Poster

[P26-1] P26-1: Anticonvulsant drugs

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[P26-1-8] Pharmacokinetic drug interactions with valproate and antiepileptic or antipsychotic drugs —still a mystery after 50 years?

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Background

Valproate has for 50 years been used as one of the main antiepileptic drugs, and is also frequently used as add on treatment for psychiatric disorders. Despite vast experience in combining valproate with other drugs, and a range of established drug interactions, the role of valproate in various enzymatic steps and pharmacokinetic processes is still unclear. Therapeutic drug monitoring (TDM)-data may be used as a source to reveal potential interactions based on different metabolic routes. The purpose of this study was to explore pharmacokinetic interactions with valproate used in combination with various antiepileptic drugs and antipsychotic drugs in various enzymatic steps.

Method:

Retrospective anonymous data from the TDM-databases at the National Center for Epilepsy, Oslo University Hospital and Center for Psychopharmacology, Diakonhjemmet Hospital, Oslo, Norway, during 2005-15 was used. Concentration/dose (C/D)-ratios was used as estimates for changes in clearance.

Results

The study included data on the following antiepileptic drugs: Clobazam/desmethyl-clobazam (CYP3A4, CYP2C19), lacosamide (CYP2C19), phenytoin (CYP2C9/2C19), lamotrigine (UGT1A4), eslicarbazepine and oxcarbazepine (UGTs) (n=1107). In addition the following antipsychotic drugs were studied: Clozapine (CYP1A2), olanzapine (UGT1A4, CYP1A2) and quetiapine (CYP3A4) (n=1915). Valproate decreased clearance of lamotrigine by 70% as marker for UGT1A4, and increased clearance of clobazam by 25% as a marker for CYP3A4. There was no effect on the C/D-ratios of lacosamide, eslicarbazepine/ oxcarbazepine or lacosamide. Valproate increased clearance of olanzapine by 22% and desmethyl-clozapine by 25%, but did not affect the C/D-ratios of clozapine and quetiapine.

Conclusions

The present study shows that valproate is involved in various pharmacokinetic drug interactions. Inhibition of UGT1A4 is well known, possible induction of CYP3A4 has not been well documented previously, and there is no evidence of inhibitory effect on CYP2C9/CYP2C19 by valproate. Such studies are important to document pharmacokinetic interactions in real-life settings and contributes to improved knowledge of how to handle important drug combinations and thus improves patient safety.