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Cartas al Director

Pharmacokinetic interaction between valproic acid and ertapenem

Dear Editor:

We present a case of significantly reduced serum valproic acid (VA) concentration associated with the coadministration of ertapenem; this interaction was to be expected from the fact that it had been previously described for other carbapenems, but had never been reported in the literature.

Case report

An 80-year-old woman with a weight of 74 kg had been primarily diagnosed with complex partial seizures secondary to severe cerebrovascular disease; she also had atrial fibrillation, peripheral artery disease, untreated high blood pressure, and advanced cognitive impairment – she only utters isolated words with a tendency to echolalia. She had an acute thromboembolic stroke two years ago, which resulted in residual left hemiplegia. She is placed on enteral tube feeding.

She is chronically treated with digoxin solution 0.150 mg every 48 hours, and VA solution 1100 mg daily in three divided doses –8 am 400 mg, 4 pm 300 mg, 12 pm 400 mg– not coincident with nutrition on an outpatient basis. Her total serum VA concentration before admission (C_{min}) was 72 μg/ml (November 10, 2005).

On December 30, 2005 she presented at the emergency room with aspiration pneumonia and abundant diarrhea episodes. On admission, in addition to her chronic therapy she was receiving amoxicillin-clavulanate. She was admitted to infectious diseases where amoxicillin-clavulanate was replaced with ertapenem 1 g/24 h. She was also prescribed omeprazole 40 mg IV/24 h, acetaminophen 1 g IV for fever, high-nitrogen solution for peripheral parenteral nutrition (1000 ml/24 h), glucosaline (1000 ml/24 h) with 2 mEq of ClK/100 ml. Metochlopramide 10 mg/8 h was given via the tube, followed one day later by magnesium metamizole 2 g/8 h, and tiapride 100 mg/24 h.

Parenteral nutrition is discontinued and enteral nutrition reinitiated on January 2; enoxaparin is prescribed subcutaneously to prevent venous thrombosis.

On January 3, following a consultation by infectious diseases, the pharmacokinetics section recommends that VA dosage be modified, since total serum concentration was found to be 36,4 μg/ml, that is, below the appropriate therapeutic range. In accordance with recommendations within the pharmacokinetic report total daily VA dose was increased to 1600 mg divided into three administrations –600, 400, and 600 mg. On January 5 total serum VA concentration was 18.42 μg/ml, with no consistency with dosage increase; as a result, daily dosage is further increased to 2000 mg divided into three fractions –700, 600, and 700 mg.

On January 9 total serum VA concentration was 1.04 μg/ml, albumin levels were 2,5 g/dl, and serum free VA concentration was non detectable. At this time the pharmacy department recommended the discontinuation of ertapenem and that VA be administered intravenously using a load dose of 800 mg and a maintenance dose of 400 mg/6 h. After having initiated this dosage scheme total serum VA levels of 14.83 μg/ml (free 1.76 μg/ml) were found on January 11, of 15.43 μg/ml (free 2.20 μg/ml) on January 13, of 23.65 μg/ml (free 3,86 μg/ml) on January 16, and of 28.92 μg/ml (free 7.12 μg/ml) on January 20. Once free VA levels had returned within the therapeutic range (5-10 μg/ml) the enteral route is reinitiated with a dosage of 1400 mg/day divided into three parts –500, 400, 500 mg– not coincidental with nutrition. With this dosage the patient kept her free VA plasma concentrations within the therapeutic range.

Discussion

The EMEA's assessment report on ertapenem[1] states that "no studies have been performed on the interaction between VA and ertapenem, but […] carbapenems reduce serum VA levels". Indeed, recent scientific literature reports on several cases of pharmacokinetic interaction between VA and panipenem[2], meropenem[2-5], or imipenem[3,5], but no reference can be found in MedLine or EMBASE describing the VA-ertapenem interaction suggested by our data.

Panipenem, meropenem, and imipenem[2-5] induce a marked decrease in plasma VA concentrations between days one and nine after antibiotic onset, which starts to recover at 24 hours following antibiotic discontinuation, and returns to normal after 3-17 days. In our case subtherapeutic VA concentrations are identified on the fourth day after ertapenem onset –they eventually fall by 97% and do not recover on increasing VA dose, but do finally ascend upon ertapenem discontinuation, and reach therapeutic free VA concentrations after eleven days.

The mechanism underlying the interaction between carbapenems and VA has not been elucidated. It is suggested[6] that panipenem increases intrinsic hepatic clearance for VA by activating liver glycogenolysis, increasing UDP-glucuronic acid levels, and enhancing VA glucuronization. Some authors[7] posit that imipenem inhibits VA intestinal absorption; others[8] claim a dual mechanism with increased renal clearance and reduced liver hydrolysis for VA-glucuronide by effect of carbapenems. Another potential mechanism is also suggested[5], according to which imipenem and panipenem would increase *in vivo* VA distribution among red blood cells, thus diminishing VA plasma concentration.

None of the studies attempting to explain the effects of carbapenem antimicrobials on VA and VA metabolite pharmacokinetics is conclusive, but fact as made up with recorded cases is. There is a highly significant pharmacokinetic interaction

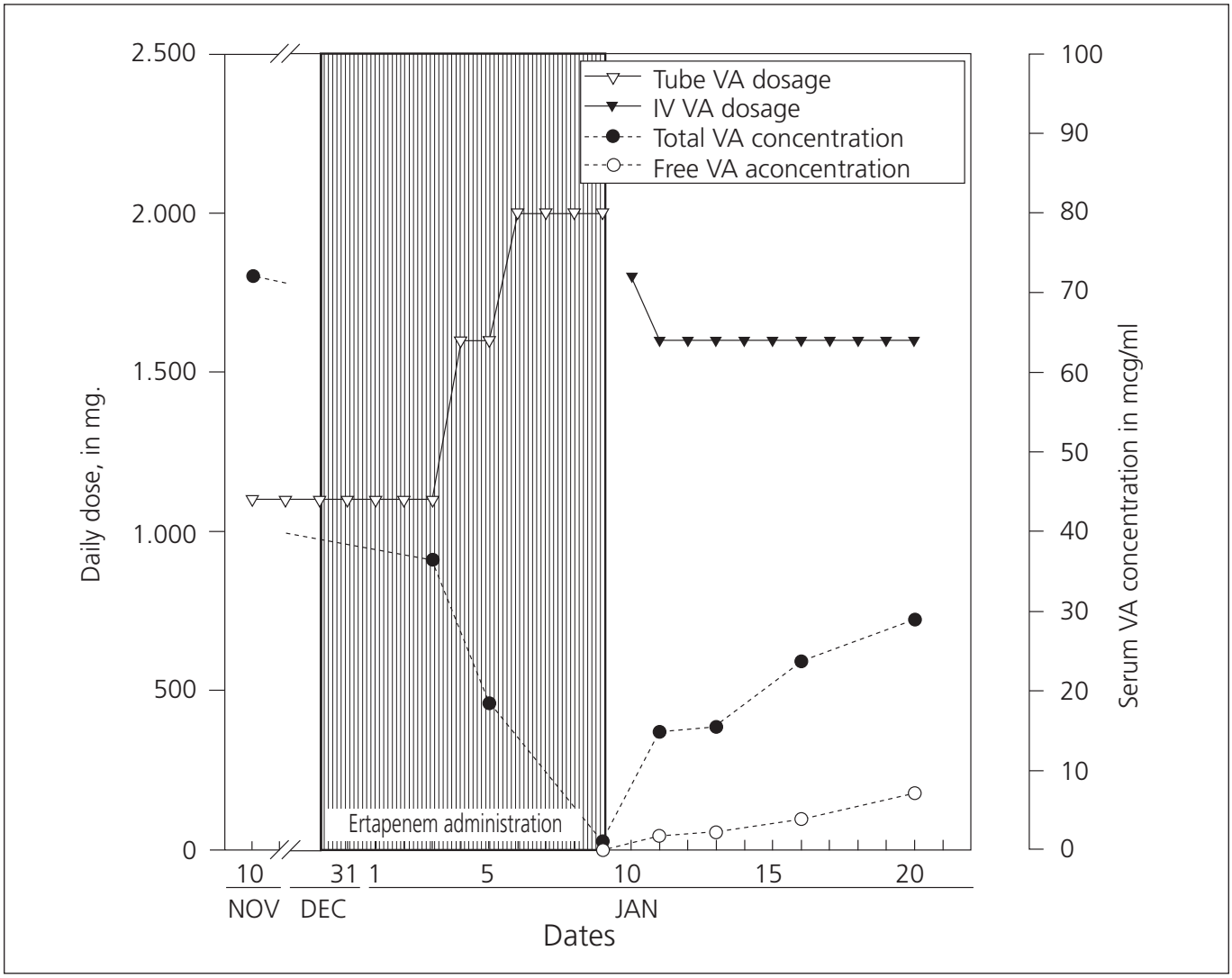

Fig. 1.- *Dosage regimen and both total and free serum valproic acid concentrations over time. The period of time during which the patient received ertapenem 1000 mg/day is indicated with vertical stripes.*

between carbapenems and valproic acid that is well documented in the literature regarding imipenem, meropenem, and panipenem, and which can be now extended to ertapenem in view of our clinical case report.

Despite the fact that ertapenem is less convulsant when compared to other carbapenems[1], the administration of any of these compounds to patients receiving VA may entail a significant risk for seizures. In such case, when both antibiotic and anticonvulsant coverage is required, a different antibiotic should be selected in accordance with the isolated organism's sensitivity, or a different anticonvulsant should be substituted for VA.

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