Poster

[P25-10] P25-10: Oncologic drugs (2)

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Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall (1F)

(Mon. Sep 25, 2017 12:30 PM - 1:30 PM Annex Hall)

[P25-10-4] Voriconazole dosing strategies in young children: challenges and recommendations

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Keywords: Voriconazole, Dosing strategy, Leukemia

Background

Voriconazole pharmacokinetics (PK) have been studied in pediatric studies and described by population pharmacokinetic modeling.[1]. Using the currently approved intravenous (IV) dosing regimen, 23 pediatric patients provided 30 trough samples resulting in a observed median (range) of 1.2 (0.11-17.4) mg/L.[1] This illustrates the highly variable pharmacokinetic (PK) profile of voriconazole in children.
The aim of this case series is to evaluate the effectiveness of dosing guidelines in combination with routine therapeutic drug monitoring (TDM) to achieve therapeutic serum concentrations of voriconazole in young cancer patients (age 0-6 years old).

Methods

At the VUmc, pediatric patients are treated using TDM. Voriconazole plasma concentrations are monitored and dosing regimens are individualized, aiming at trough levels of 1,5-6 mg/L. A case series of 4 children (age 0-6 yrs) is presented.

Results

Zoom image

The figure above illustrates the variable voriconazole exposure (n=4).
Case 1 Boy, 13 months, acute myeloid leukemia
- Loading dose 9 mg/kg tid (IV), maintenance 8 mg/kg tid (IV) resulted in supratherapeutic levels and hepatic toxicity. Root cause: CYP2C inhibition by previous itraconazole treatment.
- Therapeutic levels achieved at 6 mg/kg tid (IV).
Case 2 Boy, 5 years, acute lymphatic leukemia
-Doses varying between 7 mg/kg tid (IV) and 11 mg/kg tid (IV). Highly variable trough concentrations.
Case 3 Girl, 7 months, mixed phenotype acute leukemia
- Loading dose 6 mg/kg bid (IV), maintenance 9 mg/kg bid (PO) resulted in subtherapeutic trough levels (0.1-0.2 mg/L), possibly due to high first pass metabolism.
Case 4 Girl, 5 years, acute lymphatic leukemia
-Loading dose 10 mg/kg bid (PO), high maintenance dose of 23 mg/kg bid (PO) resulted in therapeutic levels. Higher doses of 30 mg/kg bid resulted in a more than dose-proportional increase of exposure (trough level 22 mg/L), suggesting non-linear PK.

Conclusions

Voriconazole PK is highly variable in pediatric cancer patients, which can only partly be attributed to drug interactions and co-morbidities. A starting dose of 18 mg/kg (IV) is recommended and could be administered as 6 mg/kg tid (IV).[2] Intensive TDM (at least twice weekly) and daily in-depth status reviews are recommended to achieve therapeutic drug levels.

[1] http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Assessment_Report_-_Variation/human/000387/WC500186844.pdf

[2] An optimized voriconazole dosing strategy to achieve therapeutic serum concentrations in children younger than 2 years old. T.N. Zembles, Thompson N.E., Havens P.L. eta al. Pharmacotherapy 2016