Conflict of Interest No conflict of interest

4CPS-239 POPULATION PHARMACOKINETICS OF ISAVUCONAZOLE BASED ON PHAMACOGENETICS IN IMMUNOSUPPRESSED PATIENTS

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Background and Importance Isavuconazol has a safety profile and favorable pharmacokinetic characteristics. However, studies in real-life practice have found unexpected drug levels in different groups of patients.

Aim and Objectives To develop a population pharmacokinetic model (PopPK) that describes the behaviour of isavuconazole in prophylaxis and treatment of invasive fungal infections (IFI) and to evaluate possible factors affecting dosage.

Material and Methods A prospective, multidisciplinary study including immunosuppressed patients treated with oral and intravenous isavuconazole as prophylaxis or treatment for IFI was carried out from June 2020 to January 2022. Variables considered were: demographic, clinical, biochemical and genetic (polymorphisms, presence of inductors, inhibitors and the degree of saturation -DG- of drug-metabolising enzymes of CYP3A4, CYP3A5 and CYP2B6). DG was tested using SuperCYPsPred.

Blood samples were collected predose Isavuconazole was analysed using ultra performance liquid chromatography coupled with ultraviolet detection.

Non-linear mixed effects modelling using first-order conditional estimation with interaction (FOCEI) was used to develop the PopPK model using NONMEM v7.4. Data visualisation and statistical analyses were carried out in R v.3.4.

Results A total of 31 patients (10 females) from the haematology (19) and intensive care (12) services were included in the study. The median (interquartile range) age was 58 (17) years and total body weight was 77 (17) kg. The percentage of patients who presented non-wild type genotypic was 20% for CYP3A4. 99 samples were determined and the mean concentration (standard desviation) was 1.80 (0.95) µg/mL.

Isavuconazole PK was best described by a single-compartment model with first order absorption and elimination. Isavuconazole absorption rate was fixed at 22.6 1/h as previously reported by Cojutti et al. 2021. The apparent volume of distribution was 147 L and the apparent clearance (CL/F) was described by the following equation:

$$CL/F(L/h) = 3.54*(ALB/2.9)^{-0.7}*(BS/1,9)^{1,9}*(1+0.8)^{3A4ind}$$

where serum albumin (ALB) is expressed in g/dL; body surface (BS) in m^2 and 3A4ind indicates the presence of inductor drugs for CYP3A4.

The interindividual variability for CL/F was 40% and the residual variability was 30% (additive) and 0,05 µg/mL (proportional).

Conclusion and Relevance The developed PopPK model adequately characterises the kinetic behaviour of isavuconazole and includes the ALB, BS and the presence of inductors of CYP3A4 parameters that affect its clearance.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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4CPS-244 ANALYSIS AND COMPARISON OF OLANZAPINE ADMINISTRATION IN SMOKING AND NON-SMOKING PATIENTS

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Background and Importance Olanzapine is an atypical antipsychotic that is metabolised by the cytochrome P-450 (CYP1A2 isoenzyme). This isoenzyme is induced by tobacco smoke, resulting in reduced plasma concentrations of olanzapine when both are administered concomitantly.

Aim and Objectives The aim is to analyse and compare the daily dose of olanzapine and its plasma concentration in smoking and non-smoking patients.

Material and Methods Retrospective observational study of patients on chronic treatment with olanzapine, whose levels were monitored in the clinical pharmacokinetics area of the Pharmacy Service of a regional hospital between 01/01/2021 and 08/06/2021.The daily doses administered, age, sex and results of plasma monitoring were consulted by accessing their clinical records. Therapeutic range of olanzapine considered: 20–80 mcg/mL. To evaluate the effect of CYP1A2 isoenzyme induction, the mean concentrations obtained were compared with those that should theoretically be present in the group of smokers according to the linear dose-concentration pharmacokinetic behaviour of olanzapine in non-smokers.

Results Sixty-two patients were monitored, five were excluded (four for undetectable levels and one for a self-harm attempt), so that the analysis finally included 57 patients in total: 17 smokers (29.8%) and 40 non-smokers (70.2%). 21 women (36.8%): 9 smokers and 12 non-smokers; 36 men (63.2%): 8 smokers and 28 non-smokers. Median age: 44 years (IQR=31.5–54.5).

Abstract 4CPS-244 Table 1

	Women smokers	Women non-smokers	Men smokers	Men non-smokers
Mean daily dose of olanzapine (mg)	15.3 (95% CI =10.6–20.0)	14.8 (95% CI =11.0–18.6)	22.5 (95% CI =18.0–27.0)	18.4 (95% CI =13.8–23.0)
Mean plasma concentrations (mcg/mL)	52.5 (95% CI =38.1–66.9)	80.8 (95% CI =46.8–114.8)	49.8 (95% CI =29.0–70.6)	50.1 (95% CI =37.0–63.2)

For the mean olanzapine dose observed in women and men smokers, the mean theoretical concentration would have been 83.5 mcg/mL in women and 61.3 mcg/mL in men. This is 37.1% and 18.8% higher than the results obtained, respectively.

Conclusion and Relevance In the smokers group, the mean prescribed dose was 3.3% higher in women and 18.2% higher in men, and the mean plasma concentration was 35% lower in women and 0.6% lower in men, compared to the non-smokers group.

Differences were observed between smokers and non-smokers that would correspond to the tobacco-inducible effect,

although studies with larger numbers of patients are needed to establish the tobacco-olanzapine interaction as clinically relevant.

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4CPS-245 PREVENTION OF REFEEDING SYNDROME IN PATIENTS ON PARENTERAL NUTRITION: A REVIEW OF APPROPRIATENESS

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Background and Importance Refeeding syndrome (RFS) is a metabolic disorder that can be triggered after nutritional replacement. This condition can be life-threatening, so early identification and prevention is important.

Aim and Objectives Describe a system of screening and nutritional support in patients at risk of RFS. Assess the degree of adequacy of initial parenteral nutrition (TPN) to published NICE guidelines.

Material and Methods Retrospective observational study including patients from January 2020 to September 2022 identified with RFS risk, according to NICE guidelines criteria, at the beginning of TPN.

Variables collected were: age, sex, weight, height, service, low/no intake in 5–10 days prior to starting TPN, type of RFS risk (high or extreme), kilocalories (Kcal) of TPN at baseline and at reaching total requirements, time to establishment of total kcal on TPN and development of RFS (decrease in serum levels of potassium, phosphate, magnesium in the first 72 hours).

Results 33 patients were included. The mean age was 59,6 years (SD: 15,5). 54,5% were men. The mean BMI was 20,2 (SD: 4,0). 33,3% were surgery patients; 27,3% onco-haematology; 24,2% digestive; 9.1% critical care; 6,1% others. 75,8% of the patients had low/no intake prior to the introduction of TPN. A total of 90,9% were at high risk of developing RFS. The mean kcal/kg of TPN at the start was 20,4 (SD: 3,7). In 63,6% of patients total kcals were instituted within 2 days, and in 36,4% within 3 days. 3 patients developed RFS, all at high risk, 2 of them being onco-haematological.

Conclusion and Relevance Most patients who developed RFS were onco-haematologic, a group at risk for RFS, and had little/no intake prior to the initiation of TPN.

In line with the recommendations established by NICE guidelines, the kcal/kg provided by TPN at baseline are higher than recommended (20.4 vs 10 kcal/kg). In addition, the total kcal were reached between 2–3 days, the recommendations being between 4–7 days. Only 9.1% of the patients developed RFS, so that future studies could consider a less restrictive caloric start in TPN than that proposed in the aforementioned guidelines.

The role of the pharmacist, together with the rest of the multidisciplinary team, has allowed early detection and prevention of developing RFS in 90.9% of the patients.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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4CPS-248 THERAPEUTIC DRUG MONITORING OF LINEZOLID IN SOFT-TISSUE AND OSTEOARTICULAR INFECTIONS: A RETROSPECTIVE ANALYSIS

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Background and Importance Both prospective and retrospective trials and case reports suggest that therapeutic drug monitoring (TDM) of linezolid may be useful, especially in situations when there's a potential alteration of its pharmacokinetics or an increased risk of adverse events (AE); obesity, renal failure, drug interactions or prolonged treatments.

Aim and Objectives To assess effectiveness and safety of linezolid in SOI regarding linezolid serum concentrations (LSC) and analyse the influence of glomerular filtration rate (GFR) and body mass index (BMI) in LSC.

Material and Methods Observational retrospective study including patients with SOI treated with linezolid between January/2019 and December/2021.

Demographic, prescription and clinical data were collected from hospital´s medical records. Creatinine clearance was estimated by the Cockcroft-Gault formula.

Quantification of linezolid was performed by HPLC-UV. Therapeutic target trough concentrations were settled at 2–8 mg/L.

We studied the relationship among GFR and BMI with LSC using a multivariate regression analysis with IBM SPSS® Statistics program

Results Forty-two patients (mean age 58.7 ± 16.1, 69.1% male) were included. All patients received linezolid 600mg q12h orally as initial dose. The median duration of treatment was 34.2 ± 17.4 days. No relevant drug interactions were observed.

Twenty-two patients (52.4%) had LSC outside therapeutic range (TR): 10(45.5%) above and 12(54.5%) below TR. In only 3(18.7%) patients with supratherapeutical LSC posology was modified. All infections (including ones in patients with LSC below TR) were resolved.

AE occurred in 16(38.1%) patients, 7(43.8%) over TR. Eight of them (50%) discontinued treatment due to AE (50% diarrhea, 62.5% glossitis, 25% thrombocytopenia, 12.5% anaemia).

Seven (16.6%) patients had GFR<60 ml/min, of which 4 (57.1%) were over TR. Seventeen (40%) patients had a BMI>30, of which 5(29.4%) had linezolid determinations outside the TR: 3(60%) below TR. It was not found a significant correlation between BMI and LSC (p=0.34), whereas a significant inverse correlation was found between GFR and LSC (p=0.01).

Conclusion and Relevance A great proportion of patients were outside the TR, and the variable that seems to affect the most is GFR (p=0.01), so TDM would be specially recommended in patients with a lower GFR to decrease AE, which occur frequently with high LSC. Effectiveness was demonstrated in all patients including the ones with LSC below TR.

REFERENCES AND/OR ACKNOWLEDGEMENTS

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