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Meropenem and Valproic Acid Interaction: A Systematic Review of Case Reports and Case Series

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Abstract: ***Background: This systematic review focused on the evidence regarding meropenem (MRP) and valproic acid (VPA) interaction. Method: the electronic databases consulted were PubMed, Scopus, and EBSCO, searching for cases reported related to the interaction between 1998 and 2018. Results: 35 articles were selected for this work from a total of 162 articles found in the databases, 10 selected for qualitative analysis, and 25 for quantitative analysis, with a total of 55 cases. It has been observed that: a) the VPA blood levels significantly decreased by 75-90% from the initial values (reference range 50-100 mcg/ml) 24 hours after the MRP administration; b) although VPA doses were increased, no consistent augmentation in VPA blood concentration was achieved; c) the interaction was independent of the age group; d) the VPA levels recovery could have started (between 1 and 20 days) after the MRP withdrawal. Conclusion: This systematic review proposes that the level of evidence corresponds to 3 with recommendation D level according to SING. This work has demonstrated robust evidence because of the high number and quality of cases reported. Here, the interaction was qualified as probable due to the MRP's re-entry according to the data.***

Keywords: Meropenem, valproic acid, interaction drug, systematic review

1. Introduction

In 1998 the first case of interaction between MRP and VPA was reported, in which plasma levels of VPA decreased to undetectable concentrations, resulting in seizures in many patients. The valproic acid (VPA) is an anticonvulsant mainly used to treat seizures and bipolar disorder. The meropenem (MRP) is a broad-spectrum carbapenem antibiotic commonly used for infections. The present study aimed to conduct a systematic review about meropenem and valproic acid interaction of all case report from the first appeared in 1998 until May 2018, Cochrane Handbook rules for Systematic Reviews of Interventions [1]. Moreover, it was assessed causality for this drug interaction, considering the target and precipitant drug properties, patient-specific factors, and the potential contribution of other drugs that the patient may be taking.

Different possible mechanisms have been studied in animals or in vitro tests. Kojima and colleagues [2] showed that the enterohepatic recirculation of VPA was interrupted because the enteric bacteria could not disengage the glucuronic VPA molecule preventing VPA reabsorption in the presence of meropenem. Several animal studies showed that the interaction occurs in hepatocytes; thus, the intrinsic rate of glucuronidation was increased in the presence of carbapenem with a significant increase in total body VPA clearance and the rate of biliary VPA-glucuronide excretion (Tobin et al., 2009) [3]. The most recent theory has been postulated by Suzuki et al., 2016 [4]. The interaction studied in dogs revealed that the cause is a prolonged inhibition of the VPA glucuronide hydrolysis (VPA-G) produced by acyl-peptide hydrolase, which led to a rapid decrease in VPA plasma levels and an increase in the urinary excretion of VPA-G [4].

A systematic review is a type of scientific research in which the literature on a specific topic based on a formulated question and objective is revised. Systematic and explicit methods are used to locate, select, and assess the research relevant to that question and apply protocols systematically data collect and report such investigations. The purpose of this study is to reach valid and objective conclusions about all cases reported about MRP-VPA interaction.

2. Methods

The study was conducted according to the Cochrane Manual of Systematic Reviews of Interventions (version 5.1.0) and PRISMA Guidelines (Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines)[5]based on the chosen inclusion and exclusion criteria. The search terms used to identify studies were meropenem, valproic acid, and drug interaction. Two researchers independently extracted data from each of the identified studies. The extracted data consisted of age and sex, MRP and VPA

doses, VPA or valproate baseline levels, time for the interaction appearance when MRP was added, time for VPA levels recovery and, the possibility of seizures during the interaction.

The following electronic databases were searched for papers from 1998 to May 2018: Scopus [6], PubMed (https://www.ncbi.nlm.nih.gov/pubmed/) [7]and EBSCO (http://ebsco.com)[8], without language restriction. All search results were collected and, the duplicated ones removed. Relevant reviews were examined to identify additional information to be likely used herein. The selection processes could see in the flow chart (Figure 1) according to PRISMA. It was considered to include case reports that fulfilled the inclusion criteria, and it was discarded those that had some exclusion criteria, as described below.

Inclusion criteria: 1) Patient characteristics: unrestricted age, indistinct gender, unrestricted pathology, 2) date: January 1998 to May 2018, 3) languages: Spanish and English, 4) patients medicated with VPA and MRP.Exclusion criteria: 1)Studies performed in laboratory animals, 2) computational studies, 3)languages that could not be interpreted, 4) administration of a carbapenem other than MRP, 5)reviews, comments, and others that will not comment on clinical cases.

Data collection and analysis

It was tried to get all the articles that are in virtual libraries. The data were extracted from full articles: authors, date of publication, country, language, sex of the patient, age, the dose of MRP and VPA, route of administration, plasma concentration of VPA, time to decrease blood concentration and time to recover the therapeutic levels.

Qualification of cases and interaction

Two authors reviewed the titles and abstracts articles independently. Thus, those cases that did not fulfil the inclusion and exclusion criteria were removed. Then full texts were reviewed; if there were any controversy during selection, a third reviewer would read the information and decide its inclusion. The scale developed by Agbabiaka et al. in 2008 [9] was used to rate each case. When more than one case was presented in the publication, the complete publication was valued. The rating of the interaction between VPA and MRP of each case report was made using the Drug Interaction Probability Scale (DIPS), proposed by Horn et al., 2007 [10].

Statistics

Data were presented as a minimum, maximum, mean, median, standard deviation, and coefficient of variation. We calculated 95% confidence intervals for the different variables. The Student t-test was applied to compare plasma VPA levels before and after the MRP. GraphPad Prism version 5.00 for Windows, GraphPad Software, La Jolla California USA was used.

3. Results

Initially, it was identified one hundred and sixty-two articles after eliminating duplicates of the three bases (64 papers) and discarded nineteen ones because the title indicated another type of study. Then, we had to discarded forty-four because they did not fulfil the inclusion and exclusion criteria, such as animal tests, computer tests, and comments without case reports. Finally, we obtained 35 articles, ten used for qualitative analysis, and 25 for quantitative analysis, with a total of 55 cases dictated another type of study (Fig. 1). The case analyses included patients of both sexes, with no age limit and from all over the world. The articles were written in English and Spanish. The articles' quality was evaluated based on the scale proposed by Agbabiaka et al. [9]. Each article was graded in their entirety, two published, Clause et al., 2005 [11] and De Turk et al., 1998 [12], were broke up the cases because of more than one was described with different information in them. For a quality scale between 36 and 0, an average score of 25 was obtained, with 29 being the maximum score and 16 the minimum quality (Table 1). Most of the articles were published by authors from Spain (9/35), followed in second place by the United States (6/35), in third-place Belgium (4/35) then South Korea (3/35) and Turkey (2/35), Argentine (2/35), and the followed only one: Austria, Brazil, Czech Republic, China, Chile, India, Italy, Taiwan, among others. Seventy-one per cent of articles are written in English, while 29 % in Spanish.

The years of publication of cases on the interaction between MRP and VPA range from 1998 to 2018. The date of publication of most articles was 2012 (5/35) four articles were published in 2005 and 2015, followed by three articles published in 2009. Figure 2 shows the distribution by year of publication.

Table 2 presents data of 55 cases collected, of which 11 are qualitative and 44 quantitative analysis. Three papers were case series and were classified as quantitative because they had the concentration of VPA in the blood before and after concomitantly administering MRP, thus calculating the percentage decrease.

According to reported cases, forty-two percent of patients were male, while 58% were female. The age range comprised of 2 months to 89 years, giving an average age of 47 years (Table 2 and 3).Patients presented diverse diagnoses upon admission (pneumonia, meningioma, myelodysplasia, oral candidiasis, pyelonephritis, cranial trauma, among others). Daily doses of VPA ranged from 200 mg to 2400 mg, while MRP doses varied from 0.5 g to 9 g per day. There was no relationship between MRP doses and the percentage of decrease in VPA concentration in blood. Respect for plasma VPA concentration decrease was observed in the 53/55 of cases. The results of the VPA level drop were summarized in Figure 3. The comparison of the baseline with the average value obtained with MRP has a significant difference, $\alpha < 0.0001$. The percentages of decrease ranged from 57% to 99.8% (mean 78.1%). The maximum reduction in VPA concentration was 99.8 % reported by Park and colleagues in 2012 [13]. In only two cases, the administration of the MRP unaffected AVP concentration: one was the case of a 49-year-old cirrhotic patient, detailed in the article presented by Spriet and colleagues in 2011 [14]; the other was a 19-year-old adolescent, reported by Park and colleagues in 2012 [13], as shown in Table 2.

It was observed that the VPA concentration reduction occurred at least 24 hours after the first administration of the MRP and with a maximum of nine days, with an average of 3 days after the first dose of the antibiotic. On the other hand, recovery of levels was observed at least one day after the drug's withdrawal, with a maximum period of 20 days, and an average of 8 days later. Thirteen patients had seizures after the administration of VPA and MRP of the 55 cases analysed. Four patients died during the hospitalization for different reasons: aspergillosis, cardiac arrest, septic shock, and hypoxemic refractory failure.

Three reports only described the causality of the interaction; hence it was revised the probability of the pharmacological interaction using DIPS scale to evaluate the causality of each case resulting in a probable interaction between VPA and MRP (Table 1).

4. Discussion and Conclusions

In this evaluation, patients experienced significant changes in plasma concentration of VPA below the therapeutic range in almost all cases due to concurrent administration with MRP; some of them had seizures. The interaction described was so important that it led to a change in the antibiotic or anticonvulsant medication according to the risk-benefit ratio. The anticonvulsant VPA was approved in the '70s and since the date has shown several critical drug-drug interactions. The MRP approved in 1990 with the intention that it would not produce seizures as imipenem did. A large number of publications occurred in 2012, from a range analysed between 1998 to 2018. However, only the warning was published on the package insert of these medications eleven years after the first case report [32, 31].

The contribution of the case reports was the initiative for this warning in the leaflet. While numerous studies are reporting on the interaction between VPA and MRP, this is the first review to bring together so many case reports so far. In 53 of the 55 patients included in this evaluation, they experienced significant changes in VPA elimination rate at levels below the therapeutic range (decreases from 57% to 99.8%). Daily monitoring of VPA in the blood, reducing the VPA therapeutic effect, and seizures in 13 of 55 cases warned of this problem.

Medical behaviour consists of the replacement of the antibiotic or anticonvulsant. The replacement of the MRP produced the VPA blood concentration elevations after 24 hours in some patients. No relationship was found between MRP doses on the percentage of decrease in VPA blood concentrations. On the other hand, this interaction no discriminates against its effect by gender or age.

In 3 cases, the pharmacy service alerted about this interaction and recommended changing the medication [20,26,34]. As we can see, the role of pharmacists in educating and working together with the health team is essential to prevent this type of interaction in the intensive care unit, to make clinical decisions, and to achieve adequate, effective, and safe treatment, always for the benefit of the patient.

Kohbrani et al. have demonstrated that MRP is effectively decreasing VPA concentrations, given that he clinically used MRP to produce VPA body decrease after an intoxication, proving the relationship of the interaction, constituting a piece of strong evidence [42]. Besides, in four articles included in the present analysis [24, 25, 30, 38] the interaction was tested with the MRP re-entry and confirmed the interaction between VPA-MRP.

The Information from a single case report cannot be generalized, but when there is derived from the case/report series, the quality should be assessed like in the present paper and others [43]. Because of these cases, therapeutic recommendations are used to make decisions and recommendations [44]. There are different scales to qualify the evidence proposed [45, 46, 47]. For SIGN guidelines, the evidence and the recommendation levels correspond to 3 and D, respectively. However, this systematic review demonstrated a piece of evidence strong because of the high number and quality of cases reported. Then, the level of evidence should be reviewed in systematic reviews of case reports and case series. Besides, we reviewed the qualification of this interaction, suggesting that it should be qualified as probable, based on the MRP re-entry and three retrospective observational studies conducted, that it has reviewed in this paper.

The summary of the reports analyzed indicates that the interaction between the VPA and the MRP has strong evidence with a constant decrease in the level of VPAs, which endangers the risk-benefit ratio of indicating them together. Systematic reviews of case series and case reports on adverse events and drug interactions are useful in identifying trends and treatments that lead to positive health outcomes. We encourage pharmacists to conduct more systematic reviews using the Cochrane methodology to establish therapeutic recommendations that will improve the choice of an appropriate drug for the health of patients.

5. Conflict of Interest

The authors declare that they have no competing interests.

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