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Pharmacological interaction between valproic acid and carbapenem: What about levels in pediatrics?

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ABSTRACT

Valproic acid (VPA) is the most commonly used antiepileptic drug in pediatric patients, but its major drawback is its multiple pharmacological interactions.

Objective: To study children who had been simultaneously treated with carbapenems and valproic acid, considering drug levels, pharmacological interactions and clinical follow-up.

Material and methods: Retrospective study of children who simultaneously received treatment with VPA and carbapenems between January 2003 and December 2011. Demographic variables, indication of treatment, dose, VPA plasma levels, interactions, clinical manifestations and medical management were analyzed.

Results: 28 children with concomitant treatment with both drugs were included in the study. 64.3% were males. 78.6% of the interactions were observed in the Intensive Care Unit. 60.7% of children had been previously treated VPA and its major indication were generalized seizures. Basal plasma levels of VPA were recorded in 53% and at 24 h after admittance in 60%. "40% of basal VPA levels were below therapeutic range prior to the administration of carbapenem. After the introduction of carbapenem 88% of level determinations were below therapeutic range". 54.5% of the patients that were chronically receiving VPA and had good control of epilepsy before admission had seizures during the coadministration. One patient that was on VPA before admission but with bad control of epilepsy worsened, and one patient that acutely received VPA did not achieve seizure freedom. In these cases it was necessary to either increase VPA dose or change to a different antiepileptic drug.

Conclusions: Little is known about the mechanism of pharmacologic interactions between carbapenems and VPA, but it leads to a reduction in plasma levels that may cause a loss of seizure control, so simultaneous use of both drugs should be avoided when possible. If not, VPA levels should be monitored.

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1. Introduction

Valproic acid (VPA) is the most commonly used antiepileptic drug in pediatric patients, mainly because of its easy administration (capsules, syrup, intravenous…) and the possibility of drug level monitoring.

It can be used either in monotherapy or in polytherapy to treat generalized or partial seizures with good results. Its metabolism is primarily hepatic and the resulting metabolites are removed by the kidneys, so its use is discouraged in case of liver failure and it requires dosage adjustment in renal insufficiency.[2] Its main disadvantage is that it has a very complex metabolism and has many interactions with other drugs (like other anticonvulsants, psychotropic drugs, salycilates, some antibiotics…), due to the drug's ability to inhibit certain liver enzymes. Moreover, other drugs that are enzyme inducers can increase VPA hepatic metabolism.[2,3] Many of these interactions are widely known by clinicians and have been studied and taken into account when prescribing a new treatment in patients taking VPA.[1] However, there are many other drug interactions that are unknown to many physicians that can drastically increase or reduce drug blood levels and can lead to clinical intoxication or to loss of seizure control in patients who may have been seizure free for a long time. The number of publications about interactions between VPA and other drugs has increased in recent years, especially with carbapenemic antibiotics (meropenem, imipenem, ertapenem) which are broad-spectrum antibiotics widely used in some units such as pediatric intensive care.[4–27] The concomitant use of these drugs results in a significant decrease in VPA plasma levels.[4–27]

Coadministration of VPA and carbapenems may occur in patients with any underlying neurological disease treated with VPA, which develop surgical-related or nosocomial infections that require broad spectrum antibiotics.[24]

On the other hand, critically ill patients treated with a carbapenem may require the use of VPA in the context of neurological complications resulting from their underlying disease (i.e. seizures secondary to cardioembolic stroke in patients undergoing cardiac surgery). The aim of our study was to review patients who received concomitant treatment with VPA and carbapenem and to analyze the causes of its simultaneous prescription, the consequences of the coadministration (clinical and laboratory findings), clinical outcomes and therapeutic approach.

2. Material and methods

2.1. Population

All pediatric patients who were simultaneously treated with valproic acid and carbapenems between January 2003 and December 2011 were included. They were identified by the electronic prescription record of our hospital.

2.2. Data collection

This is a descriptive, analytical, retrospective review. Data were collected from the patients' medical records. Several parameters were reviewed and included, such as age, sex, underlying disease, reason for admission, indication for treatment with VPA and with carbapenems, type of carbapenem, where and when the interaction was detected, drug doses, route of administration, antiepileptic drug levels prior to the beginning of the concomitant drug administration and subsequent monitoring levels, clinical significance and management. Total VPA plasma levels were measured in our laboratory using the Fluorescence Polarization technique on a Cobas Integra 400 analyzer (Roche Diagnostics). VPA levels were considered within therapeutic range between 50 and 100 mcg/ml. Liver enzyme levels (aspartate aminotransferase (AST), alanine aminotransferase (ALT, alkaline phosphatase (FA), gamma glutamyl transpeptidase (GGT), total bilirubin) prior to the concomitant drug administration were recorded, considering pathological levels above twice the reference values. In addition, renal function (according to creatinine plasma levels) was assessed before and after the drug coadministration.

2.3. Statistical analysis

A descriptive analysis of data was performed, using the computer program for Windows SPSS.18. Data are expressed as frequencies and proportions or as medians and interquartile ranges (P_{25}–P_{75}).

3. Results

3.1. Population and hospitalization data

We included 28 children (18 boys and 10 girls) who had received concomitant treatment with VPA and carbapenems during the study period. Table 1 shows the main characteristics of the study population, treatment dose and main baseline laboratory values (Table 2).

60.7% of patients (17 patients) were already receiving VPA at the moment of carbapenems administration, of which 64.7% had good seizure control (seizure freedom o sporadic seizures in case of patients with frequent seizures) before admission. The remaining patients (11) received carbapenem and VPA simultaneously for the first time.

In 78.6% (n = 22) of cases drug coadministration occurred in the intensive care unit followed by the pediatric floor. The leading causes of hospitalization were respiratory infection and cardiac surgery (28.6% each, 8 cases) followed by neurological disease in 21.5% (6 patients), sepsis or non-respiratory infections in 10.7% (3 patients) and airway surgery in 10.7%. Fig. 1 shows the most frequent underlying diseases.

3.2. Indication of treatment, drug type and route of administration

The main indications for antibiotic treatment were nosocomial infection (25%), respiratory tract infection (25%) and resistant organism-related infections (25%). One patient received intramuscular ertapenem and the rest received intravenous meropenem. The indications for treatment with