

## Concomitant treatment with imipenem causes a rapid and extensive decrease in the plasma concentrations of valproic acid

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### SUMMARY

**Background.** Valproic acid (VPA) is a wide-spectrum antiepileptic drug used both in children and in adults. We describe a clinically important interaction between VPA and imipenem, a carbapenem antimicrobial.

**Case presentation.** Our patient was a 19-year-old man with childhood onset of mental retardation and severe epilepsy. He was hospitalized due to pneumonia. His antiepileptic drugs, including VPA, were administered intravenously. Due to pneumonia, intravenously administered imipenem was started. After the start of imipenem treatment, a dramatic decrease in the plasma concentrations of VPA occurred within 24 hours. After the discontinuation of imipenem treatment, the concentration of VPA recovered within a few hours. The decrease in VPA levels was associated with increased seizure frequency.

**Conclusions.** The time course of the VPA–imipenem interaction suggests that mechanisms other than a change in the enzymatic elimination of VPA is the cause for this pharmacokinetic interaction. Concomitant use of VPA and imipenem should be avoided.

**Key words:** valproic acid • carbapenems • imipenem • interaction • epilepsy

### BACKGROUND

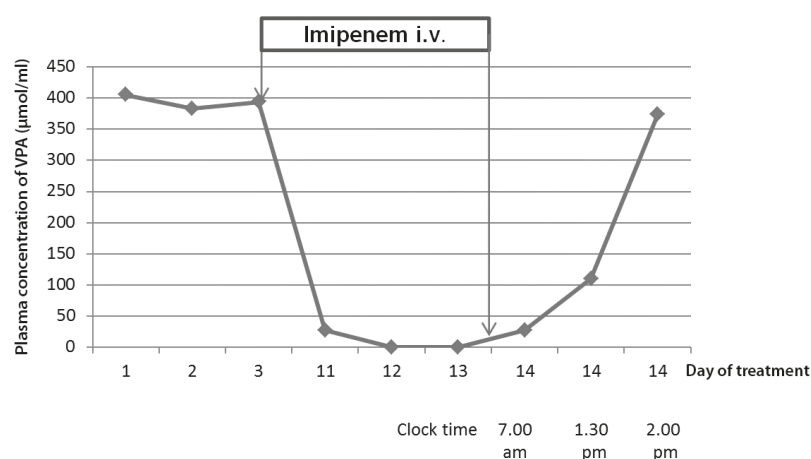
Valproic acid (VPA) is a wide-spectrum antiepileptic drug (AED) that has efficacy also as a prophylactic agent in episodic migraine, acute mania, and in the maintenance treatment of bipolar disorder (Johannesen et al., 2003). VPA has clinically significant drug interactions, most commonly with other AEDs. However, several case reports suggest that some carbapenems, administered concomitantly with VPA, cause a dramatic decrease in the plasma concentrations of VPA with a risk of exacerbation of seizures (Llinares Tello et al., 2003; Coves-Orts et al., 2005; Fudio et al., 2006; Lundde et al., 2007; Hellwig et al., 2011; Taha et al., 2013).

In the present report we document a patient in whom concomitant administration of imipenem caused an ex-

tensive decrease in the plasma concentrations of VPA. We also demonstrate that the drug interaction was rapidly reversible after the discontinuation of imipenem.

### CASE PRESENTATION

Our patient was a 19-year-old man who had childhood onset progressive mental retardation of unknown origin. The patient began having epileptic seizures at the age of 10 years. Initially he experienced tonic-clonic seizures without focal features, but his EEG showed an epileptic focus in the left frontal region. The patient was started on oxcarbazepine treatment. Later, the patient began to experience atypical absence and atonic seizures, as well as myoclonic jerks. His EEG findings pro-



**Figure 1.** Plasma concentrations of valproic acid (VPA) during concomitant treatment with imipenem. The bar shows the duration of the imipenem administration.

gesses, and, in addition to the epileptic focus, slow generalized spike and wave discharges were seen. The mobility of the patient deteriorated, and he became wheelchair bound. Two years before the current episode the patient began to have prolonged tonic-clonic seizures.

Over the years the patient was treated with a variety of AEDs, including clobazam, ethosuximide, lamotrigine, rufinamide, stiripentol and zonisamide, but the seizures remained resistant to treatment. Currently the patient was being treated with a combination of levetiracetam (LEV), clonazepam and VPA. Of all the AEDs, VPA proved to be the most effective treatment for the patient. A vagus nerve stimulator was implanted at the age of 16 without any significant treatment response.

The patient was admitted to the intensive care unit (ICU) at the Kanta-Häme Central Hospital due to pneumonia, severe ventilation difficulties and status epilepticus. After the seizures remained refractory following parenteral lorazepam, the patient received a loading dose of fosphenytoin followed by anesthesia with thiopental. The treatment with LEV and VPA was continued intravenously at doses approximately corresponding to the long-term oral doses (LEV 3000 mg/day and VPA 2700 mg/day). Also fosphenytoin was continued intravenously at a constant dose. Due to the pneumonia, a piperacillin–tazobactame antibiotic combination was started. The patient was treated at the ICU for 12 days, after which he was transferred to the neurological ward in poor condition. He continued to experience non-prolonged seizures, his ventilation was weak and a critical illness polyneuropathy was diagnosed. The bacterial culture from the tracheostomy revealed *kleb-*

*siella oxytoca*. Due to this, piperacillin–tazobactame treatment was changed to imipenem/cilastatin Ig, given three times a day intravenously. On the next day, a dramatic decrease in the serum concentration of VPA compared with previous measurements was observed (Figure 1). Despite a 300 mg increase in the daily dose of VPA, the serum concentration of the drug remained almost negligible, and the patient started having more frequent seizures. A probable interaction of VPA with imipenem was recognized four days after the start of imipenem, and the treatment was stopped. The serum concentrations of VPA increased up to reference values within a few hours thereafter. There were no clinically significant changes in the plasma concentrations of phenytoin during the episode (data not shown). Methods for the measurement of plasma concentrations of clonazepam or LEV were not available at the hospital.

## DISCUSSION

Several case reports, based on one to six adult and/or pediatric patients, have suggested that concomitant administration of various carbapenems (e.g. doripenem (Hellwig et al., 2011), ertapenem (Lunde et al., 2007), and meropenem (Llinares Tello et al., 2003; Coves-Orts et al., 2005; Fudio et al., 2006; Taha et al., 2013) with VPA is associated with a clinically significant decrease in the plasma concentrations of VPA. A series of 26 patients with concomitant meropenem and VPA treatment supports the findings of these cases (Vélez Díaz-Pallarés et al., 2012). In the literature search we conducted, we could find only three previous publications reporting an interaction between imipenem and VPA

(Llinares Tello et al., 2003; Fudio et al., 2006; Park et al., 2012). Two of these reports deal with cases in which VPA was administered enterally (Llinares Tello et al., 2003; Park et al., 2012). Perea et al. (2006) reported that the plasma concentrations of VPA failed to increase proportional to the dose when VPA was started intravenously during concomitant administration of imipenem. In our patient, treated with VPA intravenously, an extensive reduction in the plasma concentrations of VPA was observed rapidly after the start of imipenem administration. The interaction was fully reversible within hours of discontinuing imipenem treatment.

The effects of carbapenems on VPA concentrations seem to indicate a class effect (Mancl and Gidal, 2009), and the magnitude of the effects seem to be equal among various carbapenems; the decrease in VPA concentrations has been in the range of 50 to 96% (Llinares Tello et al., 2003; Coves-Orts et al., 2005; Hellwig et al., 2011; Lunde et al., 2007; Park et al., 2012; Taha et al., 2013; Perea et al., 2006; Vélez Díaz-Pallarés et al., 2012). The interaction has been observed when VPA has been administered either enterally (Park et al., 2002; Llinares Tello et al., 2003; Fudio et al., 2006; Taha et al., 2013) or intravenously (Coves-Orts et al., 2005; Lunde et al., 2007; Hellwig et al., 2011). As with our patient, the reported decrease in the plasma concentrations of VPA due to the interaction has often been associated with an exacerbation of seizures (Coves-Orts et al., 2005; Fudio et al., 2006; Lunde et al., 2007; Taha et al., 2013).

Published reports as well as our present case reveal that the plasma concentrations of VPA decrease very rapidly and reach a nadir within 48 hours of treatment initiation with carbapenem, irrespective of the route of administration of VPA (Llinares Tello et al., 2003; Coves-Orts et al., 2005; Fudio et al., 2006; Lunde et al., 2007; Hellwig et al., 2011; Taha et al., 2013). On the other hand, the recovery of VPA concentrations after the discontinuation of the concomitant carbapenem treatment has appeared to be slow in some reports: The return of VPA concentrations to levels measured prior to carbapenem treatment has taken from several days to two weeks following the cessation of carbapenem treatment (Llinares Tello et al., 2003; Coves-Orts et al., 2005; Fudio et al., 2006; Lunde et al., 2007; Hellwig et al., 2011; Taha et al., 2013). In our case, VPA levels increased very rapidly after the discontinuation of imipenem, and within 24 h, the concentrations reached similar levels to those measured prior to imipenem treatment. Quite a similar time course was observed by Hell-

wig et al., (2011) in one of their two patients who had received doripenem. The reported differences in the recovery of VPA concentrations may relate to varying actions of different carbapenems, patient-related variables, and the time course of plasma-level sampling.

Several different mechanisms relevant to the intravenous VPA-carbapenem interaction have been proposed and have been extensively discussed by Mancl and Gidal (2009). It has been suggested that carbapenems may enhance the glucuronidation of VPA (Mancl and Gidal, 2009). However, the rapid decrease in the plasma concentrations of VPA is not consistent with a hypothesis of enzyme induction as the cause, since the induction of drug metabolizing enzymes takes a longer time to become established. Furthermore, the rapid recovery of VPA concentrations observed in our patients as well as in some of the previous reported cases is not compatible with the expected time-course of de-induction. A displacement of VPA by carbapenems from the plasma protein binding is unlikely because carbapenems, with the exception of ertapenem, bind to plasma proteins only to a very low degree (Zhan et al., 2007). However, the interaction between VPA and imipenem may relate to a change in the distribution of VPA. It has been shown that carbapenems cause an accumulation of VPA in erythrocytes (Omoda et al., 2005). This mechanism is in accordance with the typical time course of the VPA-carbapenem interaction.

Some authors have advocated that VPA and a carbapenem can be used together with caution as long as plasma levels of VPA are closely monitored and the dose of VPA is adjusted to safeguard the patient (Fudio et al., 2006; Lunde et al., 2007; Hellwig et al., 2011; Llinares Tello et al., 2003). However, as demonstrated by several case reports discussed in this paper, even large dose adjustments seem to fail to maintain the therapeutic effects of VPA during concomitant administration of carbapenems. Thus, we agree with other authors that the concomitant use of VPA and carbapenems should be avoided (Mancl and Gidal, 2009; Park et al., 2012; Taha et al., 2013).

## CONCLUSIONS

The time course of the VPA-imipenem interaction suggests that mechanisms other than a change in the enzymatic elimination of VPA is the cause for this pharmacokinetic interaction. If a carbapenem is mandatory due to bacterial sensitivity issues, VPA should be substituted with another AED.

## CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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