Second-line anticonvulsive treatment in newborns with perinatal asphyxia during therapeutic hypothermia after phenobarbital – midazolam or lidocaine?

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Background
Therapeutic hypothermia has been introduced on neonatal intensive care units for neuroprotection in newborns with perinatal asphyxia. Currently, phenobarbital, midazolam and lidocaine are the drugs of first, second and third choice, respectively, for the treatment of seizures. This order is predominantly based on clinical experience and (limited) historical data under normothermia rather than on an evaluation of clinical efficacy under hypothermia. Because phenobarbital is dosed as short loading infusions and does not require additional monitoring such as blood pressure (midazolam) or electrocardiography (lidocaine), phenobarbital is a suitable drug for first-line treatment of patients in both academic and peripheral neonatal wards. Our aim was to study the efficacy and safety of anticonvulsant treatment under hypothermia and to propose a second-line treatment option.

Methods
Data were obtained from two Dutch level III NICUs (Utrecht and Zwolle) in the SHIVER study. Term born newborns with criteria of perinatal asphyxia and encephalopathy were included. Therapeutic hypothermia (33.5°C) was started within six hours after birth and was maintained for 72 hours. Neonatal seizures were treated according to the Dutch protocol, with a reduced dose for lidocaine. Responsiveness was defined as a reduction of electrographic seizure burden of >80% and no additional anticonvulsant drug was required.

Results
Seizure responsiveness under hypothermia was 65% for phenobarbital (n = 20/31) after single or repetitive loading doses. Seizure responsiveness for continuous midazolam (second line add-on) was 23% (n = 5/22) and 91% (n = 20/22) for continuous lidocaine (third line add-on). Comparing safety profiles of midazolam (hypotension) and lidocaine (cardiac arrhythmias), under midazolam the average mean arterial pressure (MAP) decrease was 6.5 mmHg and 10 mmHg from baseline, three and six hours after start of the infusion, respectively, and inotropics were required. Under lidocaine no cardiac arrhythmias were observed.

Conclusions
Phenobarbital has a relatively high clinical efficacy under hypothermia after repetitive doses. The additive anticonvulsant value of midazolam is limited compared to lidocaine. Both phenobarbital and midazolam exert their effect by stimulation of the GABA receptor. As a result of this common pathway, add-on therapy with midazolam would not result in markedly increased seizure responsiveness. The mechanism of lidocaine is GABA-independent. No cardiac arrhythmias were observed under lidocaine, whereas significant hypotension requiring inotropic support was observed under midazolam. Based on efficacy and safety numbers and on molecular pharmacology, lidocaine could be more suitable as a second-line drug than midazolam.

Keywords: hypothermia – neonates – seizures – pharmacokinetics – midazolam – lidocaine

The effect of pharmacy-based medication reconciliation on unintentional medication discrepancies in acute hospital admissions of elderly patients: a multicenter study

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Background
Evidence clearly shows the importance of pharmacy-based medication reconciliation in the emergency department. Yet, several barriers to implement patient safety interventions still exist. To address these continuing concerns about patient safety around the world, the High 5s programme was launched by the World
Health Organization (WHO) in 2006. One part of this program consisted of the implementation and evaluation of the standard operating procedure (SOP) for medication reconciliation. In accordance with the SOP the main aim of this Dutch study was to determine the effect of pharmacy-based medication reconciliation in acutely admitted patients aged 65 years and older on the frequency of medication discrepancies in participating hospitals. Secondary aims were to determine the effect on medication discrepancy types and the percentage of unintentional medication discrepancies on several time points after implementation of the intervention.

Methods
A multicenter intervention study with a pre-post design was performed in twelve Dutch hospitals. During the pre-intervention measurement period nurses and physicians were responsible for medication history taking. The SOP intervention consisted of the best possible medication history (BPMH), based on combining information on the community pharmacy record, information provided by a structured patient interview about his medication use and medication boxes to resolve discrepancies. In nine hospitals only pharmacy technicians took care of obtaining the BPMH and in three hospitals either physicians or pharmacy technicians (‘mixed model’) were used. Primary outcome measure was the proportion of patients with one or more unintentional medication discrepancies, which was stratified according to type of intervention (pharmacy-based versus mixed model). Secondary outcome measures were the type of medication discrepancies and the percentage of unintentional medication discrepancies over time.

Results
1543 patients were included. The proportion of patients with one or more unintentional medication discrepancies was reduced from 62% to 32%, resulting in an odds ratio (OR) of 0.29 (95% confidence interval [CI95] 0.23-0.37). After adjustment for type of department and hospital these results remained statistically significant with an OR of 0.20 (CI95 0.15-0.26). This effect remained stable during six months. Stratified analysis showed that no effect of the intervention was evident in the three hospitals with a ‘mixed model’ intervention, in contrast to the hospitals with a pharmacy-based intervention. The medication discrepancy types ‘omission’ and ‘dosage/strength’ occurred most frequently and were the main types influenced by the intervention.

Conclusions
Pharmacy-based medication reconciliation leads to a substantial reduction of medication discrepancies in acutely admitted elderly patients.

Keywords: pharmacy-based – medication reconciliation – standard operating procedure – medication safety – patient safety

Ineffectiveness and adverse events of nitrofurantoin in women with urinary tract infection and renal impairment in primary care

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Background
Nitrofurantoin is a systemic antibacterial used to treat uncomplicated urinary tract infections (UTIs), but is contraindicated when the estimated glomerular filtration rate (eGFR) is less than 60 mL/min. New evidence suggested that nitrofurantoin in hospitalized patients with lower eGFRs may be effective and safe. The aim of our study is therefore to determine whether treatment with nitrofurantoin in women with UTI and renal impairment in primary care is associated with a higher risk of ineffectiveness and/or serious adverse events than in women without renal impairment.

Methods
A cohort of 21,317 women treated with nitrofurantoin and a cohort of 7,926 women treated with trimethoprim, identified from the Pharma Record Linkage System, were analysed. The primary outcome was ineffectiveness of nitrofurantoin defined as the start of a second antibacterial within one month after the start of nitrofurantoin. The secondary outcome was the occurrence of serious adverse events of nitrofurantoin leading to hospitalization within ninety days. The same outcomes were determined for the trimethoprim cohort. The association between renal impairment and the risk of the outcomes was determined with Cox regression and expressed as hazard ratios (HRs).

Results
Overall, the incidence density (ID) for ineffectiveness of nitrofurantoin was 5.4 per 1000 person-days and moderate renal impairment was not associated with ineffective treatment (HR 1.1; 95% confidence interval [CI95] 0.74-1.51). Ineffective trimethoprim treatment was also not associated with moderate renal impairment (overall ID 6.3 per 1000 person-days; HR 1.1; CI95 0.60-1.88). The overall ID for adverse events with nitrofurantoin was 0.02 per 1000 person-days. In patients with renal impairment (< 50 mL/min/1.73 m²) the risk of adverse events leading to hospitalization was significantly increased (HR 4.1; CI95 1.31-13.09). The overall ID for adverse events with trimethoprim was 0.01 per 1000 person-days. The HR could not be calculated due to none adverse events leading to hospitalization in trimethoprim users with renal impairment.
Conclusions
Nitrofurantoin treatment is not associated with a higher risk of ineffectiveness and moderate renal impairment [30-50 (mL/min)/1.73 m²]. However, we found a significant association between renal impairment [< 50 (mL/min)/1.73 m²] and adverse events leading to hospitalization.

Keywords: adverse events – effectiveness – primary care – renal impairment – medication safety – urinary tract infection

Nevirapine dose escalation or immediate full dose when switching from efavirenz to nevirapine in HIV-infected patients in the ATHENA cohort study

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Background
When switching from efavirenz (EFV) to nevirapine (NVP) it is unclear whether NVP should be dose-escalated or not because of EFV-related enzyme induction. Dose escalation of NVP after EFV treatment may be associated with temporary subtherapeutic NVP plasma levels. Immediate full dose of NVP may lead to an increased risk of toxicity (e.g. skin rash or hepatotoxicity). A retrospective analysis was conducted using data from the observational ATHENA cohort to evaluate the safety and efficacy of dose escalation versus full dose of NVP in HIV-infected patients switching from EFV to NVP.

Methods
HIV-infected patients (≥ 18 years) from five Dutch hospitals with a treatment switch from EFV to NVP immediate release between 2001 and 2011 were selected from the ATHENA cohort study. Dose escalation (200 mg lead-in daily dose for 1-2 weeks followed by 400 mg/day) was compared to immediate full dose (400 mg/day). Safety and efficacy outcomes were toxicity-related discontinuation of NVP ≤ 12 weeks after start of NVP treatment and an undetectable viral load at week 24.

Results
In total 201 HIV-infected patients switching from EFV to NVP were included. The majority of patients (n = 159, 79%) switched directly to full dose NVP. There was an increase in switching to full dose over time: in the period 2001-2005, 46.2% of the patients switched to full dose NVP compared to 90.6% in the period 2006-2011 (P < 0.0001). At time of treatment switch, there were no differences between both groups in the median (IQR) CD4 cell count and the proportion of patients with an undetectable viral load: 505 (315-748) cells/mm³ versus 500 (345-690) cells/mm³ (P = 0.96) and 66.7% versus 63.5% (P = 0.74) respectively. In the first 12 weeks after initiating NVP, 13 patients (8.2%) with full dose NVP stopped NVP due to toxicity compared to 1 patient (2.4%) in the dose escalation group (P = 0.31). In a multivariable logistic regression analysis adjusting for CD4 cell count, the odds ratio for toxicity-related discontinuation within 12 weeks after starting NVP was 4.26 for patients starting with full dose (CI95 0.52-35.25; P = 0.18). No significant association was found between the starting dose of NVP and virological outcome (adjusted OR 0.97; CI95 0.34-2.73; P = 0.95).

Conclusions
In our Dutch cohort, immediate full dose NVP after switching from EFV is more frequently used than dose escalation, especially in recent years. No significant difference was found in toxicity-related discontinuations or virological failures between the two dosing strategies.

Keywords: HIV – nevirapine – efavirenz – PK/PD – dose escalation – toxicity

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A low fixed dose of prothrombin complex concentrate is cost-effective in emergency reversal of vitamin K antagonists

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Background
When switching from warfarin to other anticoagulants, the fixed dose strategy of prothrombin complex concentrate (PCC) is usually chosen. It is however unknown whether this low fixed dose of PCC is superior to variable dosing based on body weight in terms of cost-effectiveness. The present study aims to determine the effectiveness and cost-effectiveness of low fixed PCC dose strategies in the treatment of major anticoagulant-associated bleeds in a Dutch cohort of patients with atrial fibrillation.

Methods
We retrospectively analyzed a multi-center cohort of patients with major bleeding on vitamin K antagonists (VKA). A low fixed dose of PCC (1040 IU F IX) was compared to the commonly applied variable PCC dosing strategy based on body weight, taking into account the INR, the target INR, and the INR during treatment. The low fixed dose was cost- and time-effective compared to the variable dosing strategy, and preserved the INR variability.

Results
The low fixed dose was non-inferior to the variable dosing strategy in terms of effectiveness, as the fixed PCC dose was non-inferior in patients with a baseline INR below 7.5 and INR < 2, the fixed PCC dose was non-inferior in patients with a baseline INR below 7.5 and INR < 2. In the fixed PCC dose strategy, the average cost per patient was €485 and the average time per patient was 4.2 minutes. The average cost per patient in the variable dosing strategy was €745 and the average time per patient was 15 minutes. The cost-effectiveness of the low fixed PCC dose strategy was cost-effective in emergency reversal of vitamin K antagonists.

Conclusions
The low fixed dose of PCC is cost-effective in emergency reversal of vitamin K antagonists. This low fixed PCC dose strategy not only preserves the INR variability but also reduces the time and costs associated with the variable dosing strategy.
Dosing of phenytoin is difficult in children due to its non-linear pharmacokinetics, the change of pharmacokinetics as a result of growth and its variable protein binding. This protein binding can be influenced by albumin concentrations, but also other factors are known to play a role. Possible covariates for the protein binding of phenytoin have mostly been univariately investigated in small and adult populations. The generalisability of these effects to children remains unknown. Also, no equation is available to calculate the covariates-adjusted total phenytoin concentration when measurement of free phenytoin concentrations is not available. We therefore conducted a retrospective study to quantify the effect of covariates for the unbound phenytoin fraction in children and to propose an equation to calculate the unbound as well as the covariates-adjusted total phenytoin concentration.

Methods
From the Utrecht Patient Oriented Database, we extracted data on serum phenytoin concentrations, albumin, triglycerides, urea, total bilirubin and creatinine concentrations and data on co-administration of valproic acid or carbamazepine in children aged 0-18 years. Using non-linear mixed effects modelling (NONMEM) a covariate analysis was performed to evaluate the effect of covariates on the unbound phenytoin fraction.

Results and conclusions
Data of 186 children with a collection of 940 paired observations of unbound and total phenytoin concentrations were extracted. The median total phenytoin concentration was 14 mg/L (range 0.5-68.0 mg/L) and the median unbound phenytoin concentration was 1.52 mg/L (range 0.12-12.0 mg/L). The median unbound to total phenytoin concentration ratio was 0.11 (range 0.04-0.71) and the total and unbound phenytoin concentrations were highly correlated (R² = 0.839, P < 0.01). In the multivariate analysis serum albumin concentrations, serum urea concentrations and concomitant valproic acid use significantly influenced the unbound phenytoin fraction. The free fraction increased when albumin decreased, when serum urea increased or when concomitantly valproic acid was used. Although these covariates partly explained variability, the remaining interindividual and intraindividual variability of the unbound fraction was high with approximately 20%. For clinical practice we recommend that unbound phenytoin concentrations are measured routinely. However, if determination of free phenytoin concentrations is not possible, we suggest to use the proposed equations to adjust the total phenytoin concentration or to calculate the unbound concentration. Lastly, in children with uremia, hypoalbuminemia or concomitant valproic acid use, high unbound phenytoin concentrations can be expected and close treatment monitoring and possibly a priori dose reductions should be considered to prevent toxicity.

Keywords: phenytoin – unbound – albumin – urea – valproic acid
D e digita le vers i e v a n de ze e publi cat i e op pw.nl omv aat ook de abstracts van de volgende poster-presentaties

- Potentially inappropriate medications and omissions determined by Beers 2003, Beers 2012 and STOPP & START criteria in geriatric patients
- Baseline (anti)influenza serum trough levels do not predict successful down-titration or cessation of influenza in rheumatoid arthritis patients with long term low disease activity
- Effectiveness of a group-based intervention to improve medication beliefs and adherence in non-adherent patients with rheumatoid arthritis: a randomized controlled trial
- Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity: a pilot study
- The efficacy and safety of supplementation with 50,000 Units colecalciferol monthly in hemodialysis patients
- Completeness of medication-related information in discharge letters and general practitioner overviews after hospital discharge
- Clinical rule hypo- and hyperkalemia: all that glitters is not gold
- Accuracy and precision of tablet splitting methods
- HIV infection is strongly associated with hip and non-hip clinical fracture risk: a nation-wide case-control study
- Monthly colecalciferol administration in chronic hemodialysis patients: consequences on biochemical parameters and prescribed medication
- Use of metformin and survival of diabetic women with breast cancer
- The risk of venous thromboembolism in patients with multiple sclerosis: the Clinical Practice Research Datalink
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- Medication review for geriatric outpatient clinic
- Medication reconciliation and counseling by pharmacy practitioners at admission and discharge: one year in review
- Use of glucagon-like peptide 1 analogues and the risk of fracture in patients with type 2 diabetes mellitus
- Role of hospital pharmacists in optimizing pharmacotherapy in multimorbidity patients: first results from a pilot study
- Quality indicators for pharmaceutical care in surgical patients
- What is the “right” dose of rifampicin? An interim report
- The effectiveness of a medication review on the number of drug-related problems in outpatient cardiology patients: a randomized clinical trial
- Adherence and identification of factors that might influence adherence to tumour necrosis factor-antagonists in patients with rheumatoid arthritis
- Medication incidents associated with information technology
- Clinical pharmacy services in liver transplant recipients: impact on drug-related problems and cost-effectiveness
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- Physicians’ perception regarding the overall services of clinical pharmacists: a qualitative study in a tertiary care hospital in The Netherlands
- A comprehensive formulary management system improves formulary compliance
- QT interval prolongation in elderly users of selective serotonin reuptake inhibitors
- CYP3A4 phenotyping with midazolam predicts sunninitib exposure
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- Poor performance of laboratories assaying newly developed antiretroviral agents: results for darunavir, etravirine and raltegravir from The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma
- Evaluating the effect of CYP3A4 and CYP3A5 polymorphisms on ciclosporin, everolimus and tacrolimus pharmacokinetics in renal transplantation patients
- Simvastatin causes transflocation of mutant KRAS in colorectal cancer cells
- Pharmacogenetics in allogeneic stem cell transplant patients; mind the mix
- Pharmacokinetics of panitumumab in a single patient with metastatic colorectal cancer and liver dysfunction


**Effectiviteit van beslisregels in de dagelijkse praktijk**

Bart van den Bemt


In een periode van vijf maanden genereerde het systeem 2650 signalen bij 931 patiënten. Bij 10% (270) van de signalen nam de ziekenhuisapotheek een advies om de kans op bijwerkingen te verminderen. Deze adviezen behelsden vaak een dosisaanpassing (33%), het gescheiden innemen van geneesmiddelen (22%), het toevoegen van geneesmiddelen (18%) of het meten van bloedspiegels (17%).

Van de 204 adviezen namen de artsen/verpleegkundigen er uiteindelijk 128 over waardoor de therapie werd aangepast. De auteurs concluderen dat een beslissingsondersteunend systeem met medisch-farmaceutische beslisregels bruikbaar is in de praktijk, maar dat de effectiviteit van de beslisregels verbeterd moeten worden aangezien nu maar 10% van de signalen daadwerkelijk leiden tot contact met de arts/verpleegkundige en 8% tot een advies. Een verhoging van sensitiviteit en specificiteit, mogelijkerwijs door een duidelijke focus op risicogroepen, zou de efficiëntie van de beslisregels kunnen verbeteren.


Potentially inappropriate medications and omissions determined by Beers 2003, Beers 2012 and STOPP & START criteria in geriatric patients

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Background

The use of (potentially) inappropriate medications (PIMs) in the elderly is associated with adverse drug events and hospital admissions. Several screening methods have been developed to detect these PIMs, such as the Beers and the STOPP & START criteria. In contrast to the Beers criteria, the STOPP & START also detect potential omissions (POMs). The aim of our study is to compare the prevalence of PIMs detected by using the Beers 2003, the updated Beers 2012 and the STOPP criteria and detecting the prevalence of POMs by the START criteria in both inpatients and outpatients in a Dutch hospital setting.

Methods

A retrospective study was conducted in geriatric patients admitted to the geriatric ward or visiting the geriatric outpatient clinic of the Jeroen Bosch Hospital (s-Hertogenbosch). Inclusion criteria were: 1) age 65 years or older, 2) medication use and 3) patients were seen by a geriatrician for the first time. Data were collected from admission and discharge letters. The index date was the date of admission to the geriatric ward or the first visit of the geriatric outpatient clinic. The PIMs and POMs were identified by a hospital pharmacist. When information was deemed inconclusive, a geriatrician also applied the screening methods and consensus was reached. Prevalence of one or more PIMs in patients screened by the Beers 2003, Beers 2012 and STOPP criteria was calculated and tested for significance by Pearson Chi-square test.

Results

The total number of patients included was 149 (74 inpatients and 75 outpatients), the mean age was 83 (SD 6.6) years and the mean number of medications was 7 (range: 2-20). The prevalence of one or more PIMs was statistically higher with the Beers 2012 criteria (56.4%) compared with the Beers 2003 criteria (38.3%) (P = 0.002). No difference of prevalence of one or more PIMs was found between the STOPP criteria (48.3%) compared with the Beers 2003 criteria (38.3%) (P = 0.08) and between the Beers 2012 criteria compared with the STOPP criteria (P = 0.16). Prevalence of one or more POMS detected by the START criteria was 65.8%. When the STOPP & START criteria were combined prevalence of one or PIM and/or POMs was 86.6%.

Conclusions

This study showed that the Beers 2012 criteria detect more PIMs than the Beers 2003 criteria. No difference is found between the Beers 2012 criteria and the STOPP criteria. In addition, the START criteria are useful to detect potential undertreatment. Assessment of the clinical relevance of the individual criteria is important to evaluate which screening method is most relevant for use in clinical practice.

Keywords: STOPP/START – Beers – potentially inappropriate medications – omissions – geriatric patients

Baseline (anti)infliximab serum trough levels do not predict successful down-titration or cessation of infliximab in rheumatoid arthritis patients with long term low disease activity

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Background

Several studies have shown that down-titration of infliximab is feasible in part of the patients with stable RA treatment and stable disease activity. However since down-titration can also cause flares, predictors for successful down-titration are warranted. Since infliximab serum trough levels are associated with clinical effect, they might aid in predicting successful down-titration. Therefore, we conducted a prospective cohort study to investigate if baseline infliximab serum trough levels and/or anti-infliximab antibodies can predict successful infliximab down-titration or cessation in RA patients with low disease activity.

Methods

RA patients treated with infliximab who had stable low disease activity defined as DAS28 < 3.2 and stable RA treatment for more than 6 months were included in a prospective cohort study. Inclusion was from the 1st of January 2010 until 1st of April and patients were followed for a year. In all patients, infliximab was down-titrated with 25% of the original dose (3 mg/kg) every 8-12 weeks without interval change until cessation or flare. At baseline infliximab serum trough level and anti-infliximab antibodies were measured. Infliximab levels below 1.0 mg/L, between 1.0 and 5.0 mg/L and above 5.0 mg/L were categorized as low, normal and high levels.

Results

In 51 RA patients, with a mean baseline DAS28 of 2.5 (SD 0.7) and
Effectiveness of a group-based intervention to improve medication beliefs and adherence in non-adherent patients with rheumatoid arthritis: a randomized controlled trial

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Background
Medication adherence in patients with rheumatoid arthritis (RA) is suboptimal, with adherence rates between 30% and 80%. Existing interventions to improve medication adherence are mostly complex and have small effect sizes. We therefore developed a short, group-based intervention to change the balance in necessity and concern beliefs about medication, and to improve adherence to Disease Modifying Anti Rheumatic Drugs (DMARDs) in non-adherent RA patients. This randomized clinical trial aims to assess the effect of a group-based intervention on patients’ balance in beliefs about medication (primary outcome, measured with the BMQ (Beliefs about Medicine Questionnaire), and medication adherence.

Methods
Adult, non-adherent (determined with the CQR: Compliance Questionnaire on Rheumatology) RA patients using DMARDs were randomized into the intervention arm, consisting of two motivational interviewing based group sessions led by a pharmacist, a homework assignment, and a follow-up call, or into the control arm, in which participants received brochures about their currently used DMARDs. Measurements were conducted at baseline, and at one week, six months and twelve months follow-up. Generalized Estimating Equations were used to estimate intervention effects.

Results
123 RA patients (mean age 60 years, 69% female) were randomized. The group-based intervention did not increase medication adherence and also did not influence the balance between necessity and concerns about medication compared to the control group. Only at twelve months follow-up, participants in the control arm had stronger necessity beliefs about medication than participants in the intervention arm [β and CI95, corrected for baseline and with control group as reference category: –1.1 (–2.0 to –0.2)].

Conclusions
Our group-based intervention neither changed the beliefs about medication, nor improved medication adherence to DMARDs in non-adherent patients with rheumatoid arthritis.

Keywords: medication adherence – rheumatoid arthritis – disease modifying antirheumatic drugs – beliefs about medication

Dose reduction of tocilizumab in rheumatoid arthritis patients with low disease activity: a pilot study

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Background
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Results
123 RA patients (mean age 60 years, 69% female) were randomized. The group-based intervention did not increase medication adherence and also did not influence the balance between necessity and concerns about medication compared to the control group. Only at twelve months follow-up, participants in the control arm had stronger necessity beliefs about medication than participants in the intervention arm [β and CI95, corrected for baseline and with control group as reference category: –1.1 (–2.0 to –0.2)].

Conclusions
Our group-based intervention neither changed the beliefs about medication, nor improved medication adherence to DMARDs in non-adherent patients with rheumatoid arthritis.

Keywords: medication adherence – rheumatoid arthritis – disease modifying antirheumatic drugs – beliefs about medication
Background
Tocilizumab, in the registered dose of 8 mg/kg, has proven to be an effective treatment in rheumatoid arthritis (RA) patients. However, RCT data show that a substantial proportion of patients can achieve low disease activity on a lower than registered (4 versus 8 mg/kg) starting dose [1]. A lower dose might reduce dose-dependent side effects and costs. No data, however, are available on the feasibility of dose reduction to 4 mg/kg in RA patients who reached low disease activity on the registered dose of 8 mg/kg. Therefore, this study aims to assess the proportion of RA patients with successful dose reduction of tocilizumab after achieving low disease activity, and to assess the frequency of secondary ineffectiveness after re-escalation.

Methods
According to the local treatment protocol, RA patients start with tocilizumab 8 mg/kg every four weeks. After at least six months of successful treatment, the dose is reduced to 4 mg/kg if patients have low disease activity (DAS28 < 3.2 and judgement of rheumatologist). In case of loss of disease control (DAS28 > 3.2 and judgement of rheumatologist) the dose is increased again to 8 mg/kg. In this observational pilot study, patient, disease and treatment characteristics were collected as well as data on disease activity before and after dose reduction and when applicable after dose re-escalation.

Results
In 19 patients tocilizumab dose was reduced because of low disease activity. The mean disease duration in those patients was 11 years (SD 8.4), rheumatoid factor positive 68%, anti-CCP positive 81% and erosive disease 58%. The mean DAS28 at time of dose reduction was 2.4 (SD 0.9). After three and six months follow-up, respectively 73% (CI 49-90%) and 53% (CI 31-79%) of the patients still had low disease activity on the dose of 4 mg/kg. The DAS28 at respectively three and six months was somewhat (ns) higher than baseline: 2.9 (SD 1.3) and 2.8 (SD 1.0). Most RA flares (78%) after dose reduction occurred in the first 16 weeks. All patients who experienced worsening of disease activity after dose reduction regained low disease activity after dose re-escalation.

Conclusions
Dose reduction of tocilizumab is feasible in a substantial proportion of patients. Dose re-escalation after flare was effective in all patients.

References

Keywords: tocilizumab – down-titration – cost-effectiveness – rheumatoid arthritis – disease activity
Completeness of medication-related information in discharge letters and general practitioner overviews after hospital discharge

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In the study 99 patients were included. Medication-related information was complete in 62 (63%) discharge letters and 16 (16%) GP overviews. Incompleteness of discharge letters and GP overviews were mainly caused by non-documentation of medication changes and allergies. Discharge letters with uploaded TMO information were more frequently complete compared to discharge letters that included a medication list prepared by the resident (OR 26.8, CI95 7.9-90.4). Medication-related information that was communicated by discharge letters was reproduced more frequently on GP overview compared to non-communicated information (65% versus 47%, OR 2.1, CI95 1.5-2.9).

Background

The guideline transfer of medication information in the healthcare continuum stresses the importance of accurate communication between transitions in care. This study aimed to assess the completeness of medication-related information in discharge letters and general practitioner (GP) overviews after discharge.

Methods

An observational study was performed at the Sint Lucas Andreas Hospital. Discharged patients from the neurology, cardiology, pulmonology or internal medicine wards with at least one change in pre-admission prescribed medication were included. At discharge, pharmaceutical consultants made a Transitional Medication Overview (TMO) based on patient counseling and discussion with the resident. The TMO contained all pharmacotherapy, medication changes and present allergies. Furthermore, the resident had the possibility to upload the TMO information in the discharge letter. Discharge letters from all included patients were collected. Two weeks after discharge, medication files from GPs were collected. The information on the TMO was compared with the discharge letter and with the GP overview. Completeness of documentation was assessed regarding medications (including correct dose and frequency) and allergies. Descriptive data analysis was used to assess the frequency of documented information (primary outcome). Secondary, completeness of documentation was compared between discharge letters with or without the TMO uploading. Finally, completeness of documentation in GP overview was compared regarding communication versus non-communication of medication information by the discharge letter.

Conclusions

Medication-related information is lost in discharge letters and GP overviews. Information loss can result in discontinuity of care. Completeness of discharge letters can be improved through the uploading of the TMO. Completeness of GP overviews can be enhanced by communication of medication-related information by discharge letters. However, communication alone is not enough for complete GP overviews after discharge. Future studies should determine the effect of electronic infrastructures on improving information transfer and continuity of pharmaceutical care.

Keywords: patient discharge – continuity of care – medication management

Clinical rule hypo- and hyperkalemia: all that glisters is not gold

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Background

The introduction of a clinical decision support system (CDSS) with integrated patient and drug information should lead to a reduction in the occurrence of (preventable) adverse drug events. Hypo- and hyperkalemia are well known adverse drug events caused by for instance diuretics and ACE inhibitors. This study evaluates the added value of the use of a clinical rule hypo-/ hyperkalemia in the Radboud University Medical Centre.

Methods

A physician order entry system is implemented throughout our hospital. The incorporated drug-oriented CDSS shows relevant drug–drug interactions real time during prescribing. However, a feedback mechanism showing abnormal potassium levels and concurrent use of relevant medication is lacking. Following the systematics of the NVZA clinical rule, we introduced a daily review of abnormal potassium levels combined with use of relevant medication. Abnormal potassium levels were defined as potassium levels < 3.5 mmol/L or > 5.0 mmol/L. Potassium levels < 2.8 mmol/L and > 5.9 mmol/L were directly brought to the attention of physicians by a clinical chemist. Relevant co-medication for hypokalemia was defined as follows: non-potassium sparing diuretics, digoxin, antiarrhythmics and drugs that prolong QT-interval (ARIZONA list 1); and for hyperkalemia: ACE inhibitors, ATII antagonists, potassium suppletion, aliskiren, spironolactone, ciclosporin, tacrolimus and trimethoprim/co-trimoxazole.
Results
During 62 days 2471 abnormal potassium levels were measured; 73 patients with an abnormal potassium level used relevant co-medications. In 8 cases interventions were done (6 patients were hypokalemic; 2 were hyperkalemic). In 5 patients (5.8%) this resulted in a change in medication (twice advised to stop medication, three times advised to start potassium).

Conclusions
The performance of this clinical rule resulted in only 5 patients having their medication changed. Previous studies show higher intervention rates. An explanation is that we reviewed potassium levels 24-36 hours after determination, so physicians were able to act on the potassium levels themselves. Another explanation is the availability of an electronic patient record. This way, all healthcare providers, including pharmacists, have access to all relevant clinical information of a patient, and therefore have insight into the treatment plan of a patient; in this case, if there is medical attention to the issue of deviating potassium levels. The added value of a clinical rule depends on the setting in which it is used. In our hospital, this clinical rule did not have added value and therefore we stopped performing it. Evaluation of the impact of new features in CDSS is necessary to create a more efficient method of preventing adverse drug events.

Keywords: clinical rules – efficiency – adverse drug events

Accuracy and precision of tablet splitting methods
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Background
Breaking tablets in a reliable manner is essential for adequate and safe use of medicines. Therefore commonly used splitting devices should halve tablets accurately and precisely.

Methods
Hundred immediate release, round, flat, 500 mg paracetamol tablets with bevelled edges and a functional score line, RVG 53055, were selected because these tablets are widely used in inpatient and outpatient settings and commonly subdivided. The tablets were split three times with seven devices: the Lifetime, PillTool, Pilomat, Healthcarelogistics, PillAid and Fit&Healthy splitter and a kitchen knife (Blokker warehouse). The weight of the halved tablet derived from the right and left side of the splitter was determined and recalculated into the dose. Hundred tablets were also broken by hand. For splitters the Ph.Eur. test for subdivision is adapted.

Results
The accuracy and precision of the halved tablets is presented in table 1. Hand broken paracetamol tablets complied with the adapted test (200/200 parts 85-115%). They also complied when splitting with PillTool (598/600 within 85%-115%; all within 75-125%), Healthcarelogistics (598/600 within 85-115%; 1/600 within 75-125%) and Pilomat (584/600; 15/600). The tablets did not comply with Lifetime (169/600; 515/600), PillAid (148/600; 181/600) and the kitchen knife (476/600; 541/600).

Conclusions
Splitting devices are not always reliable to split paracetamol tablets into equal doses. The PillTool, Pilomat and Healthcarelogistics splitter are able to accurately and precisely halve tablets. The Lifetime, PillAid, Fit&Healthy splitter and kitchen knife are unsuitable to halve paracetamol tablets.

Keywords: medicine – pharmaceutical development – splitting device – subdivision – tablets
HIV infection is strongly associated with hip and non-hip clinical fracture risk: a nation-wide case-control study

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Keywords: bone fractures – HIV – Ziekenhuisfarmaciedagen

Aim
Hence, we studied the effects of a clinical diagnosis of human immunodeficiency virus infection on fracture risk.

Methods
We carried out a case-control study using data from the Danish National Health Service registries. We identified 124,655 fracture cases and 373,962 age- and gender-matched controls. Crude and multivariate odds ratios (OR) and 95% confidence intervals (CI) were estimated using conditional logistic regression. Potential confounders in the model were: previous fracture, alcoholism, annual income, and use of corticosteroids and sedatives. A total of 50 (0.40/1,000) patients in the fracture group and 52 (0.14/1,000) in the control group had a prior HIV diagnosis. The risk of any fracture was thus significantly increased among HIV-infected patients (age and gender-matched OR = 2.89, CI95 1.99-4.18). Similarly a significant increase in the risk of hip (OR = 8.99, CI95 2.90-28.4), forearm (OR = 3.50, CI95 1.26-9.72), and spine fractures (OR = 9.00, CI95 3.99-21.8) was observed. The observed increase in risk of any fracture stood for adjustment for potential confounders: multivariable adjusted OR 1.76 (1.14-2.71).

Conclusions
HIV infection is independently associated with a significant increase in fracture risk of almost 80% compared to that of uninfected patients. Similarly, patients diagnosed with HIV infection are at an almost 9-fold higher risk of hip fracture, although this association might be partially explained by confounders including previous fracture, alcoholism, socio-economic status, and use of opioids and other drugs. Preventive measures against fractures should be considered in HIV-infected patients, as HIV-infected populations continue ageing, and fractures potentially affect negatively both quality of life and life expectancy.

Keywords: bone fractures – HIV – Ziekenhuisfarmaciedagen

Monthly colecaciferol administration in chronic hemodialysis patients: consequences on biochemical parameters and prescribed medication

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Background
Vitamin D plays a central role in normal calcium metabolism and bone mineralization. Recent studies found that vitamin D deficiency is associated with cancer, auto-immune disease, cardiovascular disease and increased mortality. In patients with ESRD, vitamin D deficiency has a higher prevalence than in the general population, due to the lack of ability to convert vitamin D to its active form, 1,25-hydroxyvitamin D. Suppletion of vitamin D is recommended in hemodialysis patients. In this study we evaluated the effects of monthly colecaciferol suppletion on the serum 25-hydroxyvitamin D levels, other laboratory measurements and prescribed medication.

Methods
In this single centre observational study we screened all our 161 hemodialysis patients for vitamin D insufficiency, defined as a 25-hydroxyvitamin D level < 50 nmol/L, and when deficiency was present colecaciferol 50,000 IU monthly was prescribed. At baseline and every three months thereafter serum vitamin D, calcium, phosphate, PTH and AF levels were measured as well as the use of alfalcacidol, phosphate binders and cinacalcet. The follow up was twelve months.

Results
After six months 25-hydroxyvitamin D levels were raised from 28.3 ± 10.4 to 66.3 ± 27.5, which reflects a sufficient level of vitamin D in 70.2% of the patients. The serum calcium (2.28 ± 0.17 and 2.29 ± 0.133), phosphate (1.54 ± 0.50 and 1.45 ± 0.41) and AF (93.8 ± 51.8 and 97.0 ± 68.4) levels were at baseline comparable with the serum levels after twelve months. The PTH levels showed a slight decrease, with 29.9 ± 22.5 at baseline and 22.8 ± 20.0 not statistically significant. The alfalcacidol usage was decreased in 23.1% (n = 24) of the patients after twelve months.

Conclusions
Colecaciferol suppletion treated 25-hydroxyvitamin D deficiency in hemodialysis patients effectively but has no significant effects on serum calcium, phosphate and alkaline phosphatase levels.

Keywords: calcium metabolism – hemodialysis – suppletion – vitamin D
Use of metformin and survival of diabetic women with breast cancer
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Background
Breast cancer patients with diabetes mellitus have a higher mortality risk compared with their non-diabetic counterparts. Preclinical studies have suggested that metformin reduces growth of breast cancer cells. However, results from clinical trials and observational studies thus far remain inconclusive with regard to the clinical relevance of the effect.

Aim
We conducted a cohort study within the Danish national health registries to determine whether breast cancer patients who received metformin had a lower risk of all-cause and breast cancer-specific mortality as compared with women who received other oral antidiabetic drugs.

Methods
We identified 1058 adult female patients with breast cancer and prevalent type 2 diabetes. Patients were followed from the moment of breast cancer diagnosis onwards. Women with prior cancer or insulin use were excluded. During follow-up, patients were censored at the time of a first recorded insulin prescription. We performed time-dependent multivariate Cox proportional hazards analyses to assess all-cause and breast cancer-specific mortality risks associated with metformin use, adjusted for age, year of breast cancer diagnosis, comorbidity, and comedication. In a secondary analysis, use of metformin was stratified according to the cumulative number of prescriptions.

Results
During a total follow-up of 2971 person-years 349 women died (152 cases of breast cancer). Compared with nonusers, metformin use was associated with a significant reduction in overall mortality (HR 0.74 [0.58-0.96]). For breast cancer-specific mortality, a non-significant risk reduction (HR 0.88 [0.59-1.29]) was observed. Differentiation according to the cumulative number of prescriptions showed a noticeable fluctuation in risk, ranging from increased mortality risk in the lowest exposure categories to protective effects in the categories with highest cumulative use. The risk of both overall and breast cancer-specific mortality were increased in the first twelve months after discontinuation of metformin.

Conclusions
Our findings suggest that long-term metformin use may have a beneficial effect on survival in diabetic patients with breast cancer.

Keywords: metformin – breast cancer – survival

Risk of fracture in patients with muscular dystrophies
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Background
Muscular dystrophies (MDs) are inherited diseases causing muscle weakness and thereby increasing the risk of falling and detrimental effects on bone. Both are recognized risk factors for fracture. Therefore, the aim of this study was to determine the relative risk of fracture in patients with MD.

Methods
We conducted a retrospective cohort study using the UK General Practice Research Database (GPRD). It comprises the computerized medical records of 8% of all patients under the care of general practitioners and is representative for the total UK population. The study population consisted of all patients with at least one recorded diagnosis of muscular dystrophy (January 1987-August 2012). Each patient with muscular dystrophy was matched by year of birth, sex and practice to up to 6 patients without a history of muscular dystrophy. Each patient was followed up from the index date until the end of GPRD data collection or the occurrence of a fracture. Cox proportional hazards models were used in order to estimate hazard ratios of fracture risk. We statistically adjusted our analyses for age, gender, lifestyle, comorbidities, and drug exposure.

Results
As compared with control patients, risk of any fracture was statistically significantly increased in MD patients (adjusted hazard ratio [AHR] 1.40, 95% confidence interval [CI] 1.14-1.71). An increased risk of fracture was observed among MD patients with female gender (AHR 1.78, CI95 1.33-2.40) and an increasing age as compared with control patients. Stratification to Duchenne muscular dystrophy showed no association with fracture, whereas risk of fracture was two-fold increased among patients with myotonic dystrophy (AHR 2.34, CI95 1.56-3.51). MD patients had an almost tripped risk of fracture when they used oral glucocorticoids in the previous six months, as compared to non-users with a MD.
Conclusions
Patients with MD are at a 1.4-fold increased risk of fracture as compared with population-based control patients. Especially in older age groups and female gender the fracture risk of MD versus non-MD patients is increased, whereas exposure to glucocorticoids further increased fracture risk among MD patients.

Keywords: muscular dystrophy – fractures – bone

The risk of venous thromboembolism in patients with multiple sclerosis: the Clinical Practice Research Datalink

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Background
Multiple sclerosis (MS) is a progressive neurodegenerative autoimmune disease, causing a gradual loss of mobility. Previous research has shown that MS is associated with an elevated risk of venous thromboembolism (VTE). It is hypothesised that MS induces a hypercoagulable state, due to either inflammatory processes or a decreased mobility. However, prior studies lacked information on the presence of VTE risk factors in MS patients.

Aim
We conducted a cohort study within the UK Clinical Practice Research Datalink (1997-2008) to evaluate the risk of VTE associated with MS as compared with matched control subjects and to assess the effect modification by VTE risk factors, including MS treatments and comedication.

Methods
A total of 5,566 incident adult MS patients were matched (1:6) by age, sex, and practice to a reference cohort of 33,868 subjects without a record of MS anytime during follow-up. Patients were followed from the moment of MS diagnosis (or matched index date for reference cohort) onwards for the occurrence of VTE. We performed time-dependent multivariate Cox proportional hazards analyses adjusted for age, comorbidity, and drug use.

Results
Compared with the reference cohort, MS patients had a 2.5-fold increased risk of VTE (adjusted HR 2.57; CI95 2.06-3.19). During follow-up (235,836 person years), 115 VTE events occurred in the MS cohort (3.7/1000 person years) as compared with 294 events in the reference cohort (1.4/1000 person years). Within the MS population, the risk of VTE was increased in patients with a recent record of spasticity (adjusted HR 2.59, CI95 1.72-3.91), disability (adjusted HR 2.04, CI95 1.26-3.31), or treatment with high-dose glucocorticoids (crude HR 2.62; adjusted HR 2.27, CI95 1.20-4.31).

Conclusions
We found that patients with MS had an increased risk of VTE. Within the MS population, the risk varied by MS-related risk factors and medication use. Awareness of the vulnerability of MS patients to develop risk factors for VTE could enable caregivers to recognise signs of VTE at an early stage. Assessment of VTE may be considered in patients with a recent record of disability, spasticity, or treatment with glucocorticoids.

Keywords: multiple sclerosis – venous thromboembolism – systemic glucocorticoids

Medication review for geriatric outpatient clinic

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Background
Several studies have shown that approximately 5-15% of overall hospital admission in older patients and 4% of acute hospital admissions are related to adverse drug events (ADEs). Many ADEs are preventable: caused by medication errors. A study by Koekkoek et al. has shown that interventions by an outpatients care team consisting of a hospital pharmacist and a geriatrician can improve and optimize pharmacotherapy for older outpatients.

Methods
Older outpatients referred by general practitioners to the outpatient geriatric clinic of the Antonius hospital were included during a period of two years (2011 and 2012). The hospital pharmacist received GPs’ referral letters and conducted medication review based on the information these letters and data in information systems of Antonius hospital (laboratory findings, correspondence with other specialists involved, medication history). All identified (potential) drug-related problems (DRPs) were summarized in a pharmacotherapy care plan and sent by e-mail to the outpatient geriatric clinic. The geriatrician discussed the (potential) DRPs with patients and conducted interventions where necessary. The interventions were summarized on the same care plan and sent back to the hospital pharmacy.

Results
A total of 159 older outpatients were included in the study. In these 159 patients the hospital pharmacist identified 488 (poten-
Use of glucagon-like peptide 1 analogues and the risk of fracture in patients with type 2 diabetes mellitus

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Background
Although patients with type 2 diabetes mellitus (T2DM) have an increased bone mineral density as compared to healthy patients, their risk of fracture is elevated. Some anti-T2DM drugs have been associated with an increased fracture risk. Data on the effects of new antidiabetic drugs on fracture risk are limited.

Aim
To compare the risk of fracture in glucagon-like peptide-1 (GLP-1) analogue users with users of other antidiabetic drugs.

Methods
A retrospective cohort study using data from the world’s largest primary care database, the UK Clinical Practice Research Datalink (CPRD, 2007-2012) was conducted. Non-insulin antidiabetic drug (NIAD) users (N = 213,900) aged 18+ having at least one NIAD prescription since 2004, were selected. Cox proportional hazards models were used to estimate the hazard ratios (HRs) of any fracture in GLP-1 users vs. other NIAD patients. Time-dependent adjustments were made for age, sex, comorbidity and drug use.

Results
Compared with other NIAD users, users of GLP-1 analogues did not have an increased risk of fracture: fully adjusted HR 1.10 (CI95 0.94-1.28). Sex-stratified analyses did not show a different effect for men or women: adjusted HR men 1.20 (CI95 0.95-1.15), adjusted HR women 1.12 (CI95 0.92-1.37).

Conclusions
Users of GLP-1 were not at an increased risk of any fracture. GLP-1 analogue use seems not to increase the fracture risk in type 2 diabetes mellitus patients.

Keywords: bone fracture – GLP-1 analogues – diabetes mellitus
a total of 5466 actions were recorded by pharmacy practitioners of which 3482 actions concerned admission medication counseling (63.7%), 1285 actions concerned discharge medication counseling (23.5%), and 699 medication reconciliations only (12.8%). Concerning these actions 457 interventions were recorded in the pharmacy intervention registration system in Chipsoft.

Conclusions
The pilot study shows there is a high potential of on average 4 interventions per patient during medication reconciliation and counseling. A full-time ward-based medication reconciliation service by pharmacy practitioners was therefore implemented but showed significantly less interventions. Analysis of the results with the pharmacy practitioners has shown that in everyday practice too little attention is given to recording the interventions although much more interventions have been performed. The guidelines for the pharmacy practitioners have been changed in order to continuously show the added value of the pharmacy services.

Keywords: medication reconciliation – pharmacy practitioners – hospital – medication safety

Role of hospital pharmacists in optimizing pharmaco therapy in multimorbid patients: first results from a pilot study
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Background
The most common chronic condition experienced by adults is multimorbidity, the coexistence of multiple chronic diseases or conditions. Having four or five chronic conditions doubles a person’s odds of experiencing an adverse drug event. Furthermore, often many different specialists are involved in care of multimorbid patients. Yet, coordination of pharmacotherapy between these different specialists is often lacking and physicians are often reluctant to question medication choices of other physicians. Pharmacists with their patient-centered approach to pharmacotherapy and knowledge on medication safety risks can play an important role in optimizing pharmacotherapy in multimorbid patients.

Methods
Starting from February 2013 a hospital pharmacist conducted three days a week a medication review of patients admitted to the cardiology ward, taking ≥ 5 medications, with expected length of stay ≥ 3 days, and having ≥ 1 non-cardiologic conditions. All (potential) drug-related problems (DRPs) were discussed with a cardiologist during face-to-face meetings. If a DRP needed an intervention and was related to cardiovascular medication then the study cardiologist contacted the attending cardiologist to resolve this DRP. If a DRP needed an intervention and was related to non-cardiovascular medication then the study cardiologist contacted other specialists to resolve the DRP.

Results
Medication of 16 cardiology patients was reviewed by a hospital pharmacist. The patients were taking on average 9.9 medications and were having on average four chronic conditions. In these 16 patients the hospital pharmacist identified 52 DRPs (on average 3.3 per patient) of which 71.2% were accepted by the study cardiologist and followed by interventions. For 10 DRPs (19.2%) non-cardiologic specialists were contacted. In three patients, the hospital pharmacist provided additional telephone consultation to general practitioners to assure that medication changes were carried out.

Conclusions
The first results of this study suggest that medication review by a hospital pharmacist for multimorbid patients followed by interventions through collaboration with a cardiologist (the principal specialist) can reduce not only cardiovascular DRPs but also non-cardiovascular DRPs. The possibility to involve other non-cardiologic specialists through such collaborations provides new and efficient opportunity to optimize pharmacotherapy in multimorbid patients.

Keywords: medication review – clinical pharmacy – multimorbidity – medication safety – cardiology

Quality indicators for pharmaceutical care in surgical patients
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Background
Surgical patients are at risk for adverse drug events (ADEs) during hospitalization. Usually ADEs are measured as an outcome parameter of quality of pharmaceutical care. However, assessment with process measures such as quality indicators (QIs) is more manageable and efficient. The aim was to develop a set of surgical QIs and to assess the quality of pharmaceutical care of medication-related processes in surgical wards.

Methods
The QIs were developed based on medication-related QIs from literature and national and local guidelines. They consist of a
The effectiveness of a medication review on the number of drug-related problems in outpatient cardiology patients: a randomized clinical trial

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Keywords: medication review – randomized clinical trial – outpatients – drug-related problems

Background
Several studies demonstrated the effect of medication review on the reduction of drug-related problems (DRPs) and hospital (re)admissions. However, these studies had a monocenter design, focussed on elderly patients and were not conducted in an outpatient setting (Gillespie et al., 2009; Hanlon et al., 1996; Spinewine et al., 2007). Therefore, this multicenter randomised clinical trial (RCT) aims to examine the effect of medication review on drug-related problems (DRPs) in outpatient cardiology patients compared to usual care.

Methods
In this RCT, intervention patients received a multidisciplinary (physician, patient, pharmacist) medication review before their consult to the cardiologist. The control group received usual care. Adult outpatient cardiology patients without medication management assistance were included. Patients were excluded when their electronic medication records were inaccessible or a medication review in the past six months was done. There were no restrictions on age and the number of drugs used.

Results
175 patients (mean age 66.0 ± 12.4 [SD] years, 58.8% male) were included in this RCT. Intervention (n = 90) and control group (n = 85) were comparable at baseline with respect to age, gender, number of (cardiovascular) drugs and number of co-morbidities. The mean number of drugs used by each patient was 7.9 ± 3.9 of which 61% was cardiovascular related. At baseline, the mean number of DRPs did not differ between intervention and control group (1.1 ± 0.1 versus 0.9 ± 0.1). In 54% of the DRPs cardiovascular related drugs were involved. The most frequent DRPs could be categorized as “incorrect use” (16%), followed by undertreatment (15%) and insufficient drug monitoring (9%). After 1 month the mean number of DRPs was 0.3 ± 0.1 in the intervention group versus 0.8 ± 0.1 in the control group (decrease: 0.8 vs. 0.1; P < 0.001: two sample t-test). DRPs in the categories undertreatment, inappropriate drug formulation and incorrect use were most often solved.

Conclusions
This randomised clinical trial shows that medication review in patients with a scheduled visit to the outpatient cardiology ward significantly decreases the number of DRPs. Performing a medication review predominantly decreased drug-related problems in the categories of undertreatment, inappropriate drug formulation and incorrect use.

Keywords: medication review – randomized clinical trial – outpatients – drug-related problems

The effectiveness of a medication review on the number of drug-related problems in surgical patients: A randomised clinical trial

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Keywords: quality indicators – pharmaceutical care – adverse drug events – surgical patients

Background
Several studies demonstrated the effect of medication review on the reduction of drug-related problems (DRPs) and hospital (re)admissions. However, these studies had a monocenter design, focussed on elderly patients and were not conducted in a surgical population, electively admitted for at least 48 hours, from three surgical wards in the Academic Medical Centre in Amsterdam. A comparison was made with preventable ADEs found in this population.

Methods
A total of 34 QIs were developed and tested by the expert panel on acceptability, content validity and face validity. The selected 28 candidate QIs were tested for feasibility and sensitivity to change. This resulted in a complete set of 27 QIs, of which inter-rater agreements were calculated (κ = 0.92 for eligibility, κ = 0.74 for pass rate). The quality of pharmaceutical care was assessed in 252 surgical patients. The overall pass rate was 49.8%. Mean pass rates were calculated per QI domain of 65.5% for pain, 71.0% for infection, 48.6% for thrombosis, 29.4% for gastrointestinal problems, 63.0% for delirium, 31.4% for other problems and 40.0% for discharge and documentation. In this population an incidence of two preventable ADEs per 100 admissions was found, and were related to allergic reaction, hyperkalemia and excessive anticoagulation.

Conclusions
A valid set of QIs for pharmaceutical care in surgical wards was developed. Overall, the quality of pharmaceutical care of the medication-related processes in surgical wards can be improved for more than 50%. This QI set can be used as a valuable addition to ADE assessment in measuring and improving medication safety in surgery.

Keywords: quality indicators – pharmaceutical care – adverse drug events – surgical patients
What is the “right” dose of rifampicin? An interim report

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Background
Tuberculosis (TB) is a major public health problem and the second killer worldwide due to an infectious agent. In the 1960s the dose of the pivotal anti-TB drug rifampicin (10 mg/kg) was selected mainly based on costs and fear for toxicity, but actual evidence underpinning this dose is scant. A maximum tolerable dose (MTD) study was never performed. Currently, available data in mice and humans show that a higher dose of rifampicin may significantly shorten the TB treatment duration. The primary aim of this study was to assess the MTD of rifampicin to enable study of the “right” dose of rifampicin in follow-up studies.

Methods
We performed a 14-day MTD study in adult TB patients. Consecutive groups of 8 (control group) and 15 patients received 10, 20, 25, 30 or 35 mg/kg rifampicin once daily for days 1-7, complemented with standard doses of isoniazid, pyrazinamide and ethambutol for days 8-14. Safety/tolerability assessments included physical examinations, vital signs, adverse event assessments, ECG-recordings, clinical chemistry/hematology/coagulation tests and urinanalysis. The plasma pharmacokinetics of rifampicin was assessed by intensive pharmacokinetic sampling at day 14. After day 14, all subjects continued with standard anti-TB treatment. Following each dose step, a trial steering committee evaluated the adverse events and determined whether the study could be continued.

Results
All study groups completed the study. We recorded 163 adverse events in 68 patients, and 110 were possibly related (102) or related (8) to rifampicin: 88 were grade 1, 19 were grade 2, and 3 were grade 3. All 8 events considered related to rifampicin were rated grade 1. The geometric mean AUC₀–₂₄ at day 14 was 26.3 h•mg/L in the 10 mg/kg control group, increasing to 112.6, 134.5 and 189.4 h•mg/L in the 20, 25 and 30 mg/kg groups respectively, showing an initial non-linear increase followed by a more proportional increase in exposure. Geometric mean Cₘₐₓ values were 7.4, 21.6, 25.1 and 33.1 mg/L in the 10, 20, 25 and 30 mg/kg groups respectively.

Pharmacokinetic data on the 35 mg/kg group and microbiological results of all groups are pending.

Conclusions
Rifampicin up to 35 mg/kg was safe and tolerable in this MTD study, suggesting that the dose of rifampicin for TB could be strongly increased. The study will be continued and based on these interim results we will evaluate a dose of 35 mg/kg rifampicin in a phase II study in South Africa and Tanzania.

Keywords: tuberculosis – rifampicin – dose – treatment shortening – pharmacokinetics

Adherence and identification of factors that might influence adherence to tumour necrosis factor α antagonists in patients with rheumatoid arthritis

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Background
Patient adherence to a drug regimen is important to achieve an optimal treatment response. At this moment there is limited information on the adherence to subcutaneously administered tumour necrosis factor (TNF) α antagonists. Previous studies have shown adherence rates between 22 and 73%. In addition, identification of factors influencing adherence might help healthcare providers to identify non-adherent patients at an early stage and implement activities to improve adherence rates. The present study aims to determine adherence rates to subcutaneously administered TNF α antagonists and identify factors that might influence adherence.

Methods
Patients treated with subcutaneously administered TNF α antagonists for rheumatoid arthritis with more than three prescriptions between 1 January and 30 September 2012 were included in our cohort. Adherence was calculated with a medication possession ratio (MPR) as the proportion of days supply obtained during the time between index (first dispensing date within study period) and run-out date (date of last drug supply plus its days supply, truncated to the last day of the study period). Adherence was defined as MPR > 80%. A nested case-control analysis was performed to explore factors that might influence adherence. Different characteristics were compared between non-adherent (cases) and adherent patients (controls) using a univariate unconditional logistic regression model. All patients gave permission to use their data for scientific purposes.
Results
145 patients were included in our study. The mean MPR was 96.13% (SD 9.23). 6 patients were considered non-adherent (4.1%) and 139 patients (95.9%) were considered adherent. Although not statistically significant, non-adherent patients were generally younger (<50 vs. ≥50; OR = 3.6, CI95 0.7-18.9), more frequently had a history of malignant cancers (OR = 6.8, CI95 0.6-71.9) and were treated for a shorter period (<1 vs. ≥1 year; OR = 2.9, CI95 0.5-18.2). Also, non-adherent patients more often had a dosage change (OR = 3.3, CI95 0.3-31.5) and patients using concomitant methotrexate (MTX) or non-steroidal antiinflammatory drugs (NSAIDs) were less non-adherent than patients not using MTX (OR = 0.4, CI95 0.09-2.3) or NSAIDs (OR = 0.5, CI95 0.09-2.8).

Conclusions
Patients using subcutaneously administered TNF α antagonists had high adherence rates. We could not significantly identify any factors that might influence adherence, which was also related to the high adherence rates. However, the results found might be helpful to identify non-adherent patients in daily clinical practice.

Keywords: adherence – TNF α antagonists – rheumatoid arthritis

### Medication incidents associated with information technology

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#### Background
In 2001 the Institute of Medicine’s Committee on the Quality of Health System for the 21st century predicted that information technology (IT) would play a pivotal role in improving patient safety. On the other hand, IT can cause new problems for patient safety. A well-known example is the juxtaposition error in computerized physician order entry (CPOE): users may unintentionally select a wrong item or patient because the items are close to each other on the screen. To get an insight into such IT-related incidents a classification system is needed. This study aimed to provide insight into the reported IT incidents from hospitals and community pharmacies in The Netherlands, using a modified version of the classification of Magrabi et al. [1, 2].

#### Methods
For this study we used the reports of medication incidents that were sent by hospitals and community pharmacies to the Dutch Central Medication Incidents Registration (CMR) reporting system from March 2010 to February 2011. A search tool was developed to select relevant cases. The reports thus identified were independently reviewed by two researchers. They selected reports if they perceived that technology had somehow contributed to the incident. Subsequently they classified the selected reports, using the Magrabi classification. This classification consists of two axes: the principal source of the IT-related problem (‘machine-related error’ or ‘human-machine interaction-related error’) and the nature of the error (problem). Two new axes were added to the Magrabi classification. The first axis was added to classify the IT device/system involved, the second to designate the specific phase of the medication process in which the medication incident had occurred.

#### Results
In 16% (668/4161) of all CMR reports, IT had somehow contributed to the medication incident: 13% (377/2757) of the hospital reports was related to IT and 22% (351/1636) of the community pharmacy reports. Most of the incidents were classified as human-machine interaction-related incidents and concerned data entry and record manipulation (input). More than half (55%) of the incidents in hospitals were related to the CPOE, while the pharmacy information system was the most frequently implicated IT device in community pharmacies (74%). This resulted in correspondingly high percentages within the phases of the medication process of ‘prescribing’ and ‘entering prescriptions into the pharmacy information system’ respectively.

#### Conclusions
IT plays an important role in reported medication incidents. Analyzing these IT-related reports by using the adapted Magrabi classification may help to understand the underlying causes and thus to improve patient safety.

#### References

Keywords: information technology – medication error incidents – central medication incidents reporting
Clinical pharmacy services in liver transplant recipients: impact on drug-related problems and cost-effectiveness

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Background
Liver transplant recipients may be at risk of drug-related problems, because they are prescribed immunosuppressants with narrow therapeutic indexes, significant drug interactions and a high potential for adverse drug events (ADEs). Participation of clinical pharmacists in a multidisciplinary team has been shown to reduce medication errors and ADEs in different settings. Given the costs of an ADE, varying between €200 and €3600 in previous studies, clinical pharmacists have been shown to reduce healthcare costs as well. However, the impact of clinical pharmacists on healthcare outcomes in liver transplant recipients is largely unknown. Therefore, this pilot study was performed to assess the impact of a clinical pharmacist on drug-related problems in liver transplant recipients and associated costs.

Methods
Clinical pharmacists performed standardized medication reviews twice weekly for liver transplant recipients admitted to Erasmus Medical Center from July until September 2012. Identified drug-related problems that required an intervention were discussed during ward rounds. Pharmacist’s time to perform this service was recorded and associated costs were calculated. Primary outcomes were the number of drug-related problems that were identified and cost-effectiveness of the service.

Results
During this study 24 patients were included and 108 medication reviews were performed in 25 rounds (more than one review was performed for 20 patients). In total 82 drug-related problems were identified and 55 (67%) of the proposed interventions to resolve these problems were accepted by the physician. Of the accepted drug-related problems 12 (22%) had potential to cause ADEs had they not been averted. Clinical pharmacists spent a mean of 1.7 hours per round; total costs for the clinical pharmacist for 25 rounds were €3,225. To reach cost-effectiveness the costs of an ADE should be at least €269.

Conclusions
Clinical pharmacists can contribute to identifying drug-related problems and averting ADEs in liver transplant recipients. Given the range of costs of ADEs previously described, the participation of clinical pharmacists is probably cost-effective. However, we did not study whether physicians would have identified the drug-related problems themselves anyway. This should be addressed in future studies.

Keywords: liver transplantation – medication safety – adverse drug events – drug-related problems

Urea for correction of hyponatremia in patients with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH)

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Background
Hyponatremia in patients with SIADH results from water retention caused by the inability to suppress the secretion of antidiuretic hormone (ADH). SIADH therapy consists of fluid restriction, hypertonic saline infusion, sodium chloride tablets, demeclocycline capsules and loop diuretics. Vasopressin receptor antagonists (e.g. tolvaptan) are also available but very expensive. Urea treatment for SIADH is mentioned on the Uptodate website (Wolters Kluwer Health) with the remark that it is generally well tolerated but that it is not readily available in pharmacies (only as a powder). Urea acts by inducing osmotic diuresis and by promoting sodium retention. Some small case series with urea treatment for SIADH show promising results. In our hospital we received a urea request for a 63 year old woman with SIADH-induced hyponatremia who had a plasma sodium concentration of 116 mmol/L after eight days of standard therapy. We decided to accept the request and agreed to monitor all patients with urea administration during one year to acquire experience with this therapy.

Methods
Urea was provided as 30 g powder in a 100 mL bottle. Patients were instructed to dissolve the powder in water. Adding lemon syrup was allowed to mask the bitter taste. Plasma sodium, plasma urea, urine sodium, urine osmolality, co-medication and the medical dossier of all patients with urea therapy were monitored bimonthly by the hospital pharmacist i.t. (besides the standard visits/contacts of the patient with the attending physicians).

Results
10 SIADH patients received urea therapy from December 2011 to February 2013. Mean age was 66 years (47-84) and 6 patients were women. Before start with urea, 8 patients received the standard SIADH treatment but did not respond well to this therapy. Mean duration of urea administration was 52 days (3-37). Mean plasma sodium concentration was 125 mmol/L (116-133) before start of urea; 127 mmol/L (125-131) on the first day; 129 mmol (124-135) on the second day and 131 mmol/L (124-140) after discontinuation. The plasma sodium concentration increased in 8 patients and de-
creased in 2 patients during urea therapy. Mean plasma urea concentration was 5.5 mmol/L (2.2-9.1) before start of urea; 11.0 mmol/L (4.2-17.3) on the first day; 10.8 mmol (3.2-23.5) on the second day and 5.2 mmol/L (3.5-8.7) after discontinuation. Some patients complained about the bitter taste. No adverse events were reported.

Conclusions

Urea administration appears to be an effective, safe and inexpensive treatment of SIADH-induced hyponatremia. Prospective studies are necessary to further evaluate the effects of urea for SIADH treatment.

Keywords: urea – SIADH – hyponatremia

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A comprehensive formulary management system improves formulary compliance

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Background

Most hospitals maintain a drug formulary, which is viewed as an important tool to guide prescribers in choosing the safest, most cost-effective agents for treating medical problems. Reports on optimal formulary management strategies in terms of safety, productivity, and cost are conflicting. It is difficult to compare formulary management strategies and outcomes between hospitals since there is no consensus on what the best metric is to monitor formulary compliance. We developed a comprehensive hospital formulary management system and evaluated its effects on formulary compliance.

Methods

The formulary management system consisted of a formulary compliance dashboard, reviewing formulary medication use annually and providing periodic feedback to prescribers. The effect of this system was assessed by comparing average formulary compliance of a six-month period at baseline to a six-month time period three years after implementation.

Results

The number of initial orders for a nonformulary medication (nonformulary medication initiations/100 admissions) was selected as the metric for the formulary management dashboard. Interventions as a result of this continuous monitoring system decreased the use of nonformulary medications from 17.8 nonformulary initiations/100 admissions in January to June 2008 to 5.9 nonformulary initiations/100 admissions from January to June 2011, a 67% increase in compliance (P < 0.001).

Conclusions

The number of nonformulary medication initiations/100 admissions is a useful metric to monitor formulary compliance. A formulary monitoring system based on this metric increases compliance. This study addresses a practical issue in many institutions maintaining a formulary. The data required to create the formulary compliance dashboard (medication name, formulary status, and admission number) are readily available in most pharmacy information systems and hospital wide electronic medical records. Adoption by more hospitals of a similar dashboard based on the same metrics results in powerful benchmarking opportunities. This allows for identification and dissemination of successful formulary management strategies in other institutions resulting in increased efficiency and quality of the hospital medication-use process.

Keywords: formulary – compliance – dashboard – metric

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Are two intravenous iron sucrose preparations interchangeable in a hemodialysis population?

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Background

Half of the population with chronic kidney disease has an anemia. The most frequent reason to develop an anemia for this population is iron deficiency. Patients with chronic kidney disease have an increased need for iron because of the use of erythropoiesis stimulating agents (ESA). Beside this, this population has chronic dialysis-related blood loss. Patients under the normal value of hemoglobin are treated with intravenous iron and/or ESA until normal values are reached. In the last years several intravenous iron sucrose similar (ISS) preparations have been introduced for the treatment of iron deficiency anemia. But clinical comparisons with the original intravenous iron sucrose (IS) are hardly available. The investigators want to investigate whether an intravenous ISS is a good alternative for the originator intravenous IS by measuring anemia and safety parameters in hemodialysis patients, in a pilot setting in a single-centre, observational, non-interventional cohort study.

Methods

In this study two treatment periods were compared: six months of retrospective chart review, and six months of prospective data analysis. Hemodialysis patients were eligible if they had had at
least one iron sucrose administration in the first treatment period, had no switch in ESA and had had no more than one blood transfusion in the first period. In period 1 (P1) patients were treated with IS. In the second period (P2) patients received ISS. Anemia and safety parameters (e.g. hemoglobin, ferritin, TSAT, albumin and CRP) where monitored. Paired t-test was used for the analysis of the anemia and safety parameters, and Fisher's exact test for the number of blood transfusions.

**Results**
Mean hemoglobin level of the 23 included patients was higher in P2 (6.7 μmol/L in P1 vs. 7.2 μmol/L in P2; P = 0.018), while the patients required less blood transfusions (9 vs. 4; P = 0.025). This was not accompanied with a higher ESA dependency (mean ESA dose per patient 205 mg in P1 and 193 mg in P2; P = 0.55). The total anemia drug costs were reduced by 38%.

**Conclusions**
The switch from IS to ISS has led to better hemoglobin levels and had no influence on the stability of this population. Furthermore it has reduced total anemia drug costs. Since this is a pilot study with a small population, a randomized controlled trial is recommended to confirm these results.

Keywords: hemodialysis – anemia – intravenous iron sucrose similar preparation

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**Physicians’ perception regarding the overall services of clinical pharmacists: a qualitative study in a tertiary care hospital in The Netherlands**

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**Background**
Despite the limited evidence, some selective serotonin reuptake inhibitors (SSRIs) are nowadays listed as QT prolonging agents carrying a potential risk of Torsade de Pointes. It is unknown whether the risk of QT interval prolongation is a property of specific SSRIs or a class effect. The aim of our study was to investigate the association between the use of a selective serotonin reuptake inhibitor (SSRI) and the occurrence of QT interval prolongation in an elderly population.

**Methods**
A cross-sectional study was conducted among patients scheduled for outpatient preanesthesia evaluation in the University Medical Center Utrecht in the period 2007 until 2012. The index group included elderly (>60 year) users of an SSRI. The reference group of nonusers of antidepressants was matched to the index group on sex and year of scheduled surgery (ratio 1:1). The primary outcome

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**Conclusion**
The use of an SSRI by elderly patients was not associated with the occurrence of QT interval prolongation.

Keywords: selective serotonin reuptake inhibitors – QT prolongation – antidepressant agents – elderly
CYP3A4 phenotyping with midazolam predicts sunitinib exposure

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Methods
Semi-structured face to face interviews with physicians and assistant physicians from 11 departments of a 953 bed university hospital in The Netherlands were performed, using an interview guide, based upon questions used in similar studies. The researcher had no relationship with the health care providers. The interviews were audiotaped, transcribed verbatim and then coded. Atlas.ti software V 7.0.70 (ATLAS.ti Scientific Software Development Company, Berlin, Germany) was used to facilitate the coding process. A thematic analysis was performed to analyse the results.

Results
Overall, participants were satisfied with the services the clinical pharmacist offers. They also expressed their satisfaction concerning the general cooperation with the clinical pharmacist. Participants working on a ward where currently a pharmacist is involved, were positive about the contribution of the clinical pharmacist at the patient-related or medication-related discussion. Some interviewees expressed expectations concerning the role of the clinical pharmacist, e.g. participating in medication-related discussion or keeping an eye on the safe and appropriate use of medications, where they prefer personal contact instead of an automatic generated alert by the computerized physician order entry (CPOE). Additionally, suggestions to improve the involvement of the clinical pharmacist were also mentioned during the interviews, e.g. teaching physicians and assistant physicians about pharmacotherapy.

Conclusions
Our findings support the idea that involvement of a clinical pharmacist on a ward, giving clinical-pharmacological advice, is highly valued by physicians and assistant physicians in a tertiary care hospital in The Netherlands, despite having a CPOE system with automatically generated alerts. It improves awareness for drug-related problems and medication safety and contributes furthermore in the education of young doctors about pharmacotherapy.

Keywords: clinical pharmacy services – qualitative study – semi-structured interviews – thematic analysis
Association analysis of polymorphisms in genes related to sunitinib pharmacokinetics


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Background
Sunitinib is approved as systemic therapy for mRCC, GIST and pNET. Intervariable variability in the pharmacokinetics of sunitinib is high, which may have serious consequences for efficacy and toxicity of the drug. The objective of this study was to evaluate whether polymorphisms in candidate genes involved in sunitinib metabolism are related to the pharmacokinetics of sunitinib and its active metabolite SU12662.

Methods
In this multicenter study, steady state sunitinib plasma concentrations and genotypes were prospectively obtained from 115 patients. Single nucleotide polymorphisms (SNPs) and haplotypes in 8 genes encoding CYP1A1, CYP3A4, CYP3A5, ABCB1, ABCG2, NR1I2, NR1I3, and POR were evaluated as covariates in a population pharmacokinetic model describing both sunitinib and SU12662 pharmacokinetics using NONMEM. First, candidate genotypes/haplotypes were individually tested for a potential association with sunitinib or SU12662 clearance. Several (environmental) factors may also influence the pharmacokinetics of sunitinib. Interestingly, the recently identified CYP3A4*22 SNP potentially has an impact on drug exposure. Replication studies in larger groups of patients are needed to verify the role of CYP3A4*22 for sunitinib clearance.

Keywords: sunitinib – polymorphisms – pharmacokinetics – SNP – clearance

Influence of the proton pump inhibitor omeprazole on the pharmacokinetics of the HCV protease inhibitor boceprevir


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Background
By their ability to increase the pH in the stomach, proton pump inhibitors (PPIs) can limit the solubility of other drugs and hence lead to decreased absorption and lower plasma concentrations. This could lead to reduced efficacy of the drug and in case of an antimicrobial agent may contribute to the development of resistance. Chronic hepatitis C virus infected patients can now be treated with a boceprevir-containing regimen and therefore it is relevant to investigate the interaction between PPIs and boceprevir. This study was designed to investigate the influence of a frequently used PPI, omeprazole, on the pharmacokinetics of boceprevir and vice versa.

Methods
In this open-label, randomized, three-period, cross-over phase I study, healthy subjects were randomly assigned to omeprazole 40 mg once daily for five days, boceprevir 800 mg thrice daily for five days, and omeprazole 40 mg once daily + boceprevir 800 mg thrice daily for five days, or the same treatment in a different order. Every treatment period was followed by a wash-out period of nine days. After observed intake of the medication with a standardized breakfast at day 5 of every treatment period, blood samples for assessment of pharmacokinetic parameters were collected during an eight-hour period. Pharmacokinetic parameters were calculated by non-compartmental analysis (WinNonlin). Geometric mean ratios (GMR) and 90% confidence intervals (CI) were calculated for AUC0-8h and Cmax. CI90 within the 0.80-1.25 range indicates no clinically meaningful effect of omeprazole on boceprevir pharmacokinetics.

Results
All 24 subjects (all Caucasian, 15 males) completed the study and no serious adverse events were reported. The geometric mean (CI95) of boceprevir AUC0-8h and Cmax for omeprazole + boceprevir vs. boceprevir alone were 4.89 (4.37-5.48) vs. 5.34 (4.75-6.00) mg·h/L and 1.66 (1.47-1.89) vs. 1.77 (1.56-2.02) mg/L, respectively. The geometric mean (CI95) of omeprazole AUC0-8h and Cmax for
Results
The number of laboratories that participated by the end of 2012 was 44 for darunavir, 28 for etravirine, and 30 for raltegravir. A total of 357 results were evaluable for analysis. Of these, 64 (17.9%) results were reported with >20% deviation, so “inadequate” (7.6% too low; 10.4% too high). The proportion of inadequate results in 2011 was 21.3% for darunavir, 31.0% for etravirine, and 26.3% for raltegravir; in 2012 these figures improved to 8.1%, 23.2% and 8.3% for darunavir, etravirine, and raltegravir, respectively. Taking darunavir as the reference, performance for etravirine was significantly lower: OR 0.462 (CI95 0.246-0.866; P = 0.016); performance for raltegravir was not significantly different. Low concentrations were significantly more frequently reported as inadequate than medium or high concentrations: 28.6 vs. 10.6 vs. 8.8%, respectively (P < 0.001). Laboratories that used LC-MS/MS did not perform better than those using HPLC/UPLC: 41 inadequate results in 200 samples (20.5%) vs. 23 in 157 samples (14.6%) (P = 0.154). Multiple logistic regression revealed that the lower range of concentrations performed worse than medium or high concentration (P < 0.001).

Conclusions
Omeprazole did not clinically significantly affect boceprevir exposure, nor did boceprevir affect omeprazole exposure. Due to the absence of a clinically significant drug–drug interaction, omeprazole can be used simultaneously with a boceprevir-containing regimen.

Keywords: drug interactions – pharmacokinetics – hepatitis C virus – PPIs

Poor performance of laboratories assaying newly developed antiretroviral agents: results for darunavir, etravirine and raltegravir from The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma

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Background
The International Interlaboratory Quality Control Program for Measurement of Antiretroviral Drugs in Plasma was initiated in 1999. We have recently published our experiences during the first 10 years of the Program (Burger et al. TDM 2011). Since 2010, three newly developed antiretroviral agents have been added to the Program: darunavir, etravirine and raltegravir. The objective of this analysis is to describe the performance of participating laboratories measuring these newer agents in 2011-2012.

Methods
Each year laboratories received two blind samples of human plasma spiked with either a low (<1.0 mg/L), medium (1.0-5.0 mg/L) or high (>5.0 mg/L) concentration of these drugs. Laboratory results were standardized to percentages with reference to the nominal (true) concentration. Any result that deviated more than 20% of the nominal values was defined as inaccurate.

Results
The number of laboratories that participated by the end of 2012 was 44 for darunavir, 28 for etravirine, and 30 for raltegravir. A total of 357 results were evaluable for analysis. Of these, 64 (17.9%) results were reported with >20% deviation, so “inadequate” (7.6% too low; 10.4% too high). The proportion of inadequate results in 2011 was 21.3% for darunavir, 31.0% for etravirine, and 26.3% for raltegravir; in 2012 these figures improved to 8.1%, 23.2% and 8.3% for darunavir, etravirine, and raltegravir, respectively. Taking darunavir as the reference, performance for etravirine was significantly lower: OR 0.462 (CI95 0.246-0.866; P = 0.016); performance for raltegravir was not significantly different. Low concentrations were significantly more frequently reported as inadequate than medium or high concentrations: 28.6 vs. 10.6 vs. 8.8%, respectively (P < 0.001). Laboratories that used LC-MS/MS did not perform better than those using HPLC/UPLC: 41 inadequate results in 200 samples (20.5%) vs. 23 in 157 samples (14.6%) (P = 0.154). Multiple logistic regression revealed that the lower range of concentrations performed worse than medium or high concentration (P < 0.001).

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is an HMG-CoA reductase inhibitor, resulting in reduced production of farnesyl pyrophosphate and geranylgeranyl pyrophosphate. These products are lipophilic and anchor K-ras to the inner membrane which activates downstream signalling. Our hypothesis was that by preventing prenylation of K-ras, K-ras will not attach to the inner membrane, and explains our finding that the proliferation pathway had become EGFR-dependent.

Methods
LoVo (K-ras mt) and SW48 (K-ras wt) cells were seeded in NuncTM glass 8-chamber slides at density of 20,000 cells/well and cultured for 24 hours. After 24 hours, medium was refreshed with medium with or without simvastatin (2 μmol/L) and cultured for another 24 hours. Cells were fixed with 2% PFA, permeabilized using 0.1% saponin + 2% PFA, incubated with K-ras mouse anti-human antibody (1:200) and incubated with Alexa 488 goat anti-mouse antibody (1:200). Vectashield-Dapi was added to stain the nucleus.

Results
Observation with confocal microscopy revealed that K-ras is present in both wild type and mutant CRC cells. K-ras is located at the inner membrane of untreated LoVo cells and spreads throughout the whole cell in SW48 cells. LoVo cells treated with simvastatin showed translocation of K-ras from the inner membrane to the cytoplasm. In the wild type cell line (SW48), simvastatin had no effect on the location of K-ras.

Conclusions
From these results we concluded that mutated K-ras can be detached from the inner membrane in presence of low concentrations of simvastatin. These findings explain the susceptibility of LoVo cells to cetuximab in presence of simvastatin. At present, we are testing translocation of mutated K-ras in several other CRC cells.

Keywords: EGFR antibodies – simvastatin – KRAS – confocal microscopy – translocation – colorectal cancer

Evaluating the effect of CYP3A4 and CYP3A5 polymorphisms on ciclosporin, everolimus and tacrolimus pharmacokinetics in renal transplantation patients

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Background
Ciclosporin, everolimus and tacrolimus form the cornerstone of maintenance immunosuppressive therapy in renal transplantation. These drugs have small therapeutic windows and highly variable pharmacokinetics which make it difficult to maintain adequate exposure and prevent serious adverse effects. Ciclosporin, everolimus and tacrolimus are metabolized by enzymes of the CYP3A subfamily. A small part of the variability in pharmacokinetics can be explained by genetic variation in CYP3A5. Recently CYP3A4*22 was identified as a possible predictive marker for tacrolimus pharmacokinetics. The aim of this study was to investigate the effect of the CYP3A4*22 and CYP3A5 polymorphisms on tacrolimus, everolimus and ciclosporin pharmacokinetics after kidney transplantation using population pharmacokinetic methodology.

Methods
Renal transplant patients on maintenance ciclosporin (298), everolimus (97) and tacrolimus therapy (101) were included. Blood concentrations were determined with fluorescence polarization immunoassay or liquid chromatography-tandem mass spectrometry as part of routine patient care and recorded in the electronic patient record. Available data on ciclosporin (6800), everolimus (1807) and tacrolimus (921) blood concentrations were extracted. Population pharmacokinetics analysis was performed for each immunosuppressive drug using NONMEM (non-linear mixed effects modelling) and demographic factors, CYP3A4*22 (rs35599367) and CYP3A5 (rs776746) genetic polymorphisms were included as covariates. The final models were validated by using a bootstrap and visual predictive check.

Results
The pharmacokinetics of ciclosporin was best described by two-compartment model disposition model with delayed absorption. The pharmacokinetics of tacrolimus and everolimus were best described by a two-compartment model with lag-time. Body weight, prednisolone dosage (ciclosporin), ideal weight (everolimus), hematocrit (tacrolimus) were identified as demographic covariates. The effect of CYP3A4*22 on the pharmacokinetics of ciclosporin, everolimus and tacrolimus was less than 17%. Carriers of CYP3A5*1/*3 had 1.5 fold higher tacrolimus clearance than CYP3A5*1/*1 carriers. CYP3A5 had no significant influence on everolimus and ciclosporin pharmacokinetics.

Conclusions
Our data suggests that CYP3A4*22 is not likely to be suitable as a clinically relevant predictive marker for ciclosporin, tacrolimus or everolimus pharmacokinetics during maintenance therapy in renal transplantation patients. Therefore dose adjustments based on CYP3A4*22 genotype does not appear to be indicated. CYP3A5 is only suitable as a clinically relevant predictive marker for tacrolimus pharmacokinetics.

Keywords: everolimus – tacrolimus – ciclosporin – pharmacogenetics – CYP3A4*22 – kidney transplantation
Pharmacogenetics in allogeneic stem cell transplant patients; mind the mix

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Background
Currently, pharmacogenetic information is accumulating rapidly and is beginning to show consistent reproducible results for an increasing number of genetic markers for drug response. An increasing number of medical centers have acquired clinical genotyping facilities. Among the first medical centers to implement pharmacogenetics there are many highly specialized care centers with complex patient populations. These patients may present some unexpected challenges as is exemplified by the following case description.

Case description
A 20 year old female was admitted for a living related kidney transplantation. Adequate tacrolimus exposure early after transplantation is essential to prevent acute rejection of the transplant. Tacrolimus is metabolized into active and inactive metabolites by CYP3A4 and CYP3A5. Patients carrying at least one copy of the CYP3A5*1 allele have been shown to require a significantly increased tacrolimus dose to attain therapeutic blood concentrations. Therefore, all patients undergoing a kidney transplantation in the Leiden University Medical Center are pre-emptively genotyped for the CYP3A5*1 and *3 polymorphisms. The donor was autocalled, the other one was genotyped but again showed conflicting results. Results were also conflicting with results obtained with plasmid sample was genotyped but again showed conflicting results.

For this particular patient genotyping results from the two techniques were not in 100% concordance: one technique identified the patient as CYP3A5*1/*3, the other CYP3A5*1/*3. A second blood sample was genotyped but again showed conflicting results. Results were also conflicting with results obtained with plasmid controls containing the SNPs of interest. The attending nephrologist was consulted to discuss the results. It appeared that the patient had a history of allogeneic stem cell transplantation (allo-SCT), resulting in a mixed hematopoietic chimerism (28% autologous, 72% donor).

We were interested in interrogating the patient’s germline DNA. After obtaining consent from the patient and the stem cell donor, saliva samples from both subjects were collected and genotyped for both CYP3A5 polymorphisms. The donor was autocalled CYP3A5*3/*3 and the patient CYP3A5*1/*3. Based on the genotyping results, the patients genotype was finally reported as CYP3A5*1/*3. This genotype is in line with the relatively low trough level (5.5 μg/L) and area-under-the-concentration-over-time-curve of 110 μg·h/L achieved with a dose of 8 mg twice a day of tacrolimus.

Conclusions
This case description demonstrates the challenging aspects of pharmacogenetic testing in an allo-SCT recipient and illustrates the importance of proper quality control mechanisms when performing pharmacogenetic testing. Furthermore, it is essential to consider the source of the DNA used to determine the genotype, especially in a population that includes patients receiving allo-SCT.

Keywords: pharmacogenetics – pharmacogenomics – allogeneic stem cell transplantation

Pharmacokinetis of panitumumab in a single patient with metastatic colorectal cancer and liver dysfunction

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Background
Panitumumab is used for the treatment of metastatic KRAS wild type (WT) colorectal cancer (mCRC). It is likely that many of these patients will present with liver metastases and some with liver dysfunction. The pharmacokinetics in patients with hepatic impairment are unknown and dosage adjustments are undetermined. Here, we present a case of a patient with progressive mCRC and liver dysfunction.

Methods
A heavily pretreated KRAS WT mCRC patient with liver disease Child-Pugh class B was treated with two-weekly 6 mg/kg panitumumab. The patient received two doses of 490 mg iv panitumumab after which progressive disease was documented. Toxicities were graded using CTCAEv4.0. Serum samples were collected and panitumumab concentrations were determined using a validated immunoassay. Pharmacokinetic parameters after the first dose, including dose-normalized AUC from time zero to day 14, clearance (CL), and elimination half-life (t1/2), were estimated via trapezoidal non-compartmental methods. Data was compared to historical data from a normal population as reported by Stephenson (Clin Colorectal Cancer 2009). Values within the range of the mean ± 1 standard deviation (SD) were considered not deviant.

Results
Calculated AUC after the first dose of 6 mg/kg panitumumab in this patient with hepatic dysfunction was 877 μg·d/mL (Stephenson’s cohort 1: 744 ± 195 μg·d/mL). Estimated t1/2 was 3.58 days (5.28 ± 1.90 days) and CL was 6.9 mL·d−1·kg−1 (8.21 ± 3.79 mL·d−1·kg−1). Estimated pharmacokinetic parameters during the first cycle were inside reported mean ± 1 SD of historical controls without liver dysfunction. No toxicity was reported during treatment, particularly, no diarrhea and skin toxicity.
Conclusions
The pharmacokinetics of panitumumab in this patient suffering from colorectal cancer with liver dysfunction Child-Pugh class B was similar when compared to patients with adequate liver functions. Moreover, no substantial toxicity was detected. The presented data here may help clinical decision making in real life practice. Two-weekly panitumumab monotherapy seems to be safely applicable in patients with KRAS WT mCRC and hepatic dysfunction without the need for dose adjustments.

Keywords: panitumumab – pharmacokinetics – liver dysfunction – colorectal cancer