorded during the intensive phase of tuberculosis treatment after intake of drugs on an empty stomach. Plasma drug concentrations were analyzed using validated HPLC methods. PK parameters were assessed with non-compartmental methods. Descriptive statistics were calculated and PK parameters between subgroups were compared using the independent samples t-test on log-transformed data or Wilcoxon rank-sum test.

Results

41 patients were included in the study, all with adequate liver and kidney function and without co-administered drugs that interacted with tuberculosis drugs. A large inter-individual variation was shown in PK of rifampicin (range in area under the curve, AUC_{24h}: 12-119 mg·l⁻¹·h). 30% of the patients on rifampicin did not reach the reference peak plasma concentration of 8 mg/L for this drug. Co-administration of pyrazinamide was associated with reduced exposure to rifampicin (mean AUC_{24h} 40 vs. 58 mg·l⁻¹·h, p = 0.05). Use of ethambutol was associated with increased exposure to pyrazinamide (mean AUC_{24h} 429 vs. 327 mg·l⁻¹·h, p < 0.05) and smoking with reduced exposure to ethambutol (19 vs. 31 mg·l⁻¹·h, p = 0.04). Previously demonstrated reducing effects of rifampicin on the exposure to moxifloxacin were confirmed. The C_{2h} concentration of rifampicin, pyrazinamide and moxifloxacin, but not ethambutol, correlated with AUC_{24h} and C_{max}. Results for isoniazid have not been evaluated yet.

Conclusions

This study showed large variability in exposure to the key tuberculosis drug rifampicin and several possible determinants for PK variability. Limited sampling allows detection of patients with low exposures. More pharmacodynamic studies are warranted to be able to judge the clinical significance of PK variability for tuberculosis drugs.

Keywords: tuberculosis – pharmacokinetics

Lack of association between rs4606 SNP of the RGS2 gene and antipsychotic-induced parkinsonism, tremor, bradykinesia, and rigidity in Afro-caribbean inpatients

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Background

Recent literature suggests a clinically and statistically significant association between antipsychotic-induced parkinsonism (AIP) and rs4606 SNP of the RGS2 (Regulator of G-protein Signaling-2) gene in Jewish [Pharmacogenet Genom 2007;17:519-28], Caucasians, and African-American subjects [Pharmacogenom J, doi:10.1038/tpj.2008.6]. These samples include subjects that received atypical antipsychotics; 76% of the subjects in the African-American/Caucasian sample and 41% in the Jewish sample. As opposed to typical antipsychotics, atypical antipsychotics have strong HTR_{2A} binding affinities. Since RGS2 is involved in the intracellular signalling mediated by serotonin_{2A} receptor (HTR_{2A}), but not in the signalling mediated by dopamine D₂ receptors (DRD2), it is pharmacologically plausible that the possible effects of rs4606 are expressed only in those patients subjected to strong HTR_{2A} antagonism. We endeavoured to test this hypothesis by examining the association between rs4606 and AIP, rigidity, rest-tremor, and bradykinesia in 112 African-Caribbean inpatients, treated predominantly with typical antipsychotics.

Methods

Genotyping was performed according to a standard TaqMan protocol. AIP was measured with the Unified Parkinson Disease Rating Scale and data were dichotomized in presence/absence of AIP, rigidity, bradykinesia and tremor at rest. We applied Chi-square or Fisher Exact tests for the association analyses (genotype-wise and G-allele carriership-wise). We also conducted logistic regression

analyses for several models including age, gender, antipsychotic and anticholinergic dose, and carriership of rs4606 and two other putatively functional SNPs in DRD2 and HTR2C genes (-141Clns/Del and Cys23Ser, respectively).

Results

The genotype distribution (49C/C, 50C/G, and 13G/G) was consistent with Hardy-Weinberg equilibrium. There was no evidence for any significant association (even after correction for age, pharmacotherapy, and allele-carriership of -141Clns/Del and Cys23Ser polymorphisms).

Conclusions

The present study does not support an association between rs4606 and AIP or its subsymptoms. Although differences in LD patterns can not be excluded, a possible explanation may lie in the type of the antipsychotics utilized. Future studies in larger samples of patients receiving uniform antipsychotic and anticholinergic treatment are however warranted to support our hypothesis.

Keywords: pharmacogenetics – parkinsonism – antipsychotics – RGS2

Tardive dyskinesia and polymorphism of dopamine D₃, serotonin 2A and 2C receptors in Russian psychiatric inpatients

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Background

Tardive dyskinesia (TD) is a potentially irreversible motor side-effect occurring in about 30% of patients chronically exposed to neuroleptics. Genetic polymorphisms of dopamine D₃ (DRD₃), serotonin_{2A} (HTR_{2A}) and 2_C (HTR_{2C}) receptors have been examined in relation with TD in various populations, but not in Russians. The present study investigates the association between orofaciolingual (TDof) and limb-truncal dyskinesias (TDlt) and Ser9Gly (DRD₃), -1438G>A (HTR_{2A}), and Cys23Ser (HTR_{2C}) polymorphisms in Russian psychiatric patients from Tomsk.

Methods

DNA extraction and genotyping were conducted according to standard protocols. Subjects were characterized either as carriers or

Genetic combinations	TPM				LNR		LR	
	part 1 OR	P	part 2 β	P	β	P	OR	P
TDof								
9Gly-allele	2.08	0.084			1.18	0.143		
-1438A-allele	2.42	0.037			1.24	0.065		
9Gly-allele	1.27	0.635	1.10	0.499			1.85	0.161
23Ser-allele	0.19	0.034	1.36	0.366				
-1438A-allele	1.82	0.156			1.21	0.103		
23Ser-allele								
TDIt								
9Gly-allele	2.58	0.007	1.38	0.019	1.41	0.001		
-1438A-allele								
9Gly-allele	3.55	0.001	1.33	0.035	1.40	0.001		
23Ser-allele	1.76	0.399	0.72	0.053	0.75	0.031	0.166	0.097
-1438A-allele								
23Ser-allele			0.69	0.034	0.77	0.061	0.166	0.097

non-carriers of an allele. TDof and TDIt were assessed by the use of AIMS items 1-4 and 5-7, respectively. Two-part model (TPM), logistic (LR) and log-normal (LNR) regression analyses were applied to assess the effects of different variables (e.g., allele-carriership status, age, gender, and medication use) on TDof/TDIt. Model construction (for combinations of two polymorphisms) was conducted in a step-wise manner by means of Akaike's Information Criterion (AIC).

Results

In total 146 Russian Caucasians were included (95% with clinically established schizophrenia). The results of TPM, LNR, and LR analyses are presented in the Table (cells without entries indicate that the alleles in question have not been identified by AIC as explanatory for the model. P-values ≤ 0.05 are printed in *italics*). As shown in the Table, TDIt, but not TDof, exhibited an association with Ser9Gly and Cys23Ser polymorphisms (with 9Gly and 23Ser alleles exhibiting opposite effects). In all of the analyses conducted, the -1438G>A polymorphism is not associated with TDof/DIt. Furthermore, none of the polymorphisms studied could predict clinically important TDof or TDIt.

Conclusions

This is the first report on TD pharmacogenetics in Russians. Our data suggest that Ser9Gly and Cys23Ser polymorphisms are significantly associated with TDIt, but not with TDof. However, since the magnitude of the effect is rather limited, the clinical usefulness is modest. Nevertheless, our results extend and support the available pharmacogenetic data.

Keywords: dyskinesia – pharmacogenetics – antipsychotics – DRD₃ – HTR_{2A} – HTR_{2C}

Missense polymorphisms in three oxidative-stress enzymes (GSTP1, SOD2, and GPX1) and dyskinesias in Russian psychiatric inpatients from Siberia

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Background

Neuronal degeneration due to oxidative stress (OS) has been proposed as a mechanism for tardive dyskinesia (TD) pathogenesis. Cellular defense mechanisms against OS involve detoxification enzymes (e.g., glutathione peroxidase 1, GPX1; superoxide dismutase 2, SOD2; and glutathione S-transferase P1, GSTP1). Several studies have examined the pharmacogenetics of TD and oxidative-stress enzymes in different ethnic groups, but not in Russians. Here we examine the association between orofaciolingual (TDof) and limb-truncal dyskinesias (TDIt) and polymorphisms of GSTP1 (Ile105Val), SOD2 (Ala9Val), and GPX1 (Pro197Leu) genes in Russian Caucasians from Tomsk, Siberia.

Methods

In total 146 inpatients were included. TDof and TDIt were rated

with AIMS instrument items 1-4 and 5-7, respectively. Two-part model (TPM) analyses, logistic (LR) and log-normal (LNR) regressions were applied to assess the effects of different variables (e.g., genotype, age, gender, and medication use). In all of these three approaches, model construction was conducted in a stepwise manner (by means of Akaike's Information Criterion).

Results

TDof: although LR analysis does not support the association, TPM part 1 and LNR analyses suggest that Ile105Val polymorphism is significantly associated with a lower risk and severity of TDof; heterozygotes (OR = 0.41 and β = 0.78) and homozygotes (OR = 0.21 and β = 0.65). Furthermore, heterozygosity (9Ala/9Val), but not homozygosity (9Val/9Val), for the 9Val-allele (Ala9Val) was associated with significantly higher TDof risk and severity as shown by LR (OR = 4.38, p = 0.014) and LNR (β = 1.30, p = 0.064) analyses, respectively, compared to the 9Ala/9Ala genotype. In contrast to Ile105Val and Ala9Val polymorphisms, GPX1 Pro197Leu polymorphism was not selected as an explanatory variable in any of the analyses conducted, even after correction for the other relevant variables.

TDIt: TPM part 2 and LNR analyses suggest that homozygosity, but not heterozygosity, for the 105Val allele of the GSTP1 polymorphism may be associated with a lower severity of TDIt. However, Ala9Val and Pro197Leu polymorphisms did not exhibit a significant association with any measure of TDIt.

Conclusions

Pro197Leu polymorphism (GPX1) is not associated with TDof/TDIt. However, the 105Val-allele of Ile105Val (GSTP1) is probably associated with a lower risk and a severity of TDof and TDIt. Furthermore, we find evidence for an association between Ala9Val polymorphism (SOD2) and TDof, but not TDIt. However, since the magnitude of the effect is rather limited, the clinical usefulness of these associations is modest. Future studies in larger samples of comparable ethnicity are warranted to support our findings.

Keywords: dyskinesia – pharmacogenetics – antipsychotics – GSTP1 – SOD2 – GPX1

Generation of virus-specific T cell lines for treatment of viral infection after allogeneic stem cell transplantation

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Background

Infection with cytomegalovirus (CMV) or adenovirus (ADV) can cause serious morbidity and mortality during the prolonged period of immune deficiency following allogeneic stem cell transplantation

(alloSCT). Viral replication can occur in the absence of adequate numbers of virus-specific T cells, which are eradicated or impaired by the conditioning regimen and immune suppression. Progression to disseminated viral disease is associated with a high mortality, despite treatment with antiviral agents. Reconstitution of the virus-specific T cell repertoire directed against viral proteins in the first year after transplantation has been demonstrated to confer sustained protection from CMV and ADV disease. Administration of donor T cells may be used to improve antiviral immune reconstitution, but can induce lethal graft-vs.-host disease (GvHD) due to allogeneic recognition of healthy patient tissue. Adoptive transfer of donor-derived T cell lines with high specificity for viral epitopes may be an effective and durable treatment for viral disease after alloSCT, with very limited risk of GvHD. We therefore aimed to develop a method for the generation of combined CD8+ and CD4+ T cell lines, comprising cytotoxic and helper activity, with high and well defined specificity for the immunodominant CMV pp65 and IE1 or ADV hexon proteins.

Results

Pools of overlapping synthetic peptides spanning the entire CMV pp65, CMV IE1, or ADV hexon protein were used to activate virus-specific T cell populations in donor peripheral blood samples. By flowcytometric analysis, we showed the presence of high frequencies of CMV pp65-specific and IE1-specific T cells in healthy CMV seropositive donors. ADV hexon-specific T cells were only detected at very low frequencies in most healthy individuals. The phenotype of ADV hexon-specific T cells corresponded to an early memory phenotype, while CMV-specific T cells showed a more differentiated memory phenotype. Following stimulation with viral peptides, magnetic enrichment for cytokine-producing T cells resulted in efficient isolation of CD8+ and CD4+ T cells recognizing both known and novel CMV or ADV epitopes. Following a short culture period, the T cell lines contained >70% CMV-specific or ADV-specific CD8+ and CD4+ T cells. Starting with only 25·10⁶ donor peripheral blood mononuclear cells, this strategy yielded T cell lines containing 0.9-14.0·10⁶ virus-specific T cells in 15 days.

Conclusions

We conclude that we developed a GMP-grade method for the fast generation of highly CMV-specific or ADV-specific T cell lines from all healthy donors, for the treatment of CMV or ADV infection after alloSCT with very limited risk of GvHD.

Keywords: cytomegalovirus – adenovirus – allogeneic stem cell transplantation – adoptive immunotherapy

Alteration of individual 6-thioguanosine phosphate metabolite levels by co-administration of 5-aminosalicylic acid: prospective pharmacokinetics in IBD patients under steady-state azathioprine therapy

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Background

5-Aminosalicylates (5-ASA) interfere in a dose-dependent manner with thiopurines (6-MP/AZA) metabolism, increasing concentrations of 6TGN without changing MMP levels. In particular one of these metabolites, TGN-3 triphosphate, is associated with therapeutic efficacy. We performed a prospective pharmacokinetic evaluation of thiopurine metabolites in IBD patients during steady-state AZA therapy under two different 5-ASA dosages.

Methods

IBD patients on steady-state AZA monotherapy for at least 8 weeks with normal routine laboratory control values were included in our study. Study design comprised four 4 week study periods in which two different dosages of 5-ASA were used (2 and 4 g). Laboratory parameters, adverse events, 6-TG monophosphate, diphosphate and triphosphate levels (6-TGMP/6-TGDP/6-TGTP), 6-MMP levels, 5-ASA and N-acetyl-5-aminosalicylic acid (N-5-ASA) levels were determined at each visit. Differences in metabolite concentrations were evaluated using the Wilcoxon matched-pairs signed-ranks test.

Results

17 IBD patients were included (CD = 11, UC = 5, IC = 1, 6 females and mean age 42 years). Mean AZA dose at time of inclusion was 150 mg (= 2.0 mg/kg). Median baseline values of 6-TGDP, 6-TGTP and 6-MMP before initiation of 5-ASA were 52, 319 and 1676 pmol/8·10⁸ RBC respectively (ranges 13–192, 83–583 and 0–9837 pmol/8·10⁸ RBC). As expected, no 5-ASA or N-5-ASA was detected in the serum of any patient. Significant increase in 6-TGDP, 6-TGTP and total 6TGN levels was only observed after the first period of ASA co-administration (i.e. 2 g ASA daily). Median 6-TGTP levels rose with 28% to 482 pmol/8·10⁸ RBC at t = 2 after the first 5-ASA dosage regime, an absolute increase of 163 pmol/8·10⁸ RBC (p < 0.0002). Levels of 5-ASA and N-5-ASA were 175 and 1260 ng/ml at t = 2, respectively. After the second scheme of 5-ASA (t = 3), 6-TGTP levels reached median values of 483 pmol/8·10⁸ RBC and did not differ from median values at t = 2 (p = 0.669). The 5-ASA and N-5-ASA levels at t = 3 were 1295 and 3049 ng/ml, respectively. For 6-MMP levels, a significant reduction in median values from 1447 to 880 pmol/8·10⁸ RBC was seen after 5-ASA dose increased to 4 g/day at t = 3 (p = 0.0448). The ratio of individual

6TGN-metabolites did not differ significantly between all study periods; 6TGMP-levels were undetectable at each visit.

Conclusions

Introduction of 5-ASA during steady-state thiopurine therapy induces an increase of 6-TGDP, 6-TGTP and total 6TGN levels after 2 and 4 g 5-ASA daily and a reduction in 6-MMP levels during use of 4 g 5-ASA.

Keywords: azathioprine – 6-mercaptopurine – 5-aminosalicylates – inflammatory bowel disease – 6-thioguaninenucleotides – 6-methylmercaptopurineribonucleotides – drug interaction – clinical pharmacology

Improved efficiency and sustained accuracy in prescribing glucose intake using a Computerized Physician Order Entry system in the Neonatal Intensive Care Unit

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Background

Glucose control is extremely important in premature neonates. Prescribing glucose requires complex calculations because glucose is present in (par)enteral nutrition and in most drug vehicles. Computer assisted calculating systems (CPOE) may prevent errors in calculated glucose intake. Data on the effects of such systems in Neonatal Intensive Care Units (NICUs) are rare. We studied the impact of CPOE as a tool for glucose prescribing in the NICU focusing on safety and time efficiency.

Methods

The study was set up as a retrospective cohort study. CPOE (computer assisted calculating and electronic prescribing) was introduced in the NICU during April 2004. From the Nationwide Neonatal Registry and hospital information system all hypo- and hyperglycaemic episodes (glucose <2.5 mmol/L and >10 mmol/L, respectively) were selected from infants at risk for glucose imbalance [i.e. prematurity, SGA (BW<P2.5), maternal diabetes, or macrosomy] hospitalized during 2001–2007 at the NICU of the University Medical Center Utrecht. Results were expressed as number of hypo- or hyperglycaemic episodes per patient hospital days as well as number of episodes per glucose measurement for 3-months periods, 3 years before and 3 years after CPOE implementation. To assess the time needed to calculate glucose intake with and without use of CPOE, a simulation study was performed among a randomly selected group of physicians (neonatologists, fellows, residents and physician

assistants) using 3 different clinical scenarios.

Results

Before and after CPOE implementation, 3.1 hypo- or hyperglycaemic episodes per 100 patient hospital days were observed (CI95%: -0.037-0.050). In addition, no significant difference was found in number of episodes per glucose measurement before (0.016) and after (0.017) implementation (CI95%: -0.0026-0.0037). A significant time reduction of 5 minutes per prescription was noted in calculating glucose intake in the scenarios using CPOE.

Conclusions

Safety and accuracy were preserved with increased efficiency using CPOE for calculation of glucose intake.

Keywords: glucose intake – CPOE – NICU

¹³C-urea is a suitable nonradioactive marker substance for assessment of *in vivo* behaviour of oral colon-targeted dosage forms

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Background

There is a need for more specific oral colon-targeted dosage forms in Crohn's disease, colitis ulcerosa and colon cancer. In this study we report on the investigation of the suitability of ¹³C-urea as a marker substance for the assessment of *in vivo* behaviour of oral colon-targeted dosage forms. It was hypothesized that release in the colon (urease-rich segment) of ¹³C-urea from oral colon-targeted capsules would lead to fermentation of ¹³C-urea by bacterial urease into ¹³CO₂. Subsequent absorption in the blood circulation and distribution would lead to detectable ¹³C (as ¹³CO₂) in breath. If however release of ¹³C-urea occurs in the small intestine (urease-poor segment) detectable ¹³C (as ¹³C-urea) in blood was expected and no ¹³C (as ¹³CO₂) in breath. The differential kinetics of ¹³C-urea in relation to its gastrointestinal tract (GIT) segment of release could potentially describe both release kinetics as well as indicate the GIT segment of release.

Methods

The *in vivo* study consisted of three experiments, i.e. administration of uncoated ¹³C-urea 100 mg capsule, coated ¹³C-urea 100 mg capsule and coated ¹³C-sodium bicarbonate 100 mg capsule. In each experiment the same four healthy volunteers participated.

Results

It is observed that the coated capsule is able to deliver the tracer in more distal segments of the GIT compared to the uncoated capsule. This is expressed both by the t_{max} of both capsules (mean difference: 284 min, CI95%: 203-364, $p = 0.002$) and the lag-time of the coated capsule (mean: 224 min, CV: 11.5%). The lag-times as determined for the appearance of ¹³C in breath or plasma after intake of a coated capsule containing ¹³C-urea show little difference. This points to the fact that fermentation and absorption occur at the same time. The results show that the kinetic model is internally valid. The availability of ¹³C in breath as ¹³CO₂ ($F_{fermented}$) shows a range of 38-92%. The availability of ¹³C as ¹³C-urea in the volume of distribution ($F_{not-fermented}$) shows a range of 4-68%. The total recovery of ¹³C ($F_{fermented} + F_{not-fermented}$) averages 99% which indicates complete recovery of administered ¹³C via breath and blood. $F_{fermented}$ and $F_{not-fermented}$ show a high correlation ($R^2 = 0.8897$).

Conclusions

¹³C-urea is a safe marker substance to evaluate both the release kinetics of a colon-targeted oral dosage forms as well as to indicate the GI-segment of release.

Keywords: colon delivery – colon targeting – stable isotope – ¹³C-urea – fermentation – *in vivo* behaviour – bioavailability – kinetics