AN EDUCATIONAL INTERVENTION TO IMPROVE NURSES REPORTING OF ADVERSE DRUG REACTIONS

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Introduction: Adverse drug reactions (ADR) are an important cause of mortality and morbidity leading to additional costs with health. Drug safety data before commercialization is limited and incomplete, which is the reason why pharmacovigilance is important. ADR reporting system is efficient in drug safety monitoring. Nurses can have an important role in ADR reporting due to their daily activities of drugs administration (including vaccines). However, among these professionals, there a high rate of underreporting. Based on the reasons proposed by Inman for underreporting ADR, it was concluded that the main obstacles to ADR reporting among nurses were indifference (the belief that a single case cannot contribute to medical knowledge) and the lack of knowledge about the pharmacovigilance system. The aim of this study is to evaluate the quantitative and qualitative increase of ADR reports by nurses after an educational intervention.
Methods: A quasiexperimental study was performed in nurses working in primary care in Braga district, Portugal. One hundred thirteen individuals were placed in the intervention group while the control group included 590 nurses. Two educational interventions were performed to nurses working in primary care in ACES Cavado II (intervention group) that focused on the problem of adverse drug reaction, the impact on public health and spontaneous reporting. Statistical analysis were based on absolute and relative frequencies.
Results: Between January 2013 and September 2014 the Northern Pharmacovigilance Centre received 8 reports/100 nurses from the intervention group and 5 reports/100 nurses from control group.
Conclusions: The educational intervention increased 1.6 times the number of reports during the study period. The second intervention had more impact than the first one.

There was no significant increase in the quality of ADR reports in the intervention group. In the second intervention the number of reports increased only at the intervention day.

THE INFLUENCE OF NUTRITIONAL STATUS ON ACETAMINOPHEN METABOLISM IN HEALTHY SUBJECTS

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Background: Animal studies have shown that fasting and obesity are predisposing factors for acetaminophen-induced hepatotoxicity. Fasting can decrease nontoxic clearance of acetaminophen by UDP-glucuronosyltransferases (UGT1A1, UGT1A6) and sulfotranserases resulting in increased formation of the toxic metabolite N-acetyl-*p*-benzoquinone imine (NAPQI), whereas obesity can increase NAPQI-formation by induction of hepatic CYP2E1. We investigated the effect of short-term fasting and a short-term high-fat diet on acetaminophen metabolism in healthy subjects. Furthermore, changes in UGT1A1-mediated metabolism were studied by using unconjugated bilirubin, metabolised by UGT1A1, as a proxy.
Materials and Methods: Nine healthy male subjects were enrolled in a crossover intervention study. Subjects received a single oral administration of 1000mg acetaminophen after an overnight fast following 3 interventions: (1) regular diet (control), (2) 36 hours of starvation and (3) 3 days of a high-fat diet consisting of 500 mL of cream supplemented to their regular diet. The sequence of the interventions was randomly assigned. Primary endpoint was the change in acetaminophen exposure defined as the difference in area under the plasma concentration-time curve ($\Delta AUC_{0\text{-}8\ hours}$) using non-compartmental analysis. Changes in UGT1A1-mediated metabolism were investigated by comparing baseline unconjugated (indirect) bilirubin concentrations between the interventions.
Results: Short-term fasting increased acetaminophen exposure by 28.2% ($\Delta AUC_{0\text{-}8\ hours}$, $P = 0.021$) and increased unconjugated bilirubin from 8.5 μmol/L (range, 3–21 μmol/L) to 21.5 μmol/L (range, 10–56 μmol/L) ($P = 0.008$) in comparison with control. Short-term high-fat diet did not affect acetaminophen exposure ($\Delta AUC_{0\text{-}8\ hours}$=0.15%, $P = 0.374$), but decreased unconjugated bilirubin from 8.5 μmol/L to 4.0 μmol/L (range, 2–10 μmol/L) ($P = 0.013$) when compared to the control intervention.
Conclusions: Fasting increases acetaminophen exposure and decreases nontoxic UGT1A1-mediated metabolism in healthy subjects. This may lead to increased hepatotoxicity. A high-fat diet did not alter acetaminophen exposure but increased UGT1A1-mediated metabolism.

THE VALUE OF COMPUTER ASSISTED MEDICATION REVIEW IN HOSPITALISED PATIENTS

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Introduction: Polypharmacy is one of the main risk factors for adverse drug events, drug–drug interactions and undertreatment. This makes medication management in the hospital a challenging responsibility. A medication review is used to optimise therapy in a structured way. It is done manually and therefore prone to mistakes. The aim of this study was to evaluate the additional value of our CDSS to manual medication reviews compared with manual medication review alone on medication errors in the hospital.
Methods: During 4 months data were gathered by observation of the medication reviews during the weekly grand rounds at an internal and orthopaedic ward and electronic extractions were made all patients. The e-data were analysed by a Clinical Decision Support System (CDSS). After data collection, notifications obtained during the grand rounds and from the CDSS were analysed.
Results: In total 332 patients were reviewed, 219 (mean number of drugs = 9) at the internal ward (242 alerts from which 133 from cdss) and 113 (mean number of drugs = 10)at the orthopaedic ward (61 alerts from which 44 from cdss). Mean age on both wards was 67 years. Further data is shown in table.

Type of error	Total	Value CDSS
		Yes (%)
Indication without medication	59 (100)	32(54.2)
Medication without indication	48 (100)	0 (0)
Contraindications/interactions/side effects	102 (100)	88 (86,.3)
Dosage problem	34 (100)	30 (68.2)
Double medication	6 (100)	3 (50)
Wrong medication	10 (100)	0 (0)
Therapeutic drug monitoring	34 (100)	24 (70,6)
Total	303 (100)	177 (58.4)

Conclusions: The CDSS is a relevant addition to the manual performed medication reviews in the hospital. An accurate CDSS is imperative to assist the physician in performing medication reviews. Future developments include adding medical history to the clinical rules, fine-tuning the CDSS and determine relevance on patient outcome.

CHARACTERIZATION OF THE STRUCTURE OF HUMAN SERUM ALBUMIN IN PATIENTS WITH END STAGE RENAL DISEASE AFTER KIDNEY TRANSPLANTATION

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Introduction: The degree of oxidized cystein (Cys) 34 in human serum albumin (HSA) is a sensitive biomarker for diagnosis of the oxidative stress in various diseases. Although previous report suggested that the oxidation of Cys 34 in HSA was significantly increased with the progression of end stage renal disease (ESRD), a representative oxidative stress-associated disease, little is known regarding its variation in ESRD patients after kidney transplantation. The purpose of this study was to assess whether improvement of renal function after kidney transplantation had an impact on the redox state of Cys 34 in HSA.
Material and Methods: Eighteen patients with ESRD who were scheduled to undergo the first kidney allograft transplantation were enrolled. Plasma sample was collected from the ESRD patients before and 7, 14, 30, 60, 90, 180 and 360 days after kidney transplantation. Structual heterogeneity of HSA was analysed using electrospray ionization time-of-flight mass spectrometer (ESI-TOFMS).
Results and Discussion: Since creatinine clearance increased significantly from day 7 after kidney transplantation compared to before kidney transplantation and remained almost stable thereafter, it was suggested that these allograft transplantations were successful. Two major peaks, corresponding to the cysteinylation of Cys 34 (Cys-Cys 34-HSA) and reduced Cys 34-HSA in plasma samples obtained from these patients before kidney transplantation, were identified by ESI-TOFMS. A significant decrease in the ratio of Cys-Cys 34-HSA and reduced Cys 34-HSA was observed from day 7 after kidney transplantation compared to before. In addition, the gradual decrease of its ratio was confirmed until 360 day after kidney transplantation.
Conclusion: These results suggested that the redox state of Cys 34 in HSA was improved by the restoration of renal function after kidney transplantation.

RELATIONSHIPS BETWEEN PLASMA CONCENTRATIONS OF FENTANYL AND 4BETA-HYDROXYCHOLESTEROL IN CANCER PATIENTS

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Background and Introduction: Transdermal fentanyl possesses a large pharmacokinetic variation in cancer patients. Genetic polymorphism of cytochrome P450 (CYP) 3A5 influences the plasma exposure of fentanyl. Recently, the serum concentration of 4β-hydroxycholesterol has been reported as an endogenous marker of CYP3A4/5 in humans. The aim of this study was to evaluate the concentrations of plasma fentanyl and serum 4β-hydroxycholesterol based on CYP3A5 genetic polymorphisms in cancer patients.
Material and Methods: Forty Japanese cancer patients treated with transdermal fentanyl were enrolled in this study. Blood samples were obtained at day 8 or later after starting the medication. The concentrations of plasma fentanyl and serum 4β-hydroxycholesterol were measured using LC-MS/MS. The relationships between the concentrations of plasma fentanyl and serum 4β-hydroxycholesterol, and CYP3A5 genotype were evaluated.
Results: The medians of theoretical absorption rate and plasma concentration of fentanyl were 0.64 μg/h/kg and 1.74 ng/mL, respectively, in Japanese cancer patients. The plasma concentration of fentanyl normalized with theoretical absorption rate was significantly higher in the CYP3A5*3/*3 group than in the *1 allele carrier group. The median and the interquartile range of serum 4β-hydroxycholesterol concentration were 41.1 and 27.6 to 61.4 ng/mL, respectively. The serum concentration of 4β-hydroxycholesterol was significantly lower in the CYP3A5*3/*3 group than in the *1 allele carrier group. The concentration of plasma fentanyl normalized with the theoretical absorption rate was not correlated with that of serum 4β-hydroxycholesterol.
Conclusion: CYP3A5*3 affected the blood exposures of fentanyl and serum concentration of 4β-hydroxycholesterol in cancer patients. However, the blood exposure of fentanyl was not able to explain using the serum concentration of 4β-hydroxycholesterol. Nonmetabolic factors may affect the plasma exposure of fentanyl in cancer patients.

EFFECT OF CYP2D6 GENETIC POLYMORPHISM ON THE PHARMACOKINETICS OF MULTIPLE-DOSE METOCLOPRAMIDE

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Introduction: Metoclopramide is indicated for the treatment of heartburn caused by gastroesophageal reflux and is commonly used to treat nausea and vomiting. Metoclopramide is mainly metabolized by CYP2D6, and to some extent by CYP3A. Metoclopramide is also known for potent inhibitor of CYP2D6. CYP2D6 is highly polymorphic and the polymorphism of CYP2D6 significantly affects the pharmacokinetics of drugs in clinical use, such as codeine, risperidone, and fluoxetine. Therefore, we investigated the effect of *CYP2D6* genetic polymorphism on the pharmacokinetics of metoclopramide after multiple-dose.
Material and Methods: Forty one healthy Korean subjects were recruited and classified into three different groups according to *CYP2D6* genotype: *CYP2D6*wt/*wt* (**wt*= **1* or **2*, n = 11), *CYP2D6*wt/*10* (n = 15), and *CYP2D6*10/*10* (n = 15). After overnight fasting, each subject received a single oral dose of 10 mg metoclopramide. Blood samples were collected up to 24 hours after drug ingestion, and plasma concentrations of metoclopramide were determined by using validated liquid chromatography-tandem mass spectrometry system.
Results: After multiple-dose metoclopramide, C_{max} and $AUC_{0\text{-}24}$ of metoclopramide in *CYP2D6*10/*10* group were significantly higher than those in *CYP2D6*wt/*wt* group ($P = 0.014$ and $P = 0.007$, respectively). Also, apparent oral clearance (CL/F) in *CYP2D6*10/*10* group was 24.6% lower than that in *CYP2D6*wt/*wt* group ($P = 0.018$). There were no significant differences in t_{max} and $t_{1/2}$ among 3 different groups.
Conclusions: The present study showed that *CYP2D6* genetic polymorphism had significant effects on the pharmacokinetics of multiple-dose metoclopramide.

INFLUENCE OF CYP2D6 GENETIC POLYMORPHISM ON THE PHARMACOKINETIC PARAMETERS OF RISPERIDONE AND ITS ACTIVE METABOLITES

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Introduction: Risperidone is an antipsychotic drug that is used to treat schizophrenia and symptoms of bipolar disorder. Risperidone