Meropenem enhancing the clearance of valproate in the management of valproate toxicity

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Background

Despite its wide therapeutic index and acceptable safety profile, intentional overdoses with valproate requiring critical care support occasionally occur.[1] Although current management involves supportive care and decontamination, in severe cases with ingestion > 1g/kg and serum concentration > 850 mg/L, dialysis is required.[1]

Very few case reports currently exist on the use of meropenem to enhance the renal clearance of valproate in the setting of valproate toxicity. Current literature focuses how effective dialysis is in treating valproate toxicity or on the meropenem-valproate interaction.[2] Meropenem reduces valproate levels by up to 80%. by inhibiting hydrolysis of valproic acid glucuronide (Figure 1).[3-5] At toxic doses, valproate exhibits saturable protein binding making valproic acid glucuronide more readily available for removal by haemodialysis by 4 to 10 fold depending on the dialysis mode used.[5]

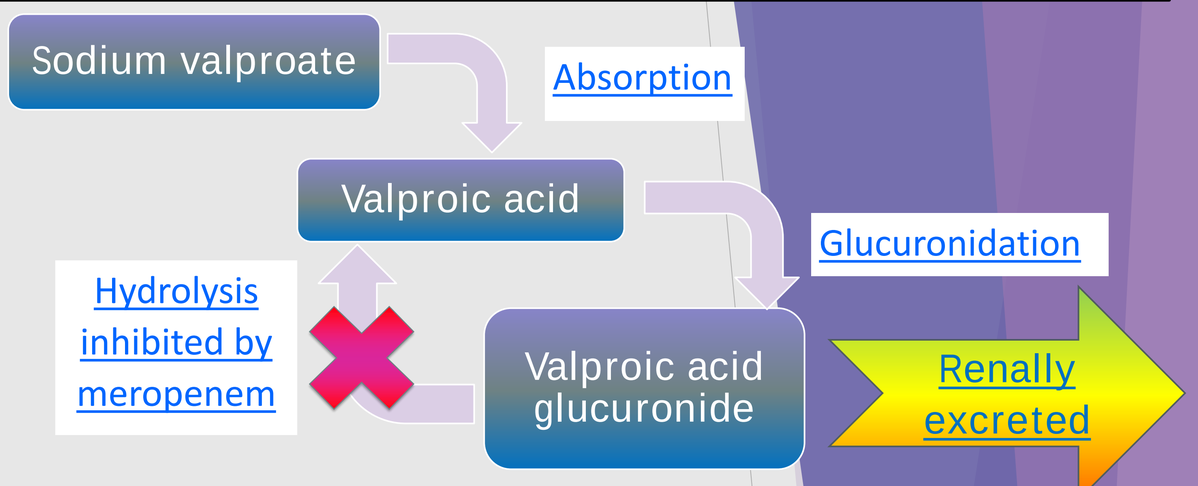

Figure 1. Meropenem-valproate drug interaction

Patient case

A 42-year-old with a history of depression presents to emergency unresponsive approximately 4 hours post polypharmacy overdose having ingested the following:

Drug	Dose ingested	Exposure
Sodium valproate	**110g**	**1.4g per kg (potentially fatal)**
Quetiapine	10g	125mg per kg
Pericyazine	1.2g	15mg per kg
Clonazepam	40mg	0.5mg per kg

Table 1. Polypharmacy ingestion per kg

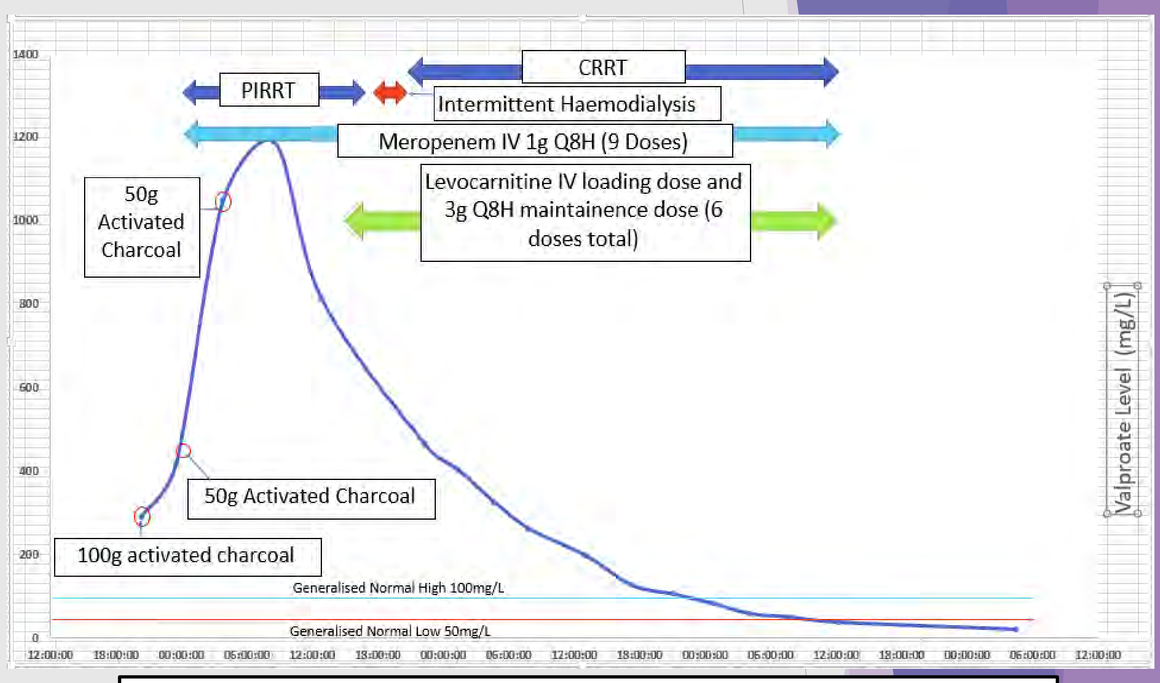

Figure 2. Valproate concentration curve over time

Intervention timeline

Initially the valproic level peaked to 1049 mg/L despite prolonged intermittent renal replacement therapy (PIRRT) and meropenem (Figure 2). Intermittent haemodialysis was initiated to further increase valproate clearance however the patient became too haemodynamically unstable. 24 hours after meropenem was commenced, the valproate level dropped to 815 mg/L, most likely due to meropenem inhibiting the conversion of valproic acid glucuronide and its subsequent elimination via dialysis. Continuous renal replacement therapy (CRRT) was commenced while meropenem and levocarnitine were continued until levels were < 100 mg/L. Levocartinine was given for hyperammonemia associated with valproate overdose however its role on reducing valproate levels remains unclear.[1]

Discussion

Dialysis exploits the pharmacokinetics of valproate and the meropenem-valproate drug interaction to further enhance rapid clearance. Literature comparing standard of care alone versus standard of care with meropenem in valproate overdoses is scarce. 2 case reports exist that describe the effectiveness of meropenem in reducing valproate levels in toxicity without dialysis and several case reports highlight the effectiveness of 3 different dialysis modes in treating valproate toxicity without meropenem. [6]

Conclusion

This case report highlights meropenem as a potential adjunct to enhancing valproate clearance in severe toxicity. Whilst dialysis remains the cornerstone of therapy, in extreme cases the meropenem-valproate interaction may be utilised to further enhance the reduction in the toxic level achieved by dialysis alone. Further studies are needed to determine the best timing and dose of meropenem in the context of intentional extreme overdose with valproate.

References

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Acknowledgements

The authors would like to extend sincere acknowledgements to the pharmacists and physicians involved in providing invaluable guidance and feedback throughout the work on this poster, notably toxicologist Dr Una Nic Ionmhain.