VALPROIC ACID-CARBAPENEM INTERACTION: REPORT OF SIX CASES AND A REVIEW OF THE LITERATURE

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SUMMARY

***Aim*:** To evaluate the drug interactions between valproic acid (VPA) and carbapenem antibiotics.

***Methods*:** The effects of concurrent use of VPA and carbapenem antibiotics were evaluated in a retrospective observational study of hospitalized adults. Patients receiving both VPA and a carbapenem with at least two plasma VPA concentrations serially measured prior to, during, and/or after this combined treatment were included.

Results: Six critically ill VPA-treated patients were identified who concurrently received meropenem (n = 4), imipenem (n = 1), or ertapenem (n = 1). As compared with values obtained while not receiving treatment with the carbapenem, mean plasma VPA trough concentrations decreased by 58% (from 51.7 [95% confidence interval {CI} 28.0-75.4] to 21.8 [95% CI 11.1-32.5] mg/L; p = 0.025). Estimated mean VPA clearance increased by 191% (from 0.0158

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[95% CI 0.0041-0.0275] to 0.0302 [95% CI 0.0169-0.0591] L/h/kg; p = 0.007). All VPA concentrations measured during concurrent VPA-carbapenem treatment were below the lower boundary of the usual therapeutic range. Five patients (83%) experienced generalized seizures during concurrent VPA-carbapenem treatment, including two with no prior history of seizures or epilepsy.

Conclusions: All recipients showed evidence of a complex pharmacokinetic and pharmacodynamic drug interaction between VPA and a carbapenem. Concurrent use of these medications should be avoided.

KEY WORDS

carbapenem, ertapenem, imipenem, interaction, meropenem, seizure, valproic acid

INTRODUCTION

Since the 1970s, valproic acid (2-propylpentanoic acid, VPA) and its various prolonged-action coordination compounds (divalproex) and salt forms (valproate sodium) have been used clinically for treatment and prevention of seizures /1,2/. In addition to its present role as a first-line or alternative agent for management of a variety of both chronic /3/ and acute seizure disorders /4,5/, VPA is widely utilized for the treatment of bipolar disorder /6/ and prevention of migraine attacks /7,8/.

Thienamycin or carbapenem antibiotics likewise are frequently used in the empiric and definitive treatment of a broad array of serious bacterial infections, particularly those associated with multiple organisms or multi-drug resistant strains /9,10/. The popularity of carbapenems largely results from their broad-spectrum antibacterial activity and proven tolerability /11-13/.

Recent accounts have described adverse clinical events recognized in conjunction with combined use of VPA and carbapenem antibiotics. These reports /14-33/, comprising a total of 76 patients, indicate that VPA and carbapenems interact with potentially detrimental consequences. Seizures have been documented frequently with combined VPA-carbapenem therapy, often in association with altered VPA pharmacokinetics and decreased VPA plasma levels. We wish to

report the details surrounding a further six patients, five of whom experienced worsening or new-onset of seizures during concurrent administration of VPA and a carbapenem.

METHODS

This study was designed as a retrospective, observational survey of hospitalized patients. Prior to data collection, the study was approved by the Colorado Multiple Institutional Review Board, the University of Colorado Hospital (UCH) Research Review Committee, and the UCH Medication Use Evaluation/Adverse Drug Reaction Subcommittee. Research was performed in a manner consistent with Health Insurance Portability and Accountability regulations. The study was conducted at UCH, a 411-bed tertiary level academic medical center located in Aurora, Colorado, USA.

The objectives of this study were to identify and evaluate relevant biochemical and therapeutic outcomes of recipients of concurrent VPA and carbapenem therapy. Adult in-patients who received VPA and imipenem, meropenem, or ertapenem during the 18-month period of observation from 1 January 2006 through 30 June 2007 were identified though utilization searches of the hospital's pharmacy computer system. Patients were selected on the basis of (1) receipt of concurrent treatment with both VPA and a carbapenem antibiotic and (2) documentation of ≥ 2 plasma VPA concentrations serially sampled and proximally measured prior to, during, and/or after this combined treatment. The medical records of consecutive VPA-carbapenem recipients were audited and relevant information was recorded. Recorded information pertained to the clinical circumstances surrounding the administration of VPA and carbapenem therapy during the first 7 days after initiation of combined treatment or sooner if discontinued or the patient was discharged.

The following data, if available, were recorded for every patient: demographics (age, gender, weight, primary diagnosis, secondary diagnoses, past medical history), lengths of intensive care unit and/or hospital stay, mortality, dosage and duration of VPA and carbapenem antibiotic therapy, concomitant treatments, direct and surrogate indicators of infection (bacterial culture results, serial white blood cell counts and leukocyte differential, core temperature), abnormal neurological findings (witnessed seizure activity, interpreted electro-

encephalographic data), and possible causes of seizures (e.g. trauma, infection, metabolic abnormalities, history of alcohol abuse). Adverse events (e.g. seizures, gastrointestinal symptoms, sedation, fatigue, dizziness, headache, ataxia, insomnia, behavioral problems, hyperammonemia, elevation of hepatic transaminases) were recorded if present and temporally related to initiation of VPA or carbapenem therapy.

Pharmacokinetic determinations were performed using trough plasma total VPA concentrations as measured by the hospital's clinical laboratory with immuno-turbidimetry assay tools. Using assumptions of first-order kinetics and attainment of steady-state, estimated total body clearance (CL) of VPA from plasma in L/h/kg was calculated using the following relationship /34/:

$$CL = \frac{D/\tau}{C_{SS}} \qquad \text{Eq. 1}$$

where D is the individual dose amount of VPA in mg/kg, τ is the dosing interval in hours, and C_{ss} is the steady-state plasma concentration of VPA in mg/L.

Using similar assumptions, estimated area under the VPA plasma concentration-time curve (AUC) for one dosing interval in mg/L·h was calculated using the following relationship /34/:

$$AUC = \frac{D}{CL} \qquad \text{Eq. 2}$$

Data presented as means were compared using Student's t-test where appropriate. All tests were 2-tailed. A p value less than 0.05 was considered significant. Data are presented as means ± 95% confidence intervals (CI).

Information in the medical literature prior to October 2008 related to VPA and carbapenem antibiotics was identified using MEDLINE and EMBASE. Search strategies comprised singular and linked database queries using the terms 'carbapenem', 'imipenem', 'ertapenem', 'interaction', 'meropenem', 'seizure', 'transporter', 'valproate', and 'valproic'. Additional references were identified from bibliographic listings of relevant articles. Studies were selected for inclusion on the basis of subject relevance, methodological soundness, and overall scientific validity as judged by the authors.

RESULTS

From existing hospital records, 17 patients were identified who received contemporaneous treatment with VPA and a carbapenem antibiotic during the designated period of observation. Eleven patients were found to have <2 VPA plasma levels and were excluded.

Six patients were identified who fulfilled pre-specified inclusion criteria. Demographic and fundamental clinical variables for these patients are sequentially displayed in Table 1. All patients were critically ill and all were treated in an intensive care unit. All patients received both VPA and a carbapenem as intermittent, divided-dose intravenous (IV) infusions.

Each patient had multiple acute and/or chronic disease diagnoses. The severity of illness present upon admission frequently led to acute or acute-on-chronic organ failure. Respiratory failure requiring mechanical ventilation was present in five cases (patients 1, 2, 3, 4, and 6 in Table 1). Liver disease was present in all patients; hepatic transaminases and total bilirubin were found to be elevated to 1.4 to 2 times the upper limit of normal in five cases (patients 1, 2, 4, 5, and 6) and severe or end-stage liver disease developed during hospitalization in one (patient 3). Renal insufficiency was found in one case (patient 6) and acute kidney failure requiring renal replacement therapy developed in two (patients 1 and 3).

Five patients were found to have clinical signs of seizures during concurrent VPA-carbapenem treatment. The occurrence of observed or suspected seizures temporally associated with initiation of concurrent treatment with VPA and antibiotic therapy with a carbapenem was clinically documented in each of these five patients and seizures were electroencephalographically confirmed in three patients. Carbapenem antibiotics associated with seizures included meropenem in three patients, ertapenem in one patient, and imipenem in one patient.

Seizures occurred during combined therapy with VPA and a carbapenem in two patients with a distant past medical history positive for seizures and in one patient with poorly controlled epilepsy. Seizures were documented in two patients with no prior history of seizures or overt epilepsy. Patients with negative seizure histories received VPA as continuation of pre-admission therapy for bipolar disorder. New onset of generalized seizures during combined VPA-

TABLE 1: Patient characteristics

Patient no.	1	2	3	4	5	6
Age, Gender	54, F	61, M	47, M	67, M	49, M	28, M
Primary diagnosis	Altered mentation	Pancreatitis	Aneurysm rupture	Hepatic cancer	Bowel obstruction	Hypoxemia
Secondary diagnoses	Fibromyalgia, sleep apnea	Anemia, ARDS[§]	Hypertension, ARDS[§]	Coma, status epilepticus	Hemicolectomy, epilepsy	Suicidal hanging, substance abuse
VPA Indication	Bipolar	Bipolar	Prophylaxis	Seizure	Epilepsy	Prophylaxis
VPA dose (mg/kg/day)	13.5	22	14	15	7.5	25
Suspected infection	Meningitis	Bacteremia	Bacteremia	Bacteremia	Prophylaxis	Pneumonia
Carbapenem dose	Meropenem 500 mg q24 h	Meropenem 1 g q 12 h	Meropenem 1g q 24 h	Meropenem 1 g q 8 h	Ertapenem 1 g q 24 h	Imipenem 500 mg q 6 h
VPA level Off*	36	28	76	82	52	36
On†	37	12	24	27	<10	22
Onset‡	<4		--	24	48	24

* Trough VPA concentration, not on carbapenem therapy, mg/L.
† Trough VPA concentration during carbapenem therapy, mg/L.
‡ Onset of observed or suspected seizure activity, recorded as approximate time of occurrence after initiation of combined VPA and carbapenem therapy, hours.
§ Acute respiratory distress syndrome.

carbapenem therapy was documented clinically in both patients and electroencephalographically confirmed in one.

As compared with VPA levels measured while not receiving carbapenem treatment, plasma VPA concentrations sampled and measured during combined therapy were diminished in five patients. Compared to off-treatment values, mean plasma VPA trough concentrations (Fig. 1) decreased by 58% during combined therapy (from 51.7 [95% CI 28.0-75.4] to 21.8 [95% CI 11.1-32.5] mg/L; $p = 0.0254$). Plasma VPA concentrations measured during combined therapy were subtherapeutic or below the lower boundary of the usual reference or therapeutic range (50-100 mg/L) /35,36/ in all cases. Recorded VPA concentrations were diminished within 24 to 72 hours following initiation of combined therapy in all affected patients.

In the single patient in whom plasma VPA levels appeared not to decline (Table 1, Patient 1), onset of seizure activity occurred less than 4 hours after completion of the first dose of IV meropenem. In this patient, blood was sampled and the plasma VPA concentration was measured in the postictal period shortly after seizures were recognized. This level showed essentially no change as compared with a VPA level measured prior to initiation of antibiotic treatment. In response, a supplemental IV dose of VPA was administered and the incremental and corresponding total daily VPA dosage was increased. Despite this, essentially no increase in plasma VPA concentration resulted. Subsequently, meropenem was discontinued and, with no further dose change, the plasma VPA concentration measured 72 hours later was within the usual therapeutic range (>50 mg/l). Hence, this patient was not spared from carbapenem-induced changes in VPA kinetics.

Conversely, VPA clearance was increased. Compared to off-carbapenem values, estimated mean VPA clearance (Fig. 2) increased from 0.0158 (95% CI 0.0041-0.0275) to 0.0302 (95% CI 0.0169-0.0591) L/h/kg ($p = 0.0068$) during combined therapy.

AUC declined. Compared to off-carbapenem values, derived mean area under the VPA plasma concentration-time curve decreased from 1,336 (95% CI 797-1875) to 522 (95% CI 272-792) mg/l·h ($p = 0.0061$) during combined therapy.

Patient outcomes varied from discharge to self care at home in one patient, to discharge to a long-term skilled nursing facility in three, and to transfer to hospice care in one. One patient expired during this

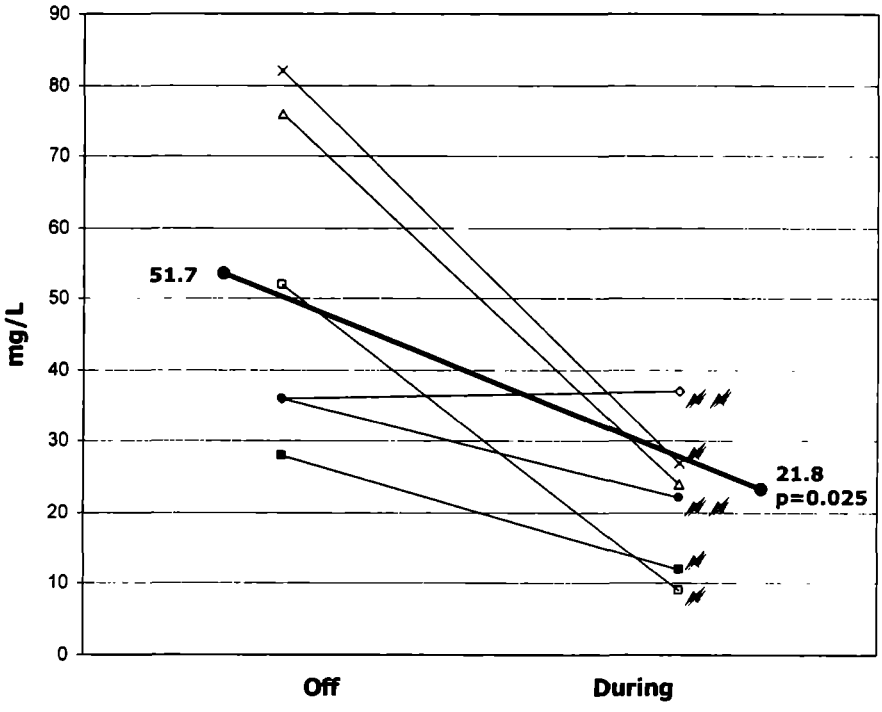

Fig. 1: VPA levels off and during concurrent carbapenem therapy. Bold line = mean for 6 patients. ↗ = worsened or recurrent seizures during combined therapy. ↗↗ = new onset seizures during combined therapy.

hospital admission; intractable intermittent seizures were cited as one of multiple factors contributing to demise.

DISCUSSION

Patients included in this evaluation experienced significant changes in estimated rates of clearance of VPA from plasma during the period when a carbapenem antibiotic was concurrently administered. These changes were associated with a decline in plasma VPA concentrations to levels that were below the lower threshold of the usual therapeutic range in all cases. These changes were associated with worsened or *de novo* seizures affecting five of six patients studied. Application of probability scaling /37/ revealed causality associations between

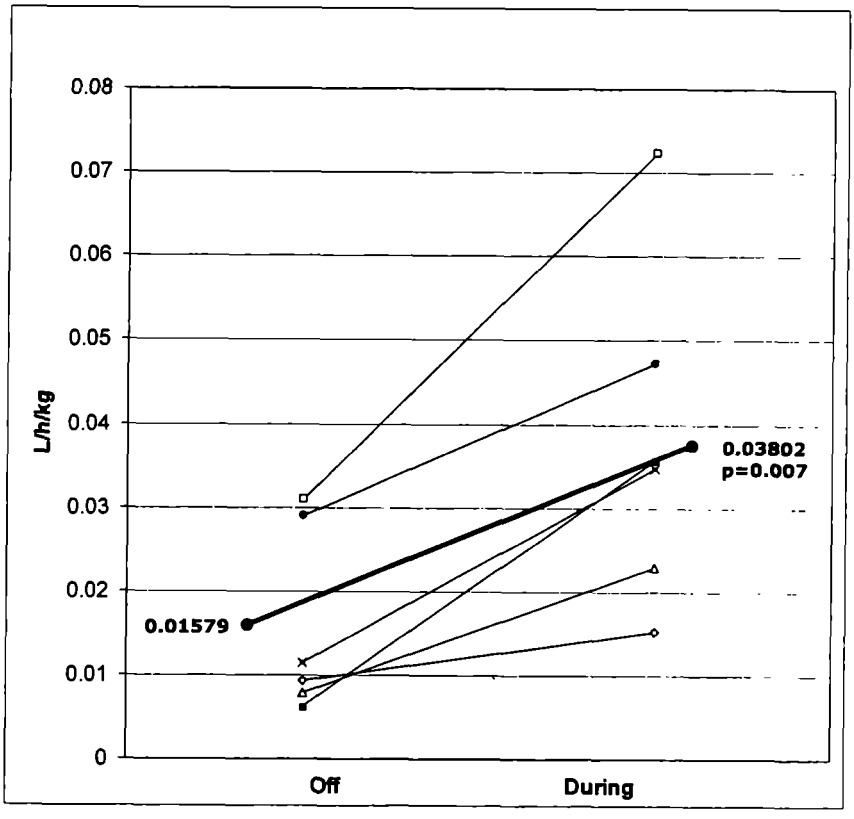

Fig. 2: Estimated VPA clearance off and during concurrent carbapenem therapy. Bold line = mean for 6 patients.

seizures and a drug interaction that were probable or highly probable in all seizure cases.

Pharmacokinetic interaction

When expressed as a fractional decrease, the magnitude of the division product of mean on- and off-carbapenem plasma concentrations of VPA exhibited by our patients (0.42) is generally comparable to those derived from previous descriptions of concurrent use of these medications /14-33/ (Table 2). These decreases in VPA levels are related to a pharmacokinetic drug interaction with the antibiotic.

TABLE 2

Reports of combined VPA-carbapenem therapy

No. of patients	VPA indication (n)			Worsened or uncontrolled seizures (n)	New onset seizures (n)	Approximate fractional VPA concentration on/off carbapenem mean (range)	Reference
	Seizure disorder	Mood disorder	Other				
3	3	–	–	2	–	0.06 (0.05-0.07)	/14/
3	3	–	–	2	–	0.30 (0.25-0.34)	/15/
2	2	–	–	0	–	0.22 (0.11-0.33)	/16/
3	2	–	–	1	–	0.40 (0.25-0.55)	/17/
3	3	–	–	0	–	0.20 (0.12-0.26)	/18/
1	1	–	–	0	–	0.20	/19/
1	1	–	–	1	–	0.27	/20/
2	2	–	–	0	–	0.40 (0.28-0.53)	/21/
1	1	–	–	1	–	0.17	/22/
1	1	–	–	1	–	0.12	/23/
2	2	–	–	0	–	0.31 (0.21-0.41)	/24/
1	1	–	–	0	–	0.31	/25/
1	1	–	–	0	–	0.51	/26/
1	1	–	–	1	–	0.10	/27/
1	1	–	–	1	–	0.54	/28/
2	2	–	–	1	–	0.22 (0.15-0.28)	/29/
7	7	–	–	1	–	0.30 (0.09-0.71)	/30/
39	38	1	–	11	–	0.34 (0.08-0.66)	/31/
1	1	–	–	1	–	<0.10	/32/
1	1	–	–	1	–	–	/33/
6	4	2	–	3	2	0.42 (0.17-1.02)	Present series

The exact mechanism for a pharmacokinetic interaction between VPA and carbapenem antibiotics is unclear. However, a number of contributing pathways for carbapenem-induced decremental changes in plasma and tissue VPA concentrations have been identified /38/. These pathways involve fundamental pharmacokinetic concepts and processes including absorption, distribution, metabolism, and excretion (Fig. 3).

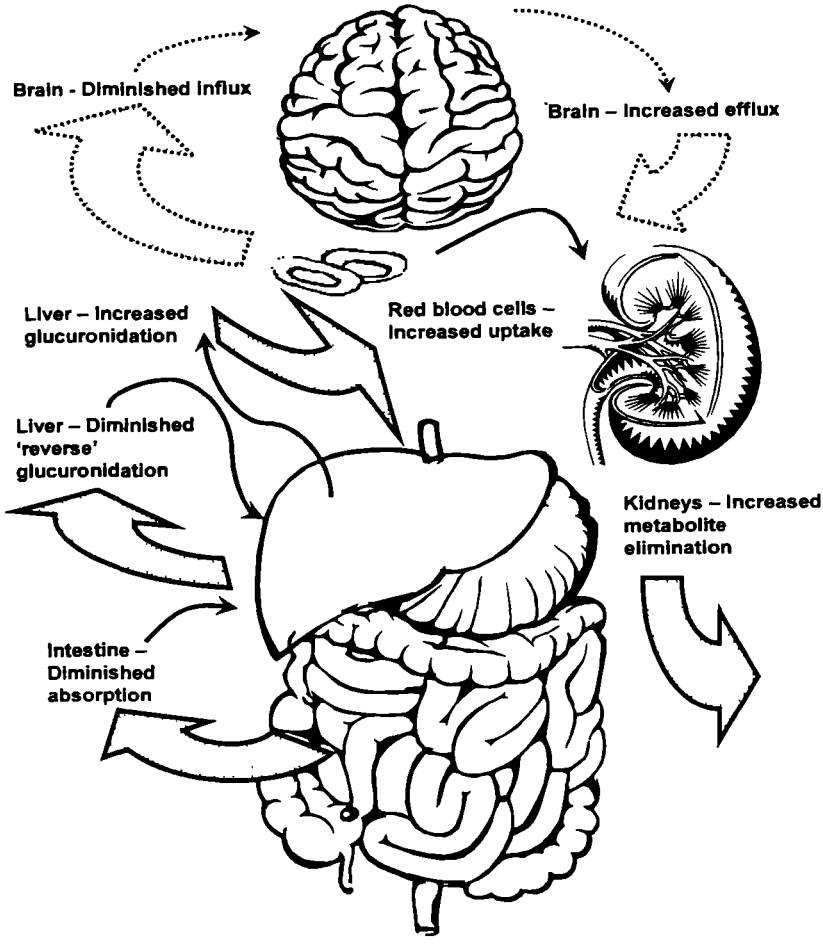

Fig. 3: Mechanisms of action for the pharmacokinetic drug interaction between VPA and carbapenem antibiotics. Dashed arrows represent actions not presently supported by clinical or strong experimental evidence.

Absorption

Carbapenem antibiotics decrease VPA absorption. Investigations in rats using large single-dose oral VPA administrations revealed that, as compared with control or IV injection, pretreatment with imipenem decreased mean peak plasma VPA concentrations by 41% and AUC by 57% (both $p < 0.01$) /39/. Decreased absorption was shown to result from altered transport across the intestinal brush-border membrane that subsequently was proven to result from carbapenem-induced inhibition of VPA transport by Caco-2 cell monolayers at the basolateral membrane of intestinal epithelial cells /40/. VPA levels additionally have been shown to be suppressed by IV co-administration of panipenem through diminished enterohepatic recirculation of VPA and antibiotic-induced decreases in the number of enteric bacteria and secondary decreases in production of β-glucuronidase /41/.

All patients in our series as well as a majority of those reported by others /16,19,21,23-25,31,32/ were critically ill and were treated with IV VPA. The degree to which altered absorption of enteral VPA contributes to a pharmacokinetic drug interaction in humans is presently unclear.

Distribution

VPA normally partitions between red blood cells and plasma in amounts that are directly proportional to concentrations of free drug in plasma /42,43/ but carbapenems affect this partitioning. In rats pretreated with IV or enteral VPA, imipenem and panipenem significantly decreased plasma VPA concentrations within 2 hours after administration. These changes resulted from increased erythrocyte distribution of VPA with increases in plasma but not whole blood VPA elimination rate constants and clearance /44/. Similar effects were found in two epileptic patients in whom imipenem was added to maintenance VPA therapy. As compared with values reported while not receiving combined treatment, imipenem administration in these patients was closely temporally associated with the prompt onset of both decreases in plasma VPA concentrations and increases in erythrocyte VPA concentrations /44/. *In vitro* studies using isolated and inverted vesicles from erythrocyte membranes have identified carbapenem-mediated effects on red blood cell membrane multidrug

resistance-associated protein (MRP) transporters that efflux VPA from erythrocytes to plasma as the predominating faction responsible for the distributive aspect of this pharmacokinetic interaction /38,45/.

Altered plasma protein binding does not appear to contribute to the interaction between VPA and carbapenems. Unlike effects of elevated VPA plasma concentrations /46/ or other organic anions such as acetylsalicylic acid /47/, co-administration of VPA and panipenem did not lead to altered protein binding or displacement of VPA from plasma protein binding sites /41,44/.

Transfer of VPA across the blood-brain barrier (BBB) and into the cerebrospinal fluid (CSF) is actively mediated by monocarboxylate transporter 1 (MCT1) /48/. The activity of this organic anion transport system has been shown to be disproportionately enhanced in a non-linear fashion by increased plasma VPA concentrations /49/. Presumably, VPA transport activity would be correspondingly non-linearly decreased by lower concentrations. Decreased plasma VPA concentrations, as documented in this and previous VPA-carbapenem interaction reports, should favor and contribute to diminished transfer of free VPA into the CSF.

Transporters governing influx of VPA into the CSF are inhibited by pretreatment with probenecid /49/ and benzylpenicillin /50/. Although influx transport inhibition has not been demonstrated with β-lactams other than penicillin, structural, physicochemical, and antibacterial pharmacological similarities among these compounds sharing a common CNS influx transporter suggest that a family or class effect on VPA influx probably exists. Accordingly, carbapenem antibiotics may be expected to suppress active transport of VPA into the CSF through this mechanism.

Efflux of VPA and its pharmacologically active β-oxidative metabolite from CSF to blood plasma is asymmetric and predominantly actuated by a distinctive energy-dependent carrier-mediated organic anion transport system located at the choroidal epithelium and brain capillary endothelium /51,52/. Members of the active transport system comprising the superfamily of adenosine-5′-triphosphate (ATP)-binding cassette (ABC) proteins or MRPs /53/, these transporters have recently been identified as MRP5 (ABCC5) /54/. Found in comparative abundance in the luminal side of brain capillary epithelial cells, brain endothelial cells, and astrocytes /55,56/, MRP5 is unique in its ability to transport and extrude cyclic

monophosphate nucleotides /57,58/, and appears to serve a protective role for brain cells by maintaining homeostasis and limiting or preventing brain exposure to potentially toxic exogenous substances such as certain antitumor /56,58-60/ and antiretroviral drugs /61/.

Both VPA and carbapenems interact with these transporters and several lines of reasoning suggest that the combined net result of these actions favors efflux or transfer of VPA from brain to blood. Expression of MRP5 is subject to induction and repression /62,63/. Detailed structural analyses /64/ and molecular modeling /65/ of human MRP5 reveal the presence of a positively charged intracellular translocation chamber that presents a high affinity recognition and binding site for organic anions as well as cyclic nucleotides. If binding and occupation of the organic ion binding site by carbapenem antibiotics is shown to induce MRP5 expression, this will be a key finding in understanding carbapenem enhancement of VPA efflux from brain tissue.

MRP5 activity is affected by VPA and carbapenems. Studies in rat erythrocyte membranes have shown that VPA inhibited MRP5-mediated low-affinity binding and transport of certain substrates whereas the carbapenem antibiotic panipenem inhibited both high- and low-affinity binding and transport /45/. Molecular modeling of MRP5 has shown that substrate binding by this transporter results in widespread conformational changes with subunit twisting and domain swapping occurring during the transport cycle /65/. Through these actions and the generally accepted theory of ion pumping /66/, the substrate VPA may be 'pumped' from high affinity binding inside CNS membranes to low-affinity binding outside CNS membranes, thereby being expelled to the extracellular space outside the BBB. Carbapenem inhibition of either VPA binding to MRP5 or the propensity of the MRP5 transporter to accept and undergo conformational variation again would favor efflux of VPA from the CNS.

One final mechanistic possibility suggests that the distributive interaction apparent between VPA and carbapenems may be caused not by the antibiotic but rather the infection being treated. Phylogenetic analyses of ABC transporters have shown that eukaryotic ABCB transporters and ABCC transporters (including MRP5) and various bacterial ABC transporters share several novel gene clusters in common and have similar repertoires of ATP-binding domains /67/. Serious infections caused by multidrug resistant gram negative

bacteria may be associated with organisms overexpressing these and related efflux transporters /68,69/. The presence of bacterial MRP5 or related efflux transporters in infected tissues such as meninges could affect membrane transport of VPA. With this in mind, it should be noted that the patient in our series, who despite no apparent change in plasma VPA concentrations suffered a first-ever generalized seizure after initiation of meropenem, was being treated for suspected bacterial meningitis.

Metabolism

Carbapenems affect the hepatic metabolism of VPA. The primary modes of biotransformation of VPA in hepatocytes are (1) conjugation with glucuronic acid in the sarcoplasmic reticulum; (2) β-oxidation in mitochondria and peroxisomes; (3) oxidation in the ω, ω_1, and ω_2 positions; and (4) γ- or δ-dehydrogenation in microsomes with subsequent glycine conjugation /70,71/, with mass balance studies generally ranking products and activity in this order /71,72/. Studies using nephrectomized and hepatectomized animal models with and without prior treatment with panipenem have demonstrated that an interaction occurs in hepatocytes such that the intrinsic rate of glucuronidation, the foremost mode of elimination of VPA, is enhanced in the presence of the carbapenem with significant resultant increases in total body VPA clearance and rate of biliary excretion of VPA-glucuronide /73/.

Pharmacological studies are divergent with regard to the mechanism of the apparent increase in rate of glucuronidation. While some indicate that liver concentrations of uridine diphosphate (UDP)-glucuronic acid, an intermediary substrate for enzymatic conversion by UDP-glucuronosyltransferase 1A6 (UDP-GT) of free VPA to VPA-glucuronide, are increased about 1.7-fold in the presence of panipenem /74/, others have failed to document these changes in liver content of this substrate /75/. Although enzymatic activity of UDP-GT has been found to be unaffected by carbapenems in some models /74/, others have reported significant drug-induced increases in UDP-GT activity of approximately 35% /38/. Investigations using primate liver slices have shown significant meropenem- and doripenem-induced inhibition of VPA-glucuronide hydrolysis, a process that contributes to decreases in plasma VPA concentrations by limiting deglucuronidation or 'reverse' conversion of VPA-glucuronide to VPA /75/. In total,

these investigations demonstrate (1) the metabolic effects of potential VPA-drug interactions are greatest in systems involving glucuronide formation, and (2) predominating effects are likely to be carbapenem antibiotic-induced enhancement of enzymatic actions within hepatocytes that affect glucuronidation.

Excretion

Carbapenems accelerate renal excretion of VPA metabolites. In rats receiving VPA with or without meropenem, the mean proportion of the VPA dose excreted in urine as VPA-glucuronide was increased from 45.6% in controls to 62.5% with meropenem ($p < 0.05$) /76/. In this investigation, the increase in total clearance of VPA was closely associated with the increase in renal elimination of VPA-glucuronide during combined treatment.

Prevalence

The pharmacokinetic interaction between VPA and carbapenem antibiotics is associated with changes in drug disposition that include increases in clearance of VPA from blood plasma, acceleration of the overall rate of elimination of VPA, and apparent enhancement of removal of VPA from the CNS. Our experience (Table 1) and that described by others (Table 2) suggests that these pharmacokinetic effects are present and measurable in most if not all patients receiving concurrent treatment with VPA and carbapenems.

Seizures have been reported infrequently in association with carbapenem treatment of infectious diseases. Large-scale clinical trials and post-marketing surveillance programs have documented the occurrence of seizures during therapy with incidence rates ranging from 1.8% with imipenem /11/ to 0.4% with meropenem /12/ and 0.2% for ertapenem /13/. In contrast, the overall incidence of seizures in the select carbapenem-treated patients who received concurrent VPA therapy displayed in Table 2 (30 [37%] of 82 total patients) is 20 to more than 100 times higher.

Consistent with comparative data from animal models /77,78/, clinical experience /11-13/ and extensive treatment surveys /79/ have documented that that the incidence of seizures associated with imipenem is higher than with meropenem or ertapenem. However, among the 30 patients listed in Table 2 who suffered from seizures

apparently resulting from a pharmacokinetic drug interaction, 22 (73%) received meropenem and two (7%) received ertapenem. Three of the five patients in our series who experienced seizures on concomitant VPA-carbapenem therapy, including both patients with new-onset seizures, received meropenem. Possible differences among drugs in the carbapenem class of antibiotics with regard to seizure liability seemingly disappear when this therapy is combined with VPA.

Pharmacodynamic interaction

In our series, new-onset seizures were identified during combined therapy with VPA and meropenem in two patients at risk but with no prior history of seizures or overt epilepsy. One critically ill patient, whose primary indication for IV VPA treatment was continuation of therapy for bipolar disorder, suffered a first-ever seizure closely associated temporally with first-dose administration of meropenem. This patient's plasma VPA concentration measured soon after the seizure was essentially unchanged from pretreatment values. Similarly, as reported by Baraboutis *et al.* /33/, one patient with progressive myoclonus epilepsy poorly controlled on VPA experienced markedly worsened seizure activity when meropenem therapy was initiated and a dramatic improvement in seizure control after its subsequent discontinuation. These changes in epileptic activity occurred despite recognition and acknowledgement of the VPA-carbapenem drug interaction with careful adjustment of VPA dosage to continuously maintain this patient's plasma VPA levels within the therapeutic range /33/.

In these patients, the occurrence of carbapenem-related seizures despite absence of change in VPA plasma concentrations indicates that a measurable pharmacokinetic interaction was unlikely to be associated with or responsible for these events. Further, these findings suggest that a pharmacodynamic interaction occurs with concurrent use of VPA and carbapenems. This interaction may occur at the level of the VPA receptor.

Mechanisms of action

γ-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the mammalian brain, and alterations in its function are

associated with many brain diseases, including epilepsy. It is generally accepted that impairment of GABAergic neurotransmission may lead to convulsions and potentiation of GABAergic neurotransmission has anti-convulsant effects. While complete functional details have long been a matter of debate, VPA, through inhibition of GABA degradation, enhancement of GABA synthesis, and/or feedback inhibition of GABA turnover, has been shown to increase presynaptic GABA levels. These increases are directly involved in elicitation of the pharmacodynamic effects of VPA, including anti-convulsant, anti-conflict, and anti-manic effects /95/.

Actions produced by VPA involve binding with multiple GABA receptor subtypes, notably including the postsynaptic $GABA_A$ receptor complex. Investigations relying on demonstration of diminished *in vivo* neuronal activity produced by exposure to known $GABA_A$ antagonists, including the benzodiazepine reversal agent flumazenil, show that most pharmacological effects of VPA are produced through enhanced non-competitive binding with this receptor /81-83/.

Carbapenems likewise have been demonstrated to interact with neuronal $GABA_A$ receptors. However, in contrast to VPA actions, carbapenem antibiotic binding to $GABA_A$ receptors is competitive, structurally and conformationally specific to $GABA_A$ /84/, and allosterically selective for the benzodiazepine region of this receptor complex /85/. Through mechanisms distinctive from penicillins, cephalosporins, and other β-lactams /85/, carbapenem binding to $GABA_A$ receptors produces antagonistic effects diametrically opposed to the GABAergic actions elicited by VPA. Results of $GABA_A$ receptor binding assays in rodent models indicate that convulsions caused by carbapenem antibiotics are produced through inhibition of $GABA_A$-mediated inhibitory transmission /86,87/ induced by blockade or inhibition of GABA agonist receptor binding /88,89/.

Comparative investigations have shown that convulsant activity associated with high-dose systemic or intracerebral administration of most carbapenems is significantly diminished by concomitant administration of $GABA_A$ agonists such as muscimol /90/. These actions, which account for experimental differences in pro-convulsive activity among various carbapenems, strongly correlate with intensity of carbapenem-induced inhibition of muscimol binding to $GABA_A$ receptors /91-94/. Although it has not been demonstrated that inhibition of VPA binding to $GABA_A$ receptors and subsequent

protective effects against carbapenem-mediated convulsant effects are altered or compromised by concurrent administration of these drugs, these receptor affinities suggest this as a strong possibility.

The pentameric $GABA_A$ receptor complex contains binding sites for convulsant antagonists such as picrotoxin and pentylenetetrazole (PTZ) /90/. Carbapenems bind to this receptor and variably enhance the convulsive activity of PTZ, shifting its dose-response curve to the left /92-94/. VPA also binds to this receptor, albeit with low potencies /95/. An *in vivo* investigation designed to evaluate the drug interaction between VPA and carbapenems demonstrated that VPA in large (800 mg/kg) doses was capable of abolishing convulsions produced by fully convulsant doses of PTZ, and that panipenem and meropenem, in doses only slightly higher than might be used therapeutically, antagonized this anticonvulsant effect of VPA by inciting seizures in a dose-dependent manner through prolongation of the duration of seizure discharges /94/. Recognizing this as the strongest evidence to date of a direct receptor-mediated interaction, the authors of this animal study extended their conclusions to suggest that clinical use of carbapenem antibiotics, including doripenem which in this experiment failed to alter VPA protection against PTZ-induced seizures, should be avoided in epileptic patients because of risk not only for adverse pharmacodynamic interaction effects but also for untoward pharmacokinetic effects that appear to be of concern for all carbapenems /94/.

Glutamate is the predominant excitatory neurotransmitter in the mammalian CNS. Glutamate activates a family of gated ion channels that originally were named for each subtype, including α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA). Excessive activation of glutamate receptors can injure or kill the cells that express these receptors. It is widely accepted that excitatory neurotransmitters such as glutamate and their transporters are etiologically involved in certain neurodegenerative diseases /96/ as well as the initiation and propagation of epileptic seizures /97/. Chronic treatment with VPA variably decreases brain glutamate concentrations in epileptic patients /98/ and increases expression of certain glutamate efflux transporter proteins /99,100/. Although controversial /80/, these effects are likely involved in some anticonvulsant actions of VPA.

In contrast, studies in epilepsy-prone mice have proven that seizures caused by imipenem toxicity result at least in part from

activation of glutamate receptors and that AMPA, kainate, and especially NMDA antagonists increase the threshold for seizures or prevent seizures induced by imipenem /90/. Untoward glutamatergic effects of carbapenem antibiotics may counteract or directly antagonize the effects of VPA on excitatory neurotransmitters potentially leading to predisposition for seizures.

Compendial statements

As provided in regulatory agency-approved product brochures or package inserts from various countries around the world, disclosure and assessment statements regarding the interaction between VPA and carbapenem antibiotics are marked by broad disparities. In Japan, evaluation of reported data concerning the clinical effects of this interaction led to conclusions that the potential consequences of combined use may be severe and, since the mid-1990s, all available pharmaceuticals containing VPA, panipenem, meropenem, and imipenem accordingly highlight VPA and carbapenems as a contraindicated drug combination /101,102/. In the United Kingdom, the product information for VPA, meropenem, and imipenem indicates only that an interaction exists but offers no estimation of either incidence or severity and provides no suggestion for management /102/. Until recently, product information in the United States for VPA and meropenem contained a precautionary statement that subtherapeutic valproic acid levels have been reported when meropenem was co-administered, again with no evaluative or management recommendations.

In March 2008, the US Food and Drug Administration mandated changes in safety labeling for VPA products and carbapenems /103/. Under warnings and precautions, a subsection of the package insert titled "Drugs for which a potentially important interaction has been observed" provides the following statement:

> A clinically significant reduction in valproic acid concentration has been reported in patients receiving carbapenem antibiotics (ertapenem, imipenem, meropenem) and may result in a loss of seizure control. The mechanism of this interaction is not well understood. Serum valproic acid concentrations should be monitored frequently after initiating carbapenem therapy. Alternative antibacterial or anticonvulsant therapy should be

considered if serum valproic acid concentrations drop significantly or seizure control deteriorates.

Although this statement presents substantively greater information concerning the interaction than what was available from product sources in the past, for a number of reasons we believe that these current recommendations for monitoring and consideration of alternative therapy are misguided.

Firstly, while it is indisputable that plasma VPA concentrations should be carefully monitored, in patients receiving VPA and carbapenems such monitoring may be unreliable and likely will fail to identify or estimate seizure risk. Unlike enzymatically-mediated oxidative drug reactions that typically require several days to a week or more to produce observable or measurable metabolic effects /104/, the interaction between VPA and carbapenems has a rapid onset. Within 24 hours after initiating carbapenem treatment, decreased plasma concentrations of VPA have been found in all patients reported to date who have had VPA levels measured at this time /16,21,29/, including 19 (100%) of 19 patients who received daily VPA monitoring in the large case series described recently by Spriet *et al.* /31/. In contrast to treatment with carbapenem antibiotics alone, in which the average onset of the uncommon occurrence of seizure activity is 7 days /105/, seizures, which are often the first sign of an interaction, may occur in less than 24 hours /25/ and frequently within 48 hours after addition of carbapenem therapy to VPA treatment /14,15,22,23,32/. Along with information suggesting that the VPA-carbapenem interaction may result in changes in tissue levels and/or pharmacological activity of VPA that are discordant or disproportionately decreased in comparison with concurrent plasma concentrations, these characteristics indicate that therapeutic drug monitoring of VPA in these situations may be misleading and potentially capable of providing a false sense of security.

Secondly, the implied recommendation that findings of a significant drop in VPA concentration should be used as a cue for consideration of alternative therapy places recipient patients at high risk for seizures. As previously described, this interaction has been shown to affect all recipient patients reported to date. Decreases in plasma VPA concentrations should be anticipated and expected in all patients receiving combined therapy with a carbapenem. Therefore, alternative therapy in these patients should be considered *a priori*.

Thirdly, deterioration of seizure control as presented in current VPA and carbapenem product information describes an adverse finding that has already happened. As before, changes in VPA levels and associated risk for seizures should be expected to affect all recipient patients and one should not wait for this adverse event before considering alternative treatments.

With all due respect, we disagree with recommendations of the FDA that alternative therapy should be considered if (and presumably when) evidence of an interaction between VPA and a carbapenem antibiotic becomes apparent. Practitioners should act preemptively and prescribe expectantly, cautiously, and in most cases conservatively. Contemporaneous use of these medications should be avoided.

Limitations

This evaluation of the interaction between VPA and carbapenem antibiotics has a number of important limitations. Our survey was performed with a retrospective, uncontrolled design and an assessment of care provided at the discretion of dedicated but autonomous clinicians. There was no institutional mandate or requirement for documentation of relevant clinical, neurological, and/or biochemical findings and, accordingly, the types and detail amounts of recorded event information were subject to the variances found in individual practice patterns. Patients were identified by a computerized search of pharmaceutical utilization records rather than associations or links to specified clinical events. The accuracy and relevance of our assessment of possible interaction-related changes in VPA pharmacokinetics is substantively limited by reliance upon assumptions of population-based variables, first-order elimination kinetics, and attainment of steady-state at the time of sampling and determination of plasma concentrations. Nonetheless, events and data displayed by our patients and those described in previously published reports reveal evidence for a drug interaction between VPA and carbapenem antibiotics that is clinically significant.

Imposition of certain exclusion criteria may have biased the apparent incidence of seizures in our patients. Among the 11 recipients of concurrent VPA and carbapenem therapy who were excluded due to documentation of <2 plasma VPA levels, treatment-related seizures were identified in one patient. Therefore, among the entire cohort of 17 treated patients whose medical records were

examined, six (35%) were affected by worsened or new-onset seizure activity. This proportion is in general agreement with the 33% incidence of seizures (25 of 76 exposed patients) recorded in previously published reports (Table 2).

CONCLUSIONS

A survey of hospitalized patients receiving VPA therapy for seizure prophylaxis or bipolar disorder and a carbapenem antibiotic for serious bacterial infection revealed significant decreases in VPA plasma concentrations to levels that were sub-therapeutic in all cases. These changes were accompanied by significant increases in estimated VPA clearance and decreases in estimated AUC. All patients showed evidence of an adverse pharmacokinetic interaction in which plasma VPA concentrations were diminished by carbapenem enhancement of removal and excretion. Data are reviewed to further suggest that this interaction affects VPA distribution such that efflux of VPA from the brain to blood is favored with resultant CNS concentrations of VPA that are disproportionately decreased.

Manifestations of the VPA-carbapenem interaction additionally involve actions of both inhibitory and excitatory neurotransmitters. Both VPA and carbapenems affect receptor binding and/or activity of central GABA and glutamate receptors. Together, these may alter and potentially decrease seizure thresholds.

Similar to findings in previously reported cases, we describe worsening or new-onset of generalized seizures during concurrent administration of VPA and a carbapenem antibiotic. Five of six patients in our series had clinical documentation of seizures, including two with no prior history of seizures or overt epilepsy. On this basis, we conclude that VPA and carbapenem antibiotics should not be used concurrently. Responsible professionals must guard against combined use of these medications.

All authors verify that they have no potential conflicts of interest to disclose.

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