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Relationship between Structure and Convulsant Properties of Some β-Lactam Antibiotics following Intracerebroventricular Microinjection in Rats

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The epileptogenic activities of several β-lactam antibiotics were compared following their intracerebroventricular administration in rats. Different convulsant potencies were observed among the various β-lactam antibiotics tested, but the epileptogenic patterns were similar. The patterns consisted of an initial phase characterized by wet-dog shakes followed by head tremor, nodding, and clonic convulsions. After the largest doses of β-lactam antibiotics injected, clonus of all four limbs and/or the trunk, rearing, jumping, falling down, escape response, transient tonic-clonic seizures, and sometimes generalized seizures were observed, followed by a postictal period with a fatal outcome. At a dose of 0.033 μmol per rat, cefazolin was the most powerful epileptogenic compound among the drugs tested. It was approximately three times more potent than benzylpenicillin in generating a response and much more potent than other cephalosporins, such as ceftriaxone, cefoperazone, and cefamandole. No epileptogenic signs were observed with equimolar doses of cefotaxime, cefonicid, cefixime, and ceftizoxime in this model. The more convulsant compounds (i.e., cefazolin and ceftezole) are both characterized by the presence of a tetrazole nucleus at position 7 and show a marked chemical similarity to pentylenetetrazole. Imipenem and meropenem, the two carbapenems tested, also showed epileptogenic properties, but imipenem was more potent than meropenem, with a convulsant potency similar to those of ceftezole and benzylpenicillin. In addition, the monobactam aztreonam possessed convulsant properties more potent than those of cefoperazone and cefamandole. This suggests that the β-lactam ring is a possible determinant of production of epileptogenic activity, with likely contributory factors in the substitutions at the 7-aminocephalosporanic or 6-aminopenicillanic acid that may increase or reduce the epileptogenic properties of the β-lactam antibiotics. While the structure-activity relationship was also investigated, there seem to be no convincing correlations among the rank order of lipophilicities and the convulsant potencies of the compounds studied. The lack of marked convulsant properties of cefixime, cefonicid, cefuroxime, and cephradine suggests that these antibiotics may interact with a binding site which is different from that by which the β-lactam antibiotics exert their convulsant effects or may demonstrate a reduced affinity for the relevant site(s).

β-Lactam antibiotics (i.e., penicillins, cephalosporins, carbapenems, and monobactams) are antibiotics widely used in clinical practice because of their high antibacterial activity (20, 21). The administration of β-lactam antibiotics into the cerebral ventricles or subarachnoidal space or directly to the cerebral cortex of chicks, cats, dogs, monkeys, mice, and rats has been reported to induce a focal or generalized epileptic state initially characterized by spike and wave discharges which are followed by clear tonic-clonic or clonic seizures (5, 7, 12, 13, 22, 23, 26, 29). More recently, seizure activity caused by imipenem-cilastatin has been also documented (11, 28, 30).

The convulsant action of penicillins and cephalosporins has been attributed to the inhibition of the γ-aminobutyric acid (GABA) system (1, 4, 5). The structural similarity of penicillin to the γ-aminobutyric acid antagonist bicuculline is of interest (3), since decreased inhibition in the hippocampus induced by penicillin contributes greatly to the epileptogenicity of penicillin (8).

The cephalosporins are a family of β-lactam antibiotics that contain the 7-aminocephalosporanic acid nucleus. They differ in their basic structure from the penicillins in that the cephalosporins contain a six-membered dihydrothiazine ring instead of a five-membered thiazolidine ring fused to the β-lactam portion. The cephalosporins resemble penicillins in their actions as both antibiotics and convulsant compounds (27). Several investigators found that the ability of penicillin derivatives to produce a seizure focus was abolished after incubation with penicillinase (12, 15, 16). Since these studies support the idea that the β-lactam ring is an indispensable structural feature for epileptogenic activity of penicillins and cephalosporins, we decided to include in our study aztreonam, a monobactam, as well as two carbapenem compounds, imipenem and meropenem, and Ro 23-9424, made up of desacetyl-cefotaxime linked to fleroxacin (14). In order to make a more accurate comparison of the convulsant activities of different β-lactam antibiotics, all compounds were administered intracerebroventricularly (i.c.v.). This route was utilized to reduce the differences in penetration of the central nervous system and in the distribution and rate of metabolism noted among the different β-lactam antibiotics when they are administered systemically (20). This route of administration does not eliminate the differences absolutely but does greatly reduce them.

In the present report, the convulsant effects of some new

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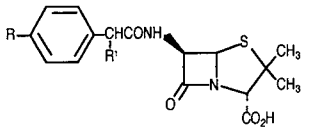


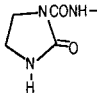
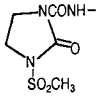
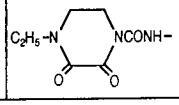
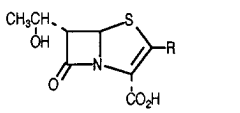
	R	R^1
Benzylpenicillin	H	H
Sulbenicillin	H	SO_3H
Ampicillin	H	NH_2
Amoxicillin	OH	NH_2
Azlocillin	H	
Mezlocillin	H	
Piperacillin	H	

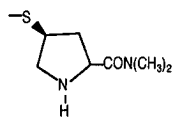
FIG. 1. Chemical structures of penicillins studied.

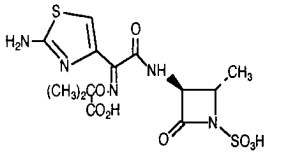
cephalosporins, penicillins, and carbapenems and a monobactam (Fig. 1 to 4) after acute injection into a lateral ventricle in freely moving rats are described. The results are compared and discussed with particular attention paid to the structure-activity relationship and the importance of lipophilicity.

MATERIALS AND METHODS

Animals and surgery. Adult male Wistar rats (200 to 250 g) were stereotaxically implanted with stainless steel guide cannulae under chloral hydrate anaesthesia, according to the atlas coordinates of Paxinos and Watson (25), to permit injection of drug into a lateral cerebral ventricle. After surgery, a minimum of 48 h was allowed for recovery before experiments were carried out. Freely moving rats were microinjected (0.2 μl/min) with an injector cannula which extended at least 1 mm below the tip of the guide cannula. The animals were placed individually in transparent cages (40 by 40 by 30 cm) and allowed to acclimatize to the new environment for 30 min. Preliminary studies to ascertain the influence of phosphate buffer solution (67 mM) in a volume of 2 or 6.6 μl injected intraventricularly showed no significant behavioral changes. A volume of 6.6 μl was used only when it was necessary to inject 3.3 μmol of some β-lactam antibiotics (i.e., cefonicid, cefuroxime, cefotaxime, ceftizoxime, cephradine, cefixime, piperacillin, meropenem, and Ro 23-9424).

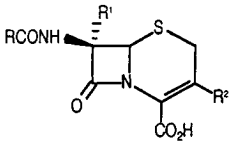


	R
Imipenem	$SCH_2CH_2NHCH{=}NH$
Meropenem	



Aztreonam

FIG. 2. Chemical structures of carbapenems studied and aztreonam.



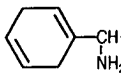
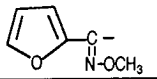
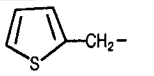
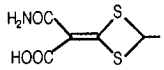
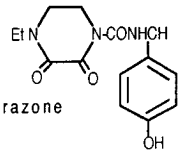
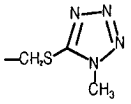
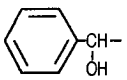
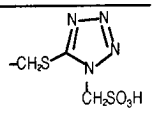
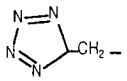
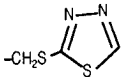
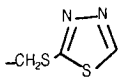
R	R^1	R^2
Cephradine 	H	CH_3
Cefuroxime 	H	CH_2OCONH_2
Cefoxitin 	OCH_3	
Cefotetan 	OCH_3	
Cefoperazone 	H	
Cefamandole 	H	
Cefonicid	H	
Ceftezole 	H	
Cefazolin	H	

FIG. 3. Chemical structures of some cephalosporins studied.

The seizure response after microinjection of cephalosporins, penicillins, aztreonam, and carbapenems was graded according to the following scale: 0, normal behavior; 1, hyperkinesia, wet-dog shake, and sniffing; 2, head tremor and nodding; 3, clonus of one limb; 4, clonus of all four limbs and/or the trunk; 5, clonus of forelimbs, rearing, and falling; 6, transient tonic-clonic seizures and escape response; 7, generalized seizures followed by postictal period with a fatal outcome.

Lipophilicity measurements. The relative lipophilicity of the compounds was measured by reversed-phase thin-layer chromatography by a previously described method (2). Briefly, silanized silica gel plates (Merck 60 F254) were used for the nonpolar stationary phase. The polar mobile phase was a 30:70 (vol/vol) mixture of acetone and phosphate buffer at pH 7. Each compound was dissolved in chloroform (3.0 mg/ml), and 5 μl of solution was applied to the plate. The experiments were repeated five times with different dispositions of the com-

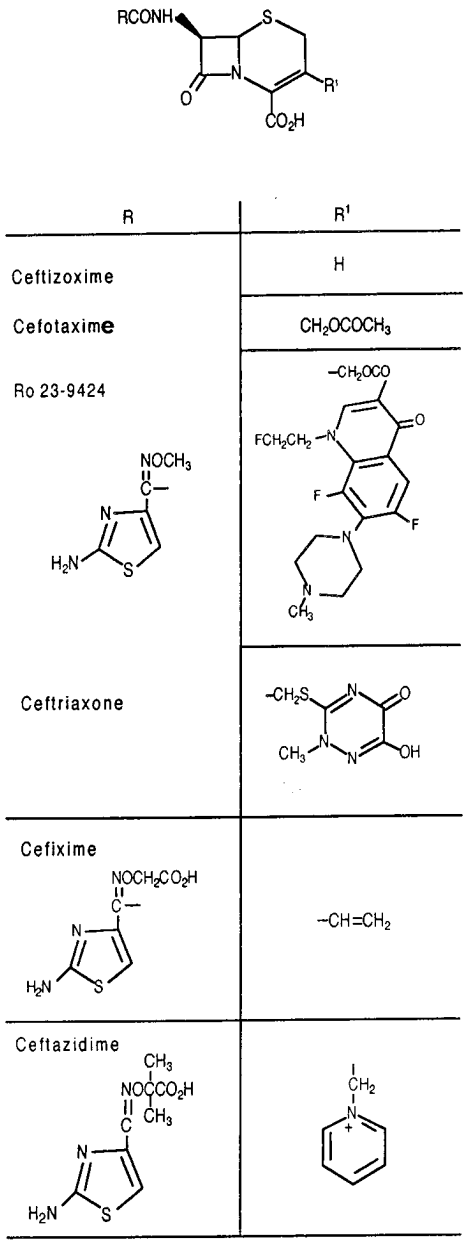


FIG. 4. Chemical structures of some cephalosporins studied.

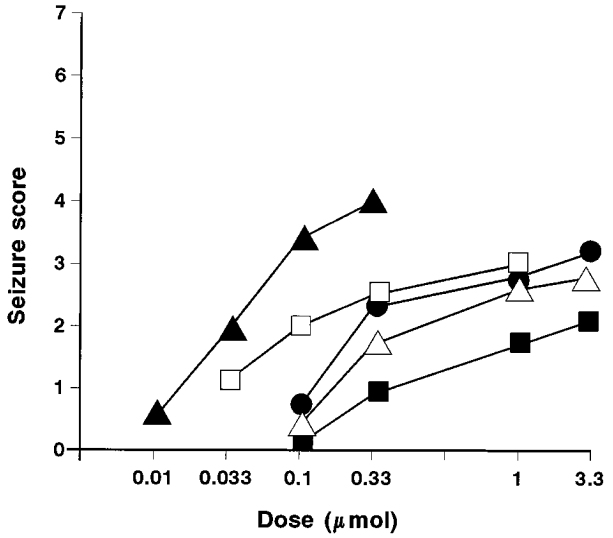


FIG. 5. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ▲, benzylpenicillin; □, aztreonam; △, amoxicillin; ●, ampicillin; ■, sulbenicillin.

pounds on the plate. R_f values were expressed as the mean values of the five determinations. Lipophilicities (R_m values) were calculated from the experimental R_f values according to the formula $R_m = \log (1/R_f) - 1$. Higher R_m values indicate greater lipophilicities.

Statistical analysis. The results of the treatment were analyzed statistically by nonparametric methods. A Kruskall-Wallis analysis of variance was first carried out, and if the result was significant, a Mann-Whitney U test was used to compare control and drug-treated animals. The convulsant doses required to induce clonic seizures (phase 3) in 50% of rats (CD_{50}s) microinjected with β-lactam antibiotics and the relative confidence limits were determined by the method of Litchfield and Wilcoxon (19). At least 32 animals were used to calculate each CD_{50}.

Drugs. The following drugs were used: benzylpenicillin, cephazolin, and ceftizoxime (Farmitalia Carlo Erba Laboratories, Milan, Italy); ceftezole and cefotetan (Schering, Milan, Italy); cefamandole (Eli Lilly & Co., Sesto Fiorentino, Florence, Italy); azlocillin and mezlocillin (Bayer Italia, Milan, Italy); cefonicid (I.S.F. Laboratories, Trezzano S/N Milan, Italy); ceftazidime (Sigma Tau Laboratories, Pomezia, Italy); cefoxitin and imipenem (Merck, Sharp & Dohme, Rome, Italy); cefotaxime (Hoechst, Frankfurt, Germany); piperacillin (Cyanamid Research Laboratories, Catania, Italy); cefoperazone, aztreonam, and cefixime (Menarini Research Laboratories, Florence, Italy); sulbenicillin (Bracco S.p.A., Milan, Italy); amoxicillin (Zambeletti, Milan, Italy); ampicillin (Proter, Milan, Italy); cefuroxime (Glaxo, Verona, Italy); Ro 23-9424 (Hoffmann-La Roche, Nutley, N.J.); ceftriaxone (Hoffmann-La Roche, Basel, Switzerland); cephradine (Squibb, Rome, Italy); and meropenem trihydrate (Ici-Pharma S.p.A., Milan, Italy).

All drugs with the exceptions of ceftazidime, cephradine, aztreonam, imipenem, and meropenem are sodium salts. Drugs in powder form were dissolved in phosphate buffer solution (67 μM) and injected at pH 7.3 to 7.4.

RESULTS

Behavioral epileptic changes. The epileptogenic properties of β-lactam antibiotics varied according to the types of substituents present on the basic structures. The behavioral seizures consisted of an initial phase characterized by wet-dog-shake episodes followed by head tremor, nodding, and clonus of limbs.

The test animals responded to the highest doses of β-lactam antibiotics with clonus of all four limbs and/or the trunk, rearing, jumping, falling down, transient tonic-clonic seizures, escape response, and generalized seizures followed by a postictal period with a fatal outcome.

All epileptic signs were dose related and were observed repeatedly, interrupted only with short pauses. Generally, the first behavioral signs were seen within 1 min after the infusion and the maximum effect was reached after a minimum lag time of 9 min after the injection. Data from dose-response curves of the epileptogenic effects induced by microinjection of various penicillins, cephalosporins, carbapenems, and aztreonam into the lateral cerebral ventricle are presented in Fig. 5 through 9 and Tables 1 and 2.

Comparison of convulsant properties of penicillins, carbapenems, and aztreonam. As shown in Fig. 5 and 6 and Table 1, benzylpenicillin was the most potent convulsant among the penicillins but was two to four times less potent than cefazolin, the most convulsant β-lactam antibiotic tested. The activity of benzylpenicillin was similar to that of imipenem, and the drug was more potent than aztreonam, ampicillin, meropenem, amoxicillin, mezlocillin, piperacillin, azlocillin, and sulbenicillin in inducing epileptic behavior. Of the two carbapenem

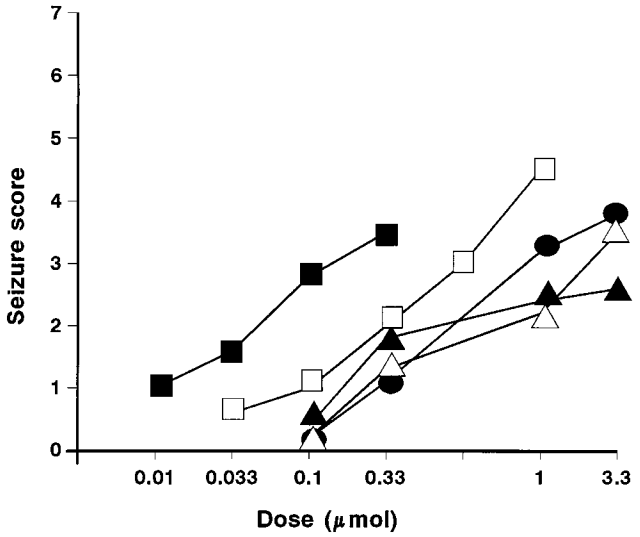


FIG. 6. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). □, azlocillin; △, piperacillin; ■, imipenem; ▲, mezlocillin; ●, meropenem.

derivatives, imipenem was 4.4 times more potent than meropenem (Fig. 6 and Table 1).

Comparison of convulsant properties of cephalosporins. As shown in Fig. 7 through 9 and Table 2, cefazolin induced the strongest activity of all the drugs tested. In addition, ceftezole, cefamandole, ceftazidime, cefoperazone, cefotetan, ceftriaxone, cefotaxime, ceftizoxime, cefoxitin, cefuroxime, cephradine, cefixime, and cefonicid, in this order, were less potent than cefazolin in inducing epileptic behavior (Table 2). By contrast, very high doses of up to 1.65 or 3.3 μmol of cefotaxime, ceftizoxime, and cefoxitin per rat were necessary in order to produce clonus of forelimbs, rearing, falling down, or transient tonic-clonic seizures and the escape response. No clear signs of behavioral seizures were noted even after administration of 1.0 and 3.3 μmol of cefuroxime, cephradine, cefixime, and cefonicid. In addition, Ro 23-9424 was also less convulsant than cefotaxime.

Physicochemical parameters. The relative lipophilicities (R_ms) and molecular weights of these β-lactam derivatives are summarized in Tables 1 and 2.

TABLE 1. Convulsant doses and relative lipophilicities of various penicillins and other β-lactam derivatives after i.c.v. administration in rats

Compound	Clonic phase CD_{50} (μmol/rat)[a]	MW[b]	R_m[c]
Benzylpenicillin	0.05 (0.03–0.09)	333.4	0.052
Imipenem	0.07 (0.04–0.12)	299.3	−1.996
Aztreonam	0.12 (0.04–0.36)	435.4	−0.753
Ampicillin	0.24 (0.18–0.36)	349.4	−0.070
Meropenem	0.31 (0.23–0.42)	383.5	−1.690
Amoxicillin	0.32 (0.24–0.43)	365.4	−0.788
Mezlocillin	0.36 (0.27–0.48)	359.6	0.269
Piperacillin	0.45 (0.31–0.65)	517.6	0.035
Azlocillin	0.51 (0.35–0.74)	461.5	−0.017
Sulbenicillin	0.76 (0.54–1.07)	414.5	−1.279

[a] All data are expressed as CD_{50}s with 95% confidence limits and were calculated by the method of Litchfield and Wilcoxon (19).
[b] MW, molecular weight.
[c] Data are expressed as R_m values and were calculated by a previously described method (2).

TABLE 2. Convulsant doses and relative lipophilicities of various cephalosporins and Ro 23-9424 after i.c.v. administration in rats

Compound	Clonic phase CD_{50} (μmol/rat)[a]	MW[b]	R_m[c]
Cefazolin	0.017 (0.012–0.024)	454.5	−0.477
Ceftezole	0.04 (0.02–0.09)	440.5	−0.477
Cefamandole	0.29 (0.16–0.53)	462.5	−0.087
Ceftazidime	0.29 (0.12–0.70)	546.6	−1.279
Cefoperazone	0.30 (0.24–0.38)	654.7	−0.140
Cefotetan	0.37 (0.29–0.47)	575.6	−1.996
Ceftriaxone	0.43 (0.25–0.74)	554.6	−0.602
Cefotaxime	0.57 (0.21–1.55)	455.5	−0.465
Ro 23-9424	0.82 (0.51–1.32)	764.8	−0.176
Ceftizoxime	1.43 (1.20–1.71)	383.4	−0.501
Cefoxitin	2.76 (1.19–6.40)	427.5	−0.231
Cefixime	ND	453.4	−0.525
Cefonicid	ND	542.6	−0.525
Cefuroxime	ND	424.4	−0.269
Cephradine	ND	349.4	−0.454

[a] All data are expressed as CD_{50}s with 95% confidence limits and were calculated by the method of Litchfield and Wilcoxon (19). ND, not detectable.
[b] MW, molecular weight.
[c] Data are expressed as R_m values and were calculated by a previously described method (2).

DISCUSSION

Previous studies have indicated that systemic administration of cephazolin to experimental animals produces epileptogenic effects (15, 16, 18, 22), and the present results further confirm these findings.

The present study used the i.c.v. route of administration to assess the convulsant effects of β-lactam antibiotics and assumed that the site of drug action is sufficiently close to the ventricular lumen that it may easily be reached by the drug. In fact, following microinjection of the highest doses, the first convulsant signs were observed within 1 min. In addition, the

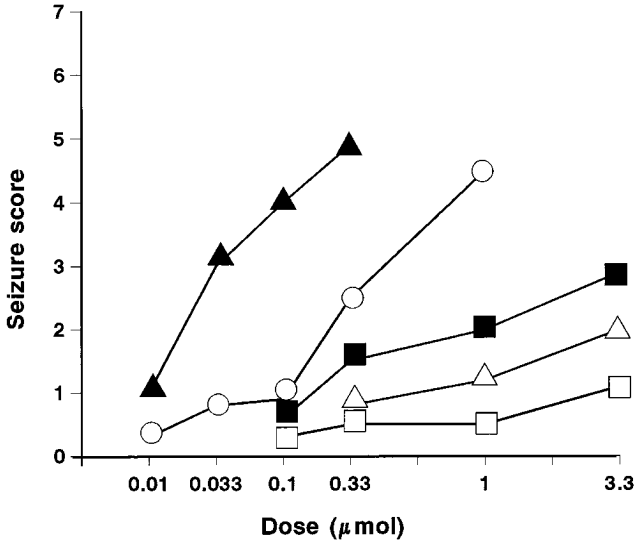


FIG. 7. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ▲, cefazolin; ○, cefoperazone; △, cefuroxime; □, cephradine; ■, Ro 23-9424.

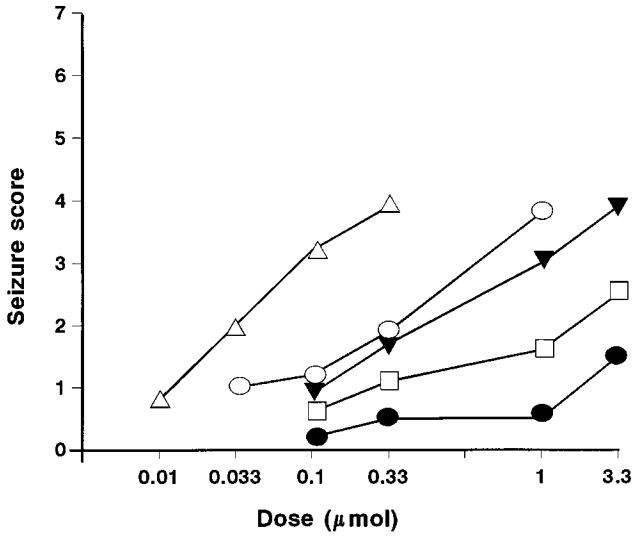


FIG. 8. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). △, ceftezole; ○, cefamandole; ▼, cefotetan; □, cefoxitin; ●, cefonicid.

present data clearly display a dose-dependent effect for several of the β-lactam antibiotics tested. Indeed, i.c.v. administration diminishes the roles played by peripheral metabolism, plasma protein binding, and drug penetration of the brain. Moreover, as the dose-response curves reflect the maximum effect but not the seizure duration, it is unlikely that the marked effects observed with some of the compounds could be attributed to their differential clearance. At the most, the latter point could be responsible for the long-lasting convulsant effects observed with some compounds.

In the present study, all β-lactam antibiotics except cefonicid, cefixime, cefuroxime, and cephradine showed clear epileptogenic activity. Cefazolin appeared the most convulsant of the compounds tested. In fact, cefazolin was two to four times more potent than benzylpenicillin. The substitution of a benzylic hydrogen in the structure of benzylpenicillin with a sulfonic group (sulbenicillin) or of an amino group (ampicillin and amoxicillin) produces a marked reduction in convulsant potency. Azlocillin, mezlocillin, piperacillin, and cefoperazone, which are all characterized by the presence of a ureido group, showed epileptogenic activities which were similar but less than those of benzylpenicillin and cefazolin. Imipenem and meropenem, which differ structurally from other β-lactam classes by a carbapenem nucleus, also possess convulsant properties, but their epileptogenic potencies differed. In fact, the potency of imipenem appeared similar to that of ceftezole, whereas the potency of meropenem was similar to that of cefoperazone. These findings are in agreement with the results of previous investigators (9, 24). Although meropenem is chemically related to imipenem, there are differences at position 2, which may account for the observed differences in convulsive liability. Aztreonam, which is characterized by having the only β-lactam ring with a heterocyclic ring at position 3, is much less convulsant than imipenem. The data suggest that the β-lactam ring is an important contributor to the epileptogenic properties observed with the β-lactam antibiotics.

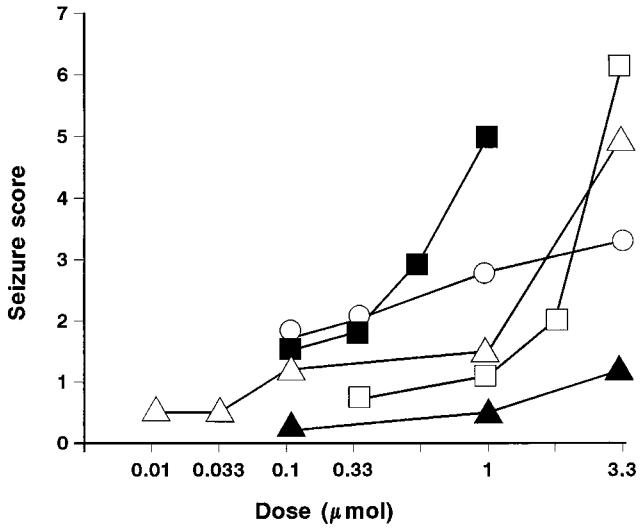


FIG. 9. Dose-response curves of seizure intensity score determined from behavioral changes after i.c.v. injection of β-lactam derivatives (see Materials and Methods for grading). ■, ceftriaxone; ○, ceftazidime; △, cefotaxime; □, ceftizoxime; ▲, cefixime.

Among the cephalosporins tested, compounds having a heterocyclic ring at position 3 and a (hetero)aromatic nucleus at position 7 of 7-aminocephalosporanic acid, such as cefoperazone, ceftazidime, cefotetan, cefamandole, and ceftriaxone, showed some evidence of epileptogenic activity but less marked than that shown by benzylpenicillin. Only ceftezole showed a potency more or less comparable to that of benzylpenicillin.

Compounds characterized by having a heterocyclic ring at position 7 of 7-aminocephalosporanic acid, such as cephradine, cefuroxime, cefoxitin, and cefixime, showed no epileptic activity, whereas cefotaxime and ceftizoxime demonstrated weak epileptic activity. Also, Ro 23-9424 showed very weak epileptogenic activity; it was 1.4 times less potent than cefotaxime.

Cefazolin and ceftezole, which have a tetrazole ring at position 7, show a marked similarity to pentylenetetrazole, a well-known convulsant drug. Such a tetrazole group could be responsible for the greater convulsant activity of these two cephalosporins in comparison with those of the other antibiotics. In addition, it is interesting that cefamandole, cefoperazone, and cefotetan, which possess a tetrazole nucleus at position 3, showed weaker epileptogenic activity than cefazolin and ceftezole. Thus, it is reasonable to presume that the presence of a tetrazole ring at position 7 in cephalosporins is more effective in increasing the convulsant potency than the same substitution at position 3, as in part previously described by Kamei and coworkers (18). It is also interesting that cefonicid, which differs from cefamandole only by the presence of a sulfonic group on the tetrazole nucleus, showed no convulsant effect.

Ceftizoxime, cefotaxime, Ro 23-9424, ceftriaxone, cefixime, and ceftazidime are all characterized by the presence of a (2-aminothiazolyl)methoxyimino moiety. However, the various degrees of convulsant activity of these antibiotics indicate that this group is not responsible for the observed effects.

There are at least two possible explanations for the lack of convulsant properties of cefixime, cefonicid, cefuroxime, and cephradine. First, perhaps these compounds cannot reach the site to induce convulsions; however, this is not very likely, inasmuch as the i.c.v. route of administration was utilized. In addition, these cephalosporins have, as mentioned above, structural characteristics different from those of the other β-lactam antibiotics which possess convulsant properties.

The second possibility is that these compounds may reach

some binding sites which are not the same as those by which the β-lactam antibiotics exert their convulsant effects. This leads to the suggestion that the β-lactam antibiotics may bind different sites which may or may not be responsible for epileptogenic activity in the brain. Though not very likely, this is an interesting idea that, if confirmed, may trigger a search for new β-lactam antibiotics without convulsant effects.

It should be noted that the failure to find an absolute correlation between the rank order of lipophilicity and the convulsant activities of these compounds may be due to several important possibilities. These include differences among β-lactam antibiotics in diffusion out of the cerebral ventricles and differences in mechanisms for producing convulsant effects. In regard to the first possibility, the different degrees of diffusion from the i.c.v. injection site were not measured for the β-lactam antibiotics examined. If such differences exist, they could account for the lack of correlation between lipophilicity and convulsant properties. In regard to the second possibility, we emphasize that β-lactam antibiotics could exert their convulsant effects by more than a simple interaction with the GABA receptor complex (3, 8). In fact, the convulsant actions of β-lactam antibiotics have been related to the reduction of GABA released from nerve terminals or to the inhibition of GABA binding to its receptor sites (1, 4, 5, 17). However, the fact that compounds such as cefazolin, ceftezole, cefonicid, and cefixime, which possess very similar lipophilicities (R_ms), showed different degrees of convulsant activity suggests the importance of other parameters. The concentrations of β-lactams able to interact with the GABA system are rather high and varied among the different β-lactam antibiotics but fit well in the concentration range used to demonstrate their convulsive or GABA-antagonistic properties in vitro (1, 15). Thus, it appears questionable whether a specific interaction of β-lactam antibiotics with GABA receptors alone can explain the convulsant activity of these compounds. An alternative mechanism, involving the increase of excitatory amino acid release in seizures induced by penicillin in cats, was suggested by Van Gelder et al. (29). Recently, we have demonstrated that some excitatory amino acid antagonists are able to counteract the seizures induced by imipenem, suggesting an involvement of excitatory amino acids in the genesis of seizures induced by this carbapenem derivative (6).

In conclusion, several factors, such as variable lipophilicity and differences in diffusion of these compounds, together with the pharmacodynamic mechanisms mentioned above deserve to be considered in explaining the convulsant properties of the various β-lactam antibiotics.

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REFERENCES

1. **Antoniadis, A., W. E. Muller, and U. Wollert.** 1980. Inhibition of GABA and benzodiazepine receptor binding by penicillins. Neurosci. Lett. **18:**309–312.
2. **Boyce, C. B. C., and B. V. Milborrow.** 1965. A simple assessment of partition data for correlating structure and biological activity using thin-layer chromatography. Nature (London) **208:**537–539.
3. **Curtis, D. R., C. A. Game, G. A. R. Johnston, R. M. McCulloch, and R. M. Maclachlan.** 1972. Convulsive action of penicillin. Brain Res. **43:**242–245.
4. **De Boer, T., J. C. Stoof, and H. Van Duyn.** 1980. Effect of penicillin on transmitter release from rat cortical tissue. Brain Res. **192:**296–300.
5. **De Sarro, A., G. B. De Sarro, C. Ascioti, and G. Nisticò.** 1989. Epileptogenic activity of some β-lactam derivatives: structure activity relationship. Neuropharmacology **28:**359–365.
6. **De Sarro, G. B., D. Ammendola, and A. De Sarro.** Effects of some excitatory amino acid antagonists on imipenem-induced seizures in DBA/2 mice. Brain Res., in press.
7. **De Sarro, G. B., M. Calò, G. Bagetta, R. Anfosso, E. Marmo, G. Nisticò, and V. Guarino.** 1983. Comparative epileptogenic properties of cefazolin and benzylpenicillin after intracaudate microinjection in rats. Acta Pharmacol. Sin. **4:**236–238.
8. **Dingledine, R., and L. Gjerstad.** 1980. Reduced inhibition during epileptiform activity in the *in vitro* hippocampal slice. J. Physiol. **305:**297–313.
9. **Drusano, G. L.** 1986. An overview of the pharmacology of imipenem/cilastatin. J. Antibiot. Chemother. **18:**79–92.
10. **Duma, R. J., A. J. Berry, S. M. Smith, J. W. Baggett, E. A. Swabb, and T. B. Platt.** 1984. Penetration of aztreonam into cerebrospinal fluid of patients with and without inflamed meninges. Antimicrob. Agents Chemother. **26:** 730–731.
11. **Eng, R. H., A. N. Munsif, B. G. Yangco, S. M. Smith, and H. Chemel.** 1989. Seizure propensity with imipenem. Arch. Intern. Med. **149:**1881–1883.
12. **Gerald, M. C., J. Massey, and D. C. Spadaro.** 1973. Comparative convulsant activity of various penicillins after intracerebral injection in mice. J. Pharm. Pharmacol. **25:**104–108.
13. **Gloor, P., and G. Testa.** 1974. Generalized penicillin epilepsy in the cat: effects of intracarotid and intravertebral pentylenetetrazol and amobarbital injections. Electroencephalogr. Clin. Neurophysiol. **36:**499–515.
14. **Gu, J., and H. C. Neu.** 1990. In vitro activity of Ro 23-9424, a dual-action cephalosporin, compared with activities of other antibiotics. Antimicrob. Agents Chemother. **34:**189–195.
15. **Gutnick, M. J., H. Van Duijn, and N. Citri.** 1976. Relative convulsant potencies of structural analogues of penicillin. Brain Res. **114:**139–143.
16. **Hartsveldt, C. V., T. L. Petit, and R. L. Isaacson.** 1975. Epileptogenic effects of several penicillins and penicillin-related compounds in rat neocortex. Epilepsia **16:**449–455.
17. **Hori, S., S. Kurioka, M. Matsuda, and J. Shimada.** 1985. Inhibitory effect of cephalosporins on γ-aminobutyric acid receptor binding in rat synaptic membranes. Antimicrob. Agents Chemother. **27:**650–651.
18. **Kamei, C., A. Sunami, and K. Tasaka.** 1983. Epileptogenic activity of cephalosporins in rats and their structure-activity relationship. Epilepsia **24:**431–439.
19. **Litchfield, J. T., and F. Wilcoxon.** 1949. A simplified method of evaluating dose-effect experiments. J. Pharm. Exp. Ther. **96:**99–113.
20. **Mandell, G. L., and A. M. Sande.** 1990. Penicillins, cephalosporins, and other beta-lactam antibiotics, p. 1271–1291. *In* A. Goodman Gilman, T. W. Rall, A. S. Nies, and P. Taylor (ed.), The pharmacological basis of therapeutics, 8th ed. Pergamon Press, New York.
21. **Neuman, M.** 1990. Vademecum des antibiotiques et agents chimiotherapiques antiinfectieux, 5th ed. Maloine, Paris.
22. **Nisticò, G., G. B. De Sarro, F. Naccari, R. Musolino, D. Rotiroti, G. Gallitto, and R. Di Perri.** 1980. Cefazolin: a valid model of experimental epilepsy? Monogr. Neural. Sci. **5:**14–19.
23. **Nisticò, G., R. Musolino, G. B. De Sarro, G. Gallitto, and R. Di Perri.** 1979. Effetti epilettogeni della cefazolina in varie specie animali. Riv. It. Elettroenc. Neurofisiol. **2:**519–523.
24. **Patel, J. B., and R. E. Giles.** 1989. Meropenem: evidence of lack of proconvulsive tendency in mice. J. Antimicrob. Chemother. **24:**307–309.
25. **Paxinos, G., and C. Watson.** 1987. The rat brain in stereotaxic coordinates. Academic Press, New York.
26. **Raichle, M. E., H. Kutt, S. Louis, and F. McDowell.** 1971. Neurotoxicity of intravenously administered penicillin G. Arch. Neurol. **25:**232–239.
27. **Rotiroti, D., G. B. De Sarro, R. Musolino, and G. Nisticò.** 1983. A new model of experimental epilepsy: the cephazolin-induced epilepsy, p. 129–144. *In* G. Nisticò, R. Di Perri, and H. Meinardi (ed.), Epilepsy, an update of research and therapy. Alan R. Liss, Inc., New York.
28. **Semel, J. D., and N. Allen.** 1991. Seizures in patients simultaneously receiving theophylline and imipenem or ciprofloxacin or metronidazole. South. Med. J. **84:**465–468.
29. **Van Gelder, N. M., I. Siatitsas, C. Menini, and P. Gloor.** 1983. Feline generalized penicillin epilepsy: changes of glutamic acid and taurine parallel the progressive increase in excitability of the cortex. Epilepsia **24:**200–213.
30. **Williams, P. D., D. B. Bennett, and C. R. Comereski.** 1988. Animal model for evaluating the convulsive liability of β-lactam antibiotics. Antimicrob. Agents Chemother. **32:**758–760.