ABSTRACT REVIEW

BAR14-0455
Pharmacokinetic/pharmacodynamic evaluation of metronidazole and cefuroxime in prophylaxis of colorectal surgery

Co-authors
M. Nogales1, A. Isla2, R. Hernanz1, S. Martinez1, A. Rodriguez2, J. Saez de Ugarte3, C. Martinez1.
1Hospital Universitario de Álava-Txagorritxu center, Pharmacy, Vitoria-Gasteiz, Spain.
2Universidad del País Vasco (UPV/EHU), Pharmacokinetic Group, Nanothechnology and Genic Therapy, Pharmacy School, Vitoria-Gasteiz, Spain.
3Hospital Universitario de Álava-Txagorritxu center, Surgery, Vitoria-Gasteiz, Spain.

Background
The antibiotics used for prophylaxis colorectal surgery (CS) must maintain appropriate plasmatic concentrations (PC) during the whole surgery to avoid surgical site infections (SSI).

Purpose
To determine the suitable of a single dose of metronidazole and cefuroxime for prophylaxis of CS, assessing the relation between antibiotic PC and the minimum inhibition concentration (MIC) of the microorganisms often isolated in SSI.

Materials and Methods
Prospective study involving 64 patients undergoing CS in a tertiary hospital. Each patient was administered a single dose of 1.5g metronidazole and 1.5g cefuroxime by intravenous infusion over 20-60 minutes during induction of anesthesia. 4-5 blood samples were taken; the first at the time of starting the infusion and one of them at the end of surgery. Mean surgery duration was 2.68h (range 0.75-6.83h). We assessed whether dosing regimens used ensured concentrations of both drugs above the MIC of the microorganisms commonly isolated in SSI, during the whole intervention. The target concentration was 8mg/L, the highest susceptibility breakpoint for bacteria expected to be found in these procedures.

Results
Metronidazole PC at the time of closure of peritoneal cavity ranged from 8.60mg/L to 49mg/L, all values above 8mg/L. Cefuroxime PC at the time of closing ranged from 2.72mg/L to 72.63mg/L. In 6 cases, where surgery was prolonged over 2.6h, cefuroxime concentrations at closing time was less than 8mg/L. Considering that the elimination half-life of cefuroxime is 1.3h and after 2.6h (two elimination half-lives) plasma levels fall below the target value, a second dose of 1.5g of cefuroxime should be recommended in surgeries that extends over 2h to ensure target concentration during all surgery.

Conclusions
Single dose of 1.5g of metronidazole is able to maintain suitable levels of drug in plasma for the entire surgery. In the case of cefuroxime, it would be necessary to administer additional doses when the surgery is extended over 2 hours.

No conflict of interest

Keywords
Metronidazole; Cefuroxime; Pharmacokinetic/pharmacodynamic;

Authors letter
Relevance: 3 Innovation: 2 Implication for future hospital practice of this abstract: 3. This study have given awareness to surgeons how important is to repeat the doses when the surgery takes more than 2 hours to protect the patient from surgical site infection.

Score: 240

Remarks all reviewers:
Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications

1.
Modifications needed: ;
Nominee: No

Last sentence in the M&M section : the target concentration was 8 mg/L, of which drug correct the numbers: 72.63 mg/L is not realistic --> 73 mg/L 2.72 --> 2.7
Langebrake, Claudia: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications

2.
Modifications needed: ;
Nominee: No

Please comment on the high metronidazole-dose of 1.5g.
Bar14-0458
Relationship between vancomycin trough concentrations and nephrotoxicity

Co-authors
1Hospital Costa del Sol, Pharmacy, Marbella, Spain.
2Hospital Torrecárdenas, Pharmacy, Almería, Spain.
3Northampton Hospital, Pharmacy, Northampton, United Kingdom.

Background
High vancomycin trough concentrations have been correlated with good anti-MRSA and other gram-positives activity. However, the rate of nephrotoxicity varies markedly among studies and optimal dosage regimen remains somewhat controversial.

Purpose
To compare the incidence of vancomycin-related nephrotoxicity in patients with high (>15 mg/L) vs low (<15 mg/L) trough concentrations.

Materials and Methods
Retrospective study conducted from January 2009 to August 2013. Inclusion criteria: patients over 18 years-old who completed a course of vancomycin (duration≥72 h), had baseline (pre-vancomycin) and intratherapy serum creatinine determined, and had at least one steady-state (2 to 4 days into therapy) vancomycin trough concentration determined. According to their trough levels, the patients were included into one of the following categories: those in which vancomycin trough was <15mg/L (hereafter group 1) and those with vancomycin trough ≥15mg/L (hereafter group 2). Pharmacokinetic data were estimated using a Bayesian approach (Abbottbase PKS, Abbott®). Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL or a >50% increase from the baseline for two consecutive determinations.

Results
30 patients included, 18 belonging to group 1 and 12 to group 2. Demographics: mean age 68.1, female 33%. Data among groups were consistent throughout the population.

Median (CI95%) pharmacokinetic data: AUC=585 [507-664], clearance=3.2 L/h [2.6-3.8], dose=1,820mg [1,569-2,075], and duration of treatment 13.5 days [11.0-16.1]. No nephrotoxicity in group 1 vs 2 patients (16%) in group 2.

Conclusions
The incidence of nephrotoxicity was relatively low in patients with trough concentrations above 15 mg/L. A vancomycin dosage regimen aimed to maintain trough concentrations over 15mg/L did not compromise renal function in our cohort. In addition, the episodes registered were moderate in severity and reversible after vancomycin discontinuation. Nonetheless, a larger population would be necessary to address these and other safety issues.

No conflict of interest

Keywords
Vancomycin; Nephrotoxicity; Trough concentrations;

Authors letter
The rate of nephrotoxicity varies markedly among studies and optimal dosage regimen remains somewhat controversial. We wanted to compare the incidence of vancomycin-related nephrotoxicity in patients with high (>15 mg/L) vs low (<15 mg/L) trough concentrations, to check the safety of the treatment.

Score: 200

Remarks all reviewers:
Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
1. Modifications needed:
Nominee: No

Langebrake, Claudia: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
2. Modifications needed:
Nominee: No

Please comment on concommitant treatment, especially other nephrotoxic drugs. Were there differences regarding PK-data between group 1 and group 2?
Severe hepatotoxicity in a patient treated with chemotherapy and phytotherapy: a case report

Co-authors

N. Fonts1, M.E. Moreno1, G. Anguera2, M.C. Pallarès1, M.A. Mangues1.

1Hospital de la Santa Creu i Sant Pau, Pharmacy, Barcelona, Spain.
2Hospital de la Santa Creu i Sant Pau, Oncology, Barcelona, Spain.

Background

A large proportion of cancer patients are estimated to use herbal medicines. Because of the possibility of unwanted side effects or interactions with conventional treatments and chemotherapy is important to know if patients are taking herbal medicine and supplements.

Purpose

To report severe liver toxicity in a patient treated with paclitaxel and carboplatin who took concomitantly a herbal preparation containing echinacea and propolis.

Materials and Methods

A 78-year-old man, former smoker, with a history of hypertension, dyslipidemia and thrombosis in his left eye, treated with enalapril 10 mg/day, simvastatin 20 mg/day, aspirin 100 mg/day and omeprazole 20 mg/day. The patient was diagnosed with lung adenocarcinoma (T4N0M1, stage IV, adrenal), Karnofsky index 90%. He was initially treated with carboplatin AUC 5 + paclitaxel 175 m² (day 1, 21-day cycles).

After the first cycle, the patient showed grade 3 liver toxicity with an increase in aspartate aminotransferase (AST) from 9.6 IU/L to 184 IU/L, alanine aminotransferase (ALT) from 30.6 IU/L to 280 IU/L, alkaline phosphatase (ALP) from 72 IU/L to 365 IU/L and gamma-glutamyl transpeptidase (GGT) from 24 IU/L to 409 IU/L. It was decided to stop chemotherapy and other potentially hepatotoxic drugs such as simvastatin and omeprazole.

The patient was asked about the use of other medication apart from that described. The patient explained that due to his persistent hoarseness, a symptom of the disease, he was taking a phytotherapeutic product indicated for a sore throat that contained propolis, echinacea and vitamin C.

A literature review was carried out.

Results

A case of echinacea-induced severe acute hepatitis is described in the literature. Echinacea has been thought to have potential for liver toxicity because of the presence of pyrrolizidine alkaloids, which cause vasospasm and may lead to hypoxia and liver necrosis. It is recommended to avoid association with hepatotoxic drugs. In addition, echinacea is a CYP3A4 inhibitor and paclitaxel is a CYP3A4 substrate. Consequently, echinacea can potentiate the hepatic toxicity of paclitaxel, described in the literature as an increase in FA (22%), AST (19%), bilirubin (7%) and hepatic encephalopathy or necrosis (<1%). It is recommended to avoid this association.

With regard to propolis, acute hepatitis has been described in two patients taking this substance.

After normalization of hepatic enzymes, the chemotherapeutic scheme is changed to carboplatin AUC 4 + Gemcitabine 800 mg/m², to avoid possible liver toxicity associated with paclitaxel. The patient is being treated with this new treatment scheme without liver toxicity.

Conclusions

Echinacea and propolis may have interacted with paclitaxel and other hepatotoxic drugs enhancing the hepatotoxicity that appeared in the patient. It is important to question the patients on their use of herbal treatment. The pharmacist has a role in the prevention and detection of possible side effects or interactions between herbs and chemical drugs.

No conflict of interest

Keywords

hepatotoxicity; echinacea; paclitaxel;

Authors letter

1.- Impact on efficacy and security of chemotherapy treatment. 2.- Currently there are very few data available in the literature that examine the risk and hepatic side effects of using herbal products, such as echinacea and propolis. 3.- Question the patients on the use of herbal treatment should be a routine practice before starting chemotherapy treatment.

Score: 140

Remarks all reviewers:

Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted
Nominee: No

this is an important n=1 report
Langebrake, Claudia:

Rejected
Word count 456 --> abstract too long
BAR14-0758
Tacrolimus plasmatic levels in adults during hematopoietic stem cell allotransplant

Co-authors
P. CARMONA OYAGA1, G. Liceaga Cundin1, I. Fernández González1, O. Valbuena Pascual1, A. Asensio Bermejo1, J. Barral Juez1, M. Umérez Igartua1, M.T. Artola Urain2, J.J. Ferreiro Martinez2, M.P. Bachiller Cacho1.
1Donostia University Hospital, hospital pharmacy, San Sebastián, Spain.
2Donostia University Hospital, haematology, San Sebastián, Spain.

Background
When an unrelated donor is used for an allogenic hematopoietic stem cell transplant (AlloHSCT) high immunosupresive therapy is needed during early post-transplant period as prophylaxis against acute graft versus host disease (aGVHD). Tacrolimus is one the drugs used with a target level of 5-15 ng/mL.

Purpose
To compare the accuracy of real plasmatic tacrolimus levels with target levels in the immediate post-transplant period.

Materials and Methods
A retrospective revision was made between 2008/01/01 and 2013/09/30 of all aGVHD prophylaxis that included tacrolimus. Data were obtained from electronic medical history records and Pharmacy intravenous Unit database.

Results
Tacrolimus was used in 46 patients (17 women) with a median of 51 years old (17-69). In all cases the first dose of tacrolimus was administered on day -1 at 0.03mg/kg/day by intravenous continuous infusion.

Only half of patients, 23 (50%) were on therapeutic range when the first measure was made. Supratherapeutic levels were found in 15 patients and infratherapeutic in 8 patients.

This first tacrolimus plasmatic level was obtained between day +2 and day +11.

Conditioning was made with myeloablative regimens (fludarabine-busulphan for 13 patients, Total body irradiation and cyclophosphamide for 5 patients) and non myeloablative regimens (fludarabine-melphalan for 7 patients, fludarabine-busulphan for 17 patients and fludarabine-cyclophosphamide for 3 patients).

Antibiotic prophylaxis was made in all cases with ciprofloxacin and antifungal prophylaxis was fluconazole for 42 patients, voriconazole for 3 patients and caspofungin in one case.

There is not a direct relationship between the day of measurement, the conditioning regimen, the antibiotic or antifungal prophylaxis and the tacrolimus plasmatic level obtained.

Conclusions
There is a great discordance among theoretical tacrolimus plasmatic levels and real levels.

After this revision a pharmacokinetic drug interaction among drugs used during conditioning regimes or antibiotic or antifungal prophylaxis is excluded. A deep revision of the circuit of tacrolimus samples obtention and manipulation is mandatory.

No conflict of interest

Keywords
Tacrolimus;allogenic hematopoietic stem cell transplant;Plasmatic level;

Authors letter
This abstract has a hard implication for future hospital pharmacy practice because there is a problem worldwide with tacrolimus plasmatic levels. Exactly, is not known why we can't manage to reach therapeutic levels. Therefore, it's necessary to study everything that might influence.

Score: 200

Remarks all reviewers:
Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted.
Nominee: No

Langebrake, Claudia: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
Nominee: No

Please comment on the influence of renal function and other possible factors that influence tacrolimus
BAR14-0772
Analysis of patients with digoxin intoxication admitted to hospital as emergencies

Co-authors
S. Cobo Sacristan¹, E. Leiva Badosa¹, ME. Miquel Zurita¹, N. Méndez Cabaleiro¹, A. Alcorta Lorenzo¹, E. Santacana Juncosa¹, R. Juvany Roig¹, R. Jódar Masanes¹.
¹Hospital Universitari de Bellvitge. IDIBELL. Pharmacy, L'Hospitalet de Llobregat, Spain.

Background
Digoxin, the oldest cardiovascular drug, has been used for the treatment of heart failure and in frequency control strategies in atrial fibrillation (AF) patients. American College of Cardiology/American Heart Association (ACC/AHA) guidelines from 2009 and European Society of Cardiology (ESC) guidelines from 2012, on the management of acute and chronic heart failure (CHF), recommend digoxin for symptom relief and reducing hospital admissions. The ESC-recommended serum digoxin levels used for treating of CHF are 0.8–1.5 nmol/l (0.6–1.2 ng/ml) and equivalent ACC/AHA guidelines recommend 0.6–1.2 nmol/l (0.5–0.9 ng/ml). A serum digoxin level ≥3.0 nmol/l (2.5 ng/ml) is considered to be toxic.

Purpose
The aim of our study is to analyse a patient population admitted to emergencies for digoxin intoxications in a third-level hospital.

Materials and Methods
This a retrospective single-centre study of patients admitted at emergencies with the diagnosis of digoxin intoxication from January 2010 to May 2012. Variables collected from medical records: demographic data (sex, age), antecedents (diabetes, acute (ARF) and chronic (CRF) renal failure, hypertension, dyslipidaemia, CHF), digoxin treatment data, reason of intoxication, analytical data at admission and treatment at discharge. All categorical variables are reported as frequency and percentage, while the continuous variables were reported as mean±standard deviation.

Results
136 out of 237,068 patients admitted to hospital as emergencies had digoxin intoxication (106 women, 81.8±8.7 years). 36.1% diabetic, 53.5% and 35.6% suffered ARF and CRF, 86.7% hypertensive, 45.9% dyslipidaemia and 69.2% CHF). 47.8% were treated with digoxin for AF and 47% for CHF and AF. The mean daily dose of digoxin was 0.163±0.050 mg. The main reasons for digoxin intoxication were ARF (34.5%), acute kidney injury in CRF (22.7%) and no dosage adjustment (21.8%). The mean digoxin serum levels were 3.36±1.29 mcg/L and creatinine 167.9±121.4 μmol/L. Two patients required treatment with antidigoxin antibody and three were admitted to the ICU. At discharge, digoxin treatment was stopped (53.2%), dose adjusted (23.4%) or changed to another drug (12.9%) in most of the cases.

Conclusions
According to our results, the population at most risk of suffering digoxin intoxication are old women with renal failure. Therefore, early recognition is important for close monitoring and reduce admissions.

No conflict of interest

Keywords
digoxin; intoxication; serum levels;

Authors letter
1) Digoxin intoxications are important given the high prevalence of treatment with digoxin. 2) This is an observational study of an old cardiovascular drug. 3) However, it can be very useful to determine the population at risk for digoxin intoxication.

Score: 240

Remarks all reviewers:
Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted
Nominee: No
Langebrake, Claudia: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications
2.
Modifications needed: ;
Nominee: No
Drug Interactions with azole antifungals in patients treated with Hematopoietic Stem Cells

Background
The incidence of invasive fungal infections is increasingly important in patients treated with hematopoietic stem cells. These infections are the leading cause of morbidity and mortality in these immunocompromised patients.

Fluconazole and Voriconazole are the main azole prescribed in the service of Hematology and Transplant at the National Center for Bone Marrow Transplant.

These two molecules are both substrates and inhibitors of cytochrome P-450 which is the source of many drug interactions with drugs metabolized by these enzymes.

Purpose
The objective is to evaluate the prevalence of drug interactions in patients treated with azole (Voriconazole and Fluconazole) and investigate the possible consequences of these interactions.

Materials and Methods
A retrospective study was performed on 1067 daily drug prescriptions of 38 patients (61% men and 39% women) treated with hematopoietic stem cells and hospitalized during 2012 in the service of hematology and transplant.

Results
The average number of drugs per prescription is 5 drugs with a minimum of 3 and a maximum of 17.

The average number of interactions is 2 per prescription, ranging from 2 to 18 interactions.

60% of prescriptions collected contain an azole antifungal, with a slight predominance of Voriconazole 34% versus 26% for fluconazole.

74% of prescriptions containing an antifungal azole have at least one interaction with this antifungal drug.

In one patient (or 2.63%), an association was noted against-indicated. This interaction involved the co-prescription of voriconazole and rifampicin (an enzyme inducer responsible for the decrease in the concentration of voriconazole in the blood of more than 95%).

Also a not recommended interaction was observed in another patient between voriconazole and sirolimus.

The majority of interactions are precautions for use (3rd level of risk):

- Voriconazole: ciclosporine, Lowen et Gaviscon
- Fluconazole: ciclosporine, Sintrom et Gaviscon

Azole, by their enzymatic inhibition of CYP3A4, increase plasma concentrations of ciclosporine and thus the risk of nephrotoxicity.

Conclusions
Understanding the mechanisms of drug interactions allows clinicians to avoid certain interactions and develop a possible strategy to minimize iatrogenic events. This is facilitated by the establishment of a computerized system in the service to prevent iatrogenic drug and ensuring patient safety.

No conflict of interest

Keywords
interaction; drug; azoles;

Authors letter
- Management of drug interaction is capital to prevent iatrogenic events. - the presence of clinical pharmacy in a clinical department can be important to manage such drug interaction

Score: 120

Remarks all reviewers:
Neef, Cees: Conclusion warranted
Conflict of interest clear
Accepted, but Author modifications 1.
Modifications needed: ;
Nominee: No

use only generic names: Lowen, Sintrom, etc
Langebrake, Claudia: Conclusion NOT warranted
Conflict of interest clear
Rejected
2.6.
Reason for reject: ;
The described interactions are all well-known. In the setting of allogeneic HSCT, the concommittant application of an azole and a calcineurin-inhibitor or an m-Tor-inhibitor is common and drug levels are usually monitored.