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COMPARATIVE EPILEPTOGENIC PROPERTIES OF CEFAZOLIN AND BENZYLPENICILLIN AFTER INTRACAUDATE MICRO-INJECTION IN RATS

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ABSTRACT The epileptogenic properties of cefazolin given unilaterally into the caudate nucleus of rats were compared with those by equimolar doses of benzylpenicillin. Cefazolin produced a dose-dependent increase in locomotor activity, circling, stereotyped behavior and myoclonic jerks associated with high voltage spikes and other bioelectric paroxysmal discharges. In comparison to benzylpenicillin, cefazolin was more powerful on a molar basis and the epileptogenic disorders were longer-lasting.

KEY WORDS cefazolin; benzylpenicillin; epilepsy; caudate nucleus; rats

Several models of epilepsy have been developed during the last decades including local application of convulsant metals, acute electrical stimulation, kindling, local freezing of cerebral cortex, etc.[1] Benzylpenicillin applied to the cortex, given into some areas of the brain or given systemically produced motor and electrocortical epileptogenic discharges[1,2]. We have developed a new model of epilepsy, i. e., cefazolin-induced epilepsy[2-4]. Cefazolin is a parenteral cephalosporin which shares with benzylpenicillin the antibacterial action. Experimental evidence exists on the convulsant properties of cephalosporins[5]. The aim of this paper was to compare epileptogenic properties of cefazolin and benzylpenicillin after microinfusions into the caudate nucleus of rats.

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METHODS

Adult Wistar-Morini rats, 290 ± (SD) 23 g, were anesthetized with chloral hydrate. Stereotaxic implantation of cannulae into the head of the caudate nucleus was performed according to De Groot's atlas[6]. The volume of infusate was 1-2 μl for each microinjection. Cortical electrodes were implanted as previously described[7]. Rats were tested at least 48 h after operation. Drugs were dissolved in pyrogen-free saline, pH adjusted to 6.8-7. Control infusion was carried out with 1-2 μl of apyrogenic distilled water used to dissolve benzylpenicillin and cefazolin and did not produce significant changes in overt behavior and electrocortical activity which was recorded by an 8-channel OTE EEG machine.

The electrocortical spikes were counted at 5-min intervals by a Berg-Fourier analyzer (OTE Biomedica)[2].

Cefazolin sodium (Carlo Erba, Milan); benzylpenicillin sodium (Farmitalia, Milan).

RESULTS AND DISCUSSION

The unilateral microinjection of cefazolin 0.25 and 0.5 μmol into the caudate nucleus (at least 12 experiments/dose) produced a dose-dependent increase in locomotor activity, contralateral circling and stereotyped behavior (licking, grooming, sniffing, contralateral turning and occasionally biting and gnawing). Myo-

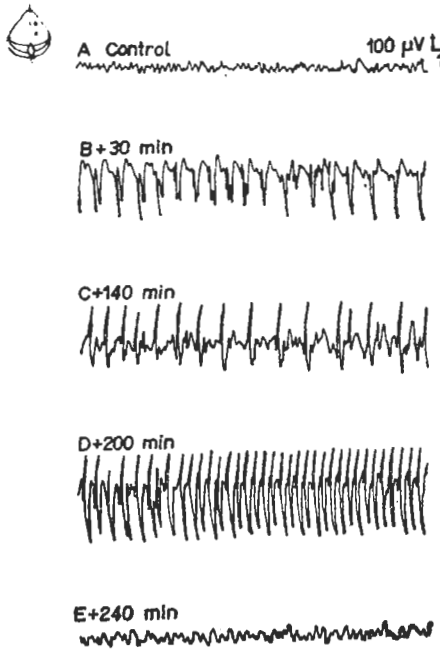

Fig 1. Effects of an intracaudate injection of cefazolin 0.5 μmol on electrocortical activity in a rat. A. Control electrocortical pattern. B–D. High voltage electrocortical spikes after 30, 140 & 200 min. E. Return of ECoG to normal after 240 min.

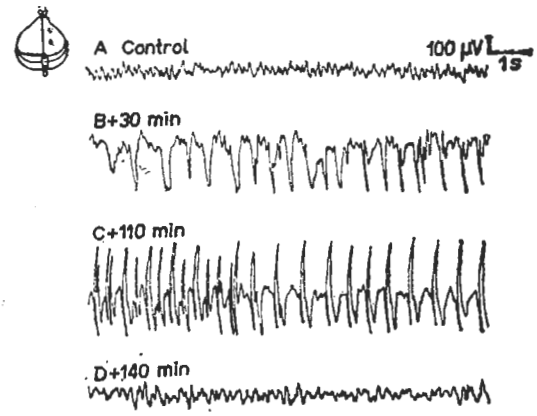

Fig 2. Effects of an intracaudate injection of benzylpenicillin 1 μmol on electrocortical activity in a rat. A. Control. B,C. High voltage ECoG spikes after 30 & 110 min. D. Return of ECoG to normal after 140 min.

clonic movements of the contralateral limbs were seen and in some occasions these merged into tonic–clonic convulsions. Cefazolin 0.5 μmol induced myoclonic jerks of contralateral limbs associated with initially ipsilateral and then bilateral high-voltage spikes and such epileptic phenomena lasted 212 ± (SD) 36 min (n = 18). Benzylpenicillin 0.5 μmol (n = 6) failed to produce epileptic seizures; however, 1 μmol (n = 12) induced similar behavioral and electrocortical disorders, although of significantly ($p<0.01$) shorter duration (121 ± 42 min).

Penicillin is a convulsant agent[1,2]. Its epileptogenic properties have been ascribed to both increased excitation in synaptic transmission[8] and decreased inhibition[9–12]. It was

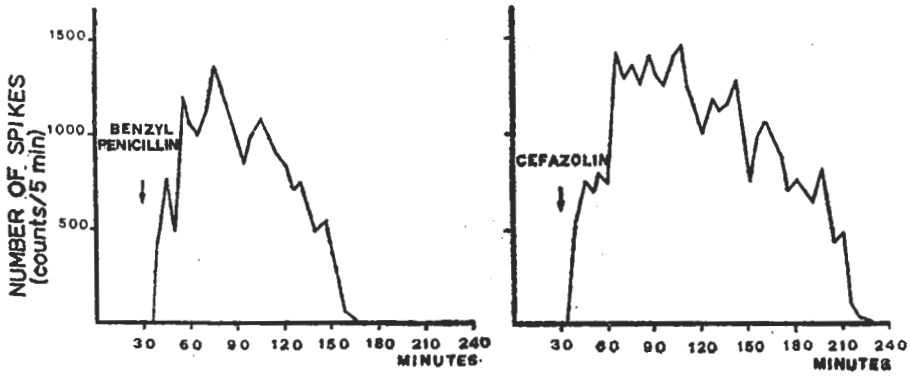

Fig 3. Number of electrocortical spikes (counts every 5 min) after an intracaudate injection of cefazolin 0.5 μmol or benzylpenicillin 1 μmol. The total number of spikes was significantly ($p<0.01$) higher after cefazolin in comparison to benzylpenicillin.

considered as an antagonist at GABA receptors[13] and also benzodiazepine receptors[14].

The mechanism of action of cefazolin is not known. It acts possibly in a similar way as penicillin. Both antibiotics given unilaterally into the corpus striatum of rats served as good models of focal myoclonic epilepsy which resembled that evoked by intrastriatal infusion of picrotoxin and bicucullin, two GABA receptor antagonists[15]. However, in comparison with benzylpenicillin for epileptogenic agents, cefazolin is more powerful and longer-lasting. Hence the cefazolin model is more suitable for drug testing especially when the drugs require a long latency period (e. g., GABA-transaminase inhibitors).

In conclusion, the cefazolin model of epilepsy is simple, reproducible and gives rise to epileptogenic bioelectric and motor changes reversible but longer-lasting than those evoked by benzylpenicillin.

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