Dear Sir,

I read with great interest the paper by Keränen and Kuusisto (2016) reporting a rapid and substantial decrease in the plasma concentration of valproic acid (VPA) within 24 hours after beginning concomitant treatment with imipenem. When imipenem treatment was stopped four days later, the VPA plasma concentration increased within a few hours. The authors conclude that this time course suggests that mechanisms other than a change in the enzymatic elimination of VPA are the cause for the pharmacokinetic interaction. This conclusion is not in line with data presented in an extensive review on the VPA-meropenem interaction by Rösche et al. (2014). At that time 21 reports with one or two patients, with a total of 28 treatment episodes in 25 patients, and nine case series with at least three cases each corresponding to 158 treatment episodes in 155 patients were available. In a patient with decompensated liver cirrhosis (Child-Pugh score 13) there was no interaction with VPA and meropenem (Spriet and Willems, 2011). Therefore liver function may be crucial for the VPA carbapenem interaction, which is commonly regarded as a class effect (Mancl and Gidal, 2009). The decrease of the VPA plasma concentration within 48 hours after meropenem application was 56% (SD 27%) in five patients with intravenous VPA administration and 84% (SD 15%) in 10 patients with enteral VPA administration (p = 0.03) (Rösche et al., 2014). Further treatment resulted in a maximal decrease of 79% (SD 14%) for VPA administered intravenously and 89% (SD 10%) for VPA administered enterally. The small delay of the decrease of the VPA plasma concentration may be an effect of the avoidance of the first pass effect of hepatic metabolism of VPA when administered intravenously. Given that the enhancement of VPA glucuronidation was considered to be the mechanism for the decline of plasma VPA levels, the range of the recovery time after stopping the carbapenem from a few hours (Keränen and Kuusisto 2016 for imipenem) to even 48 days (Gonzáles and Villena 2012 for meropenem) is difficult to explain. After all the small delay of the decrease of the VPA plasma concentration after application of a carbapenem when VPA is administered intravenously may be of limited clinical relevance, since a decrease of 50% in the first 48 hours also will lead in most patients to a subtherapeutic plasma concentration. After 48 hours of combination with meropenem a therapeutic plasma concentration is difficult to achieve. In the only treatment episode of a combination of VPA and meropenem with a VPA plasma concentration in the therapeutic range published before 2014 a daily dose of 12 g VPA was used (Spriet et al., 2007). There are no safety data for such a high dose of VPA. The combination of VPA with a carbapenem should be avoided.

REFERENCES


Keränen T., Kuusisto H.: Concomitant treatment with imipe-


