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Title Page

Pharmacokinetic Interaction between Valproic acid, Meropenem and Risperidone

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Acknowledgments and Statement of Interest

Mr. Kuzin and Dr. Paulzen declare no conflict of interests.

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Case report

Combining different drugs is a common clinical practice, also for treating somatic diseases in psychiatric patients. Pharmacodynamic or pharmacokinetic drug-drug interactions can thereby lead to desired effects, attenuated effects, undesired harmful effects or even to serious adverse reactions. Treatment with several drugs enhances the risk of adverse drug reactions (ADR) and drug-drug interactions. The probability of interactions increases with the number of applied drugs. Even in complex clinical cases, valid interaction checks are still difficult, especially to assess whether an indicated potential interaction risk is clinically relevant or not.

The addition of the beta-lactam antibiotic meropenem (MER) for antimicrobial chemotherapy to an ongoing therapy with valproic acid (VPA) leads to a well-known decrease of VPA serum concentrations [1, 2]. Largely unknown is the influence of this pharmacokinetic interaction on a concurrent treatment with the second generation antipsychotic risperidone (RIS). We therefore show a clinically complex case where the interaction between VPA, MER and RIS led to unexpected effects.

Mr. A is a 43-year-old inpatient diagnosed with a multiple drug use dependence syndrome (ICD-10: F19.2) and a paranoid schizophrenia (ICD-10: F20.0). He was treated successfully with a combination of VPA 1,800 mg and RIS 4 mg per day with a stable psychopathology and no signs of acute psychosis in the sense of missing positive symptoms such as hallucinations, delusions or bizarre behavior. Due to multiple bilateral phlegmons of the forearms with bone involvement in the course of an ongoing intravenous drug abuse, he had to undergo plastic surgery with overlap surgery of both forearms. MER was added at a daily dose of 3,000 mg because of infections of the skin transplants. Therapeutic drug monitoring (TDM) of VPA and RIS was performed as part of an individualized treatment optimization. Drug concentrations were measured once a week as trough levels under steady state conditions. According to the metabolic ratio between risperidone (RIS) and its active metabolite 9-OH risperidone (9-OH-RIS) with much higher levels for RIS than for 9-OH-RIS (mean RIS/9-OH-RIS ratio of 5.3, SD 2.0, see table. 1), it was assumed that the patient was phenotypically a cytochrome P450 2D6 (CYP2D6) poor metabolizer (PM). Genotyping of cytochrome P450 2D6, 2C9 and 2C19 was performed to complete the clinical diagnostic.

Due to stable clinical conditions with regard to the psychosis and serum levels of the active moiety (RIS + 9-OH-RIS) reaching the upper value of the therapeutic reference range (20-60 µg/l, [3], the administered daily dose of RIS was reduced from 4 mg to 2 mg before the start of the antimicrobial chemotherapy with MER (see table. 1). The mean concentration-by-dose ratio (C/D) for the active moiety (calculated as serum concentration divided by the applied dose) was 15.3 (SD 5.2) during this first period. The daily dose of VPA remained unchanged. After starting the antimicrobial chemotherapy, VPA mean serum concentrations decreased dramatically (minus 83 %) from 37 µg/mL (SD 6) to 6 µg/mL (SD 0.6).

Despite a reduction of the prescribed daily dose of risperidone from 4 to 2 mg, the serum concentration of RIS decreased only by 31 percent after adding MER (mean serum concentration: 50 ng/ml, SD 15 ng/ml before, 34 ng/ml, SD 8 ng/ml after addition of MER). Mean serum concentrations of the metabolite 9-OH-RIS decreased in an expected range, namely by 54% (12 ng/mL, SD 6 ng/ml; after adding MER: mean 5 ng/mL, SD 2 ng/ml).

‚place tab. 1 about here'

Interestingly, serum levels of RIS and 9-OH-RIS changed differentially after the addition of MER: the concentration-by-dose ratio (C/D, drug concentration divided by daily dose) for RIS increased from 12.4 to 17.1 indicating a lower clearance of RIS while C/D for 9-OH-RIS slightly decreased (from 2.9 to 2.7). C/D for the active moiety increased from 15.3 to 20.0 (see table. 1 and fig. 1.) After termination of the antimicrobial chemotherapy, the C/D ratio for RIS, and active moiety decreased again. The ratio RIS/9-OH-RIS temporarily increased from 5.0 (SD 1.92) to 6.6 (SD 1.19) under MER co-medication and decreased again to 5.5 (SD 2.80) after ending the MER therapy. Cytochrome P450 genotyping showed a poor metabolizer (PM) status (*4/*4) for CYP2D6, an extensive metabolizer status (*1/*1) for 2C9 and a rapid metabolizer status (*1/*17) for 2C19.

‚place fig. 1 about here'

Discussion

Several mechanisms are hypothesized to explain the decrease of VPA after the addition of carbapenem antibiotics, such as meropenem. They include an effect at the intestinal absorption site, the liver site (decrease of the uridine 5'-diphospho-glucuronic acid (UDPGA) level by carbapenem antibiotics, a direct activation of uridine 5'diphospho-glucuronosyltransferase (UGT) by carbapenem antibiotics, or an inhibition of β-glucuronidase) and/or at the distribution site of VPA in blood (for more details, see [4]). The metabolism of both VPA and meropenem is independent from CYP2D6 activity while RIS is mainly metabolized via CYP2D6 to the active metabolite 9-OH-RIS. This pharmacokinetic interaction between 3 drugs is complexified by the CYP2D6 poor metabolizer status. Because homozygotes for the null alleles of *CYP2D6* such as *4 do not have any functional CYP2D6 protein, it was not expected that the preexisting high ratio of RIS/9-OH-RIS, indicating a CYP2D6 poor metabolizer status, was influenced by MER. However, after starting MER, not only VPA serum levels decreased but also serum levels of the active moiety of RIS increased, an effect mostly driven by a higher concentration by dose ratio (C/D) for RIS despite a small decrease of 9-OH-RIS concentration by dose ratio suggesting a reduced formation of 9-OH-RIS from RIS. Of note, although CYP2D6 is the main

isoform responsible of RIS metabolism, a contribution of CYP3A to RIS metabolism has also been suggested by several interaction studies with CYP3A inducers [5, 6], or inhibitors [7, 8].

We therefore hypothesize that the observed inhibition of RIS metabolism in a CYP2D6 poor metabolizer is due to the blockade of secondary metabolic pathways, mediated by CYP3A and/or other isoforms. An increasing importance of CYP3A4 in the metabolism of clozapine, a drug mainly metabolized by CYP1A2, has thus been demonstrated in patients with blocked CYP1A2 activity [9]. Concerning risperidone, in CYP2D6 poor metabolizers, CYP3A could be important for the production of 9-hydroxy risperidone [10] and a case study suggested that CYP2D6 genotype may influence susceptibility to a clinically important interaction with carbamazepine, a CYP3A inducer [11]. If true, a weaker inhibitory effect of MER on RIS pharmacokinetics would probably be observed in a CYP2D6 extensive metabolizer, if observed at all. We can however not exclude that the observed interaction is mediated by changes in VPA serum concentrations, in that case the mechanism remaining unclear. Luckily, due to the relatively short period of decreased VPA serum concentrations, no changes in psychopathology were observable. VPA was administered for affective control and against impulsivity but decreasing VPA levels did not lead to a reoccurrence of any of those symptoms.

Finally, the present complex case of pharmacokinetic interaction between 3 drugs, possibly also depending on the metabolic status of the patient, underscores the clinical usefulness of TDM for treatment optimization. Luckily, during the entire duration of the inpatient treatment, before, during and after the antimicrobial treatment with meropenem and although the daily dose of risperidone was halved, the clinical condition of the patient was stable and no psychotic symptoms recurred.

Table legends

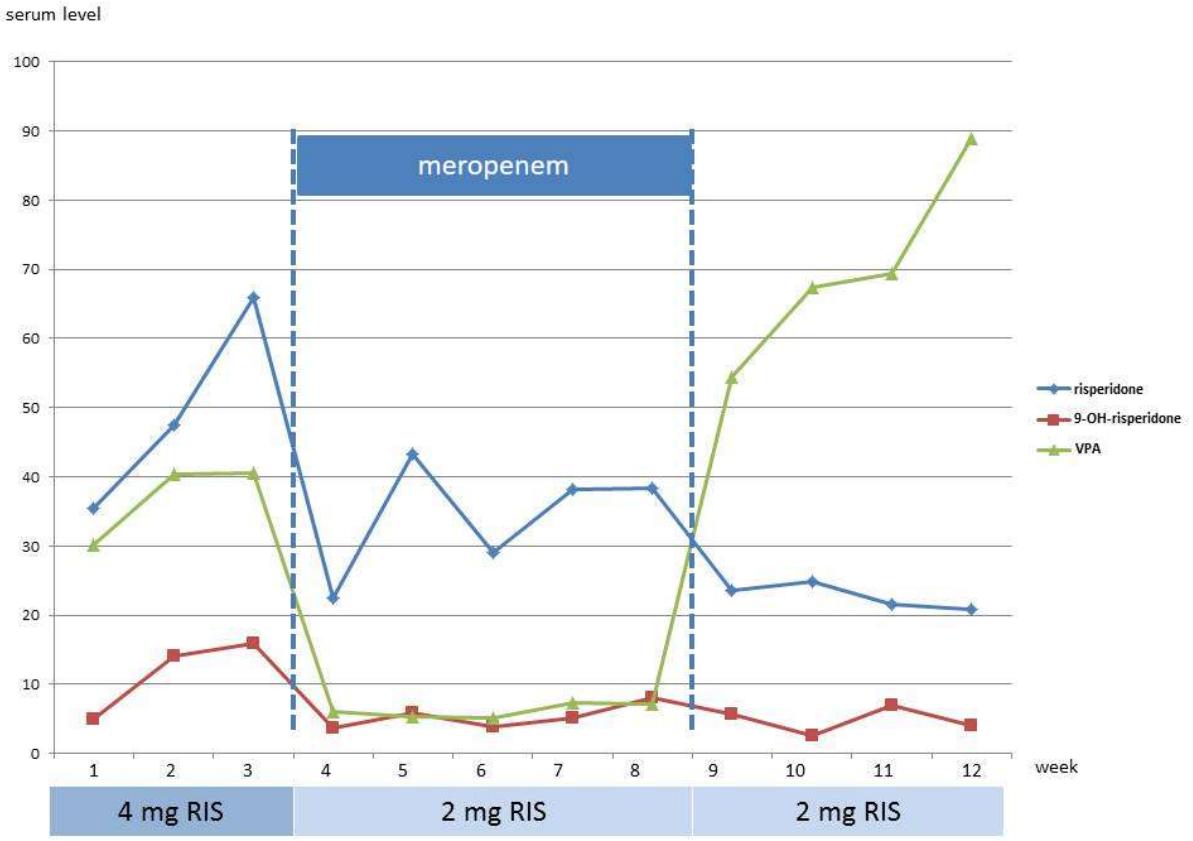
Tab. 1: Daily doses of risperidone (RIS) and valproic acid (VPA), and serum levels of RIS, 9-OH-RIS and VPA before, during and after a concomitant treatment with meropenem (MER)

Figure legends

Fig. 1: Risperidone, 9-OH-risperidone and valproic acid (VPA) serum-levels before, during and after concomitant medication with meropenem. Serum levels of RIS and 9-OH-RIS in ng/mL, VPA serum-levels in µg/mL. Daily dose of RIS was reduced from 4 mg to 2 mg. Meropenem treatment started at week 4 and ended with week 9.

	risperidone				concomitant treatment with MER						risperidone				
week	1	2	3	**mean**	4	5	6	7	8	**mean**	9	10	11	12	**mean**
DD risperidone	4	4	4	**4**	2	2	2	2	2	**2**	2	2	2	2	**2**
RIS	35.5	47.4	66.0	**49.6**	22.4	43.3	29.1	38.2	38.3	**34.3**	23.5	24.8	21.5	20.9	**22.7**
C/D (RIS)	8.9	11.9	16.5	**12.4**	11.2	21.7	14.6	19.1	19.2	**17.1**	11.8	12.4	10.8	10.5	**11.3**
9-OH-RIS	4.9	14.1	16.0	**11.7**	3.6	5.9	3.9	5.2	8.1	**5.3**	5.6	2.6	7.0	4.0	**4.8**
C/D (9-OH-RIS)	1.2	3.5	4.0	**2.9**	1.8	3.0	2.0	2.6	4.0	**2.7**	2.8	1.3	3.5	2.0	**2.4**
RIS + 9-OH-RIS, AM	40.4	61.5	82	**61.3**	26	49.2	33	43.4	46.4	**39.6**	29.1	27.4	28.5	24.9	**27.5**
C/D AM	10.1	15.4	20.5	**15.3**	13	24.6	16.5	21.7	23.2	**19.8**	14.6	13.7	14.3	12.5	**13.7**
Ratio RIS/9-OH-RIS	7.2	3.7	4.1	**5.0**	6.2	7.3	7.5	7.4	4.7	**6.6**	4.2	9.5	3.1	5.2	**5.5**
DD VPA	1,800	1,800	1,800	**1,800**	1,800	1,800	1,800	1,800	1,800	**1,800**	1,800	1,800	1,800	1,800	**1,800**
VPA	30.1	40.3	40.5	**37.0**	6.0	5.4	5.2	7.3	7.1	**6.2**	54.4	67.4	69.4	89	**70.1**

DD – daily dose, value in mg; C/D – concentration by dose ratio, values given in (ng/mL)/(mg/day); values for RIS, 9-OH-RIS and AM, active moiety = RIS + 9-OH-RIS, are given in ng/mL; values for valproate, VPA, are given in µg/mL.



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