

#### 4CPS-081 EVALUATION OF THE STANDARD DOSAGE REGIMEN OF VORICONAZOLE IN A PAEDIATRIC AND ADULT POPULATION THROUGH THERAPEUTIC DRUG MONITORING

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**Background** Voriconazole is an antifungal drug used for invasive fungal infection with high pharmacokinetic variability and narrow therapeutic range and, therefore, therapeutic drug monitoring (TDM) is recommended.

**Purpose** The objective was to evaluate the standard dosage regimen of voriconazole in a paediatric and adult population through TDM.

**Material and methods** Retrospective observational study (January 2015 and October 2017). Inclusion criteria: adult and paediatric patients treated with voriconazole (oral/intravenous) with at least one trough plasma concentrations ( $C_{trough}$ ) of voriconazole at steady state (>5 days) with the standard dosage and without concomitant use of potent inducers or inhibitors. Standard dose was: paediatric 8 mg/kg IV BID or 9 mg/kg PO BID, and adult 4 mg/kg IV BID or 200 mg PO BID. Variables: age, weight, indication (treatment or prophylaxis) and  $C_{trough}$  at steady state. Data was stratified by paediatric and adult patients. Primary outcome was: percentage of patients with  $C_{trough}$  at steady state of voriconazole within the therapeutic range at the standard dose (therapeutic window by indication: treatment: 1–5 mg/L; prophylaxis: 0.5–5 mg).

**Results** A total of 56 patients were included (26.7% children and 73.2% adults). In the paediatric group, the mean age and weight was 6.4 years (95% CI: 3.9 to 9.0) and 25.5 kg (95% CI: 16.4 to 34.5). The mean age and weight for the adult patients were 61.0 years (95% CI: 56.4 to 65.6) and 69.9 kg (95% CI: 65.3 to 74.5). 17.7% of the patients were treated with voriconazole for prophylaxis and 82.2% for treatment.

The median  $C_{trough}$  in paediatrics was lower than in adults: 0.7 mg/L (p25–75: 0–5.5) vs 2.5 mg/L (p25–75: 0.1–8.0), respectively (p<0.05).

66.7% and 22% of patients had infra-therapeutic  $C_{trough}$  in paediatrics and adults (p<0.05), respectively. However,  $C_{trough}$  above the therapeutic window was similar between groups (6.7% of paediatrics and 7.3% of adults).

**Conclusion** The  $C_{trough}$  with the standard maintenance dose of voriconazole were within the therapeutic range in only 26.7% in paediatrics, while in the adult group it was 70.7%. Given the high variability observed in the  $C_{trough}$ , it was necessary to perform TDM at the beginning of the treatment to make an individualised dosage adjustment in both paediatric and adult patients.

#### REFERENCES AND/OR ACKNOWLEDGEMENTS

[https://www.ema.europa.eu/documents/product-information/vfend-epar-product-information\\_es.pdf](https://www.ema.europa.eu/documents/product-information/vfend-epar-product-information_es.pdf)

No conflict of interest.

#### 4CPS-082 NEPHROGENIC DIABETES INSIPIDUS INDUCED BY LIPOSOMAL AMPHOTERICIN B: A CASE REPORT

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**Background** Nephrogenic diabetes insipidus (NDI) results from the inability of the late distal tubules and collecting ducts to respond to vasopressin. The lack of ability to concentrate urine results in polyuria and polydipsia. NDI is almost always drug-induced, however, there are other causes such as electrolyte abnormalities.

**Purpose** To describe a case of NDI associated with the high-dose and long-term use of liposomal Amphotericin B.

**Material and methods** Data were obtained from electronic medical records. Bibliographic research was conducted to find similar cases. The Naranjo algorithm was used to estimate the probability of adverse drug reactions.

**Results** A 39-year-old man diagnosed with diffuse large B-cell non-Hodgkin lymphoma underwent an allogeneic bone marrow transplant. After 2 months, disease progression was detected, and immunosuppressive treatment was withdrawn and rescue treatment initiated. One month later, the patient was diagnosed with graft-versus-host disease grade III (GVHD). Immunosuppressive therapy was started with cyclosporine, micophenolate, sirolimus, methylprednisolone, and oral and rectal beclometasone. Additionally, meropenem, acyclovir, levofloxacin, cotrimoxazole and caspofungin were used as antimicrobial prophylaxis. During hospitalisation, the patient developed invasive pulmonary aspergillosis with isolations of *Aspergillus fumigatus* and *Aspergillus flavus*. The patient was treated with liposomal amphotericin B 6 mg/kg (440 mg) for 41 days with a cumulative dose reaching 18.04 g. Voriconazole and Posaconazole were discarded because of concomitant treatment with sirolimus and parenteral nutrition respectively. On day 5, the serum potassium level began to decrease achieving <1.5 mEq/L and urine output increased >6 L/day. The patient was transferred to the medical intensive care unit and treated with vigorous potassium administration. NDI was diagnosed and treated with desmopressin 10 mcg/12 hour nasal drops, hydrochlorothiazide 50 mg/24 hour and spironolactone 50 mg/24 hour. According to the Naranjo algorithm, this event would be classified as a possible reaction because of the temporal correlation between NDI and treatment with liposomal Amphotericin B. Several cases were reported related to NDI induced by Amphotericin B,<sup>1,2</sup> regardless of formulation.

**Conclusion** It is very important to understand the etiology and symptoms related with nephrotoxicity and NDI. The association of other nephrotoxic drugs and persistent hypokalaemia also contributed to this event. Specific intervention is required to prevent nephrotoxicity in patients receiving Amphotericin B.

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