Case Report: Ganciclovir Subtherapeutic Dosing in a Pediatric Patient on Extracorporeal Membrane Oxygenation

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Introduction

Limited data exists regarding antivirals and extracorporeal membrane oxygenation (ECMO). ECMO provides additional challenges in appropriate dosing due to multiple factors, including, increase volume distribution (Vd), direct extraction by the circuit, and altered clearance. As most antivirals are renally cleared, the use of continuous renal replacement therapy (CRRT) during on ECMO likely delays clearance, as seen in patients on CRRT who are not on ECMO. 1 ECMO without CRRT produces an increased Vd secondary to the ECMO circuit along with increased urinary clearance rate due to high fluid volumes which may lead to underdosing of critically needed antimicrobials.

We present a case of pharmacokinetics of ganciclovir in an immunocompromised patient with respiratory failure requiring venovenous ECMO support without CRRT.

Case History

- 4 year old with history of rhabdoid tumor, required an autologous bone marrow transplant after intensive chemotherapy 80 days prior to illness
- Presented with respiratory failure and developed acute respiratory distress syndrome
- Was initially started on Cefepime, Vancomycin, Trimethoprim/Sulfamethoxazole, Voriconazole and Ganciclovir
- Placed on VV-ECMO on Day 8 of ICU admission due to air leak syndrome
- Did not have kidney injury throughout illness and did not require renal replacement therapy

ICU Timeline

- On day 10 of ICU stay, 2 days after ECMO initiation, CMV PCR levels increased from 1161 to 138,000
- Foscarnet added due to the concern for ganciclovir resistance
- Ganciclovir levels drawn on day 17 of ICU admission, after first sample failed to run.
- CMV PCR levels down trended after foscarinet was added
- Foscarnet discontinued after ganciclovir dose was therapeutic on day 20

Results

We used a one compartment model to characterize the pharmacokinetic profile of ganciclovir based on the available literature. Sawchuk-Zaske equations were used to estimate the AUC based on 2 concentrations. Although literature is sparse on what the goal AUC for treatment dose ganciclovir should be, we decided upon an AUC target of at least 45 mcg/mL * h was based on pharmacokinetic and pharmacodynamic literature reports in solid organ transplant patients demonstrating efficacy.2 3 The timing of our levels was based on average ganciclovir peak and trough times from a study by Padulles Caldes et al. in 20 solid organ transplant adults.4

Serum levels were checked on day 17 and followed up on day 20 after new dosing regimen started. In this interval, patient had an increase with his total volume due to positive fluid balance. This created a discordance between our predicted and actual pharmacokinetics.

Discussion

This is the first case report of pharmacokinetics of ganciclovir dosing in either pediatric or adults while on ECMO. Standard recommended dosing of 5mg/kg every 12 hours provided a low AUC that was shown not to be therapeutic both clinically, with the increasing CMV DNAemia, and based upon pharmacokinetic analysis. After increasing the dose to 10 mg/kg, we were able to achieve targeted AUC24 for ganciclovir. By the time dosing was adequate CMV PCR had already down trended, likely due to the initiation of the foscarnet. The CMV resistance panel was negative for resistance, which supports the ganciclovir being subtherapeutic.

This case also demonstrated vastly different volume distribution in a small time frame that affected our predicted and actual pharmacokinetics. Our predicted AUC was set at to be greater than 65, but with the increase in volume, nearly double, decreased the expected Cmax and decreased the AUC to 50. This ended up still being therapeutic, but lower than anticipated.

Conclusion

- Higher dosing of ganciclovir may be required in patients on ECMO without CRRT. In our patient 10mg/kg every 12 hours was determined to be therapeutic.
- Therapeutic Drug monitoring may be of benefit in the these clinical situations.
- Further pharmacokinetic/pharmacodynamics studies are needed of antivirals in patients on ECMO.

References