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Topiramate potentiates the antiseizure activity of some anticonvulsants in DBA/2 mice

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Abstract

Topiramate (1–50 mg/kg, intraperitoneally (i.p.)) was able to antagonize audiogenic seizures in DBA/2 mice in a dose-dependent manner. Topiramate at dose of 2.5 mg/kg i.p., which per se did not significantly affect the occurrence of audiogenic seizures in DBA/2 mice, potentiated the anticonvulsant activity of carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital and valproate against sound-induced seizures in DBA/2 mice. The degree of potentiation induced by topiramate was greatest for diazepam, phenobarbital and valproate, less for lamotrigine and phenytoin and not significant for carbamazepine and felbamate. The increase in anticonvulsant activity was associated with a comparable increase in motor impairment. However, the therapeutic index of the combination of all drugs + topiramate was more favourable than that of antiepileptics + saline, with the exception of carbamazepine or felbamate + topiramate. Since topiramate did not significantly influence the total and free plasma levels of the anticonvulsant drugs studied, we suggest that pharmacokinetic interactions, in terms of total or free plasma levels, are not probable. However, the possibility that topiramate can modify the clearance from the brain of the anticonvulsant drugs studied cannot be excluded. In addition, topiramate did not significantly affect the hypothermic effects of the anticonvulsants tested. In conclusion, topiramate showed an additive effect when administered in combination with some classical anticonvulsants, most notably diazepam, phenobarbital, lamotrigine, phenytoin and valproate.

Keywords: Epilepsy; Topiramate; Carbamazepine; Phenytoin; Valproate; Felbamate; Anticonvulsant; Audiogenic seizure; DBA/2 mouse

1. Introduction

Seizures can be controlled with antiepileptic drugs by (a) blocking seizure spread or (b) elevating seizure threshold. Carbamazepine and phenytoin, active only in the maximal electroshock seizure test, are believed to act by blocking seizure spread (Swinyard et al., 1989; White, 1997). In contrast, valproate and felbamate display activity in both maximal electroshock and chemically induced seizures and have a broad spectrum of action clinically (Swinyard et al., 1989; Harden, 1994; Britton and So, 1995; Meldrum, 1997).

With regard to mechanisms that may lead to seizure activity, much attention has been focused on the existence of inhibitory and excitatory amino acid neurotransmitters in the central nervous system. Impairment of γ-aminobutyric acid (GABA)ergic transmission by a variety of drugs, such as benzodiazepine, phenobarbital and primidone, may result in focal or generalized seizures, whilst enhancement of GABAergic inhibition may prevent seizures in several animal models of epilepsy (Meldrum, 1984, 1997; McLean and MacDonald, 1986; Upton, 1994; Macdonald and Meldrum, 1995).

Topiramate (McN-4853, RWJ-17021-000), one of a series of structurally novel anticonvulsants, contains a sulfamate functionality and is derived from the naturally occurring monosaccharide D-fructose (Maryanoff and Gardocki, 1985; Maryanoff and Margul, 1989; Maryanoff et

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al., 1987). Topiramate was selected for development as an anticonvulsant based on its potency, high protective index and long duration of action (Graves and Leppik, 1993; Ben-Menachem, 1995). In initial animal studies, topiramate resembled carbamazepine and phenytoin in displaying antiseizure activity in the maximal electroshock test and not against chemically induced seizures (Gardocki et al., 1986; Edmonds et al., 1991, 1992; Jiang et al., 1991; Shank et al., 1991, 1994; Vaught et al., 1991; Kimishima et al., 1992; Wauquier and Zhou, 1996).

Neurochemical studies of the possible mechanisms of action of topiramate show that it acts at voltage-sensitive Na^+ channels so as to stabilize neuronal membranes, thus inhibiting the release of excitatory amino acids (Coulter et al., 1993; Sombati et al., 1995; Hanaya et al., 1998; Taverna et al., 1999). In addition, in an animal model of epilepsy that may predict the clinical spectrum of antiepileptic drugs, topiramate blocked both absence-like and tonic seizures, whereas carbamazepine and phenytoin blocked tonic seizures but not absence-like seizures, and ethosuximide blocked absence-like seizures but not tonic seizures (Nakamura et al., 1994). Such findings support clinical efforts to determine whether topiramate has a broad spectrum of therapeutic action (Privitera 1997).

If topiramate does indeed have a broad therapeutic spectrum, this may reflect multiple mechanisms of topiramate action. Of the four antiseizure actions by which antiepileptic drugs are believed to act: (1) modulation of voltage-dependent Na^+ ion channels: (2) enhanced γ-aminobutyric acid (GABA)-mediated inhibitory neurotransmission; (3) modulation of voltage- and receptor-gated calcium ion channels; and (4) blockade of excitatory neurotransmitters (Macdonald and Meldrum, 1995), topiramate may have effects on three pathways (Brown et al., 1993; Coulter et al., 1993, 1995; Gordey et al., 1995; Sombati et al., 1995; White et al., 1995a, 1995b). For example, in cultured hippocampal cells displaying spontaneous epileptiform discharge, topiramate reduced the duration and frequency of action potentials associated with sustained repetitive firing, presumably by state-dependent inhibition of voltage-sensitive Na^+ channels. In this effect, topiramate resembles carbamazepine and phenytoin (Coulter et al., 1993, 1995; Sombati et al., 1995). Like the benzodiazepines, topiramate increased GABA-induced chloride influx, although topiramate appears to act at a novel GABA receptor that is not modulated by a benzodiazepine (Gordey et al., 1995). A third potential mechanism of topiramate action is the reduction of neuronal excitability via the blockade of glutamate-related excitatory neurotransmission. Specifically, topiramate inhibited the excitatory responses of hippocampal neurons elicited by selective activation of the kainate receptor subtype (Coulter et al., 1995).

The aim of the present study was to investigate the effects of pretreatment with topiramate on the anticonvulsant properties of carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital and valproate against audiogenic seizures in DBA/2 mice. The effects of the combination of topiramate with the above reported anticonvulsant drugs on rotarod performance, body temperature and total and free plasma levels of antiepileptics also were studied.

2. Materials and methods

2.1. Animals

Male and female DBA/2 mice weighing 8–12 g (22–26 days old) or 20–28 g (48–56 days old) were used (Charles River, Calco, Como, Italy). The animals were housed in groups of 8–10 under a 12-h light/dark cycle (lights on at 7:00 a.m.) with food and water available ad libitum. Procedures involving animals and their care were conducted in conformity with international and national laws and policies.

2.2. Experimental design

DBA/2 mice were exposed to auditory stimulation 60, 120 or 180 min following intraperitoneal (i.p.) administration of topiramate (1–50 mg/kg) or saline and 45 min following i.p. injection of some antiepileptics. Each mouse was placed under a hemispheric perspex dome (diameter 58 cm) and 1 min was allowed for habituation and assessment of locomotor activity. Auditory stimulation (12–16 kHz, 109 dB) was applied for 1 min or until tonic extension occurred. As previously reported, the seizure response (De Sarro et al., 1984) was assessed using the following scale: 0 = no response, 1 = wild running, 2 = clonus, 3 = tonus, 4 = respiratory arrest. The maximum response was recorded for each animal. Rectal temperature was recorded immediately prior to auditory testing using an Elektrolaboratoriet thermometer type T.E.3. Behavioural changes were observed during the period between drug administration and auditory testing.

2.3. Determination of the plasma levels of the antiepileptic compounds

DBA/2 mice, 48–56 days old, were administered i.p. either saline + one of antiepileptic compounds or topiramate + one of antiepileptic drugs. The animals were lightly anaesthetized with ethyl ether and killed by decapitation at appropriate times and blood samples of approximately 1 ml were collected into Eppendorf tubes. The felbamate and lamotrigine assay was carried out by high-performance liquid chromatography (HPLC) analysis (Rizzo et al., 1997).

Blood samples were centrifuged at 2000 rpm for 15 min for carbamazepine, diazepam, phenytoin and phenobarbital

determination. The plasma was put into a system MPS-1 (Amicon, Danvers, MA, USA) for the separation of free from protein-bound microsolutes. Plasma samples of 60 μl were transferred to special sample cups and inserted into an Automatic Clinical Analyser (ACA II, du Pont, Wilmington, DE, USA) which uses a method based on the homogenous enzyme immunoassay technique. For the magnesium valproate assay a serum sample of 50 μl was diluted twice with Tris buffer and analysed with the same method. Control drug solutions were put before and after the respective antiepileptic experimental samples.

2.4. Effects on motor movements

Behavioural changes and their onset and duration were recorded after drug injection until the time of the rotarod test. In particular, two independent observers followed gross behavioural changes consisting of locomotor activity, ataxia, squatting posture and possible piloerection. These behavioural changes were noted but not statistically analysed.

Groups of 10 DBA/2 mice, 8–12 g and 22–26 days old, were trained to do coordinated motor movements continuously for 2 min on a 3-cm diameter rotarod turning at 8 rev min^{-1} (U. Basile, Comerio, Varese, Italy). Impairment of coordinated motor movements was defined as inability of the mice to remain on the rotarod for a 2-min test period (Dunham and Miya, 1957). The ability of the mice to remain on the rotarod was tested 45 min after the i.p. administration of saline + one of the conventional antiepileptics or after the combined treatment with topiramate + one of the antiepileptic drugs.

2.5. Statistical analysis

Statistical comparisons among groups of control and drug-treated animals were made using Fisher's exact probability test (incidence of the seizure phases) or analysis of variance (ANOVA) and Dunnett's test (rectal temperature). The percent incidence of each phase per dose of compound administered and dose–response curves were fitted using linear regression analysis. ED_{50} values (with 95% confidence limits) for each compound and each phase of seizure response were estimated using a computer program of the method of Litchfield and Wilcoxon (1949); the relative anticonvulsant activities were determined by comparison of respective ED_{50} values. The lines of best fit of conventional antiepileptic drug + saline or in association with topiramate were compared using Chi-squared analysis, with results expressed for position, parallelism and heterogeneity. TD_{50} values (with 95% confidence limits) for each compound were estimated using the method of Litchfield and Wilcoxon (1949). The plasma levels of the drugs are expressed as means ± S.E.M. of at least eight determinations. Student's *t*-test was used for statistical comparisons.

2.6. Drugs

The sources of the drugs used were: carbamazepine, (Novartis, Basel, Switzerland), diazepam (Hoffmann-La Roche, Basel, Switzerland), felbamate (Schering-Plough, Milano, Italy), sodium phenobarbital (Bracco, Milano, Italy), sodium phenytoin (Recordati, Milano, Italy), lamotrigine (Glaxo-Wellcome, Verona, Italy) and magnesium valproate (Sigma-Tau, Pomezia, Italy). Topiramate was extracted with ethyl chloroform from commercial tablets (Topamax, Janssen-Cilag, Cologno Monzese, Milano, Italy).

3. Results

3.1. Anticonvulsant properties of topiramate in DBA/2 mice

To allow better evaluation of topiramate anticonvulsant effects, we exposed the animals to the auditory test at different times after topiramate administration. Topiramate (10, 20, 30, 40 and 50 mg/kg i.p.), produced a dose-dependent significant protection ($P < 0.01$) against the clonic or tonic phase of the audiogenic seizure response in DBA/2 mice 60 min after administration (Fig. 1). Significant protection against the wild running phase was observed after topiramate 30, 40 and 50 mg/kg i.p. After topiramate 1, 2.5 and 5 mg/kg i.p., no significant anticonvulsant activity or behavioural changes were observed. When the auditory test was carried out 120 min following topiramate administration (20, 30, 40 and 50 mg/kg i.p.) a

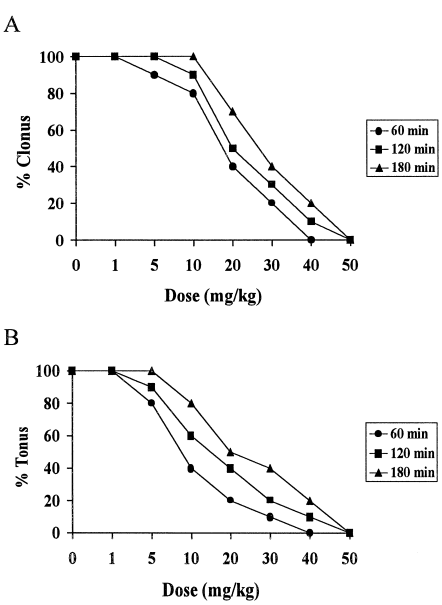

Fig. 1. Dose–response curves for the anticonvulsant effect of topiramate 1–50 mg/kg at (●) 60 min, (■) 120 min and (▲) 180 min after i.p. administration. Abscissae shows the doses, ordinate shows (A) % of clonic seizures, (B) % of tonic seizures.

significant protection against the clonic and tonic phases of audiogenic seizures was observed in DBA/2 mice. Doses of 40 and 50 mg/kg of topiramate administered 120 min before auditory testing were able to significantly protect against the wild running phase of the audiogenic seizures. After topiramate 1, 2.5, 5 and 10 mg/kg i.p. no significant anticonvulsant activity or behavioural changes were observed. When the auditory test was carried out 180 min after the i.p. administration of topiramate (30, 40 and 50 mg/kg) the clonic and tonic phases of the audiogenic seizures were significantly antagonized in DBA/2 mice. The dose of 50 mg/kg i.p. significantly reduced the incidence of wild running, whereas no protection was observed after topiramate 1, 2.5, 5, 10 and 20 mg/kg i.p. ED_{50} values (±95% confidence limits) of topiramate administered 60, 120 and 180 min before the auditory test are reported in Table 1. The doses of topiramate studied did not reduce locomotor activity or produced ataxia and a decrease in rectal temperature. Since topiramate exerted its maximal anticonvulsant activity at 60 min (Table 1), we decided to use this pretreatment time for the following studies. In addition, according to previous studies, all the conventional anticonvulsants were administered 45 min before auditory testing (De Sarro et al., 1992, 1996, 1998).

3.2. Influence of topiramate on the anticonvulsant activity of conventional antiepileptic drugs against audiogenic seizures

As shown in Table 2, diazepam, carbamazepine, felbamate, lamotrigine, phenobarbital, phenytoin and valproate exhibited anticonvulsant activity in the audiogenic seizure model of DBA/2 mice. Pretreatment (15 min before anticonvulsant administration) with topiramate (2.5 mg/kg i.p.) was able to produce a consistent shift to the left of the dose–response curves of conventional antiepileptics with some exceptions for carbamazepine or felbamate compared with concurrent groups, suggesting an increase in anticonvulsant activity (data not shown). All dose–response curves were parallel except those for carbamazepine or felbamate plus topiramate. There was no significant heterogeneity, i.e., any residual variation was consistent with binomial sampling. The degree of potentiation by topiramate varied among the anticonvulsant drugs, being greatest for diazepam, phenobarbital and valproate, less for lamotrigine

Table 1
ED_{50} values (±95% confidence limits) of topiramate on audiogenic seizures in DBA/2 mice following various pretreatment times
All data above reported are expressed in mg/kg and were calculated according to the method of Litchfield and Wilcoxon (1949).

Pretreatment time (min)	Seizure phase		
	Wild running	Clonus	Tonus
60	22.9 (15.8–33.9)	16.2 (11.3–23.1)	9.9 (6.9–14.2)
120	33.0 (25.9–43.1)	19.1 (13.5–27.1)	13.9 (8.7–22.3)
180	44.0 (35.0–55.4)	23.3 (17.6–30.9)	17.5 (12.4–24.6)

Table 2
ED_{50} values (±95% confidence limits) of saline + antiepileptic drugs or topiramate (2.5 mg/kg i.p.) + antiepileptic drugs against audiogenic seizures in DBA/2 mice
All reported data are expressed in mg/kg and were calculated according to the method of Litchfield and Wilcoxon (1949). Significant differences in the ED_{50} values among concurrent groups of saline + antiepileptic drug and topiramate + antiepileptic groups are denoted by $^{b}P < 0.05$ and $^{a}P < 0.01$.

Seizure phase	Drug + saline	Drug + topiramate
Wild running		
Carbamazepine	10.6 (8.1–13.8)	6.4 (4.5–9.1)[b]
Diazepam	0.49 (0.34–0.71)	0.23 (0.15–0.35)[a]
Felbamate	114.6 (92–142.7)	87.4 (52.5–145.5)
Lamotrigine	6.1 (4.6–8.1)	3.6 (2.2–5.9)[b]
Phenobarbital	7.1 (5.6–9)	3.3 (2.1–5.2)[a]
Phenytoin	4.3 (3.1–6)	2.1 (1.4–3.1)[a]
Valproate	84 (63–114)	42 (26–67.8)[a]
Clonus		
Carbamazepine	4.4 (3.6–5.4)	3.4 (1.9–6.1)
Diazepam	0.28 (0.2–0.39)	0.12 (0.08–0.18)[a]
Felbamate	48.8 (35.4–67.2)	39.6 (27.9–56.2)
Lamotrigine	3.5 (2.4–5.1)	2.1 (1.5–2.9)[b]
Phenobarbital	3.4 (2.3–5)	1.5 (0.9–2.5)[a]
Phenytoin	2.5 (1.8–3.5)	1.3 (0.8–2.1)[b]
Valproate	43 (33–56)	19.7 (15.1–25.7)[a]
Tonus		
Carbamazepine	3.0 (2.6–3.8)	1.8 (1.1–2.9)[b]
Diazepam	0.24 (0.15–0.39)	0.11 (0.07–0.17)[a]
Felbamate	23.1 (12.1–44)	16.2 (8.9–29.5)[b]
Lamotrigine	1.1 (0.7–1.8)	0.6 (0.4–0.9)[a]
Phenobarbital	2.4 (1.7–3.4)	1.1 (0.7–1.73)[a]
Phenytoin	2.0 (1.6–2.5)	0.8 (0.6–1.07)[a]
Valproate	31 (22–43)	14.3 (10.5–19.5)[a]

Table 3
TD_{50} values (with 95% confidence limits) of saline + various antiepileptics and topiramate + antiepileptics obtained in the rotarod test
All data are expressed as mg/kg and were calculated according to the method of Litchfield and Wilcoxon (1949). TD_{50}/ED_{50} = therapeutic index, which represents the ratio between TD_{50} and ED_{50} from the clonic phase of the audiogenic seizures. No significant differences were observed between concurrent groups.

Treatment	TD^{50} locomotor deficit	TD^{50}/ED^{50}
Saline + carbamazepine	46.5 (37.9–57)	15.5
Topiramate + carbamazepine	40.1 (24.4–65.9)	11.9
Saline + diazepam	3.8 (3.0–4.8)	13.5
Topiramate + diazepam	2.0 (1.4–2.86)	18.2
Saline + felbamate	816 (590–1024)	16.7
Topiramate + felbamate	546 (426–699.8)	13.8
Saline + phenytoin	48.3 (50.9–68.4)	19.3
Topiramate + phenytoin	25.6 (20.3–32.3)	19.7
Saline + lamotrigine	81 (55–118)	23.1
Topiramate + lamotrigine	71 (53–95.1)	33.8
Saline + phenobarbital	139 (115–168)	40.9
Topiramate + phenobarbital	74 (51–107.4)	49.3
Saline + valproate	290 (240–251)	7.3
Topiramate + valproate	185 (121–283)	9.4

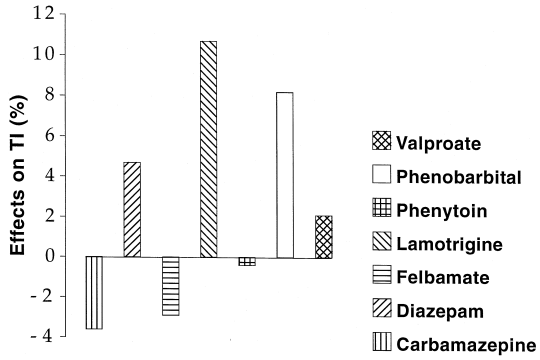

Fig. 2. Effects of a single administration of topiramate (2.5 mg/kg, i.p.) in combination with some antiepileptics on percent changes in the therapeutic index (TI). Note that the combined treatments of topiramate (2.5 mg/kg, i.p.) with diazepam, lamotrigine, phenobarbital, phenytoin or valproate resulted in a favourable therapeutic index, whereas a combination of topiramate with carbamazepine or felbamate caused an increase of motor impairment.

and phenytoin, and not significant for carbamazepine and felbamate.

3.3. Influence of topiramate on the motor impairment induced by antiepileptic drugs

When applied in doses equal to their ED_{50} values against the clonic phase of the audiogenic seizures, carbamazepine (4.4 mg/kg), diazepam (0.28 mg/kg), felbamate (48.8 mg/kg), lamotrigine (3.5 mg/kg), phenytoin (2.5 mg/kg), phenobarbital (3.4 mg/kg) and valproate (43 mg/kg) did not influence the motor performance of DBA/2 mice. Larger doses were necessary to produce motor impairment (Table 3). Topiramate administered at doses up to 100 mg/kg did not significantly affect locomotor performance. Concomitant treatment with carbamazepine and topiramate or felbamate and topiramate resulted in an increase of motor impairment, whilst considerable impairment of locomotor performance was not observed when topiramate was administered with phenobarbital, lamotrigine, diazepam and valproate (Table 3). In fact, the therapeutic index of the combination of phenobarbital + topiramate, lamotrigine + topiramate, diazepam + topiramate or valproate + topiramate was more favourable than that of phenobarbital + saline, lamotrigine + saline, diazepam + saline or valproate + saline (Fig. 2).

3.4. Effects of combined treatment of topiramate with antiepileptic compounds on body temperature

Body temperature was recorded in animals administered saline + anticonvulsant drugs or topiramate + anticonvulsant drugs. We observed hypothermic effects only after administration of saline + the highest doses of carbamazepine (20, 30 and 50 mg/kg i.p.), diazepam (3 and 5 mg/kg i.p.) and valproate (100, 200 and 300 mg/kg i.p.). No significant differences among groups treated with saline + felbamate, lamotrigine, phenytoin, phenobarbital or low doses of carbamazepine, diazepam or valproate were evident (data not shown). Groups treated with topiramate (2.5 mg/kg i.p.) + different antiepileptic drugs showed no significant changes in hypothermic effect when compared with the effect of concurrent saline + antiepileptic drugs.

3.5. Influence of topiramate on the total and free plasma levels of antiepileptic drugs

Blood concentrations of carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital and valproate are presented in Table 4. The doses of topiramate studied did not significantly modify the plasma levels of carbamazepine (15 mg/kg, i.p.), felbamate (100 mg/kg,

Table 4
Influence of topiramate on total and free plasma levels of some antiepileptic compounds (carbamazepine, diazepam, felbamate, lamotrigine, phenytoin, phenobarbital, and valproate) in DBA/2 mice
Drugs were administered i.p. Saline or topiramate (2.5 mg/kg i.p.) + lamotrigine 45 min, carbamazepine, diazepam, and felbamate 60 min, phenobarbital 60 and 120 min, phenytoin 120 min and valproate 30 and 60 min before blood samples were collected. Values are means (μg/ml) of at least eight determinations ± S.E.M. Student's *t*-test was used for statistical analysis of the data.

Treatment (time) (dose mg/kg)	Saline + compound		Topiramate + compound	
	Total	Free	Total	Free
Carbamazepine (60 min) (15 mg/kg)	5.2 ± 0.7	0.62 ± 0.2	5.2 ± 0.5	0.61 ± 0.2
Diazepam (60 min) (5 mg/kg)	2.1 ± 0.2	0.15 ± 0.05	2.1 ± 0.3	0.15 ± 0.05
Phenytoin (120 min) (10 mg/kg)	8.8 ± 1.8	0.9 ± 0.1	9.2 ± 2.0	1.0 ± 0.1
Phenobarbital (60 min) (20 mg/kg)	35.3 ± 3.1	4.4 ± 0.3	35.2 ± 3.2	4.5 ± 0.4
Phenobarbital (120 min) (20 mg/kg)	22.4 ± 2.5	3.1 ± 0.3	22.3 ± 2.4	3.0 ± 0.3
Valproate (30 min) (200 mg/kg)	251 ± 22	40.2 ± 3.9	251 ± 23	40.3 ± 3.9
Valproate (60 min) (200 mg/kg)	309 ± 29	49.4 ± 4.1	310 ± 31	49.6 ± 4.2
Felbamate (60 min) (100 mg/kg)	4.2 ± 0.3	3.1 ± 0.3	4.1 ± 0.3	3.0 ± 0.3
Lamotrigine (45 min) (10 mg/kg)	1.8 ± 0.2	0.67 ± 0.07	1.9 ± 0.2	0.69 ± 0.1

i.p.), lamotrigine (10 mg/kg, i.p.), phenytoin (10 mg/kg, i.p), phenobarbital (20 mg/kg, i.p), valproate (200 mg/kg, i.p.) and diazepam (5 mg/kg, i.p.).

4. Discussion

The present results clearly demonstrated that topiramate, at doses which did not significantly affect or slightly influenced the audiogenic seizures elicited in DBA/2 mice by auditory stimulation, markedly enhanced the anticonvulsant properties of diazepam, lamotrigine, phenytoin, phenobarbital and valproate in this strain of audiogenic seizure-sensitive mice.

A pharmacokinetic interaction does not seem to be responsible for the potentiation by topiramate of the antiseizure effects of the anticonvulsant drugs studied. In fact, it has been demonstrated in humans, following single as well as repeated administration of topiramate, that this compound does not affect the plasma concentrations of conventional antiepileptics. In particular, topiramate does not significantly affect carbamazepine, valproate (Heater et al., 1997), phenobarbital or primidone (Doose et al., 1995) plasma concentrations in most patients. In addition the plasma clearance of phenytoin may be reduced by up to 20% when metabolism is nearly saturated, causing an increase in phenytoin plasma concentrations with the addition of topiramate (Gisclon et al., 1994). Thus, topiramate has no pharmacokinetic interactions with other anticonvulsants (Doose et al., 1995; Heater et al., 1997). Conversely, some conventional antiepileptics, namely, carbamazepine, phenytoin and phenobarbital, affect the pharmacokinetics of topiramate (see Bourgeois, 1995; Glauser, 1997; Privitera, 1997; Rosenfeld, 1997). Based on in vitro studies with P450 isoforms, topiramate is not expected to have clinically relevant interactions with other anticonvulsants (Levy et al., 1995; Heater et al., 1997). The present study clearly shows that, in the absence of pharmacokinetic interactions, topiramate increases the anticonvulsant potency of some conventional antiepileptics as reported in various clinical studies (Rosenfeld et al., 1995, 1997a, 1997b; Ben-Menachem et al., 1996; Tassinari et al., 1996; Faught, 1997; Glauser, 1997). In addition, we clearly demonstrated that topiramate did not affect the total or free plasma levels of carbamazepine, diazepam, felbamate, lamotrigine, phenobarbital and valproate. However, the present data do not exclude the possibility that topiramate modifies the time course of anticonvulsants which penetrate the brain or their clearance from the cerebral area. The first hypothesis appears unlikely since topiramate did not significantly modify the changes in body temperature induced by the antiepileptic drugs studied. Furthermore, topiramate 2.5 mg/kg in combination with valproate, diazepam, lamotrigine, and phenobarbital caused some motor impairment but still showed a favourable therapeutic index (Table 3 and Fig. 2), whereas a combination of topiramate and carbamazepine or felbamate caused an increase of motor impairment. Topiramate shows a new and different mechanism of action from that of the conventional antiepileptic drugs used in the present study (Privitera, 1997). It could be suggested that the observed increase of antiseizure activity of the antiepileptics might be partially related to the synergic effects elicited by drug acting with different mechanism of actions (Leach, 1997).

In our opinion, the combination in therapy of some antiepileptics with topiramate would not only allow the dosage of the former to be decreased, which might be important for reducing their adverse effects, but would also allow the dosage of topiramate to be reduced as well. These adverse effects might be the result of pharmacodynamic interactions. We performed an acute study, which may have some importance for chronic therapy even if different effects exist under such different conditions.

Finally, such experimental data showing a potentiation of effects of certain conventional antiepileptic agents induced by topiramate in DBA/2 mice suggest that further investigations are warranted, particularly in those forms of human epilepsy that are resistant to the classical antiepileptic drugs.

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