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Prediction of clinically relevant adverse drug events in surgical patients

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Background

Risk stratification of hospital patients for adverse drug events (ADE) would enable targeting patients who may benefit from interventions aimed at reducing drug-related morbidity. It can support clinicians and hospital pharmacists in selecting patients to deliver a more efficient health care service. This study aimed to develop and test a prediction model that helps to identify patients at the day of hospital admission, who are at increased risk of developing a clinically relevant, preventable adverse drug event during their stay on a surgical ward.

Methods

Data of the P-REVIEW study were used. This study was designed to assess the impact of a multifaceted educational intervention on clinically relevant, preventable adverse drug events in surgical patients [1]. Thirty-nine variables were evaluated in a univariate and multivariate logistic regression analysis, respectively. Model performance was expressed in the Area Under the Receiver Operating Characteristics (AUROC). Bootstrapping was used for model validation.

Results

6780 admissions of patients at surgical wards were included during the pre-intervention period of the PREVIEW trial. 102 Patients experienced a clinically relevant, adverse drug event during their hospital stay that was deemed potentially preventable. The prediction model comprised five variables: age, number of biochemical tests ordered, heparin/LMWH in therapeutic dose, use of opioids and use of cardiovascular drugs. The AUROC was 0.86 (95% CI 0.83-0.88). At a cut-off point for an increased risk of developing an ADE of 1.6%, the model had a sensitivity of 80.4% and a specificity of 73.4%. The positive and negative predictive value were 4.5% and 99.6% , respectively. The bootstrap procedure did not significantly affect model parameters.

Conclusion

The combined use of a limited set of easily ascertainable patient characteristics can help physicians and pharmacists to identify, at the time of admission, surgical patients who are at increased risk of developing ADEs during their hospital stay. This may serve as a basis to take extra precautions to safeguard medication safety in those patients.

Literatuur

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A 25% higher vancomycin maintenance dose is required in neutropenic hematologic patients

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Background

Neutropenic hematology patients with severe sepsis and neutropenic patients with a predisposition for penicillin resistance are indicated for treatment with a glycopeptide antibiotic like vancomycin. There is accumulating evidence that this specific group of patients requires higher dosages vancomycin and that the increased required dose is likely associated with the presence of neutropenia. To prevent longlasting sub-therapeutic exposure and inefficacy of treatment, it is of utmost importance to obtain adequate exposure from the first dose onwards, with as little as dose titration necessary. We, therefore, aimed to quantify the effect of neutropenia on the pharmacokinetics of vancomycin.

Methods

We selected patients within the period from 2010-2016 that were treated with vancomycin for at least 2 days and from whom at least 1 vancomycin concentration was available. To be able to compare pharmacokinetics of vancomycin between various patient populations, patients were divided in three matched cohorts, i.e. 1) patients with a hematologic malignancy, 2) patients with a solid tumor, and 3) patients not known with cancer. Data, including general patient characteristics, vancomycin dose, and peak and trough plasma concentrations were retrospectively collected by analysis of the Electronic Healthcare Record System (EHRS) and by the use of the Santeon Farmadatabase (SFD). Pharmacokinetic analysis was performed by means of non-linear mixed effects modelling, with the software package NONMEM V7.3. Presence of neutropenia was investigated as a binary covariate on clearance and volume of distribution of vancomycin.

Results

A total of 116 patients were included (39 hematologic patients, 39 solid tumor patients and 38 pts not known with cancer). In total, 742 paired time-concentration observations were available for the pharmacokinetic analysis. When investigating the presence of neutropenia as a covariate for clearance of vancomycin, we found that neutropenia relevantly and significantly ($P = 0.018$) increased the clearance of vancomycin in neutropenic patients by 23% (95% confidence interval 3%-48%). The presence of neutropenia did not significantly impact volume of distribution ($P = 0.20$).

Conclusion

The clearance of vancomycin is increased in patients with neutropenia by 23%. For rapid pharmacokinetic target attainment, the maintenance dose of vancomycin should be increased by 25% in hematologic patients. Since the volume of distribution seems unaffected, no adjustment in loading dose is indicated. These dose adjustments do not rule out the necessity of further dose individualization by means of therapeutic drug monitoring.

Intrathecal morphine/bupivacaine for laparoscopic segmental colonic resection. A randomized controlled trial

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Background

Pain after laparoscopic surgery is intense, but relatively short-lived when compared to open surgery. Analgesia should be tailored accordingly. Post-operative pain management after laparoscopic colonic resections remains controversial. Enhanced Recovery After Surgery (ERAS) program-guidelines recommend to limit opioid use by administration of multimodal analgesics, which includes regional anesthesia techniques and Patient Controlled Intravenous Analgesia (PCIA). In this randomized controlled trial, we compared the intrathecal administration of an admixture of morphine/bupivacaine with the standard analgetic procedure within an ERAS-program. The goal of the study was to investigate whether intrathecal morphine/bupivacaine would lead to an enhanced recovery and limited need of systemic opioids after laparoscopic colonic surgery as compared to the standard procedure.

Methods

A single-center, double-blinded randomized controlled trial was performed. Patients scheduled for laparoscopic segmental intestinal resections were considered. Exclusion criteria were patients in whom contra-indications were present for spinal anesthesia, conversion to open surgery and gastric and rectal surgery. A sterilised intrathecal admixture of morphine/bupivacaine was formulated and produced by the hospital pharmacy. The intervention group received a single shot intrathecal morphine/bupivacaine (12.5 mg/300 mcg), just prior to the laparoscopic surgery. The control group received a sham procedure and a bolus of piritramide (0.1 mg/kg). Both groups received standardized general anesthesia and a PCIA-pump as postoperative analgesia. A decrease in days to "fit-for-discharge" was the primary outcome parameter.

Results

56 patients were enrolled. Patients in the intervention

group had an earlier "fit-for-discharge" rate (median of 3 versus 4 days, P = 0.044). Furthermore, there was a significant decrease in opioid-use and lower pain scores on the first postoperative day in the intervention group. Besides a higher incidence of pruritus in the intervention group (41% versus 8%), there were no differences in adverse events, time-to-mobilisation, fluid administration or patient satisfaction.

Conclusion

This RCT shows that intrathecal morphine is a more effective method of postoperative analgesia in laparoscopic surgery than intravenous opioids. These results have led to the admission of the morphine/bupivacaine intrathecal product into the hospital formulary. Studies to investigate the use of intrathecal morphine/bupivacaine in other indications are currently performed.

The effect of an improved collaboration between secondary and primary care on drug-related problems post-discharge

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Background

A hospital discharge is a critical period with respect to patient safety. Lack of communication, inadequate transfer of information between secondary and primary care and the patient can result in drug-related problems (DRPs). The objective of this study was to investigate the effect of an improved collaboration between secondary and primary care on the amount of DRPs post-discharge.

Methods

A prospective controlled multicenter study was conducted in two hospitals (OLVG and BovenIJ) and fifty community pharmacies in Amsterdam. Patients discharged from the internal medicine-, neurology-, cardiology- and pulmonology departments were included if at least one medication change was initiated during admission. Usual care patients received routine care: medication reconciliation at hospital admission and discharge by pharmacy technicians and pharmaceutical consultants (specialized pharmacy technicians). Intervention patients additionally received teach back at hospital discharge to assess whether the patient could specify which medication had changed during admission. Also, primary care providers (i.e. community pharmacy, general practitioner, home healthcare nurses) received a medication overview listing (reasons for) all in-hospital medication changes. Finally, the patient's community pharmacist performed a home visit ≤5 days post-discharge.

Four weeks post-discharge DRPs (adverse drug events, practical problems, doubts and concerns on the effectiveness and safety of medication) were assessed during a structured telephone interview (primary outcome). Also, knowledge regarding all medication changes implemented in the hospital and satisfaction with medication use were measured. Data were analysed by means of descriptive statistics. The independent T test was used for continuous variables and the Chi square test for frequencies. Ordinal logistic regression analyses were performed adjusting for confounders. P-values and adjusted odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results

In total 456 patients were included (usual care: n = 234, intervention: n = 222). DRPs decreased significantly from 66% in the usual care group to 52% in the intervention group (P < 0.01, adjusted OR 0.57 (95% CI 0.37-0.89)), primarily due to decreased post-discharge adverse drug events (25% versus 16%; P < 0.05).

Furthermore knowledge regarding all medication changes implemented in the hospital improved significantly in the intervention group (30% versus 42%; P < 0.05). In total, 82% of the patients in the intervention group reported that they were satisfied with their medication compared to 68% in the usual care group (P < 0.01).

Conclusion

This study highlights the importance of an improved collaboration between primary and secondary healthcare providers to ensure continuity of care and to reduce patient harm due to medication. DRPs were significantly reduced.

Effect of *CYP3A4*22*, *CYP3A5*3* and *CYP3A* combined genotypes on tamoxifen metabolism

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Background

Tamoxifen is the cornerstone of endocrine therapy for breast cancer. Recently, the decreased activity *CYP3A4*22* allele and the loss of function *CYP3A5*3* allele, have been described as potential factors that could help to explain the inter-patient variability in tamoxifen metabolism. The aim of this study is to analyze the impact of *CYP3A4*22*, *CYP3A5*3* and *CYP3A* combined genotypes in addition to CYP2D6 genotype on tamoxifen metabolism.

Methods

DNA from 667 women participating in the CYPTAM study (NTR1509) was genotyped for *CYP2D6*, *CYP3A4*22* and *CYP3A5*3*. Tamoxifen and metabolite concentrations were measured in serum, and metabolic ratios were calculated. The impact of *CYP3A4*22*, *CYP3A5*3* and *CYP3A* combined genotypes was examined by multiple linear regression analysis. A two-sided Student's t-test was used for comparisons between mean concentration levels and metabolic ratios.

Results

Among *CYP3A4*22* carriers, a tendency towards higher endoxifen levels was observed ($P = 0.088$), and significantly higher concentration levels of tamoxifen, N-desmethyl-tamoxifen and 4-hydroxy-tamoxifen were found. The Metabolic ratio tamoxifen/N-desmethyl-tamoxifen was significantly higher in *CYP3A4*22* individuals (0.59 versus 0.52, $P < 0.001$). At the same time, *CYP3A4*22* genotype contributed to improving the explained inter-variability between patients (R2 of the (log-transformed) metabolic ratio tamoxifen/N-desmethyl-tamoxifen improved from 21.8 % to 23.9 %, $P < 0.001$).

*CYP3A5*3* carriers did not show any significant difference in tamoxifen and its metabolites mean concentration levels. However, *CYP3A5*3* genotype marginally improved the explained variability of the (log transformed) metabolic ratio 4-hydroxy-tamoxifen/-endoxifen (from 44.9 % to 46.2 %, $P < 0.038$). In line with these results, *CYP3A* combined genotypes did not significantly contribute to improving the explained variability between patients.

Conclusion

Our data demonstrate that CYP3A genotype slightly contributes to explaining the variability between patients in tamoxifen metabolism. However, the effect is small, and therefore, it is unlikely to have any significant clinically relevance for the efficacy of tamoxifen. ■