STRUCTURE-ACTIVITY RELATIONSHIPS OF CARBAPENEM AND PENEM COMPOUNDS FOR THE CONVULSIVE PROPERTY

Sir:

Induction of convulsion is a well known side effect of β-lactam antibiotics, such as penicillins and cephalosporins[1~3]. Carbapenem antibiotic imipenem, administered in combination with the renal dehydropeptidase (DHP) inhibitor cilastatin, was also reported to induce convulsion in the clinical use[4,5]. We have recently studied the adverse effects in the central nervous system of meropenem, a DHP-I-stable 1β-methylcarbapenem in comparison with that of imipenem. The distribution to the brain of meropenem following intravenous administration to mice was similar to that of imipenem. That is, there was no difference in their blood-brain barrier permeability. However, neurotoxic activity of meropenem, unlike imipenem, was not observed in the intravenous or intraventricular injections to mice and rabbits[6,7]. In another comparative study of imipenem/cilastatin and meropenem in mice by PATEL *et al.*, both imipenem alone and imipenem/cilastatin, but not meropenem, were found to cause a significant potentiation of metrazole-induced seizures[8]. From these results, it was considered that the neurotoxic activity in carbapenems was related to the presence of β-methyl group at the C-1 position or the structure of C-2 side chain but not to the carbapenem skeleton itself. With the aim of clarifying this problem, we have studied on the structure-activity relationships of 1β-methylcarbapenem, carbapenem and penem compounds having various C-2 side chain for the convulsive property.

The compounds examined here were prepared in our laboratories according to the reported procedures[9~15]. The intraventricular administration of the compounds to mice was carried out as follows[7]. Groups of ten *ddY* mice weighting about 25 g were used. Each dose (0.3~300 μg/head) of the compounds dissolved in 20 μl of saline was injected into the left lateral ventricle of mice using a microsyringe. Incidence of clonic and tonic convulsions and mortality were observed for 30 minutes after the administration.

The convulsant activity of the examined com-

Fig. 1. 1β-Methylcarbapenem, carbapenem and penem compounds.

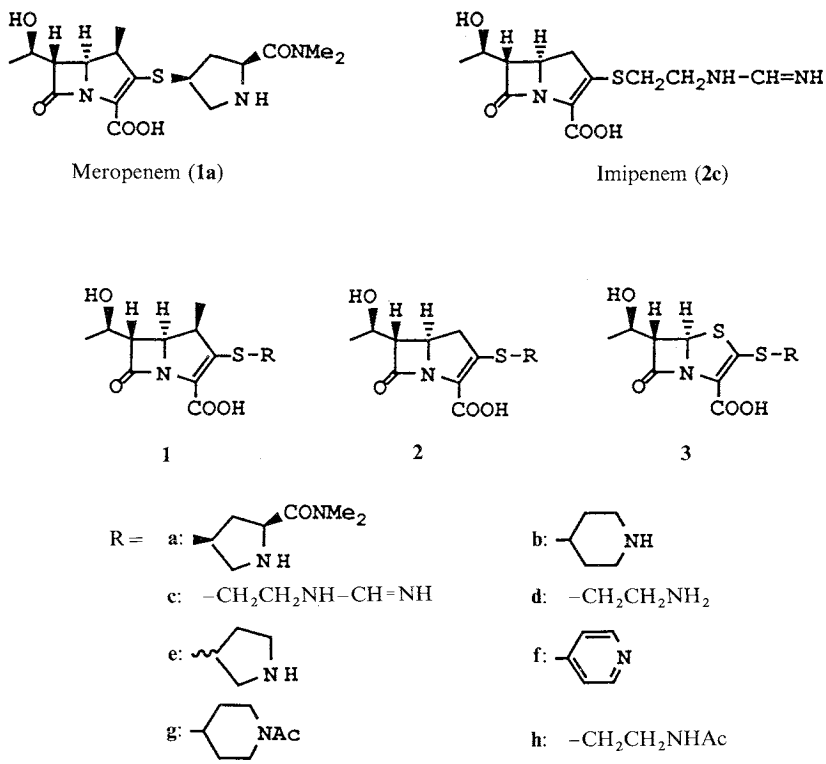

Table 1. Comparison of 1β-methylcarbapenem, carbapenem and penem compounds for induction of convulsion in mice by intraventricular injection.

Compound	ED_{50}* (μg/head)		LD_{50} (μg/head)
	Clonic convulsion	Tonic convulsion	
1a	>300	>300	>300
2a	>300	>300	>300
3a	120	120	120
1b	1.7	2.2	2.4
2b	2.0	2.6	2.8
3b	0.4	0.6	0.7

* ED_{50} indicates the dose required to cause the convulsion in 50% of mice.

Table 2. Comparison of carbapenem compounds with various C-2 side chains for induction of convulsion in mice by intraventricular injection.

Compound	ED_{50}* (μg/head)		LD_{50} (μg/head)
	Clonic convulsion	Tonic convulsion	
2c	11.3	16.6	16.6
2d	14	19	29
2e	2.8	3.6	4.9
2f	64	83	83
2g	>300	>300	>300
2h	>300	>300	>300

* See the footnote in Table 1.

pounds is summarized in Tables 1 and 2.

First, the structural effects of 1β-methylcarbapenem, carbapenem and penem compounds were investigated in 3′-(5′-dimethylaminocarbonyl)pyrrolidinyl and 4′-piperidinyl series. As shown in Table 1, the compounds having 3′-(5′-dimethylaminocarbonyl)pyrrolidinylthio group (**1a**, **2a** and **3a**) exhibited no or extremely low convulsant activity, while the 4′-piperidinylthio derivatives (**1b**, **2b** and **3b**) induced convulsions at high incidence. There was no significant difference in the induction of convulsion between 1β-methylcarbapenem and carbapenem. However, both penem derivatives showed higher convulsant activity, compared to their corresponding 1β-methylcarbapenem and carbapenem derivatives. Consequently, it was found that introduction of β-methyl group at the C-1 position of carbapenem did not significantly affect the convulsant activity and that the convulsive property was closely related to the structure of C-2 side chain.

In Table 2, the convulsant activities of the carbapenems having a variety of C-2 side chain are compared. The pyrroridinyl derivative (**2e**) showed to be extremely convulsive as well as **2b**. Pyridyl derivative (**2f**) was less convulsive, compared to **2c**, **2d** and **2e**. Comparison of imipenem (**2c**) and thienamycin (**2d**) demonstrated that introduction of *N*-formimidoyl group was not effective to reduce the convulsant activity. On the other hand, acetylation of the amino group as in **2g** and **2h** significantly blocked the induction of convulsion. These results suggested that the presence of the amino groups in the C-2 side chain was an important factor to induce convulsions and the strength of basicity of the amino group was correlated with the convulsant activity.

However, comparing the induction of convulsions in **2a** and **2e**, the effects of C-2 side chain can not be explained solely in terms of the basicity of the amino group. It is possible that there are other factors, for example steric crowding around the amino group by the 5′-dimethylaminocarbonyl group, to affect the convulsant activity. Further investigation on the correlation between the structure and the convulsant activity is in progress.

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