



Short communication

Influence of cimetidine on the anticonvulsant activity of conventional antiepileptic drugs against pentetrazole-induced seizures in mice

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Abstract:

The aim of this study was to evaluate the effects of acute (1 day) and chronic (7 days) administrations of cimetidine, an H₂ histamine receptor antagonist, on the protective activity of conventional antiepileptic drugs (AEDs) against pentetrazole (PTZ)-induced seizures in mice. Cimetidine (up to 100 mg/kg), given alone either acutely or chronically, did not alter significantly PTZ-induced seizures in mice. However, the drug (at 20 mg/kg, administered acutely) potentiated the anticonvulsant activity of ethosuximide (ETX) by reducing its ED₅₀ from 134 to 103 mg/kg ($p < 0.05$). This effect was associated with a 74% elevation of plasma ETX level ($p < 0.01$). In contrast, chronic (7 days) administration of cimetidine (20 mg/kg) did not affect the anticonvulsant activity of ETX in the PTZ test and its plasma levels. On the other hand, cimetidine (20 mg/kg), given either acutely or chronically, when co-administered with valproate, clonazepam, and phenobarbital had no significant impact on the anticonvulsant properties of these AEDs against PTZ-induced seizures and their plasma levels in mice. The results indicate that there may be no risk in prescribing cimetidine for other than epilepsy reasons in patients treated with valproate, clonazepam or phenobarbital.

Key words:

cimetidine, antiepileptic drug, pentetrazole, drug interaction, clonic seizures

Introduction

In clinical practice, H₂ histamine receptor antagonists are commonly used for the treatment of patients with peptic ulcers and gastric acid-related disorders [7]. Although these drugs are administered at relatively low doses, they easily penetrate *via* blood-brain bar-

rier into the central nervous system and sometimes in elderly patients with renal dysfunction or during polytherapy, the drugs can produce serious side effects (especially, schizophrenic-like syndrome and/or seizures) [3, 4, 11]. Cimetidine was the first synthesized and clinically used drug possessing the antagonistic properties at H₂ histamine receptors. Noteworthy, the drug is still used in patients with peptic ulcers.

In this study, we examined the effects of cimetidine administered acutely or chronically (once daily for 7 days) on the anticonvulsant activity of conventional antiepileptic drugs (AEDs) against pentetrazole (PTZ)-induced seizures in mice. Finally, to characterize possible pharmacokinetic profiles of such combinations, the influence of cimetidine on plasma AED levels was evaluated.

Materials and Methods

The experiments were conducted on male Swiss mice weighing 20–27 g. The animals were kept in colony cages, under standard laboratory conditions. Animals were randomly assigned to the experimental groups, consisting of 8–12 animals. All experimental procedures were approved by the Local Ethics Committee at the Medical University of Lublin.

The following drugs were used: ethosuximide (ETX; Sigma, St. Louis, MO, USA), valproate magnesium (VPA; ICN Polfa Rzeszów, Poland), clonazepam (CLO), phenobarbital (PB) and cimetidine (all three drugs from Polfa Warszawa, Poland). PTZ (Sigma, St. Louis, MO, USA), ETX, PB, cimetidine and VPA were dissolved in distilled water, whereas CLO was suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in distilled water. All drugs were administered intraperitoneally (*ip*) in a volume of 0.01 ml/g, except for PTZ which was given subcutaneously (*sc*) in a volume of 0.005 ml/g. VPA and CLO were administered 30 min, ETX and PB – 45 min, and cimetidine – 60 min before the tests. Mice were injected *sc* with PTZ (at a dose of 99 mg/kg, being its CD_{97} value (i.e. the dose of PTZ necessary to evoke clonic seizures in 97% of animals tested). Subsequently, the mice were placed individually into transparent cages and observed for 30 min for the occurrence of clonic and tonic seizures.

This study comprised two experiments: (1) acute experiment, in which animals were injected *ip* with a single dose of cimetidine and one of the AEDs and (2) chronic experiment, in which the animals were given 7 consecutive injections of cimetidine (once daily for 7 days) and on the last day the mice were co-administered with one of the AEDs studied. Details concerning experimental designs have been presented in our previous study [10]. The measurements

of plasma AED concentrations were performed with fluorescence polarization immunoassay technique, using an Abbott TDx analyzer and reagents exactly as described by the manufacturer (Abbott Laboratories, Irving, Texas, USA). The procedure of plasma sampling has been described in detail earlier [10].

Median effective doses of AEDs (ED_{50} s with their 95% confidence limits) were calculated and statistically analyzed by computer probit analysis, according to Litchfield and Wilcoxon [5]. Plasma levels of AEDs were statistically analyzed using unpaired Student's *t*-test.

Results

Cimetidine (up to 100 mg/kg) administered either acutely or chronically (for 7 days) was without any significant effect on PTZ-induced seizures in mice. During the evaluation of acute and chronic effects of cimetidine on the antiseizure properties of AEDs, the former drug was administered at a constant dose of 20 mg/kg. In our previous study [9], we have found that cimetidine at the dose of 40 mg/kg elevated electroconvulsive threshold, both acutely or following chronic administration, being without effect upon this parameter at the lower (20 mg/kg) dose.

The combined acute administration of cimetidine (20 mg/kg) with ETX resulted in a significant increase in the anticonvulsant activity of ETX. The ED_{50} value of ETX, against PTZ-induced clonic seizures, was decreased from 134 (120–149) mg/kg to 103 (92–116) mg/kg ($p < 0.05$; Fig. 1). In contrast, the protective activity of VPA, PB and CLO co-administered with cimetidine (20 mg/kg; in the acute study) was not significantly affected as compared to these AEDs given alone (Fig. 1). The chronic (7-day) treatment with cimetidine (20 mg/kg) did not alter the anticonvulsant activities of all the studied AEDs in the PTZ-test (Fig. 1).

Pharmacokinetic verification of the observed interactions revealed that cimetidine, given acutely at a dose of 20 mg/kg and co-applied with ETX, markedly raised (by 74%) the total plasma ETX level (from 42 ± 11.3 to 73 ± 14.7 $\mu\text{g/ml}$; $p < 0.01$). On the other hand, cimetidine (administered singly at 20 mg/kg) did not affect the free plasma levels of VPA, PB or CLO (data not shown). Moreover, cimetidine (admin-

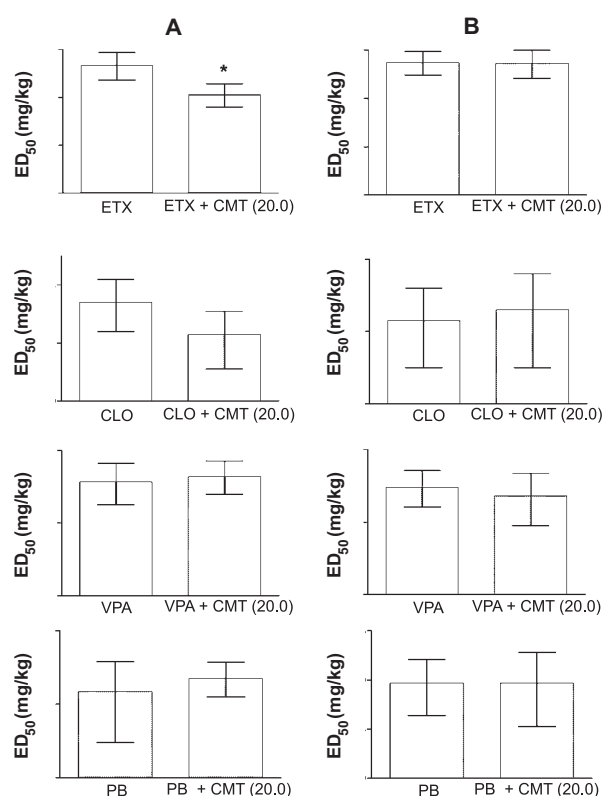


Fig. 1. Influence of cimetidine, administered once and chronically (for 7 days), on the protective activity of conventional antiepileptic drugs against pentetrazole-induced seizures. Results are presented as median effective doses (ED_{50} in mg/kg; with 95% confidence limits as the error bars). Statistical evaluation of data was performed with probit analysis according to Litchfield and Wilcoxon [5]. Clonazepam (CLO) and valproate (VPA) were administered *ip* 30 min, ethosuximide (ETX) and phenobarbital (PB) – 45 min before the PTZ-test. * $p < 0.05$ vs. ETX. (A) Cimetidine was given *ip* at a single dose of 20 mg/kg, 60 min before the PTZ test; (B) Chronic *ip* administration of cimetidine (at 20 mg/kg; once daily for 7 days)

istered chronically at 20 mg/kg) had no significant impact on plasma AED concentrations (data not shown).

Discussion

The presented study indicates that cimetidine given once or chronically did not affect anticonvulsant properties of VPA, CLO or PB. On the other hand, co-administration of cimetidine with ETX resulted in pharmacodynamic as well as pharmacokinetic interactions between these drugs. Also, acute cimetidine treatment at the subthreshold dose of 20 mg/kg enhanced the anticonvulsant activity of carbamazepine whilst, following chronic administration, it dimin-

ished the efficacy of PB [9]. Numerous experimental and clinical studies have reported that the administration of cimetidine or other H_2 histamine receptor antagonists may be associated with a high risk of convulsive attacks [1, 3, 8, 11]. Moreover, it has been found that seizures evoked by cimetidine or other H_2 histamine receptor antagonists were blocked by muscimol, a $GABA_A$ receptor agonist [8]. On the other hand, endogenous brain histamine plays a protective role against the seizure development in PTZ-kindled rats [12]. However, the brain concentration of endogenous histamine seemed to be independent of administration of H_2 receptor antagonists [2]. Relatively recently, Cannon et al. [2] have suggested that some cimetidine-like drugs (i.e., famotidine, tiotidine, ranitidine and impropogran) do not produce seizures *via* H_2 and $GABA_A$ receptors, but by other, unknown as yet, mechanisms that might be involved in their CNS adverse effects.

Several lines of evidence indicate that cimetidine may increase plasma levels of co-administered AEDs through the inhibition of some isoforms of hepatic enzymes [6]. In the present study, the increased plasma level of ETX, following the acute administration of cimetidine, does not seem to be a result of inhibition of hepatic cytochrome P450 enzymes, since the chronic (7-day) treatment with cimetidine had no impact on plasma ETX levels in experimental animals.

Finally, based on current preclinical data, the utmost caution is advised during the concomitant administration of cimetidine with ETX in order not to expose the epileptic patients to unpredictable pharmacokinetic interactions. However, there seem to be no contraindications to combine cimetidine with VPA, CLO or PB.

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