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Interaction of topiramate with conventional antiepileptic drugs in mice

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Abstract

Topiramate [2,3:4,5-bis-*O*-(1-methyl-ethylidene-)-β-D-fructopyranose sulfamate], administered intraperitoneally (i.p.) up to 5 mg/kg, did not influence the threshold for electroconvulsions. In doses of 10–30 mg/kg, topiramate significantly raised the threshold. This novel antiepileptic drug, in subprotective doses, enhanced the protective activity of i.p. given valproate, carbamazepine, dihenylhydantoin and phenobarbital against maximal electroshock-induced convulsions in mice. The potentiation induced by topiramate (2.5–5 mg/kg) was most profound for carbamazepine and phenobarbital. The anticonvulsive activity of valproate and diphenylhydantoin was potentiated by topiramate only at 5 mg/kg. Topiramate (5 mg/kg) combined with valproate, phenobarbital and diphenylhydantoin did not alter their free plasma levels but its combination with carbamazepine resulted in an increased free plasma level of this antiepileptic drug. Treatment with topiramate (5 mg/kg) alone or in combination with the studied antiepileptics (providing 50% protection against maximal electroshock) resulted in no adverse effects, as measured in the chimney test (motor coordination) or passive avoidance task (long-term memory). In contrast, valproate administered alone at its ED_{50} against maximal electroshock impaired motor coordination. It is noteworthy that valproate and carbamazepine at their respective ED_{50} values of 248 and 11.2 mg/kg disturbed long-term memory. The results provide an experimental basis for rational polytherapy. © 2000 Elsevier Science B.V. All rights reserved.

Keywords: Topiramate; Antiepileptic drug; Electroshock, maximal; Drug interaction; Seizure

1. Introduction

Satisfactory seizure management is not attainable in as many as 30% of patients treated with conventional antiepileptic drugs such as diphenylhydantoin, carbamazepine, valproate and phenobarbital (Loiseau, 1986). Moreover, their metabolic pathways and interaction profiles, in particular enzyme induction, enzyme inhibition and displacement from protein binding, may result in a wide range of toxic and idiosyncratic reactions (Cloyd, 1991; Perruca, 1996). There is, therefore, a constant demand for the development of new drugs, which possess improved efficacy and tolerability as well as reduced toxicity and drug interactions.

Many of the novel antiepileptic drugs introduced in recent years have been demonstrated to potentiate the effects of conventional antiepileptic drugs and are mainly used as adjuvants. These include gabapentin, felbamate, topiramate, lamotrigine and vigabatrin (Fisher and Blum, 1995; Ben-Menachem, 1996; French, 1996; Cramer et al., 1999). Moreover, numerous potential antiepileptics are being studied in experimental animal models of epilepsy. For example, 7-acetyl-3-(4-aminophenyl)-8,9-dihydro-8-methyl-7 *H*-1,3-dioxazolo [4,5-h] [2,3]-benzodiazepine (LY 300164), a novel antagonist of the AMPA/kainate receptor, was demonstrated to enhance the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced convulsions in mice (Czuczwar et al., 1998) and that of clonazepam against amygdala kindling in rats (Borowicz et al., 1999). The same was evident for another AMPA/kainate receptor antagonist, 1-(4-aminophenyl)-4-methyl-7,8-methylenedioxy-5-2,3-benzodiazepine (GYKI 52466; Borowicz et al., 1995), as well as

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some competitive NMDA-receptor antagonists (Borowicz et al., 1996).

Several of the conventional anticonvulsants act as inducers of the hepatic microsomal cytochrome *P*450 enzymes, thereby increasing the metabolism of other drugs metabolized by the liver. These include diphenylhydantoin, phenobarbital, primidone and carbamazepine. In contrast, valproic acid inhibits hepatic metabolism and thus may increase the levels of other antiepileptic drugs. The available studies involving novel antiepileptic drugs have shown that these drugs, generally, induce fewer drug interactions and, therefore, co-medication with conventional anticonvulsants can result in an improved tolerability (Patsalos and Duncan, 1993).

Topiramate (2,3:4,5-bis-*O*-(1-methyl-ethylidene-)-β-D-fructopyranose sulfamate) is a sulphate-substituted monosaccharide derived from D-fructose and is structurally unrelated to other antiepileptic drugs. It has multiple modes of action involving different pharmacological targets (Shank et al., 1991, 1994; Shank, 1995; Zona et al., 1997; Kuzniecky et al., 1998). Topiramate is well absorbed from the gastrointestinal tract, is negligibly bound to plasma proteins and has a relatively long half-life of 18–24 h (Gram, 1996; Perruca, 1996).

The objective of the present study was to examine the influence of topiramate on the anticonvulsant efficacy of conventional antiepileptics against maximal electroshock-induced seizures in mice.

2. Materials and methods

2.1. Animals

The experiments were conducted on female Swiss mice, weighing 20–25 g. The animals were housed in colony cages, under standard laboratory conditions, with free access to food and tap water. All mice were maintained at an ambient temperature of 20 ± 1°C and on a natural light–dark cycle. After the adaptation period of 10 days, experimental groups consisting of 8–10 animals were chosen randomly. Each mouse was used only once.

2.2. Drugs

The following drugs were used: the novel anticonvulsant topiramate [2,3:4,5-bis-*O*-(1-methyl-ethylidene-)-β-D-fructopyranose sulfamate] and four conventional antiepileptic drugs: valproate magnesium (Dipromal, Polfa Rzeszów, Poland), carbamazepine (Amizepin), diphenylhydantoin (Phenytoinum) and phenobarbital sodium (Luminalum Natrium, all three from Polfa Warsaw, Poland). Valproate and phenobarbital were dissolved in distilled water, while topiramate, carbamazepine and diphenylhydantoin were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA). All drugs were administered intraperitoneally (i.p.) in a volume of 0.1 ml/kg body weight, valproate magnesium and carbamazepine — 30 min, phenobarbital — 60 min, diphenylhydantoin — 120 min prior to the test. According to Shank et al. (1994), topiramate's anticonvulsant activity was nearly constant at 60–240 min after administration. In the present study, topiramate was given 120 min before convulsive and behavioral tests. The doses of topiramate, phenobarbital and valproate refer to their free forms.

2.3. Electroconvulsions

Electroconvulsions were induced by an alternating current (50 Hz) delivered via ear-clip electrodes by a Hugo Sachs (Type 221, Freiburg, Germany) generator, the stimulus duration being 0.2 s. Tonic hindlimb extension was taken as the criterion for the occurrence of seizure activity.

In order to estimate the convulsive threshold, at least four groups of mice (eight animals per group) were challenged with electroshocks of various intensities. Subsequently, an intensity–response curve was constructed, according to Litchfield and Wilcoxon (1949), from which a CS_{50} (current strength 50%) value was calculated. Each CS_{50} value represents the current strength (in mA) necessary to induce tonic hindlimb extension in 50% of the animals tested.

The anticonvulsant activity of the investigated drugs was determined by using the maximal electroshock test and evaluating the respective ED_{50} values (in mg/kg), i.e., the calculated dose required to block the hindlimb tonic-extensor component of the maximal electroshock seizure in 50% of the animals tested. Again, at least four groups of mice, consisting of 8–10 animals, were used. The animals, pretreated with different doses of the tested drugs, were challenged with maximal electroshock (fixed current intensity of 25 mA and the duration of 0.2 s). In order to estimate ED_{50} values of drugs, a dose–effect curve was constructed, based on the percentage of the animals protected.

2.4. Chimney test

The effects of the antiepileptic drugs alone or combined with topiramate on motor performance were evaluated with the chimney test of Boissier et al. (1960). The animals had to climb backwards up a plastic tube (3-cm inner diameter, 25-cm length). Motor impairment was indicated by the inability of mice to climb backwards up the tube within 60 s. The mice were pretrained 24 h before treatment and those unable to perform the test were rejected from experimental groups (each group consisted of 12 animals). All substances were administered i.p. The results are shown as the percentage of animals that failed to perform the test.

2.5. Passive avoidance acquisition and retention testing

According to Venault et al. (1986), the step-through passive avoidance task may be regarded as a measure of long-term memory acquisition. The animals were placed in an illuminated box ($10 \times 13 \times 15$ cm) connected to a larger ($25 \times 20 \times 15$ cm) dark compartment equipped with an electric grid floor. In this test, entry into the dark compartment was punished by an electric footshock (0.6 mA for 2 s; facilitation of acquisition). The mice that did not enter the dark compartment within 60 s were excluded from the experiment. On the following day (24 h later), the same animals were again placed in the illuminated box and those avoiding the dark compartment for longer than 180 s were regarded as remembering the task. Retention was evaluated as the mean time (in seconds) required to enter the dark compartment.

2.6. Estimation of the free plasma levels of antiepileptic drugs

Plasma levels of antiepileptic drugs were measured according to Czuczwar et al. (1989). The animals were given either one of the studied antiepileptic drugs and saline (control group) or combinations of topiramate (5 mg/kg) with one of these drugs. Mice were decapitated at times scheduled for the convulsive test, and blood samples of approximately 1 ml were collected into Eppendorf tubes. Samples of blood were centrifuged at 10000 rpm (Abbott centrifuge, Irving, TX, USA) and the obtained plasma samples were pipetted into a micropartition system, MPS-1 (Amicon, Danvers, MA, USA). Then the samples were centrifuged again and the free plasma levels of the investigated drugs were determined by immunofluorescence, using an Abbott TDx analyzer (Abbott). Control plasma samples of each antiepileptic drug were used to verify the calibration. Plasma levels are expressed in microgram per milliliter as means ± S.D. of eight determinations.

2.7. Statistics

Both CS_{50}, ED_{50} values and their statistical evaluation were calculated by computer probit analysis, according to Litchfield and Wilcoxon (1949). The data obtained in the chimney test were compared statistically by using Fisher's exact probability test. The results from the passive avoidance task were statistically verified with the Mann–Whitney test. An unpaired Student's *t*-test was used for the statistical evaluation of the plasma levels of antiepileptic drugs.

3. Results

3.1. Effects of topiramate upon the electroconvulsive threshold in mice

Topiramate in doses of 10 and 20 mg/kg, given 120 min prior to the test, raised the electroconvulsive threshold from 6.9 to 8.1 and 10.4 mA, respectively, whereas it was ineffective at 5 mg/kg (Fig. 1). The ED_{50} of topiramate against maximal electroshock was 62.1 [(55.3–72.1) mg/kg; result not shown in tables].

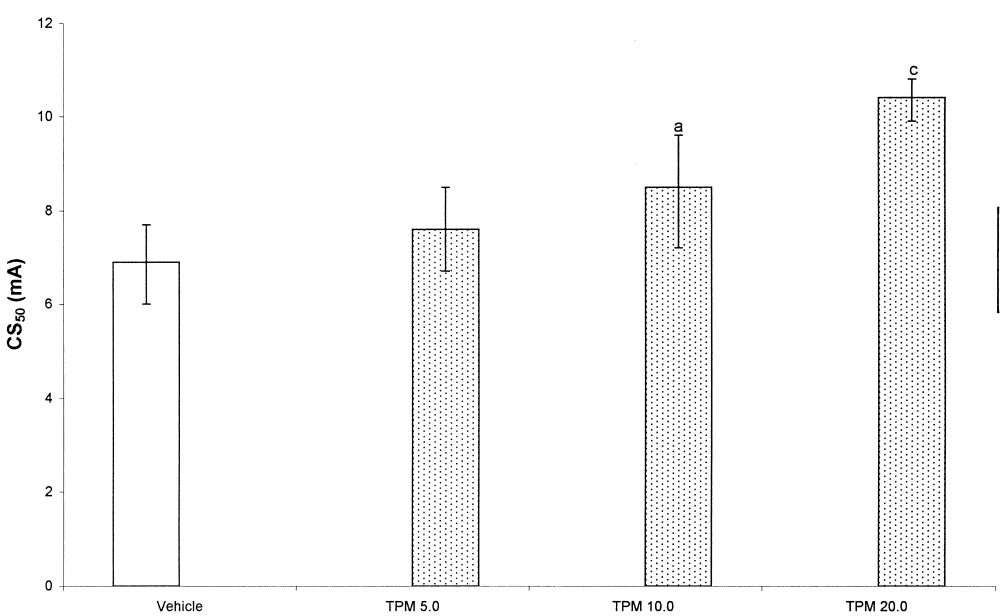

Fig. 1. Effects of topiramate (TPM) upon the electroconvulsive threshold in mice. TPM was given i.p. 120 min before testing. The control group received distilled water. The experimental groups consisted of at least eight animals. The data are CS_{50} values (with 95% confidence limits), calculated and statistically compared according to Litchfield and Wilcoxon (1949). $^{a}P < 0.05$, $^{c}P < 0.001$.

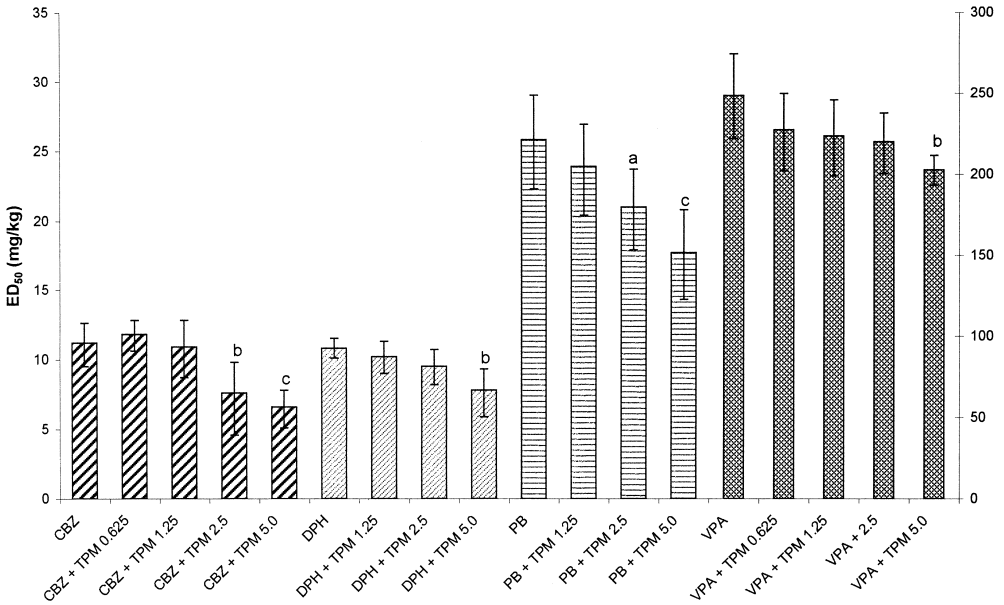

Fig. 2. Influence of TPM upon the protective activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice. TPM was given i.p. in doses ranging from 0.625 to 5.0 mg/kg, 120 min before testing. Valproate (VPA) or carbamazepine (CBZ) was given i.p. 30 min, phenobarbital (PB) 60 min and diphenylhydantoin (DPH) 120 min before testing. The control group received distilled water. The experimental groups consisted of at least eight animals. The data are the ED_{50} values of conventional antiepileptic drugs (with 95% confidence limits), calculated and statistically compared according to Litchfield and Wilcoxon (1949); the scale on the left is for CBZ, DPH and PB, and that on the right is for VPA. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$.

3.2. Influence of topiramate on the protective activity of antiepileptic drugs against maximal electroshock-induced seizures in mice

Topiramate (5 mg/kg), when combined with valproate, significantly reduced the ED_{50} of valproate from 248 to 203 mg/kg (Fig. 2). Topiramate (2.5 and 5.0 mg/kg) also enhanced the protective action of carbamazepine, which was reflected by a decrease in the ED_{50} value of carbamazepine (from 11.2 to 7.6 and 6.6 mg/kg, respectively)

Table 1
Motor impairment after administration of antiepileptic drugs, topiramate, or a combination of topiramate with an antiepileptic in mice

Treatment (mg/kg)	Mice impaired (%)
Vehicle	0
Phenobarbital (25.8)	25
Phenobarbital (17.7)	8.3
Phenobarbital (17.7) + topiramate (5.0)	8.3
Carbamazepine (11.2)	8.3
Carbamazepine (6.6)	0
Carbamazepine (6.6) + topiramate (5.0)	8.3
Valproate (248)	33.3[a]
Valproate (203)	16.6
Valproate (203) + topiramate (5.0)	25
Diphenylhydantoin (10.8)	16.6
Diphenylhydantoin (7.8)	8.3
Diphenylhydantoin (7.8) + topiramate (5.0)	8.3
Topiramate (5.0)	8.3

The results are expressed as a percentage of animals that failed to perform the chimney test during a 60-s observation period. Antiepileptics alone or combined with topiramate provided 50% protection against maximal electroshock. Drugs were given i.p.: topiramate 120 min, valproate and carbamazepine 30 min, phenobarbital 60 min, and diphenylhydantoin 120 min before testing . Experimental groups consisted of 12 mice.

[a]$P < 0.05$ (Fisher's exact probability test).

Table 2
Effects of antiepileptic drugs, topiramate, or a combination of an antiepileptic with topiramate on the retention of a passive avoidance task in mice

Treatment (mg/kg)	Medians (25, 75 percentiles)	
Vehicle	180	(180, 180)
Phenobarbital (25.8)	180	(87.7, 180)
Phenobarbital (17.7)	180	(90.7, 180)
Phenobarbital (17.7) + topiramate (5.0)	180	(157.5, 180)
Carbamazepine (11.2)	138.5	(126, 180)[a]
Carbamazepine (6.6)	180	(180, 180)
Carbamazepine (6.6) + topiramate (5.0)	180	(180, 180)
Valproate (248)	138.5	(82,166.7)[b]
Valproate (203)	164.5	(83.5, 180)
Valproate (203) + topiramate (5.0)	156	(49.3, 180)
Diphenylhydantoin (10.8)	180	(180, 180)
Diphenylhydantoin (7.8)	180	(180, 180)
Diphenylhydantoin (7.8) + topiramate (5.0)	180	(180, 180)
Topiramate (5.0)	180	(180, 180)

Presented values are the medians with 25 and 75 percentiles of 10 determinations. The retention was quantified as the time (in seconds) the animals avoided the dark compartment. For treatment times and number of animals per group refer to Table 1.

[a]$P < 0.05$ (two-tailed Mann–Whitney *U*-test).

[b]$P < 0.01$ (two-tailed Mann–Whitney *U*-test).

Table 3
Influence of topiramate on the free plasma levels of antiepileptic drugs

Treatment (mg/kg)	Plasma levels
Phenobarbital (17.7)	12.2 ± 0.39
Phenobarbital (17.7) + topiramate (5.0)	12.1 ± 0.69
Carbamazepine (6.6)	0.38 ± 0.086
Carbamazepine (6.6) + topiramate (5.0)	0.56 ± 0.082[a]
Valproate (203)	140 ± 17.32
Valproate (203) + topiramate (5.0)	133 ± 13.77
Diphenylhydantoin (7.8)	0.65 ± 0.08
Diphenylhydantoin (7.8) + topiramate (5.0)	0.73 ± 0.049

Presented values are the means in microgram per milliliter of plasma ± S.D. of eight determinations. Blood samples were taken at times scheduled for the convulsive test.

[a] $P < 0.01$ (unpaired Student's *t*-test).

(Fig. 2). Topiramate (5.0 mg/kg) co-administered with diphenylhydantoin reduced the ED_{50} of diphenylhydantoin from 10.8 to 7.8 mg/kg (Fig. 2). Combined treatment with topiramate (2.5 and 5 mg/kg) and phenobarbital resulted in a reduction of the ED_{50} of phenobarbital from 25 mg/kg to 21 and 17.7 mg/kg, respectively (Fig. 2).

3.3. Chimney test and passive avoidance task

Topiramate (5 mg/kg) given alone or combined with conventional antiepileptics, in doses providing 50% protection against maximal electroshock, did not produce any motor impairment. Similarly, carbamazepine, diphenylhydantoin and phenobarbital, (applied at doses equal to their ED_{50} values against maximal electroshock-induced convulsions) did not influence the performance of mice in the chimney test. Motor impairment was noted only in the case of valproate given at its ED_{50} of 248 mg/kg (Table 1). Phenobarbital and diphenylhydantoin, when given at doses equal to their ED_{50} against maximal electroshock, did not impair long-term memory in mice (Table 2). Memory impairment occurred only in mice that were given valproate or carbamazepine at their ED_{50} values of 248 and 11.2 mg/kg, respectively. Topiramate (5 mg/kg) and the combined treatment of topiramate (5 mg/kg) with the remaining antiepileptics, in doses providing 50% protection against maximal electroshock, did not affect the performance of mice in the memory task (Table 2).

3.4. Effects of topiramate upon the free plasma levels of antiepileptic drugs

Topiramate increased the free plasma levels of carbamazepine but did not significantly affect the levels of valproate, diphenylhydantoin or phenobarbital (Table 3).

4. Discussion

The results from these experiments indicate that topiramate increased the electroconvulsive threshold at the dose of 10 mg/kg and was ineffective at the dose of 5 mg/kg. Topiramate in subthreshold doses considerably potentiated the protective activity of all tested antiepileptic drugs (magnesium valproate, diphenylhydantoin, carbamazepine and phenobarbital) against maximal electroshock in mice. The respective ED_{50} values for the above mentioned drugs were reduced by 18%, 28%, 41%, and 31%.

Studies carried out so far have established that topiramate is highly effective in the maximal electroshock test and relatively weak against pentylenetetrazol-induced seizures (Shank et al., 1994). Based on the available in vitro studies, a number of mechanisms of action for the anticonvulsant activity of topiramate have been suggested. It was shown to exert an attenuating effect on voltage-dependent sodium channels (Coulter et al., 1993; Zona et al., 1997). Topiramate was observed to enhance γ-aminobutyric acid (GABA)-stimulated Cl^- fluxes into cultured cerebellar granule cells (Brown et al., 1993; Kuzniecky et al., 1998). It was suggested that topiramate enhanced GABA activity through a new binding site at the $GABA_A$/benzodiazepine receptor complex. Topiramate also inhibited excitatory pathways through an antagonistic action at the kainate/AMPA subtype of the glutamate receptor (Shank, 1995). Another mode of action displayed by topiramate is a weak inhibition of carbonic anhydrase (Shank et al., 1994). There are data indicating that the bicarbonate ion can induce depolarization at the moment $GABA_A$ channels have been opened by GABA (Staley et al., 1995). This effect can be decreased by a carbonic anhydrase inhibitor, which may explain the anticonvulsant activity of topiramate. The available data indicate that blockage of voltage-dependent Na^+ channels as the mechanism underlying the anticonvulsant activity of topiramate is also the mechanism of some of the conventional antiepileptic drugs, such as diphenylhydantoin, carbamazepine and valproate (Macdonald, 1989; Macdonald and Meldrum, 1995; Meldrum, 1996; Ragsdale and Avoli, 1998). The potentiation of GABA-ergic inhibition exhibited by topiramate is, in turn, found with valproate, barbiturates and benzodiazepines (Staley et al., 1995). Furthermore, there is increasing evidence that several of the basic drugs may also affect glutamatergic excitation (Coulter et al., 1993; Shank, 1995). It may be concluded, therefore, that the anticonvulsant activity of topiramate is mostly due to a combination of the mechanisms responsible for the anticonvulsant effect of the older antiepileptic drugs (Rogawski and Porter, 1990; Löscher, 1998; Ragsdale and Avoli, 1998).

Shank et al., (1994) used the isobolographic method to examine the possible interactions between topiramate and three traditional antiepileptic drugs (carbamazepine, diphenylhydantoin and phenobarbital) in the mouse maximal electroshock test. Mice were administered graded oral doses of topiramate in combination with reference conventional antiepileptic drugs in fixed ratios (0.75/0.25, 0.50/0.50, or 0.25/0.75) of their individual ED_{50} values.

An analysis of the isobolograms created for several dose combinations of topiramate and diphenylhydantoin showed that the anticonvulsant activity of these drugs was additive. When topiramate was combined with carbamazepine or phenobarbital, the anticonvulsant activity was slightly synergistic at certain ratios.

The results obtained from our experiments are consistent with the evidence provided by Shank et al. (1994). However, in our study, apart from the three antiepileptic drugs tested by these authors (carbamazepine, diphenylhydantoin and phenobarbital), we also added another conventional ''antiepileptic drug-magnesium valproate''. In addition, we examined the adverse effects induced by the tested drug combinations and the possible pharmacokinetic interactions by estimating the free plasma levels of the antiepileptic drugs studied. Topiramate did not affect the free plasma levels of valproate, diphenylhydantoin and phenobarbital (thus, a pharmacokinetic interaction with these drugs does not appear to be probable), but significantly increased the levels of carbamazepine. In the available clinical studies, however, topiramate had no appreciable effects on the pharmacokinetics of carbamazepine or of other traditional antiepileptic drugs (Bourgeois, 1996). This may be due to the relatively long period of therapy and different drug concentrations used in the clinical trials, which may have resulted in some possible changes in the pharmacokinetic interactions (e.g. the induction of the hepatic cytochrome *P*450 enzymes following prolonged administration of carbamazepine or diphenylhydantoin).

Combined treatment with topiramate and the antiepileptic drugs resulted in no adverse effects, as measured in the chimney test (motor coordination) and passive avoidance task (long-term memory). Motor and long-term memory impairment was noted only in the case of valproate administered alone at its ED_{50}, which is in agreement with the study of Borowicz et al. (1995). Consequently, the combined treatment with topiramate and valproate was superior to valproate alone, as regards adverse effects. These results provide a rational experimental basis for polytherapy with topiramate and conventional antiepileptic drugs. The clinical trials indicate, however, that administration of topiramate may lead to a number of side effects such as paresthesia, nephrolithiasis, mild weight loss, fatigue, somnolence and impaired concentration (Shorvon, 1996). These adverse effects observed in clinical trials appear to be mainly dose related (the methodology entailed quick dose adjustment and titration of many patients to their maximal tolerated dose, i.e., to a daily dosage, which elicited a dose-limiting adverse effect) and are thought to be caused predominantly by the inhibition of carbonic anhydrase by topiramate.

In some patients, seizure control will not be possible with presently available traditional antiepileptic drugs (so-called refractory or intractable epilepsy). In addition, the therapeutic effectiveness of the older anticonvulsants is usually significantly limited by their profound adverse effects and narrow therapeutic ratio (Loiseau, 1986). The aim of concomitant administration of topiramate with conventional antiepileptic drugs is to provide benefits in terms of efficacy, tolerability and adverse effects. Clinical experience to date indicates that despite some mild side effects and a relatively narrow therapeutic ratio, this novel anticonvulsant is generally well tolerated as add-on therapy and is especially efficacious in the management of refractory partial-onset seizures in both adults and children (Elterman et al., 1999; Moreland et al., 1999; Uldall and Buchholt, 1999). Topiramate adjunctive therapy was also demonstrated to effectively reduce the number of drop attacks and major motor seizures in Lennox–Gastaut syndrome — a multiple-type seizure disorder in which conventional antiepileptic drugs alone are particularly ineffective (Glauser, 1999; Sachdeo et al., 1999). Despite these very encouraging results, however, a thorough assessment of the efficacy and adverse effects of topiramate is not yet fully possible because the potential for infrequent adverse reactions or reactions occurring only after long-term use is still largely unknown and remains to be further tested. It is also noteworthy that the acute administration of drugs against maximal electroshock-induced convulsions, which are a model of generalized tonic–clonic seizures in humans (Löscher and Schmidt, 1988), in non-epileptic mice may have limitations for the prediction of therapeutic efficacy against intractable seizures in epileptic patients.

Finally, in the same seizure model, another novel antiepileptic drug, felbamate, failed to enhance the anticonvulsant activity of conventional antiepileptic drugs. It is remarkable that felbamate, when given in doses that increased the electroconvulsive threshold, still did not enhance the protection offered by carbamazepine, phenobarbital and valproate (Borowicz et al., 2000). This indicates that some combinations of novel and conventional antiepileptics may not be effective. In spite of the limitations of animal studies, the present data provide an experimental basis for rational polytherapy in epileptic patients.

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