

Penetration of Intact Blood-Brain Barrier by Doripenem[▽]

Doripenem is a new carbapenem with broad-spectrum activity against bacterial pathogens that cause serious (mostly nosocomial) infections.

There are no data on the penetration of the blood-brain barrier (BBB) by doripenem in humans.

In 5 neurosurgical patients with spasticity, a pump for intrathecal administration of baclofen was implanted. An indwelling catheter was inserted in the spinal subarachnoid space. None of the patients had active neurological diseases or infections, and therefore the blood-brain barrier was considered intact. To reduce the risk of surgical infection and nosocomial meningitis, a regimen of doripenem (500 mg as a 30-min intravenous infusion prior to the operation) followed by vancomycin (1 g as a 2-hour infusion prior to the operation) was used as preoperative prophylaxis. The catheters were inserted in the spinal subarachnoid space at different time intervals after initiation of antibiotic infusion in each patient. A single cerebrospinal fluid (CSF) sample was collected from each patient through the catheter to ensure its proper placement. The time of sample collection was dependent on the time that catheter placement needed to be checked during the operation. All CSF samples were immediately transferred in ice after the addition of an equal volume of buffer (morpholinepropanesulfonic acid [MOPS], 1 M) to prevent drug degradation and stored at -70°C . The concentration of doripenem was measured with a high-performance liquid chromatography assay (4). The plasma drug concentration was also measured for comparative purposes.

The study was approved by the Hospital Ethics and Research Committee, and written informed consent was obtained from all patients.

No adverse effects relating to the administration of doripenem were noted.

The results of this preliminary study (Table 1) showed that doripenem penetrates the intact blood-brain barrier to a small but measurable extent. It seems that CSF levels are consistent with slow drug distribution, since shortly after doripenem administration, high plasma levels were followed by low CSF levels, as shown in Table 1.

The lack of knowledge of doripenem pharmacokinetics in CSF is a drawback for its use in the treatment of CNS infections, although its antimicrobial spectrum is favorable (2, 5, 7–9). Furthermore, doripenem probably has a wider spectrum (1, 6) and a lower epileptogenic potential than that of other carbapenems (3).

Moreover, doripenem is effective *in vitro* against many multiresistant strains of *Acinetobacter* spp. (10), among the most dreaded strains that can cause postoperative meningitis (12), especially the biofilm-producing strains (11).

The limited number of biological samples collected from each patient in the present study do not allow concrete pharmacokinetic estimations. Nevertheless, important clinical implications arise from these results. Doripenem concentrations achieved in CSF during the 3-hour time frame would probably not achieve the accepted time above the MIC of 40 to 50% for maximum efficacy of this antimicrobial agent against pathogenic microorganisms with a MIC of $>0.25\ \mu\text{g/ml}$. It should be mentioned, however, that the doripenem CSF concentration

TABLE 1. Duration of intravenous infusion, sampling time, and levels of doripenem in CSF and plasma from patients with intact BBB

| Duration of i.v. ^a infusion (min) | Sampling time (min) ^b | CSF concn ($\mu\text{g/ml}$) | Plasma concn ($\mu\text{g/ml}$) | Patient wt (kg) |
|--|----------------------------------|--------------------------------|-----------------------------------|-----------------|
| 33 | 10 | 0.11 | 32.8 | 75 |
| 38 | 17 | 0.14 | 18.7 | 65 |
| 41 | 22 | 0.21 | 14.9 | 70 |
| 27 | 71 | 0.38 | 12.9 | 75 |
| 34 | 176 | 0.48 | 9.5 | 75 |

^a i.v., intravenous.

^b Minutes after the end of intravenous infusion.

was measured after administration of a single dose, while therapeutic levels are achieved after multiple-dose administration.

This study provides evidence that doripenem penetrates the intact BBB but to a small extent. Further pharmacokinetic studies in both intact and inflamed meninges are necessary to establish doripenem use in the treatment of central nervous system infections.

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