The effect of pre operative pharmacotherapeutic consultations by a pharmacy technician on an orthopaedic ward

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Background: Patients who are admitted to our hospital are interviewed three times about their home medication by three different employees. In addition, the hospital pharmacy claims the histories of home medicine use from community pharmacies, which are used by the physicians for the prescription of drugs. This is an inefficient process which leads to differences in information regarding the actual medicine use. By implementing pre operative pharmacotherapeutic consultations by a pharmacy technician, we aim to improve this process.

Aims
1. Creating a clear, complete and accurate overview of the home medication.
2. Reduction of mistakes in the prescriptions of hospital medication.
3. Having a screened prescription sheet on the day of admittance, instead of a delay of one day.
4. Reduction of time towards administering the medication from a screened prescription sheet on the ward.
5. Enlarging the contentment of health professionals on the new working process.
6. Standardising the new working process.

Methods: During a period of four months pre operative pharmacotherapeutic consultations about home medication were held with patients who were admitted for elective orthopaedic surgery. During these consultations a screened prescription sheet was created. These sheets were compared with the histories of home medicine use of the patients. Discrepancies were scored as mistakes.

Results: 58 consultations were held. In 72% one or more mistakes (mean ± SD: 1.3 ± 1.2 per patient) were found in the histories of home medication use. The mean number ± SD of prescriptions per patient was 3.4 ± 2.7. In figure 1 the different categories of the scored mistakes are given.

Conclusion: Implementing pre operative pharmacotherapeutic consultations revealed an occurrence of 72% mistakes compared with the history of home medicine use. The working process has been improved and standardized. A large quality improvement in medication safety has been established.

The effect of statins on urinary albumin excretion and glomerular filtration rate: A RCT and an observational cohort study

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Background: Statins have shown to improve cardiovascular outcome, but hard evidence on their effect on renal outcome is limited. Both a fall and a rise in albuminuria have been reported, and evidence on renal function outcome is mostly limited to post-hoc analyses from cardiovascular trials.

Aim of the study: To know the effects of statins on urinary albumin excretion (UAE) and glomerular filtration rate (GFR) in two settings: an RCT and an observational cohort study.

Methods: We used data from the PREVEND-IT study and from the PREVEND observational cohort study. In PREVEND-IT 788 subjects were included with a UAE 15–300 mg/day who received...
pravastatin 40 mg/day vs placebo and/or fosinopril 20 mg/day vs placebo in a 2 × 2 factorial-RCT design. In PREVEND cohort study 3440 subjects were included of whom complete information of their clinical and pharmacy data were available from the first and second (4 years later) screening. The main outcome was percentage change in UAE and GFR, and being progressor of albuminuria in relation to statin use. Progressor in albuminuria defined as change in UAE at least 50% and change class from normoalbuminuria (UAE < 30 mg/d) to microalbuminuria (UAE 30–300 mg/d) or macroalbuminuria (UAE > 300 mg/d). Multivariate-regression was used to estimate the effects of statins on UAE and GFR.

Results: In the observational cohort statin use was associated with a significant rise in UAE (12.1%) compared with no statin use (3.6%).

The impact of hormonal contraceptives on blood pressure, urinary albumin excretion and glomerular filtration rate
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Background: In short-term studies, hormonal contraceptives (HC) suggested to induce a rise in blood pressure (BP) and urinary albumin excretion (UAE), and decrease in renal function (GFR). Data on long-term and withdrawal effects of HC-use on these outcomes are however, not available.

Aim of the study: To know whether start and cessation of HC induce changes in BP, UAE and GFR.

Methods: We used data from the PREVEND-Study, a prospective cohort of subjects aged 28–75 years. Eligible were women aged ≤45 years old with complete clinical and pharmacy data on baseline and follow-up screening (4- yrs later). Multivariate regression analysis was used to estimate the effects of HC on BP, UAE and GFR in those who started (n = 73), stopped (n = 117) or continued (n = 183) with those who never used (n = 286) as reference group.

Results: BP increased among starters (2.8% +/− 9.1 for systolic and 3.6% +/− 8.5 for diastolic) and fell (−2.3% +/− 7.2 for systolic and −1.4% +/− 7.5 for diastolic) in stoppers. These changes were statistically significant compared to never-users (0.3 +/- 8.5 and 1.4 +/- 8.0 for systolic and diastolic, resp), also after adjustment for relevant variables. UAE increased 14.2% in starters (p = 0.074) and fell 10.6% in stoppers (p = 0.021), while GFR fell 6.3% in starters (p < 0.001) and did not change in stoppers. The effects of stopping HC on UAE and GFR were significantly different compared to changes among never-users, also after adjustment for other variables (p = 0.023 and 0.036 resp).

Conclusions: The start of HC is independently associated with worsening of BP, UAE and GFR, while stopping HC-use resulted in an improvement. These data suggest that long-term HC-use may be deleterious from cardiovascular and renal point of view, but stopping may result in correction of these effects.

Cost-effectiveness of losartan in patients with hypertension and LVH: An economic evaluation for the Netherlands based on the LIFE-Study
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Introduction: The Losartan Intervention For Endpoint Reduction (LIFE) in hypertension study was a randomised, double-blind trial comparing effects of losartan with atenolol on cardiovascular morbidity and death. A population of 9,193 hypertensive patients with left ventricular hypertrophy (LVH) in different countries was studied. As compared to atenolol, losartan reduced the combined risk of cardiovascular morbidity and mortality by 13% (p = 0.021), and reduced risk of stroke by 25% (p = 0.001), despite comparable blood pressure control. Our objective was to conduct a cost-effectiveness analysis of losartan compared with atenolol from the Dutch health care perspective.

Methods: Utilisation of losartan and atenolol within the trial period and an estimation of direct medical costs of stroke for the Netherlands were combined with estimates of reduction in life expectancy through stroke. Medication cost and stroke incidence during 5.5 years of patient follow-up were estimated separately, adjusted for the baseline degree of LVH and Framingham risk score. To estimate lifetime stroke costs, the cumulative incidence of stroke was multiplied by the lifetime direct medical costs attributable to stroke. All costs (Dutch prices in 2004) and effects were discounted at 4% annually.

Results: Prevention of stroke resulted in a gain of 5.1 discounted life years. As a consequence, losartan treatment resulted in 0.081 life years gained per patient. Losartan reduced stroke related cost by €946. After inclusion of study medication cost, net cost per patient was €237 higher for losartan than atenolol. The net cost per life year gained was €4017 which is below the Dutch pharmacoeconomic threshold of €20,000/LYG for accepting interventions. The corre-
Biomarkers for the course-to-course evaluation of the cardiac side effects of anthracyclins
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Introduction: Anthracyclines (ACs) cause myocardial damage, which eventually may result left ventricular failure (LVF). The clinical assessment of the myocardial damage after AC-therapy is difficult, as the symptoms of LVF occur late. Hence, identification of (bio)markers of early cardiac damage may be useful. Levels of the N-terminal split product of pro Brain Natriuretic Peptide (Nt-proBNP) and QT-interval change after completion of chemotherapy. The course-to-course effect of anthracyclin administration on Nt-proBNP and QT-intervals would be additional evidence for the usefulness of these markers.

Methods: We studied 12 patients (10F/2M) scheduled for at least 4 courses of three-weekly AC-chemotherapy, without cardiologic abnormalities, nor did they use other cardiotoxic medication. Nt-proBNP blood levels and ECG-recordings were taken pre-dose, immediately afterwards and at 24 hr after each course of AC. QTc-times were calculated according to Bazett. Statistical analysis was by mixed model analysis of variance after log-transformation.

Results: Nt-proBNP did not increase immediately after cessation of AC administration, but markedly increased at 24 h after each course. Arise of 269% (95% CI: 167–409%) was found at 24 hr for the first course, whereas similar 2–3 fold increases were observed after the 2nd, 3rd and 4th course (fig. 1). Nt-proBNP levels had returned to baseline before the start of each subsequent AC course. At cessation of the first course of AC therapy QTc prolongation was small, but increased by 2.56% (0.21–4.95%) after 24 hrs. A similar pattern was observed for the subsequent AC courses (fig. 2). The pre-dose QTc increased slightly over the observation period.

Conclusion: We conclude that Nt-proBNP and QTc may be useful markers for course-to-course evaluation of anthracyclin-induced cardiotoxicity. The relation to LVF is to be established.
Treatment for patients with type 2 diabetes in primary care: Quality of preventive cardiovascular care

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Background: Many initiatives have been taken to support both patients and general practitioners to improve the quality and outcomes of diabetes care. Primarily the focus was on better glycaemic control but in recent years it has been stressed that more attention should be paid to cardiovascular preventive care. Doubts have been raised whether this has been sufficiently implemented in primary care.

Aims: To evaluate the quality of cardiovascular preventive care treatment for patients with type 2 diabetes in two primary care populations.

Methods: We used the GIANTT database (1) which contains information collected from electronic medical records from 50 general practitioners (GPs) as well as a regional diabetes service. Clinical measures (HbA1c, total cholesterol, HDL and blood pressure levels) and patient information (age, gender, diabetes-duration, BMI, diet, insulin-use) were assessed in 8073 patients attending the regional diabetes service and 1822 patients visiting only their general practitioner for their diabetes management in 2004. Prescribed cardiovascular treatment could be retrieved for a sample of 1121 patients seen by the diabetes service and all 1822 patients managed by the GPs alone. Levels of cardiovascular treatment in patients not achieving target cholesterol and blood pressure levels were assessed, looking also at specific age groups.

The association between antidepressant use and hypoglycemia in diabetic patients: a nested case-control study


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Introduction: Hypoglycemia is a limiting factor for glycemic management of diabetes with intensive insulin and/or oral antidiabetic drug regimen. Evidence from literature [1], mainly case reports [2], suggests that antidepressants may interfere with blood glucose metabolism in patients with Diabetes Mellitus increasing the risk of both hypo- and hyperglycemia. Comorbid depression treated with antidepressive agents therefore could further complicate glycemic control.

Aims: Assessment of the risk of hospital admitted hypoglycemia associated with the use of antidepressants.

Methods: A nested case-control study was conducted using data from the Dutch Pharmo system. The base cohort consisted of diabetic patients treated with insulin and/or oral antidiabetic drugs between 1991–2002. Cases were those individuals who were admitted to the hospital for the first time with a primary or secondary diagnosis of hypoglycemia. Up to four controls were selected from the base cohort. They were assigned the same index date as the corresponding case and had not been admitted to the hospital for hypo- or hyperglycemia before the index date. Exposure to antidepressants and potential confounding factors (age, gender, hypo- and hyperglycemia inducing co-medication, type of diabetic medication and extent of chronic co-morbidity, measured by Chronic Disease Score) were determined on index date. Conditional logistic regression was used to estimate the strength of the association.

Results: From the base cohort (40 600 patients), 553 (1.36%) cases were identified and 1912 controls were selected. Current use of any antidepressant was not associated with a significantly higher risk of hospital admitted hypoglycemia (OR: 1.42 (95% CI: 0.89–2.29)). Current use of antidepressants with high affinity for the norepinephrine reuptake transporter, however, was associated with a significantly increased risk of hospital admitted hypoglycemia of 1.87 (95% CI: 1.04–3.36) and in particular after three years use 5.30 (95% CI: 2.27–12.38).

Conclusions: The risk of hypoglycemia should be considered in diabetic patients using antidepressants. It is important for these patients to pay attention for symptoms of hypoglycemia and strict blood glucose self-monitoring. This could increase quality of life and prevent life threatening situations.

Encapsulation of vecuronium by the modified γ-cyclodextrin sugammadex: a new concept in clinical pharmacology

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Introduction: Cycloextrins are ring-shaped sugar molecules with a lipophilic inner cavity and hydrophilic outer surface, enabling formation of unique host-guest complexes with hydrophobic molecules. Cycloextrins have been applied for improving the bioavailability of poorly soluble drugs, and increasing the concentration of drugs at the target site. The present study investigates whether cycloextrinsics can be used for preventing the action of drugs, by evaluating the effects of the modified γ-cyclodextrin sugammadex on vecuronium-induced moderate neuromuscular block in surgical patients.

Materials and methods: After ethics committee approval and written consent, 40 patients (age 19–84 years) received 0.1 mg/kg vecuronium. Patients were randomly allocated to receive placebo or 0.5, 1.0, 2.0, 4.0 or 8.0 mg/kg sugammadex, administered at moderate neuromuscular block (reappearance of T2). Neuromuscular block was monitored by accelerometry (TOF-Watch® SX). The primary end-point was time to recovery, defined by time from administration of sugammadex until recovery from neuromuscular block (T4/T1 ratio of 0.9). The relation between the dose of sugammadex and recovery from neuromuscular block was studied by using weighted non-linear regression analysis. Pharmacokinetic analysis was performed in 22 patients. Safety of sugammadex was evaluated by analysing adverse events and vital signs.

Results: Compared with placebo, sugammadex accelerated the recovery from vecuronium-induced neuromuscular block in a dose-dependent way (see table).

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>Time to recovery (min (SD))</th>
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<tbody>
<tr>
<td>placebo</td>
<td>48.8 (27.9)</td>
</tr>
<tr>
<td>0.5</td>
<td>7.7 (2.6)</td>
</tr>
<tr>
<td>1.0</td>
<td>2.5 (0.8)</td>
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<tr>
<td>2.0</td>
<td>2.3 (0.8)</td>
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<tr>
<td>4.0</td>
<td>1.5 (0.5)</td>
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<tr>
<td>8.0</td>
<td>1.4 (0.5)</td>
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Plasma concentrations of sugammadex appeared to be proportional to the administered dose. Vecuronium plasma concentration – which includes both free and sugammadex encapsulated vecuronium – showed some increase within the first 15 minutes after administration of sugammadex. Two serious adverse events were reported, constipation and muscle hemorrhage, which were not considered to be related to sugammadex.

Conclusion: The modified γ-cyclodextrin sugammadex encapsulates vecuronium, thereby preventing its action at the nicotinic receptor. Sugammadex causes effective reversal of vecuronium-induced moderate neuromuscular block. The safety data indicate that sugammadex was well tolerated.

Tacrolimus concentration measurement with the dried blood spot method

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Introduction: Lifetime therapeutic drug monitoring of blood tacrolimus concentrations in transplant patients is necessary. Venous blood samples have to be drawn by experienced phlebotomists. Capillary blood obtained by fingerprick by the patients themselves could be an alternative sampling method. Consecutively the blood is applied as a spot on sampling paper and sent to the laboratory by mail. Such a procedure has logistic and practical advantages. Usefulness of capillary blood obtained by fingerprick has been reported recently [1]. However a method for dried blood spot sampling has not yet been described in literature.

Objectives: Development of a dried blood spot method for therapeutic drug monitoring of tacrolimus. The method was compared with our routine assay in venous blood.

Methods: Our routine tacrolimus assay in venous blood is based on a HPLC tandem mass spectrometric method, described in literature, with some modifications [2]. Blood spots were collected in round spots drawn on standardized sampling paper. After overnight drying at ambient room temperature 7.5 mm diameter punches were made, extracted with methanol/acetonitril (4 + 1) and injected into the HPLC tandem mass spectrometer. The dried blood spot assay was validated and compared with our routine assay in venous blood by measuring trough concentrations of 24 stable kidney transplant patients in the outpatient department.

Results: Analytical validation. Inter- and intra-assay precision and accuracy of self prepared controls in EDTA blood were <7.5 and <15% respectively. The precision of the commercial ClinChek® control was also <7.5%. The accuracy however was far above the 15% level: 23%. The lower limit of quantitation was at least 3 µg/l. Linearity (3–30 µg/l) was satisfactory: R² > 0.9915 + 0.0039 (n = 18).

Stability of blood spot samples: Blood spots of patients, calibration standards, and controls were stored at various temperature conditions (−20, +4, 20 and 37°C) up to 31 days. No decrease of tacrolimus concentrations was observed.

Method comparison: Results of the conventional and the dried blood spot assays were nearly identical: the intra-class correlation coefficient for method agreement was ≥0.965 and ≤0.978. The Bland Altman plot showed no significant bias and all points lied within or near the 2 SD limit.

Discussion: Thoroughly filling of the round on the sampling paper proved crucial. Erratic lower results are obtained if haemolytic blood is used. Therefore concentrations below specifications were found for the haemolytic ClinChek® control.
Conclusion: We have developed a dried blood spot method for the assay of tacrolimus. The method has been validated and is suitable for stable outpatients.

Influence of polypharmacy on adherence with drug use in patients with diabetes mellitus type 2: A questionnaire study
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Introduction: Long-term complications of diabetes mellitus type II (DM-2) include both macro- (cardiovascular disease) and microvascular complications (nephropathy, neuropathy, retinopathy). In addition to the treatment of cardiovascular disorders (hypertension, obesitas and hyperlipidaemia), prevention of long-term complications requires a strict glycaemic control. Treatment often includes changes in lifestyle and the use of several drugs. Patients should use their drugs according to the advice of their doctors. Several studies, however, have shown that many patients are compliant with drug treatment. Questionnaire studies report a good compliance of 65 to 80% of the patients (Guillausseau 2005) but studies on the basis of pharmacy dispensing data found good compliance between 25 and 80% of the patients (Guillausseau 2005). Good compliance therefore widely differs. Patient-related factors (age, socio-demographic background, ethnicity), disease status (severity and duration, depression) and drug use (number of drugs used and dose frequency) have been found to influence compliance with treatment. In the literature, however, conflicting results on the precise effect of each factor are reported.

Aims: To assess adherence with the use of drugs of DM-2 patients. To study the influence of polypharmacy on adherence.
Methods: A questionnaire study among DM-2 patients. Patients were selected using the pharmacy information system of four pharmacies in Amstelveen (Amsterdam area). Inclusion criteria: use of oral antidiabetics between oktober 2004 and september 2005, to be reached by telephone and ability to fill in the questionnaire. The questionnaire included questions about patients’ demographics, severity and duration of the disease, co-morbidity, drug use and the missing of doses during the past two weeks.
Results: Of 1099 patients using oral antidiabetics 229 were invited to participate. 199 patients agreed and were sent a questionnaire. With 147 evaluable questionnaires returned the response amounted to 64.2%. 53.7% of the patients were male and the mean age was 68.9 ± 10.7 years. 6.1, 12.2, 12.9, 13.6 and 55.2% used respectively 1, 2, 3, 4 and 5 or more drugs daily. 19.7, 21.8, 3.4 and 40.8% used respectively monotherapy with metformin, a sulphonylurea, a thiazolidine compound and a combination of these drugs. 80.3% of the patients reported not to have missed a dose during the past two weeks. 15.6% of the patients reported to have missed one or more doses of one or more drugs. No relationship between the number of drugs patients use and the missing of doses was found.
Conclusion: Adherence assessed by means of self report was good in at least 80.3% of the patients. The missing of doses was not influenced by the number of drugs patients use.

Evidence for bisphosphonates in prostate cancer: Systematic review of clodronate, etidronate, pamidronate and zoledronate
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In prostate cancer, metastases in bone occur in 80% of men with advanced disease, with the majority experiencing bone pain. These metastases are caused by increased bone formation. A number of studies have investigated the role of bisphosphonates in metastasised prostate cancer, however, the overall potential of this group is not clear.

Aim: Review of literature to determine evidence for the clinical effect of bisphosphonates in prostate cancer.

Methods: Systematic literature search of PubMed and EMBASE with the terms: ‘bisphosphonates’ and ‘prostatic neoplasms’ and categorization according to CBO guidelines:

A1: systematic reviews with trials of level A2 with consistent results.
A2: large randomized comparative trials with consistent results and of high quality
B: small randomized comparative trials of poor quality. Meta-analyses and randomised placebo controlled and comparative double blind clinical trials were included. Abstracts and level C and D evidence were excluded. Conclusions were categorized level 1 to 4.

Results: 11 studies were included. No systematic review was found. Studies were grouped according to 3 primary endpoints: reduction of pain, reduction of skeletal related events (SRE), and change in bone mineral density (BMD).
Six studies investigated the effect of bisphosphonates on the reduction of pain. One study investigated pamidronate (90 mg i.v.), five studies investigated clodronate (0.3–1.5 g i.v. and up to 3.2 g p.o.) and one study etidronate (7.5 mg/kg i.v. + 0.4 g p.o). No positive effect on the reduction of pain was shown (level of evidence: 2).
Two studies investigated reduction of SRE. One large study was performed with zoledronate (4 or 8 mg i.v.). Another trial studied clodronate (2.08 g p.o). Zoledronate reduced the chance for a SRE with 11%. Clodronate was not effective. There was no consistent evidence for reduction of SRE’s. (level of evidence 3). Two trials studied the effect on BMD. Both trials, one with pamidronate (90 mg i.v.) and one with zoledronate (4 mg i.v.) showed a significant increase of BMD. The results of these studies suggest that a positive effect on BMD is plausible (level of evidence: 2).
Conclusion: There is insufficient evidence for the use of bisphosphonates in metastasised prostate cancer, since no obvious reduction in pain was seen. Only one study with zoledronate showed a reduction of SRE. Only two relatively small studies showed an effect on BMD. No head-to-head studies were performed.
Intoxications with citalopram – two divergent cases

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Introduction: Citalopram is an anti-depressant within the group of selective serotonin reuptake inhibitors (SSRI) and is one of the most prescribed SSRI’s in the Netherlands, together with paroxetine and amitriptylin. The acute toxicity of SSRI’s in humans has been reported to be considerably less than that of tricyclic antidepressants. The two following cases illustrate that citalopram overdose can result in unpredictable clinical courses that can be unexpectedly life threatening.

Case 1: A 46-year old woman was admitted to our hospital 2 to 4 hours after ingestion of 170 tablets of citalopram 20 mg and 60 tablets of sulpiride 50 mg. She had a history of depression and post-traumatic stress disorder, she had no history of suicide attempts. On admission she had a generalized tonic clonic seizure. Immediately, rectal diazepam was administered. At admission, blood pressure was 125/85 mmHg, heart rate was 120 beats per minute and respiratory rate was normal. ECG showed a sinus rhythm with normal conducting times, however, 10 minutes later followed by a left bundle branch block configuration with notching, with a widened QRS complex up to 0.15 sec. The EMV score was 4-6-4. Serum concentration of citalopram was 7.5 mg/L (therapeutic range: 0.03–0.1 mg/L) and serum concentration of sulpiride was 2 mg/L (therapeutic range 0.04–0.6 mg/L). She was given activated charcoal and sodium sulphate as a laxative. Laboratory values were all within the normal range. The patient was transferred to the ICU. Three hours later the ECG showed a sinus rhythm again. She recovered within a couple of hours and was discharged two days later.

Case 2: A 17-year old girl was found unconscious on the road. At admission to the emergency ward, her pupils were dilated and non-responsive to light. Because of motoric agitation and an EMV score of <7, she was sedated and put on mechanical ventilation and a toxicological screening was carried out. Laboratory tests revealed a metabolic acidosis with a pH 7.21, pCO2 of 4.5 kPa, and base excess −13.8 mmol/L. Temperature on admission was 36.1°C. Her blood pressure was 137/60 mmHg and her heart rate was 157 beats per minute. Toxicological screening showed a citalopram concentration of 0.5 mg/L and oxazepam of 1.2 mg/L (therapeutic range: 1–2 mg/L). Drugs and alcohol were not detectable. One day later, the serum concentration of citalopram was declined to 0.2 mg/L and that of oxazepam to 0.4 mg/L. No activated charcoal and sodium sulphate were administered. The patient recovered within 2 days.

Discussion: These cases show that the course of an intoxication with citalopram in combination with other drugs is not predictable. One must be aware that an intoxication with even a relatively small dose of citalopram may cause severe adverse events.

Towards rational usage of Prothrombin Complex Concentrate

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Introduction: Prothrombin Complex Concentrate (PCC, Cofact®) is used to antagonize coumarins in patients with major bleedings or urgent surgery, when vitamin K suppletion alone is not appropriate.

An unexplained increase in usage of costly PCC in our hospital was reason for a retrospective analysis. In addition, a new guideline for the application of PCC was evaluated, including a fixed dose of 20 or 40 ml, depending on the indication of PCC.

We calculated that the maximum dose of PCC is 40 ml, based on minimum levels (0%) of vitamin K dependent coagulation factors and their haemostatic levels. However, a much higher dose (70 ml on average) is recommended by the manufacturer.

Aim: To obtain a more appropriate application of PCC.

Methods: Clinical outcome (clinical stabilisation of major bleeding or invasive procedure without bleeding complications) and INRs prior to and after administration of a fixed dose of 20 or 40 ml of PCC were the main endpoints.

Patients with intracranial bleeding were excluded from the prospective analysis. Dosage of PCC in these patients was to the discretion of the neurologist. This was documented, as well as INRs prior to and after PCC and clinical effects.

Results: Retrospectively, 55 patients were evaluated over a 6 months period. Of these, 40% had no valid indication (minor bleeding: 4 patients, elective invasive procedure: 9 patients, asymptomatic INR above target range: 6 patients, no coumarin: 3 patients). Mean dosage of PCC was 67 ml [range 10–200 ml]. Two patients developed fatal pulmonary embolism, death of another 14 patients was not related to PCC. Mean INRs prior to and after PCC were 5.46 [range 1.12–9] and 1.80 [range 1.2–3.9], respectively.

Prospectively, until now 31 patients have been enrolled in 4 months. Of these, 5 (17%) had no valid indication (elective surgery, 3; asymptomatic INR above target range, 2). Major bleeding and urgent surgery were reasons for PCC administration in 14 and 12 patients, respectively. Mean dose of PCC was 34 ml [range 10–40 ml]. Mean INR decreased from 5.7 [range 1.92–9] to 1.9 [range 1.2–4.1] through administration of PCC. Three patients died, their death was judged not to be related to PCC treatment. Clinical outcome was as aimed in all other patients.

In 8 excluded patients with intracranial bleeding mean INR decreased from 3.8 [1.68–6.0] to 1.8 [1.6–2.3] after 40 ml of PCC and to 1.5 [1.0–1.9] after an average actual dose of 48 ml [range 20–90].

Conclusion: Our simple guideline resulted in a more appropriate and safer application of PCC at a much lower dose to antagonize coumarins.
Cost-effectiveness of a potential future helicobacter pylori vaccine in the Netherlands; the impact of varying the discount rate for health

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Introduction: The two most important clinical conditions, which are associated with Helicobacter pylori infection, both in numbers and costs are peptic ulcer disease and gastric cancer. In 1999 these two conditions were responsible for more than 2000 deaths and €94,9 million in the Netherlands. In this paper we calculate the cost-effectiveness of a potential Helicobacter pylori vaccine. Additionally, the impact of changing the discount rate for health, as is now suggested for the Netherlands, is shown.

Methods: Cost estimates were available for 1999. The birth cohort of 1999 was chosen to be in line with the cost estimates underlying the analysis. Plausible assumptions of doses for a full vaccination and the vaccine price per dose (including administration) were made. The percentage of peptic ulcers and gastric cancers attributable to Helicobacter pylori infection were estimated using Attributive Risks. For peptic ulcer disease and gastric cancer the number of deaths per age group in 1999 was taken. The corresponding estimation of the total number of life years lost was discounted using the current discount rate of 4% and the currently discussed discount rate of 1.5%. To calculate life years gained and financial savings a vaccine effectiveness at 80% was assumed (base case analysis). In the model different distributions for the estimation of uncertainty for the different variables were used. A second order Monte-Carlo simulation was performed. The 10,000 sampled cost-effectiveness ratios of the Monte-Carlo simulation were used to construct cost-effectiveness acceptability curves. Multiple scenarios for different vaccine prices were performed.

Results: In the base case analysis the cost-effectiveness ratio for the 4% discount rate is €14,300 compared to €2600 for the 1.5% discount rate for health. For the different scenarios investigated all median cost-effectiveness ratios for the 4% discount rate are relevantly below the median cost-effectiveness ratios obtained with a 1.5% discount rate for health.

Conclusion: Using the current prescribed discount rate for health effects the cost-effectiveness ratio for a potential newly developed Helicobacter pylori vaccine is below the Dutch threshold of €20,000 per life year gained. Introducing a new, lower discount rate for health will greatly benefit the cost-effectiveness ratio for vaccines in general, as is shown here for the Helicobacter pylori vaccine. This benefit will be true for all programs (e.g. screening programs) which have their benefits in the future and cost in present time.

New scaling factor for dosing in (preterm) newborns and infants based on morphine and its glucuronides as a model drug

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1Department of Clinical Pharmacy, St. Antonius Hospital, P.O. Box 2500, 3430 EM Nieuwegein, The Netherlands, 2Leiden/Amsterdam Center for Drug Research, Leiden, The Netherlands, 3Department of Pediatric Surgery, Erasmus MC-Sophia Children’s Hospital, Rotterdam, The Netherlands, 4LAP&P Consultants, Leiden, The Netherlands, 5Department of Pediatric Pharmacology and Pharmacogenetics, Hopital Robert Debre, Paris, France, 6Division of Pediatric Clinical Pharmacology, Children’s National Medical Center, Washington, DC, USA

Introduction: In order to predict drug concentrations in (preterm) newborns to infants of 3 years old, we studied the influence of different patient characteristics (body weight, birth weight, postnatal age, postconceptional age, gestation) on the pharmacokinetics of morphine (M) and its glucuronides (morphine-3-glucuronide (M3G, main metabolite) and morphine-6-glucuronide (M6G)) as continuous covariates.

Methods: The analysis was based on 2159 morphine and glucuronide concentrations from 248 infants ranging in body weight from 500 g to 18 kg (median of 2.8 kg), receiving 2400 µg/kg/24 h intravenous morphine (van Dijk et al., 2002; Simons et al., 2003). Population pharmacokinetic modeling was performed using NONMEM V.

Results: Body weight proved to be the most predictive covariate for both formation clearances to M3G and M6G and elimination clearances of these glucuronides. The clearances could all be described using an allometric equation based on body weight, with an exponential scaling factor of 1.5. For the volumes of distribution, this factor was not significantly different from 1. Postnatal age less than 10 days was an additional covariate for formation clearance to glucuronides, resulting in 25% higher concentrations of the parent compound.

Conclusions: In contrast to the previously reported value of 0.75, the exponential scaling factor for formation and elimination clearance proves to be 1.5. This implicates that drugs undergoing glucuronidation should be given in a fixed dose expressed in µg/kg1.5 instead of µg/kg in order to obtain similar concentrations in all infants ranging from 500 g to 18 kg body weight. For term and preterm newborns younger than 10 days, formation clearance to glucuronides is impaired.

Antipsychotic drug use and the risk of pneumonia in the elderly


Old people Drugs & Dysregulations study group

Department of Geriatrics, UMC Utrecht; Department of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, The Netherlands

Introduction: Antipsychotic drugs (APDs) are frequently prescribed to elderly patients for a variety of mental health problems. Recent studies (Schneider et al., 2005; Wang et al., 2005) showed an increased risk of death in elderly using atypical and conventional antipsychotics. The potential mechanism through which antipsychotics might increase the risk of death is unclear: cardiovascular events and pneumonia have been suggested.

Objective: To investigate the association between use of antipsychotics and risk of pneumonia in the elderly.

Method: A case-control analysis nested within a cohort of patients aged 65 and older with at least one prescription for APDs between 1985 and 2003 was performed. Data were derived from the PHARMO record linkage system containing drug-dispensing records from community pharmacies and linked hospital discharge records of approximately 950,000 subjects. Cases were defined as patients with a hospital diagnosis of pneumonia (ICD-9 codes 480–486 and 507). For each case we randomly selected four controls matched on index date.

APD use in the year before index date was classified as current use, recent past use or past use.

No prescription for an antipsychotic in the year before the index date was considered as no use.

The strength of the association between use of antipsychotics and the development of pneumonia was estimated by multivariate logistic regression analysis and expressed as odds ratios (OR) with 95% confidence intervals (CI) taking into account potential confounding covariates.

Results: The study population consisted of 543 cases and 2163 controls. Current use of APDs was associated with an almost twofold increase in the risk of pneumonia (adjOR 1.7; 95%CI, 1.3–2.2). In current users, the risk of pneumonia was highest during the first week after initiation of an APD (adjOR 4.7; 95%CI, 3.0–7.6). Associations were similar for users with or without a prescription of antibiotics. Users of atypical agents showed a higher risk of pneumonia (adjOR 2.8; 95%CI 1.7–4.7) than users of conventional agents (adjOR1.6; 95%CI 1.2–2.0). There was no clear dose-response relationship.

Conclusions: Use of antipsychotics in the elderly is associated with an increased risk of pneumonia.

The risk is highest shortly after initiating treatment of the antipsychotic drug. The potentially larger effect on atypical antipsychotics might be related to their antihistaminic potency.

The relationship between polypharmacy and undertreatment

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Introduction: Polypharmacy is very common among geriatric patients and is often indicated. Recently it has been shown that, despite of the use of many medicines, undertreatment is frequently seen in the elderly. (Sloane et al. Arch Intern Med 2004;164: 2031–2037, Higashi et al. Ann Int Med 2004;140:714–720). We have studied the nature and prevalence of undertreatment in patients referred to the Geriatric department and its relation to polypharmacy.

Method: Between October 2004 and February 2005 data were collected regarding diagnoses and prescribed medication from all patients who were admitted at or referred to the outpatient clinic or day clinic of the Geriatric department. Patients gave permission to examine their records. Indication for drug treatment was based on general practitioner standards or national guidelines.

Table 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Missing drug</th>
<th>Number of patients</th>
<th>Percentage of undertreatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine use</td>
<td>Laxative</td>
<td>13</td>
<td>61.5%</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>Beta-blocker</td>
<td>15</td>
<td>60%</td>
</tr>
<tr>
<td>Heart failure</td>
<td>ACE inhibitor</td>
<td>21</td>
<td>47%</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>Coumarine derivative</td>
<td>18</td>
<td>42%</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>Bisphosphonate</td>
<td>43</td>
<td>29%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>Statine</td>
<td>13</td>
<td>23%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>Antihypertensive</td>
<td>56</td>
<td>23%</td>
</tr>
<tr>
<td>Indication trombocyte aggregation inhibition</td>
<td>Trombocyte aggregation inhibitor</td>
<td>53</td>
<td>21%</td>
</tr>
<tr>
<td>NSAID use</td>
<td>Stomach protection</td>
<td>21</td>
<td>21%</td>
</tr>
</tbody>
</table>
Introduction: To increase the use of folic acid among women planning a pregnancy, it is important to get insight in the determinants that predict this behavior. According to the theory of planned behavior, women planning their pregnancy should have a positive attitude towards folic acid, which is partly formed by having correct knowledge, in order to use folic acid. Although many studies about periconceptional folic acid use have been published, these yielded only scarce valid prospective data about folic acid use by women planning their pregnancy. The aims of this study are therefore to evaluate use of folic acid among women with a short term pregnancy wish, and to investigate determinants associated with this use.

Methods: Questionnaires were sent to women aged 25 to 35 from 23 pharmacies that visited their pharmacy to collect their oral contraceptives. Out of 154 patients, 150 gave permission, 64% female, average age 30 ± 7 years. Average drug use 6 ± 3 drugs (range 0–17) with 61% using 5 or more drugs.

In 53 patients (35%) undertreatment was found. Of patients with polypharmacy 48% were undertreated, as opposed to 15% of patients without polypharmacy (p < 0.001). The chance (likelihood-ratio) for undertreatment increased significantly with the number of drugs used.

Conclusion: This study shows a clear relationship between polypharmacy and undertreatment. It is possible that guidelines are not applicable to the very elderly. Nevertheless prescribers should be aware of undertreatment, especially in case of polypharmacy.

Use and predictors of use of folic acid among women with self reported short term child wish

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2MediClara Projects, Abcoude, The Netherlands

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Stimulation of platelet production in healthy volunteers by a novel, pegylated, peptide-based thrombopoietin (TPO) receptor agonist

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2Johnson & Johnson-PRD, Beerse-Be, High Wycombe-UK and Springhouse, PA-US

Introduction: A novel, pegylated TPO receptor agonist (peg-TPOmp), without homology to endogenous TPO, was tested for the first time in humans to evaluate its tolerability, effects, and pharmacokinetics (PK).

Methods: In a randomised, double-blind, placebo-controlled study in 40 healthy males, single iv doses of 0.375, 0.75, 1.5, 2.25 and 3.0 µg/kg were administered. Per dose group, 8 subjects were randomised in 6:2 ratio to receive peg-TPOmp or placebo. The effect of peg-TPOmp was measured as platelet count elevation. Levels of endogenous TPO, EPO, IL-6, and IL-11 were measured using immunoassays. Antibody formation was measured with a biosensor immunoassay. Peg-TPOmp levels were determined in platelet poor plasma using a validated ELISA. Treatment response was tested using ANCOVA with baseline as co-variate.

Results: The compound was well tolerated at all doses and there were no serious adverse events (AEs). The most frequently observed AEs were mild headache and fatigue, occurred equally after active drug and placebo. No antibodies against peg-TPOmp were detected. A dose-dependent increase in platelet counts occurred and the estimated difference to placebo (with 95% confidence intervals) are listed in the table.

<table>
<thead>
<tr>
<th>dose (µg/kg)</th>
<th>0.375</th>
<th>0.75</th>
<th>1.5</th>
<th>2.25</th>
<th>3.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>% increase</td>
<td>9.2</td>
<td>19.4</td>
<td>19.0</td>
<td>29.5</td>
<td>51.7</td>
</tr>
<tr>
<td>95% CI</td>
<td>-3± 23</td>
<td>+6± 35</td>
<td>+5± 34</td>
<td>+15± 46</td>
<td>+35± 71</td>
</tr>
</tbody>
</table>

Peak platelet levels were reached at Day 10–12, and counts returned to baseline within 3–4 weeks (fig. 1). Mean (SD) peak platelet levels ranged from 315±10×10^9/L at 0.375 mg/kg to 685±10×10^9/L at 3 mg/kg. Endogenous TPO levels increased dose-dependently with peak levels at 3 days post-dose, indicating displacement from platelets and thereby altered clearance. No change was observed in collagen-induced platelet aggregation, EPO, IL-6, and IL-11.

PK analysis showed that multiple peaks were present (range for median Tmax: 0.09–2 hrs). Cmax ranged from 8.1 ng/mL (0.375 µg/kg) to 62 ng/mL (3.0 µg/kg). PK analysis indicated dose-related kinetics of peg-TPOmp, but at doses of 0.75 µg/kg or lower, concentrations were generally below the LOQ of 6.25 ng/mL at or prior to 12 hours post-dose. This is also reflected in the terminal half-life for peg-TPOmp estimated for the different doses, which ranged between 18–36 hrs (fig. 2).

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**Conclusion:** This study shows that peg-TPOmp potently stimulates platelet production in man after iv administration. There was no indication of an antibody response. Although the pharmacokinetics of the compound are not fully elucidated, further testing of the peg-TPOmp in patients is warranted.

**Figure 1**

**The association between 5-HT2c polymorphisms and the metabolic syndrome in patients using antipsychotics**

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**Background:** The use of antipsychotics is associated with metabolic side effects, which puts the patient at risk for cardiovascular morbidity. The high interindividual variability in antipsychotic-induced metabolic abnormalities suggests that genetic make-up is a possible determinant.

**Objective:** This cross-sectional study investigates whether genotypes of the HTR2C receptor are associated with the metabolic syndrome in patients using antipsychotics.

**Methods:** Patients were identified from a schizophrenia disease management programme. In this programme patients blood pressure, triglycerides, HDL-cholesterol, weight and waist circumference are measured regularly during follow-up. Primary endpoint was the prevalence of the metabolic syndrome as classified by the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP: ATP III). Primary determinants were polymorphisms in the HTR2C receptor gene (rs518147:G > C (−697 G/C), rs3813929:C > T (−759 C/T), rs3813928:G > A (−997 G/A), rs1414334:C > G and HTR2C:c.1–142948(GT)n).

The association between HTR2C genotypes and the metabolic syndrome was evaluated with logistic regression and expressed as adjusted odds ratios (OR) with 95% confidence intervals (95%CI). Potential confounders were age, sex, type and dosage of antipsychotic drug, polypharmacy and the concomitant use of drugs that influence weight, glucose metabolism or lipid metabolism.

**Results:** In total, 112 patients with chronic psychiatric disorders were included. The included patients mainly (>80%) used atypical antipsychotics (clozapine, olanzapine and risperidone). The table shows the association between HTR2C genotypes and the metabolic syndrome.

<table>
<thead>
<tr>
<th>Genotype</th>
<th>OR Metabolic Syndrome (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs518147 C</td>
<td>2.66 (1.02–6.94)</td>
</tr>
<tr>
<td>rs1414334 C</td>
<td>4.09 (1.41–11.89)</td>
</tr>
<tr>
<td>HTR2C:c.1–142948(GT)n, Z-6</td>
<td>3.32 (1.20–9.22)</td>
</tr>
</tbody>
</table>

**Conclusions:** HTR2C genotypes are associated with an increased risk of the metabolic syndrome in patients taking antipsychotics.

Exposure to rifampicin is reduced by 53% in tuberculosis patients with Diabetes Mellitus

H. Nijland, R. Ruslami, J. Stalenhof, B. Alisjahbana, R. H. H. Nelwan, Danusantoso, R. Aarnouitse, & R. van Crevel

Introduction:

For the treatment of late onset neonatal infections with Staphylococcus spp., rifampicin is added to vancomycin or flucloxacinill, when the infection is persistent. Few reports have addressed rifampicin plasma concentrations in neonates, whereas data on neonatal rifampicin pharmacokinetics are completely lacking.

Objectives:

Measurement of rifampicin plasma concentrations, determination of the pharmacokinetic parameters, and investigation of the influence of covariates.

Methods:

Twenty-one neonates, treated with vancomycin and rifampicin in our neonatal ward, with Gestational Age (GA) 29.9 ± 4.1 weeks (mean ± SD) and Post Natal Age (PNA) 24.8 ± 13.4 days were included. Rifampicin dose was 5–10 mg/kg intravenously once a day. Plasma concentrations of rifampicin and its metabolite, 25-O-desacetylrifampicin (DES), were determined with HPLC in 123 surplus plasma samples from routine vancomycin assays. In 8 study patients, plasma concentrations of rifampicin and DES were measured again after two weeks of therapy. Pharmacokinetic parameters were calculated according to a one compartment open model with iterative two-stage Bayesian fitting (MWP/PHARM 3.60, Mediware, The Netherlands). Pharmacokinetic parameters of a preceding gentamicin course were calculated for 12 patients. Statistical analysis was performed using SPSS 12.0 (Chicago, IL, USA).

Results: Rifampicin plasma concentrations and pharmacokinetics.

Rifampicin peak and trough concentrations after the second dose were 4.66 ± 1.47 and 0.21 ± 0.20 mg/L, respectively after a dose of 8.5 ± 2.1 mg/kg. A linear relationship between dose and peak plasma concentrations was found, but inter-patient variability was high. In all samples DES was detected. Total body clearance corrected for body weight (CL/W), elimination half-life (t1/2), and volume of distribution corrected for body weight (V/W) were 0.28 ± 0.11 L/kg, 4.9 ± 1.7h, and 1.84 ± 0.59 L/kg, respectively. After two weeks of therapy CL/W was significantly increased with 67 ± 50% (p = 0.007, n = 8).

Covariates:

Correlations were found between CL/W rifampicin and the covariates CL/W gentamicin (r = 0.837, n = 12), I/plasma creatinine (r = 0.728, n = 17), and GA (r = 0.600, n = 21).

Discussion:

Strong correlation of CL/W rifampicin with gentamicin clearance and plasma creatinine indicates that glomerular filtration is an important route for the elimination. However, metabolism is also involved as indicated by the presence of DES. Rifampicin clearance increases during two weeks therapy in neonates. It is not possible to provide a definite dosing scheme because information about effective pharmacodynamics of rifampicin, the role of protein binding, and pharmacodynamic interaction with coadministered vancomycin or flucloxacinill is insufficient.

Conclusions:

Because of the large inter-patient variability in rifampicin plasma concentrations and in CL/W increase during therapy, the authors suggest monitoring of rifampicin plasma concentrations. More research is needed to determine well-founded dosing guidelines.
Adherence to different drugs in patients with type II diabetes

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Introduction: Poor metabolic control in type II diabetic patients leads to a higher risk for long term complications. (UKPDS 33, UKPDS 34) The average adherence rate of drugs used by diabetic type II patients varies between 36 and 93%. (Cramer, 2004) Unreported side effects and lack of confidence in benefit are recorded as the main predicting factors for suboptimal adherence. (Grant et al., 2003; Sabaté, 2003) Adherence rates vary between various oral antidiabetic drugs in diabetic type II patients (Cramer, 2004), however it is unknown what factors predict adherence rates in different therapeutic drug classes.

Aim: The aim of this study is to investigate differences in beliefs about, and adherence to different drugs used in type II diabetic patients.

Methods: A total of 54 GPs in The Netherlands were asked to select a maximum of 6 type II diabetic patients in their practice according to the following inclusion criteria: (1) the patient was older than 40 years, (2) the patient was prescribed at least one oral anti-diabetic (OAD) drug, and (3) the patient should use additionally at least a proton pump inhibitor (PPI) or a statin. Patients were interviewed at home according to a questionnaire containing questions about their beliefs about medicines (BMQ-questionnaire), their adherence to a higher risk for long term complications. (UKPDS 33, UKPDS 34) The average adherence rate of drugs used by diabetic type II patients varies between 36 and 93%. (Cramer, 2004) Unreported side effects and lack of confidence in benefit are recorded as the main predicting factors for suboptimal adherence. (Grant et al., 2003; Sabaté, 2003) Adherence rates vary between various oral antidiabetic drugs in diabetic type II patients (Cramer, 2004), however it is unknown what factors predict adherence rates in different therapeutic drug classes.

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VKORC1 and CYP2C9 genotypes and acenocoumarol anticoagulation status: interaction between both genotypes affects overanticoagulation

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2Hospital Pharmacy Midden-Brabant, TweeSteden Hospital and St.Elisabeth Hospital, Tilburg, The Netherlands
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5Salto, GP Laboratory and Thrombosis Service, Utrecht, The Netherlands

Introduction: The protein Vitamin K reductase complex subunit I (VKORC1), encoded by the homonymous gene VKORC1, has been recently identified as the target of coumarins which act by inhibiting VKOR activity. Several studies demonstrated an association between the presence of VKORC1 polymorphisms and a reduced dose need of warfarin as well as acenocoumarol. Effects of the CYP2C9 genotype on coumarin anticoagulation status has already been well studied.

Aim: To assess the effects of VKORC1 and CYP2C9 genotypes on acenocoumarol status during the initial phase of treatment.

Methods: We conducted a prospective follow up study at two anticoagulation clinics in the Netherlands. We assessed the CYP2C9 genotype (CYP2C*2 and CYP2C9*3 alleles) and the VKORC1 C1173T genotype of the subjects and collected data on international normalized ratio (INR), dose, comedication and comorbidity. We used Cox proportional hazard models to assess differences in over-anticoagulation (INR > 6.0) and time to achieve stability and we used multiple regression models to assess differences in acenocoumarol dose requirements.

Results: Of the 231 patients in the cohort, 150 (64.9%) had a VKORC1 C1173T polymorphism and 84 (36.4%) had a CYP2C9*2 or CYP2C9*3 allele. Only carriers of a combination of a CYP2C9 polymorphism and a VKORC1 polymorphism had an increased risk of overanticoagulation compared with subjects with no polymorphism or only one polymorphism (hazard ratio [HR] 3.83, 95% confidence interval [CI] 1.62–9.05). The time to achieve stability was associated with the CYP2C9 genotype, not with the VKORC1 genotype. (CYP2C9*3 allele compared with CYP2C9 wild type HR 0.59, 95% CI 0.40–0.87). Patients with a VKORC1 polymorphism required significantly lower daily doses than VKORC1 wild type sub-
Postprandial hypotension in elderly: effectiveness of midodrine and desmopressin vs placebo assessed with the portapress; a pilot study
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Background: Postprandial hypotension (PPH) is defined as a fall of systolic blood pressure of at least 20 mm Hg within 90 minutes after a meal. PPH may cause syncope, falls, myocardial and cerebrovascular infarction. Prevalence increases with age and comorbidity, ranging from 24% to 75%. A number of pathologic processes are likely involved, including autonomic dysfunction, baroreceptor dysfunction, and vasoactive peptide related disorders. This controlled cross over pilot was designed to investigate whether an oral dose of midodrine 10 mg just before breakfast and/or desmopressin 0,4 mg in the evening before breakfast is effective in treating PPH in the morning.

Methods: Patients were selected at the geriatric ward by one or more of the following criteria: age of 70 years or above, or complaints of dizziness after a meal, or autonomic dysfunction and/or earlier diagnosis of PPH. Patients with atrial fibrillation, hypertension (>160/100), an acute illness, renal insufficiency, using contraindicated medication and inability to undergo the tests or to give informed consent were excluded. Systolic blood pressure was measured beat to beat with the portapress (PP) and each 6 minutes with the spacelab (SL). PP data were averaged each two minutes. Measurements started 15 minutes before breakfast (which started approximately at 10 o’clock am). The subjects received a standardised meal. After breakfast, the test continued for 90 minutes. Patients had PPH when the systolic blood pressure after breakfast dropped 20 mm Hg or more in comparison with the lowest systolic blood pressure before breakfast, assessed by PP. During the test, the subjects watched a documentary video. Patient with PPH were selected to endure three more tests in randomised order using placebo, midodrine (10 mg 45 minutes before breakfast) and desmopressin (0,4 mg 12 hours before the test.)

Table 1

| Inclusion Placebo Midodrine Desmopressin |
|-------|-------|-------|------|
| PP    | 6     | 1     | 2    | 4    |
| SL    | 4     | 2     | 4    | 2    |
Results: 25 subjects succeeded the measurements for selection. Mean age of all volunteers was 73 years (52–91). Seven subjects (28%) had PPH (established with the PP). One patient did not continue the other tests. In the 6 remaining selected PPH subjects, the results of PPH could not be reproduced at the time of placebo, desmopressin or midodrine use (table 1). Outcomes of PPH measured with the PP and SL, established at the same test, were not comparable (table 1).

Discussion: The contrast with earlier results of diagnosing PPH by use of the PP in the elderly, might be due to the use of the video, which is responsible for a more stable and alert arousal state. Earlier results may have been biased by a boredom induced sleepy state.

Conclusion: the effects of pharmacological interventions in PPH can not be assessed because of a disappointing reproducibility and reliability of the results, both with PP and SL.

Sublingual administration of tacrolimus: A pilot study
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2Internal Medicine and Nephrology, University Hospital of Maastricht, The Netherlands

Introduction: The immunosuppressant tacrolimus has a narrow therapeutic index and high inter- and intra-individual variability of its pharmacokinetics. Oral bioavailability is low and highly variable (25%(4–93%)). A pilot study by Reams et al. [1, 2] demonstrated that lung transplant patients achieve therapeutic blood levels after sublingual administration comparable with oral administration. Inspired by these results, we have measured 0–12 hour blood concentration time curves after sublingual administration of tacrolimus to kidney transplant patients before transplantation.

Objectives: Investigation of sublingual tacrolimus as an alternative for the oral administration with more predictable pharmacokinetics.

Methods: Three kidney transplant patients were treated with 0,04 mg/kg tacrolimus s.l. two days before transplantation and also with 0,1 mg/kg orally one day before transplantation. A tacrolimus capsule was opened and the content dispersed under the tongue. During 15 minutes the patient was not allowed to swallow and afterwards the patient was told to spit out saliva and rinse its mouth with 250 ml of water. Oral administration the next day was with 100 ml water. Blood samples were taken at t = 0, 1/4, 1/2, 1, 2, 4, 8, 12 and 24 hours postdose. Tacrolimus blood levels were analyzed by HPLC and tandem mass spectrometry (LOQ = 1 µg/l). Also a volunteer has been treated with 0,04 mg/kg tacrolimus s.l. both with a capsule and with a solution for injection from an ampoule.

Discussion: We could measure only very low tacrolimus concentrations after sublingual administration in comparison with oral administration. A possible explanation for the contradictory results with the study of Reams et al. could be that patients were not told not to swallow, to spit out saliva and rinse its mouth after 15 minutes. Therefore unintended oral ingestion of tacrolimus can not be excluded.

Conclusions: Sublingual administration demonstrates negligible absorption of tacrolimus and does not seem a suitable alternative for oral administration


Capsaicin-induced vasodilatation in the human skin as a pharmacodynamic model to test CGRP antagonists in vivo
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Introduction: Application of capsaicin on the skin, results in the activation of the transient receptor potential vanilloid type 1 (TRPV1) receptor, located on the Aδ- and C-fibre nociceptors. In turn, these primary sensory afferent neurons release vasoactive mediators,
resulting in dermal vasodilatation as part of a reaction known as neurogenic inflammation.

**Aims:** We investigated the period-to-period and arm-to-arm reproducibility of the capsaicin-provoked vasodilatation (part I) as well as the involvement of the following mediators: calcitonin-gene related peptide (CGRP), prostaglandins (PG) and nitric oxide (NO).

**Methods:** In part I, a 2-period open label study, capsaicin (1000 µg/20 µL) was locally applied to the volar surface of both proximal forearms. In part II, responders (i.e. subjects showing an increase of >100% in dermal blood flow (DBF) in both arms in the two periods of part I) participated in a randomized, single-blind, 3-way, cross-over study. After capsaicin application, CGRP <sub>8-37</sub> (1200 ng.min<sup>-1</sup>. dL<sup>-1</sup> forearm), indomethacin (5 µg.min<sup>-1</sup>. dL<sup>-1</sup> forearm) or N<sub>G</sub>-monomethyl-L-arginine (L-NMMA, 0.2 mg.min<sup>-1</sup>. dL<sup>-1</sup> forearm) was infused in the brachial artery of the non-dominant arm. DBF was assessed by laser Doppler perfusion imaging before and at 10, 20 and 30 minutes after capsaicin application. DBF response was summarized by the percentage increase at 30 minutes (t<sub>30</sub>, %) and the area under the curve from 0 to 30 minutes (AUC<sub>0-30</sub>, %.min).

**Results:** Part I: The increase in DBF averaged 390% and 5035%.min for t<sub>30</sub> and AUC<sub>0-30</sub>, respectively (n = 11 subjects). Table 1: Period-to-Period and arm-to-arm reproducibility:

<table>
<thead>
<tr>
<th></th>
<th>t&lt;sub&gt;30&lt;/sub&gt; Mean difference (%)</th>
<th>AUC&lt;sub&gt;0-30&lt;/sub&gt; Mean difference (%.min)</th>
<th>Interarm 36 ± 114</th>
<th>Interarm 36 ± 114</th>
</tr>
</thead>
<tbody>
<tr>
<td>Interperiod</td>
<td>49 ± 157</td>
<td>1119 ± 3091</td>
<td>0.41</td>
<td>0.34</td>
</tr>
</tbody>
</table>

Data are mean ± SD; ICC, intraclass correlation coefficient.

Part II: See Figure 1, (*p = 0.003, paired Student t-test)

**Conclusion:** The capsaicin-induced increase in DBF shows a high arm-to-arm within subject reproducibility. This response is largely inhibited by CGRP<sub>8-37</sub>, but not by L-NMMA or indomethacin. These findings suggest that the capsaicin-induced DBF response can be used as a pharmacodynamic model to test CGRP antagonists *in vivo* in humans.

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**Unanticipated recovery from a status epilepticus after administration of levetiracetam**

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Levetiracetam is registered for the adjuvant treatment of epilepsy. However, there is more and more evidence that levetiracetam is also effective in the treatment of generalized epilepsy. Refractory status epilepticus (RSE) is defined as status epilepticus that fails to respond to first- and second-line therapy.

We here present a 20-year old woman with a history of M. Hodgkin stage IVB. She was successfully treated with 8 BEACOPP-escalated courses. Hereafter she was in complete remission. Approximately 4 weeks later she was admitted to our hospital with pain in her back. She had severe hypotension and bradycardy. Hereafter, she needed recussituation during eight minutes and she still had severe oxygenation problems. She was in a status epilepticus which was unresponsive to several combinations of the following drugs: phenytoin, propofol, pentobarbital, valproic acid, midazolam, and topiramate. Therapeutic drug monitoring of the anti-epileptic drugs was performed during the whole treatment and plasma concentrations were maintained within the therapeutic range.

Since two case report have been published in which levetiracetam shows good response in a few patients with posthypoxic myoclonus, levetiracetam was also added to the medication of this patient<sup>1,2</sup>. The administered dose of levetiracetam was 500 mg *bid*. After two days of coadministration of levetiracetam, the EEG still showed myoclonic activity and therefore the dose of levetiracetam was increased to 500 mg *tid*.

After 10 days the patient recovered neurologically; she could speak short sentences and was able to perform some simple tasks. On day 15 after the start of levetiracetam she was dismissed from the intensive care unit to the department of neurology.

The adding of levetiracetam to several antiepileptic drugs resulted in an unanticipated recovery of RSE in a 20-year old patient. Levetiracetam should be considered as adjuvant treatment in patients with RSE who do not respond to conventional therapy.

Levetiracetam is not metabolized by cytochrome P450 (CYP450), and therefore interactions between inducers or inhibitors of CYP450 are not anticipated. However, recently, it was demonstrated that plasma concentrations of levetiracetam were lowered during concomitant administration of phenytoin and phenobarbital. No rela-
tionships could be demonstrated between the exposure to levetiracetam in plasma and anti-epileptic effectiveness. Plasma concentrations of levetiracetam were measured twice in this patient (8.2 and 4.2 mg/L), and were somewhat lower than plasma concentrations reported in the literature [10.4–14.7 mg/L].


Clinical pharmacology of oral gemcitabine in patients with advanced solid tumors

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Introduction: Gemcitabine (dFdC) is an anticancer agent used i.v. in the treatment of a number of solid tumor types including pancreatic and non-small cell lung (NSCL) cancer. dFdC is metabolised to dFdU by cytidine deaminase particularly in the liver and as a prodrug it has to be intracellularly phosphorylated by deoxycytidine kinase to its main active triphosphate metabolite (dFdCTP) (Heinemann et al., 1992). Preclinical models reveal high activity of continuous exposure compared with intermittent exposure. In patients the most optimal therapy to achieve continuous exposure is by applying oral dosing.

Aims: To determine safety and any antitumor activity, and to assess the pharmacokinetics (PK) and – dynamics after continuous oral gemcitabine at two different dosing schedules.

Methods: Patients were treated daily for 14 days (21-day cycle, A) or every-other-day for 21 days (28-day cycle, B). Dose-escalation with 3 patients per dose level was performed. dFdC and dFdU in plasma and intracellular levels of dFdCTP in peripheral blood mononuclear cells (PBMCs) were measured on day 1, 14, 21 (A) and day 1, 21 and 28 (B) using LC-MS/MS.

Results: 30 patients have been included. Oral gemcitabine was well tolerated, and toxicity was mild (mainly gastro-intestinal). 1 patient developed hepatic- and renal failure in cycle 2, etiology unclear. No partial remission was reported and in 5 patients stabilisation of disease was observed. Plasma levels of dFdC were low (<10 ng/mL) with high interpatient variability (%CV) due to high first pass metabolism into dFdU (see Table 1). dFdU had a long t1/2 due to liver accumulation and slow release into the systemic circulation. dFdCTP levels in PBMCs were low and variable, but increased with dose.

Conclusions: After oral dosing gemcitabine has poor bioavailability and is extensively converted to dFdU. This may have implications for the toxicity and for further development of this drug.


Cardiovascular risk management in diabetes: which information regarding risk factors triggers the start of medication?

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Background: In patients with diabetes, timely initiation of cardiovascular treatment is important. Guidelines on cardiovascular risk management recommend the use of total risk assessment for initiating medication treatment. Many risk tables and risk calculators are available, but few doctors formally assess cardiovascular risk. They estimate risk subjectively based on their ‘clinical judgment’, and seem to focus on a limited number of risk factors. To counter current undertreatment, insight is needed in the use of risk factor information for the decision to start cardiovascular treatment.

Aims: To obtain insight in the use of information about blood pressure (systolic/diastolic) and cholesterol (total cholesterol and lipid ratio) levels for the decision of general practitioners to start cardiovascular treatment in diabetes patients.

Methods: We used data from the GIANTT database (1), containing clinical information and prescriptions collected from electronic medical records from general practitioners as well as a specialised diabetes service in the region. Included were 970 patients with type II diabetes managed by 33 general practitioners. Data from 2003–2004 were used. The influence of the risk factors’ level

Table 1
Mean PK parameters (%CV) of dFdU

<table>
<thead>
<tr>
<th>Part A (Day 14)</th>
<th>1*</th>
<th>2*</th>
<th>4</th>
<th>6</th>
<th>8*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose level (mg)</td>
<td>78</td>
<td>74</td>
<td>324 (17)</td>
<td>389 (23)</td>
<td>631</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>1675</td>
<td>1395</td>
<td>6530 (18)</td>
<td>8790 (26)</td>
<td>13750</td>
</tr>
<tr>
<td>AUCτ,ss (ng*h/mL)</td>
<td>8</td>
<td>12*</td>
<td>16</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>366 (19)</td>
<td>698</td>
<td>926 (18)</td>
<td>905 (20)</td>
<td>905 (20)</td>
</tr>
<tr>
<td>AUCτ,ss (ng*h/mL)</td>
<td>14125 (19)</td>
<td>24823</td>
<td>33235 (20)</td>
<td>32552 (32)</td>
<td>32552 (32)</td>
</tr>
</tbody>
</table>

*Values of two individual patients were available.
Dynamic modelling for estimating the cost-effectiveness of a Chlamydia trachomatis screening program

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2Foundation for STI control, Utrecht, The Netherlands

Objective: To estimate the cost-effectiveness of a systematic Chlamydia trachomatis (CT) screening program including partner treatment for the Netherlands using a dynamic approach.

Methods: Data on infection prevalence, participation rates and sexual behaviour were obtained from a large pilot study conducted in the Netherlands. We developed a dynamic SIS model, that is widely used in exploring the transmission dynamics of other infectious diseases, to estimate the impact of the screening program on the incidence and prevalence of CT in the population. Subsequently, a progression-of-disease tree was used to calculate the complications averted by the screening program. Cost-effectiveness is expressed as the net costs per major outcome averted (MOA). We compared doing nothing both with a one-off screening program and with screening on various time intervals.

Results: Compared to doing nothing the one-off screening program is estimated to cost €373 per MOA. However, restricting the screening to women only the program is estimated cost saving. Even though screening on various time intervals advert more serious complications, a one-off screening program is estimated more cost effective as the screening related costs increase relatively more (i.e. bi-annual screening is estimated to cost €3000 per MOA).

Conclusions: Our cost-effectiveness analysis shows that society had net to pay for the prevention of CT complications. Furthermore, as the prevalence returns to the steady state only very slow the one-off screening program is pharmaco-economically more favourable than screening on various time intervals. One could argue that €373 per MOA, for the one-off screening program, is a reasonable cost. A screening program consisting of screening women only should always be adopted from a pharmaco-economic point of view.

Antipsychotic drug use and hypothermia. Reported cases in literature and WHO database

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2OLDY (Old people Drugs & Dysregulations) study group
3Netherlands pharmacovigilance Centre (Lareb), Department of Pharmacotherapy and Pharmaceutical Care, RU Groningen, The Netherlands

Introduction: Antipsychotic drugs (APDs) can influence thermoregulation. The hypothermic effect of antipsychotic drugs, often leading to ICU admission, seems less well known than the risks of developing hyperthermia. Risk factors for hypothermia in AP users are not well known.

Method: We performed a literature search for case reports of hypothermia in AP users in Medline and Embase. Secondly we searched the WHO international database for Adverse Drug Reactions for reports of hypothermia and APD use.

Results: Our search resulted in 31 publications (42 patients, 45 events) and 9 non-published cases. Characteristics are shown in table 1. In the WHO database, 339 reports of hypothermia associated with APD use were registered (compared to 326 reports of APD related hyperthermia) (table 2).

Conclusions:
1. Hypothermia risk is increased in the first days following start or dose increase of APDs.
2. 63% of hypothermia reports are for atypical APDs.
3. APDs with strong 5-HT2 antagonism seem to be more involved in hypothermia.
4. Patients with schizophrenia seem to be at increased risk.
5. Hypothermia incidence equals hyperthermia incidence.
The association between antihypertensive drug combinations and the risk of myocardial infarction


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Introduction: In hypertension trials testing with individual antihypertensive drugs, thiazide diuretics and ACE-inhibitors were found to be most effective in reducing cardiovascular events. Most patients require more than one antihypertensive drug to control their hypertension. It is unresolved which combination of antihypertensive drugs has better effects on cardiovascular morbidity.

Aim: To compare different combinations of two antihypertensive drugs with the combination of thiazide diuretics and ACE-inhibitors (proved to be most effective) on the risk of myocardial infarction (MI).

Methods: In a population-based registry of pharmacy records linked to hospital discharge records (PHARMO) we used a nested case-control design to assess the association between antihypertensive 2-drug combinations and the risk of MI. Among users of antihypertensive drugs we selected subjects hospitalised for MI as cases if they had at least one prescription for antihypertensive drugs in the 3 months prior to their first MI and were registered in PHARMO for at least 1 year. Controls met the same eligibility criteria as the cases, but were not hospitalised for MI. To each case up to 12 controls were matched on age, gender and region.

All subjects were assigned an indexdate, for cases this was the date of their MI and for controls this was the same date as for the case to whom they were matched.

All subjects were recruited through community pharmacies that participate in PHARMO and were asked to fill in a questionnaire about demographics, cardiovascular diseases and risk factors. Only hypertensive subjects who used 2 antihypertensive drugs at the indexdate were included.

Logistic regression analysis was used to calculate odds ratios (OR) and 95% confidence intervals (CI) and to adjust for the potential confounding factors smoking, hypercholesterolemia, diabetes mellitus, obesity, use of aspirin, coumarins, statins and fibrates, history of cardiovascular disease, and family history of MI.

Results: We included 117 responding cases and 785 controls. Compared to users of thiazide diuretics and ACE-inhibitors combination, the risk of MI was statistically significant higher among users of thiazide diuretics and calcium channel blockers (OR 4.25; 95% CI: 1.45–12.50) and beta-blockers and calcium channel blockers.

Table 1
Characteristics cases in literature

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>41%</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>52.5 (24.4)</td>
</tr>
<tr>
<td>Reported body temperature (mean (SD))</td>
<td>32.6 (2.0)</td>
</tr>
<tr>
<td>Diagnosis known (n = 34)</td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>59%</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>18%</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>15%</td>
</tr>
<tr>
<td>Dementia</td>
<td>9%</td>
</tr>
<tr>
<td>Drug change</td>
<td></td>
</tr>
<tr>
<td>Start or dose increase</td>
<td>80%</td>
</tr>
<tr>
<td>No change</td>
<td>16%</td>
</tr>
<tr>
<td>Interval drug change detection hypothermia</td>
<td></td>
</tr>
<tr>
<td>&lt;2 days</td>
<td>58%</td>
</tr>
<tr>
<td>2–7 days</td>
<td>16%</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3.8%</td>
</tr>
<tr>
<td>ICU admission</td>
<td>2.2%</td>
</tr>
<tr>
<td>Hospitalisation (incl. prolonged)</td>
<td>69.8%</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Reports (n)</th>
<th>Reported OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pipamperon</td>
<td>10</td>
<td>42.40 (22.57–79.64)</td>
</tr>
<tr>
<td>Chloorprothixeen</td>
<td>4</td>
<td>22.58 (8.41–60.67)</td>
</tr>
<tr>
<td>Zuclonphenthixol</td>
<td>11</td>
<td>22.26 (12.25–40.44)</td>
</tr>
<tr>
<td>Tiapride</td>
<td>3</td>
<td>10.95 (3.51–34.13)</td>
</tr>
<tr>
<td>Flupentixol</td>
<td>5</td>
<td>6.13 (2.54–14.78)</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>31</td>
<td>4.68 (3.28–6.68)</td>
</tr>
<tr>
<td>Chloorpromazine</td>
<td>15</td>
<td>4.04 (2.43–6.71)</td>
</tr>
<tr>
<td>Perfenazine</td>
<td>2</td>
<td>1.78 (0.44–7.12)</td>
</tr>
<tr>
<td>Sulpride</td>
<td>2</td>
<td>1.80 (0.45–7.21)</td>
</tr>
<tr>
<td>Droperidol</td>
<td>1</td>
<td>1.32 (0.19–9.57)</td>
</tr>
<tr>
<td>Risperidol</td>
<td>111</td>
<td>11.12 (9.18–13.46)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>10</td>
<td>4.92 (2.64–9.17)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>29</td>
<td>3.26 (2.26–4.71)</td>
</tr>
<tr>
<td>Clozapine</td>
<td>61</td>
<td>2.36 (1.83–3.04)</td>
</tr>
<tr>
<td>Ziprasidon</td>
<td>3</td>
<td>2.50 (0.81–7.78)</td>
</tr>
</tbody>
</table>

ROR = (a/c) / (b/d); (a = no. of reports of adverse drug reaction with suspected drug; b = no. of reports of adverse drug reaction in total database; c = no. of reports regarding the suspected drug in database; d = total no. of reports in database).
The risk of fractures in patients currently or previously using lithium

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Conclusion: In the Afro-Caribbean population studied the association between TD parameters and genotype are clearly gender dependent and differ strongly between orofacial and axioappendicular dyskinesia.

The risk of fractures in patients currently or previously using lithium

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(OR 3.35; 95% CI 1.57–7.12). The risk of MI was not significantly different for users of beta-blockers and thiazide diuretics (OR 1.33), thiazide diuretics and AT1-blockers (OR 0.36), beta-blockers and ACE-inhibitors (OR 1.45), ACE-inhibitors and calcium channel blockers (OR 1.77), calcium channel blockers and AT1-blockers (OR 0.99) and other antihypertensive drug combinations (OR 1.52).

Conclusion: Thiiazide diuretics and ACE-inhibitors, which as single agents are more effective on cardiovascular endpoints than beta blocker and CCB also in combination appear to be more effective than combinations of other antihypertensive drugs.
Background: Lithium is one of the major long-term treatment options for patients with bipolar disorders. A recent case-control study (Vestergaard et al., 2005) reported a decreased risk of fracture for those ever having been on lithium treatment, within four years prior to the date of fracture. An association between exposure to lithium and the risk of fractures could be the result of either a pharmacological effect of the element itself (Wnt signalling or secondary hyperparathyroidism), the underlying disease (accident inducing behaviour related to mania or depression), or both. The objective of the present study was to further explore the relation between exposure to lithium and the risk of fractures, focussing on the relation with duration of use and time since discontinuation.

Methods: A large case-control study was conducted within the General Practice Research Database (GPRD). Cases were patients ≥18 years, with a first record of any fracture during GPRD follow-up. To each case one control-patient, without a history of fracture, was matched on age, gender and practice. As determinant for fractures we investigated current and past lithium use. Furthermore, using spline regression analysis, we investigated in current users the association between the risk of fractures and duration of use. For each case one control-patient, without a history of fracture, was matched on age, gender and practice. As determinant for fractures we investigated current and past lithium use. Furthermore, using spline regression analysis, we investigated in current users the association between the risk of fractures and duration of use and in past users the association between the risk of fractures with time since discontinuation.

Results: We included 231 778 cases and 231 778 controls. We found a decreased risk of fractures (OR 0.75; CI 95% 0.64–0.88) in current users, not varying with duration of use (r² = 0.035). For those having discontinued lithium ≥1 year, we found a trend for a higher risk of fractures, (OR 1.31; CI 95% 0.99–1.74), increasing with longer time since discontinuation (r² = 0.66).

Discussion: We found a decreased risk of fractures in those currently using lithium, and a trend towards an increased risk of fracture in past users, increasing with longer time since discontinuation. Further research is needed to elucidate whether the observed higher risk of fractures in past users of lithium can be attributed to more risk full behaviour resulting from deterioration of the underlying mood disorder. In addition, more research is warranted to unravel the mechanism responsible for the observed decreased risk of fractures in those currently using lithium.


A tool for assessing the relation between adverse drug events and medication errors

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Background: Medication safety is a prime concern in health care as medication errors (MEs) can result in patient harm and may have negative socio-economic implications. In studies that have evaluated medication safety, different methods have been used to identify and classify MEs and adverse drug events (ADEs) caused by such errors. However, the causal relationship between MEs and ADEs has not been assessed clearly in most studies. In the framework of our study on the effect of a computerized Physician Order Entry system on Medication Safety (the POEMS-study) an algorithm was developed to assess the causal relationship between MEs and ADEs in hospitalised patients.

Objective: To develop a tool for the standardised assessment of the likelihood that an ADE is caused by a medication error.

Method: The NCC MERP index was selected for the classification of MEs according to whether an adverse clinical outcome (e.g. ADEs) has occurred and the severity thereof (http://www.nccmerp.org). To assess the causal relationship between ADEs and MEs the Yale algorithm was chosen and slightly adapted (Kramer et al.). During two expert meetings of medication safety researchers and (hospital) pharmacists an algorithm was designed to link the Yale algorithm to the NCC MERP index. The feasibility of this new algorithm was tested in a sample of five patients in an additional meeting.

Results: Causality assessment was needed to link ADEs with an earlier ME that had reached the patient. For this assessment the questions of the Yale algorithm concerning previous general experience with the drug, alternative etiologic factors and timing of events were applicable to this study only. Originally, the Yale algorithm was developed to assess the likelihood that a specific drug caused a specific ADE. Therefore, the algorithm was slightly adapted so that the starting point for these questions became the ME instead of the drug. For example: when a drug was not administered as a result of omitted transcription by a nurse, return of disease symptoms for which the drug had been prescribed could be an ADE. If the likelihood had been assessed as possible or probable, the ADE was considered the outcome of the ME and was supposed to be preventable. Subsequently the severity of the ME could be classified. Testing showed that our algorithm was feasible. Individual assessment of the causal relationship between ADEs and MEs and the classification of MEs by the experts showed variation but consensus was reached on all cases.

Conclusion: Our algorithm is a tool to facilitate the assessment of the likelihood that an ADE is caused by a medication error in a standardised manner. Further study is necessary to test the performance of this tool.