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Overview of Seizure-Inducing Potential of Doripenem

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Abstract

The seizure-inducing potential of carbapenems has been debated since the introduction of imipenem/cilastatin over 20 years ago. Doripenem is a new carbapenem, recently approved in the US for the treatment of adults with complicated urinary tract infections (cUTI) or complicated intra-abdominal infections (cIAI), and additionally in the EU for nosocomial pneumonia, including ventilator-associated pneumonia. Here, the seizure-inducing potential of doripenem is evaluated, using data from *in vitro* and *in vivo* animal studies, doripenem clinical trials and doripenem postmarketing reports of seizures. Animal studies indicate that doripenem has low binding affinity for GABA receptors and does not induce seizures at doses greater than seizure-inducing doses of imipenem or meropenem. In clinical studies of cUTI or cIAI, no seizures were reported in the 1332 patients treated with doripenem (500-mg infusion every 8 hours). In two studies, patients with nosocomial pneumonia were treated with doripenem 500 mg (1- or 4-hour infusion every 8 hours), and the incidence of seizures was lower for doripenem (1.2% [6/485]) than imipenem (3.8% [10/263]) or piperacillin/tazobactam (2.7% [6/221]). For patients with seizure-predisposing conditions, seizures occurred during treatment for 3/193 (1.5%) in doripenem, 1/66 (1.5%) in piperacillin/tazobactam and 6/116 (5.2%) in the imipenem group. The review of data from both clinical trials and postmarketing surveillance supports the low seizure-inducing potential of doripenem. The seizure potential of doripenem should be evaluated further in patients at increased risk for seizure.

The propensity of β-lactam antibacterial agents to produce seizures has been noted since the introduction to clinical practice of crystalline penicillin G, and studied in various *in vitro* and *in vivo* animal models.[1] The generally accepted mechanism of carbapenem-associated neurotoxicity is a result of their effects on central neuroinhibitory tone. The binding of GABA, the principal inhibitory central neurotransmitter, to receptor sites in the CNS is antagonized to varying degrees by various carbapenems, resulting, in some cases, in CNS excitation and convulsions.[2]

The first marketed carbapenem, imipenem/cilastatin,[3] introduced more than 20 years ago, was noted to have a seizure-inducing propensity.[4-6] There have been many subsequent reports on the risk of seizures, with rates as high as 6%, especially when dosing with respect to renal function was not carefully adjusted and monitored.[7,8] A meta-analysis of 37 papers published

between 1984 and 1999, showed a seizure rate of 1.4% among nearly 6000 adults treated with imipenem/cilastatin.[5]

The pro-convulsant activity of imipenem/cilastatin has limited its usefulness in the treatment of individuals at high risk of seizures, such as those with CNS infections, especially meningitis,[9-11] chronic or acute CNS injury, and generally in critically ill patients with compromised renal function and lowered threshold for seizure activity.

The pro-convulsant activity of meropenem, introduced into the market in the early 1990s,[12] has been shown to be less than that of imipenem/cilastatin in a large meta-analysis of over 5000 meropenem-treated and 1800 imipenem/cilastatin-treated patients with serious infections.[13] In this analysis, the incidence of drug-related seizures was 0.8% for meropenem and 2.8% for imipenem/cilastatin, despite the fact that patients with CNS disorders, including seizures, were excluded from the trials. A more recent review of over 6000 patients treated with meropenem reinforced the favourable safety profile of meropenem.[14] A review of the neurotoxicity of carbapenems concluded that meropenem appeared less neurotoxic in animal studies and was associated with a lower risk of seizures in patients.[6,15] Meropenem is the only carbapenem currently indicated specifically for the treatment of individuals with bacterial meningitis, a category of high-risk patients.

Ertapenem, introduced into world markets in 2001 and 2002,[16] appears to have a low seizure-inducing potential, similar to that of meropenem.[17] In clinical trials,[18] 1954 patients with community-acquired pneumonia, skin, urinary tract, intra-abdominal or pelvic infections were treated with at least one dose of ertapenem 1 g daily. Of these, three patients (0.2%) experienced a seizure considered to be drug related, compared with 2 of 774 patients (0.3%) who received piperacillin/tazobactam and none of the 942 patients who received ciprofloxacin. Three of these five patients had underlying neurological disease and two had pre-existing seizure disorders. However, it should be noted that ertapenem, unlike its predecessors, imipenem and meropenem, has limited *in vitro* activity against *Pseudomonas aeruginosa* and *Acinetobacter* species, and is more suited to the treatment of serious community-acquired infections than nosocomial infections.[18] Therefore, patients treated with ertapenem might be less critically ill than those treated with other carbapenems and potentially at lower risk of seizures.

Here, the seizure-inducing potential of doripenem, a new carbapenem, is evaluated using data from *in vitro* and *in vivo* animal studies, *post hoc* analysis of doripenem clinical trials, and doripenem postmarketing reports of seizures.

1. Doripenem

Doripenem is a new carbapenem antibacterial agent approved in Japan (July 2005) for the treatment of moderate to severe bacterial infections, in the US (October 2007) for the treatment in adults of complicated intra-abdominal infections (cIAI) and complicated urinary tract infections (cUTI) including pyelonephritis, and in the EU (August 2008) for the treatment of cIAI and cUTI, and nosocomial pneumonia (NP), including ventilator-associated pneumonia (VAP).[19] The *in vitro* antibacterial potency of doripenem is similar to that of imipenem/cilastatin against Gram-positive pathogens and to that of meropenem against Gram-negative pathogens.[20] Importantly, doripenem has been shown to be at least 2-fold more potent than imipenem/cilastatin and meropenem against *P. aeruginosa* isolates collected from patients with serious infections.[21]

1.1 Preclinical Studies with Doripenem

Horiuchi et al.[22] investigated the convulsive activities of doripenem in a series of studies using different animals and compared them with β-lactam antibacterials, including other commonly used carbapenems. One study compared the competitive inhibition of ^{3}H-muscimol binding to the GABA receptors by various drugs in mouse brain synaptic membrane samples. Doripenem showed low affinity for GABA receptors at all concentrations (0.3, 1, 3, 10 mmol/L) and was lower than those of other carbapenems, including imipenem/cilastatin, meropenem and panipenem/betamipron (figure 1). The maximum concentration

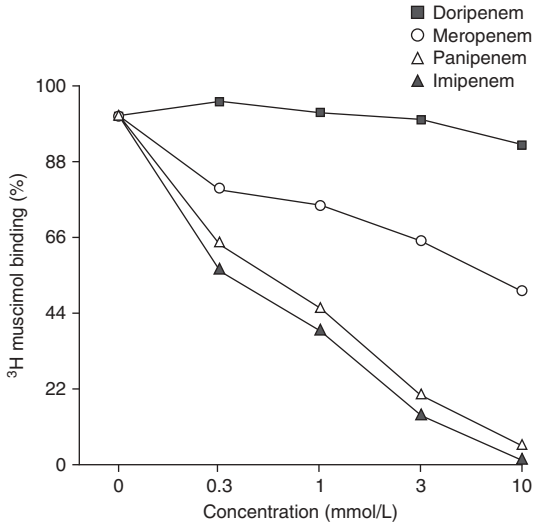

Fig. 1. Competitive inhibition of muscimol binding to GABA receptors *in vitro* with selected carbapenems. Data adapted from Horiuchi et al.[22]

of doripenem tested was well in excess of concentrations achievable in human serum or biological tissues with clinically used doses. The typical peak plasma concentration (C_{max}) after receiving a single dose of 500 mg of doripenem intravenously over 1 hour is 23 μg/mL.

Another study evaluated the effect of carbapenem drugs on the EEG and behaviour in dogs. Doripenem (100, 300 and 1000 μg/dog), imipenem/cilastatin and meropenem were administered directly into the lateral ventricles of dogs weighing 9.3–10.8 kg. Doripenem did not affect EEG or behaviour even at the highest dose tested (1000 μg/dog), which was ten times the dose of imipenem/cilastatin (100 μg/dog) and more than three times the dose of meropenem (300 μg/dog) that caused clonic convulsions.[22]

In other studies, doripenem (100, 200, 400 mg/kg) caused no changes in the EEG and behaviour in rats, whereas imipenem/cilastatin at 400/400 mg/kg produced seizure discharges on EEG accompanied with clonic convulsions in rats. Imipenem, panipenem and cefazolin induced clonic convulsions in a dose-dependent manner in mice. Doripenem and meropenem did not induce convulsions at up to 100 μg/mouse. Additional studies in rats and mice indicated that doripenem did not cause, enhance or have an effect on convulsive thresholds for electroshock or pentetrazol-induced seizures at the equivalent doses that induced convulsions with imipenem/cilastatin or meropenem.[22]

Horiuchi et al.[22] concluded that doripenem has no convulsive activity and suggests that its neurotoxicity may be negligible at doses used in clinical practice.

Nakajima et al.[23] studied the drug interactions between carbapenems (doripenem, panipenem/betamipron, meropenem) and valproic acid using *in vivo* and *in vitro* methods with monkeys and rats.[23] In monkeys, the plasma concentration of valproic acid at 2 hours after intravenous administration of valproic acid decreased rapidly with coadministration of carbapenems. Additional experiments investigated the inhibitory activity of carbapenems in rats and possible mechanisms for the drug interaction between valproic acid and carbapenem (e.g. inhibition of hydrolytic enzymes). This has been confirmed with a similar interaction in humans with doripenem.[24]

1.2 Seizures in Doripenem Clinical Trials

In eight clinical pharmacology studies, none of the 202 patients who received doripenem up to 1 g had seizures (study identifiers: DORI-01, -02, -04; DORI-NOS-1001, -1004, -1005, -1006, -1007). The doripenem clinical development programme also included one phase II study (DORI-03) and six phase III studies in three indications, cUTI, cIAI and NP including VAP (table I).

1.2.1 Treatment of Complicated Urinary Tract Infections

Patients with cUTI were treated intravenously with 500 mg of doripenem every 8 hours in a randomized, double-blind, levofloxacin–controlled, multicentre study (DORI-05; n = 748); in a single arm, multicentre study (DORI-06; n = 423); and in a dose-finding study (DORI-03; n = 56). No seizures were documented in the 855 patients treated with doripenem. Among the 372 patients with cUTI who received levofloxacin 250 mg once daily intravenously, one seizure occurred after the patient was switched from intravenous

Table I. Summary of the six doripenem phase III studies in the treatment of complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI) or nosocomial pneumonia (NP)

Study identifier	Study design	Dosage regimen	www.ClinicalTrials.gov identifier
Treatment of cUTI			
DORI-05	Randomized, double-blind	Doripenem IV 500 mg over 60 min q8h (10 d) Levofloxacin IV 250 mg over 60 min q24h	NCT00229021
DORI-06	Single-arm	Doripenem IV 500 mg over 60 min q8h (10 d)	NCT00210990
Treatment of cIAI			
DORI-07[a]	Randomized, double-blind	Doripenem IV 500 mg over 60 min q8h (5–14 d) Meropenem IV bolus (3–5 min) 1 g q8h	NCT00210938
DORI-08	Randomized, double-blind	Doripenem IV 500 mg over 60 min q8h (5–14 d) Meropenem IV bolus (3–5 min) 1 g q8h	NCT00229060
Treatment of NP, including VAP			
DORI-09[b]	Randomized, open-label	Doripenem IV 500 mg over 60 min q8h (7–14 d) Piperacillin/tazobactam IV 4.5 g over 30 min q6h	NCT00211003
DORI-10[c]	Randomized, open-label	Doripenem IV 500 mg over 4 h q8h (7–14 d) Imipenem IV 500 mg over 30 min q6h or 1 g over 60 min q8h	NCT00211016

a See Lucasti et al.[25] for more information on the study.

b Includes non-ventilator-associated NP and early onset VAP. See Rea-Neto et al.[26]

c Includes early- and late-onset VAP. See Chastre et al.[27]

IV = intravenous infusion; **q*x*h** = every *x* hours; **VAP** = ventilator-associated pneumonia.

study drug therapy to oral levofloxacin; the seizure occurred at their home and was considered not drug related.

1.2.2 Treatment of Intra-Abdominal Infections

Patients with cIAI were treated with 500 mg of doripenem every 8 hours in two randomized, double-blind, meropenem-controlled, multicentre studies (DORI-07 [n = 471]; DORI-08 [n = 486]).[25] No seizures were documented in either patients who received meropenem (n = 469) or the patients treated with doripenem (n = 477).

1.2.3 Treatment of Nosocomial Pneumonia, Including Ventilator-Associated Pneumonia

Patients with NP, including early-onset VAP, were treated intravenously with 500 mg of doripenem infused over 1 hour every 8 hours in a randomized, open-label, piperacillin/tazobactam–controlled, multicentre study (DORI-09 [n = 444]).[26] Piperacillin/tazobactam 4.5 g every 6 hours was administered intravenously to 221 patients and doripenem to 223 patients. Additionally, patients with VAP (DORI-10 [n = 525]), including both early and late onset, were treated with the same dose (500 mg) of doripenem (n = 262) administered as a 4-hour infusion in a randomized, open-label, imipenem-controlled, multicentre study.[27] Imipenem/cilastatin 500 mg (n = 263) was administered every 6 hours or 1000 mg every 8 hours via 30- or 60-minute intravenous infusions, respectively.

Both the NP studies included a significant proportion of patients with a history of seizures and other baseline predisposing neurological conditions that constituted a high risk for seizures (193 patients and 180 patients in the doripenem and comparator groups, respectively). For a *post hoc* analysis of seizure incidence for patients with predisposing conditions, the medical history of all treated patients were reviewed for a limited number of terms describing conditions that may have predisposed subjects to seizures (e.g. stroke/haemorrhage/tumour) as the study was not designed to collect this information *a priori*. Metabolic conditions or medications that could potentially lower the seizure threshold were not included and, therefore, the analysis potentially underestimates the total number of patients with predisposing conditions for seizures. The most prevalent predisposing conditions were stroke/CNS haemorrhage or tumour (75 in each treatment group) and traumatic head injury (80 in the

doripenem and 59 in the comparator group). Other predisposing conditions included drug abuse or drug (including alcohol) withdrawal syndromes, coma or alteration in mental status not otherwise specified, primary seizure disorder unrelated to any of the syndromes previously listed, or others such as raised intracranial pressure.

Table II summarizes the presence of baseline neurological conditions predisposing to seizure in the nosocomial pneumonia studies, the incidence of seizures during the study and whether the seizure occurred during drug treatment or post-therapy.

Despite the high seizure risk in both studies, the overall incidence of seizures during study therapy and in the 30-day period after therapy was relatively low; 6/485 (1.2%) in doripenem-treated patients, 6/221 (2.7%) in piperacillin/tazobactam-treated patients, and 10/263 (3.8%) in imipenem/cilastatin–treated patients. Of the patients with seizure-predisposing conditions in the VAP study (DORI-10), 3/131 (2.3%) had seizures in the doripenem treatment group compared with 10/116 (8.6%) in the imipenem group.

All six doripenem-treated patients who had seizures had underlying predisposing neurological conditions. Three patients who received the 4-hour infusions of doripenem experienced seizures; one patient with a history of cocaine abuse had a subarachnoid haemorrhage and continued on doripenem therapy with no further seizures; the second had a subarachnoid haemorrhage and had a seizure 11 days after the end of doripenem therapy; and the third had a history of epilepsy. Among the three patients with seizures who received the 1-hour infusions of doripenem, one had a subarachnoid haemorrhage and a seizure 1 day after doripenem had been discontinued; the second patient was experiencing tremors from alcohol withdrawal at the time of the seizure and continued on doripenem therapy without further seizures; and the third had recently experienced a stroke and had a prior history of seizures.

All seizures in piperacillin/tazobactam-treated patients occurred in those with underlying predisposing illness. The ten imipenem/cilastatin-treated patients who experienced seizures had underlying predisposing conditions. Seven patients had seizures while on study drug. Two patients reported a seizure 1 day after discontinuing study therapy, and one patient experienced a seizure 8 days after discontinuing study therapy. One patient had possible intermittent seizure activity 8 days after discontinuing the study drug. One patient had a seizure when given non-study imipenem/cilastatin nearly 3 weeks after having been withdrawn from study drug therapy; although

Table II. Prevalence [n (%)] of baseline neurological conditions predisposing to seizures in the DORI-09 and DORI-10 nosocomial pneumonia (NP) studies and incidence of seizures (see table I for study information)

Patients with NP	DORI-09: 1-h infusion of doripenem[a]			DORI-10: 4-h infusion of doripenem[b,c]		
	doripenem	piperacillin/tazobactam	total	doripenem	imipenem	total
No. of patients	223	221	444	262	263	525
Incidence of seizures while on study	3 (1.3)	6 (2.7)	9 (2.0)	3 (1.1)	10 (3.8)	13 (2.5)
Incidence of seizures while receiving IV study drug	3 (1.3)	1 (0.5)	4 (0.9)	1 (0.4)	6 (2.3)	7 (1.30)
Patients with predisposing condition	62 (27.8)	66 (29.9)	128 (28.8)	131 (50.0)	116 (44.1)	247 (47.0)
Seizure history	12 (19.4)	12 (18.2)	24 (18.8)	21 (16.0)	21 (18.1)	42 (17.0)
Incidence of seizures	3 (4.8)	6 (9.3)	9 (7.1)	3 (2.3)	10 (8.6)	13 (5.2)
while receiving IV study drug	2	1	3	1	6	7
post-therapy	1	5	6	2	4[d]	6

a Includes non-ventilator-associated NP and early onset VAP.

b Includes early and late onset VAP.

c Post-therapy is defined as 30 days after last dose.

d One patient started non-study imipenem/cilastatin on the same day the seizure occurred.

IV = intravenous infusion; **VAP** = ventilator-associated pneumonia.

the seizure was not related to imipenem/cilastatin administered as the study drug, it may have been related to the imipenem/cilastatin that was started the same day the seizure occurred.

1.3 Doripenem Postmarketing Reports of Seizure

The estimated number of patients exposed to doripenem is approximately 508 176 through December 2008. A cumulative, postmarketing review of seizures reported with doripenem was conducted as part of ongoing pharmacovigilance activities to identify all events associated with any formulation or dosage form of doripenem received as of May 2008.[28] The search conducted for the review included all spontaneous reports from postmarketing studies, the literature, trial registries, and solicited and health-authority reports.

A total of ten cases of seizures were reported, with eight from Japan. The cases in which sex and age was reported included six males and three females, with a mean age of 70 years (range 31–89). Two of the ten cases did not provide sufficient information for medical assessment. Two cases presented an implausible temporal relationship as the onsets of the convulsive seizures were 12 and 2 days after the last dose of doripenem. Five of the six remaining cases had multiple confounders known to be associated with seizures, including underlying disease, concomitant medications and electrolyte abnormalities. The last case described a patient who did not have an underlying CNS disorder, but was receiving dialysis for acute renal failure. This review of the postmarketing reports to date supports the low seizure-inducing potential of doripenem.[28]

2. Discussion

Animal studies suggest that doripenem has less potential to induce seizures than imipenem/cilastatin and meropenem. Comparative data with ertapenem are not available. Data from worldwide clinical trials and postmarketing experience support the low seizure-inducing potential of doripenem. There were no seizures reported in cIAI studies in which meropenem was the active comparator, and relatively few seizures in either the doripenem or imipenem/cilastatin treatment arms of the nosocomial pneumonia studies, in which almost all patients who experienced seizures were at high risk due to underlying neurological conditions. Even though the incidence of baseline risk factors for seizure was slightly higher among doripenem-treated patients than imipenem/cilastatin-treated patients in one clinical trial, the seizure rate during doripenem therapy (1/131; 0.8%) was lower than that for imipenem/cilastatin therapy 6/116 (5.2%), suggesting that doripenem may have a lower seizure-inducing potential than imipenem/cilastatin in high-risk patients.

Meropenem is the only carbapenem currently indicated specifically for the treatment of bacterial meningitis, a category of high-risk patients. Imipenem is not approved for meningitis because of increased risk of seizures.[6,9] The *in vitro* and animal studies, and the clinical studies, indicate that doripenem may be comparable with meropenem in the incidence of seizure with the treatment of the meningitis. An ongoing clinical study is comparing doripenem (1 g every 8 hours) and imipenem therapy in patients with high morbidity and mortality (e.g. VAP patients) [www.ClinicalTrials.gov identifier: NCT00589693]. Carbapenems reduced serum valproic acid concentrations to sub-therapeutic levels in healthy volunteers and, therefore, serum valproic acid concentrations should be monitored if a carbapenem is administered concomitantly with valproic acid and alternative therapies should be considered.[29]

In the doripenem clinical trials, dosage adjustment for renal impairment was carefully enforced in all treatment arms, potentially contributing to a lower incidence of seizures with doripenem as well as comparators. Doripenem-treated patients with severe renal impairment (e.g. creatinine clearance values of 10–30 mL/min) may be expected to have a higher exposure to doripenem, even after appropriate dose adjustments, compared with patients with normal renal function, and yet no cases of seizures were seen in these patients.

Carbapenems are often prescribed for patients with risk factors for seizures, such as renal and

neurological impairment, and hard to treat infections, such as those caused by *P. aeruginosa*. In these patients, proper dosing is important to provide maximal antibacterial coverage with minimal risk of CNS toxicity. Dosage adjustment for renal impairment with doripenem is based only on creatinine clearance, whereas with imipenem/cilastatin, bodyweight as well as creatinine clearance must be taken into consideration. Finally, a significant association between *P. aeruginosa* infection and risk of seizure with imipenem/cilastatin therapy has been noted, likely to be due to dose escalation.[30] Alternatively, for more difficult to treat infections, doripenem can be given as an extended infusion (e.g. over 4 hours), which would potentially result in improved bacterial coverage without increasing total drug exposure. Thus, doripenem may be a valuable alternative to imipenem/cilastatin therapy for all infections, but particularly in patients with pseudomonal infections[31,32] or at high risk for seizures.

3. Conclusions

Animal studies, worldwide clinical trials, and postmarketing monitoring support the low seizure-inducing potential of doripenem. Doripenem is a potentially valuable therapy for serious infections, particularly in patients with pseudomonal infections or at high risk for seizures. The seizure potential of doripenem should be evaluated further in patients at increased risk for seizure.

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