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Original article

Sotalol enhances the anticonvulsant action of valproate and diphenylhydantoin in the mouse maximal electroshock model

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ABSTRACT

Background: Sotalol as a drug blocking β-receptors and potassium KCNH2 channels may interact with different substances that affect seizures. Herein, we present interactions between sotalol and four conventional antiepileptic drugs: carbamazepine, valproate, phenytoin and phenobarbital.
Methods: Effects of sotalol and antiepileptics alone on seizures were determined in the electroconvulsive threshold test, while interactions between sotalol and antiepileptic drugs were estimated in the maximal electroshock test in mice. Motor coordination and long-term memory were evaluated, respectively, in the chimney test and passive-avoidance task. Brain concentrations of antiepileptics were determined by fluorescence polarization immunoassay.
Results: Sotalol at doses up to 100 mg/kg did not affect the electroconvulsive threshold. Applied at doses 60–100 mg/kg, sotalol potentiated the antielectroshock action of valproate, while at doses 80–100 mg/kg that of phenytoin. Sotalol (up to 100 mg/kg) did not affect the action of carbamazepine or phenobarbital in the maximal electroshock. Sotalol alone and in combinations with antiepileptics impaired neither motor performance nor long-term memory in mice. Finally, sotalol did not change brain concentration of valproate and phenytoin, so pharmacokinetic interactions between the drugs are not probable.
Conclusions: As far as obtained data may be extrapolated into clinical conditions, sotalol may be considered as an arrhythmic drug that does not reduce the action of classical antiepileptic drugs and thereby can be used in epileptic patients with cardiac arrhythmias.

Introduction

Chronic spontaneous recurrent seizures in both animals and humans cause sympathovagal imbalance and cardiorespiratory autonomic dysfunctions, including tachycardia with profound proarrhythmogenic effects (prolongation of QT interval) or bradycardia with accompanying apnea [1,2]. Status epilepticus (SE) can be even accompanied by reduced ejection fraction, decreased ventricular contractility and increased blood pressure [3].

Seizure-induced autonomic cardiorespiratory changes play a crucial role in pathogenesis of sudden unexpected death in epilepsy (SUDEP) [4,5]. Although the exact mechanisms of autonomic cardiorespiratory dysfunction in people with epilepsy is unclear, we know that seizures cause microglial activation in both experimental and clinical conditions [6,7]. Short term microglial activation (e.g. during acute seizures) is considered beneficial [8,9], in contrast chronic microglial activation may be injurious [10]. Furthermore, destructive microglial activity during chronic seizures may contribute to neurodegeneration and brain cell death in the course of SUDEP and temporal lobe epilepsy [11].

The established relationship between seizures and severe arrhythmias makes co-treatment with antiepileptic and β-blockers very probable. Furthermore, a representative of β-blockers, atenolol, prevented all status epilepticus-induced cardiac dysfunctions in rats, including reduced cardiac output, decreased ventricular contractility and relaxation, increased blood pressure, and prolonged QT interval. This opens the way for the use of β-blockers in epileptic patients during seizures. One of the most frequently used antiarrhythmics is sotalol, a very interesting medicine from many points of view.

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Sotalol, a racemic mixture of D- and L-isomers in a ratio 1:1, is a non-selective competitive β-adrenergic receptor blocker, without intrinsic sympathomimetic or membrane stabilizing activity, that also exhibits class III antiarrhythmic properties. Blockade of β-receptors is almost entirely caused by L-isomer, while lengthening of cardiac repolarization by both isomers [12]. Like bretylium or amiodarone, sotalol prolongs the ventricular action potential duration without significantly depressing cardiac conduction velocity [13]. Due to the dual action, sotalol is often used preferentially to other beta blockers as treatment for atrial and ventricular tachyarrhythmias. Like antiarrhythmic drugs of class Ia, Ic and III, sotalol can prolong the QT interval, thereby increasing the risk of life-threatening torsade de pointes.

Sotalol non-selectively binds to both β1- and β2-adrenergic receptors preventing production of cAMP and decreasing calcium influx. Sotalol also blocks potassium voltage-gated channel subfamily H member 2 potassium channels (KCNH2), inhibiting influx of K+ ions during repolarization, and causes a delay in relaxation of the ventricles. Moreover, sotalol passes through blood-brain barrier. Blockade of β-adrenoceptors may contribute to antiseizure properties, while blockade of KCNH2 potassium channels can lead to just opposite effect. Mutation of KCNH2 channels may be a potential link between epilepsy and some arrhythmias (long QT-2 syndrome) [14]. Therefore, it is impossible to predict an effect of sotalol on seizure phenomena. Although significant β-blockade occurs at oral doses as low as 25 mg, and significant class III effects are seen only at daily doses of 160 mg and above, therefore anticonvulsant action of sotalol administered at therapeutic doses is more probable [12]. Interestingly, sotalol does not bind to plasma proteins and is not metabolized. This reduces possibility of pharmacokinetic interactions. The usual antiarrhythmic dose of sotalol is 160–320 mg daily [12].

It should be remembered that a number of β-blockers exhibited anticonvulsant action in a variety of experimental models of epilepsy. The most examined medicine was propranolol, probably because of its local anesthetic effects and good penetration through blood brain barrier. This β-blocker showed protective effects in maximal electroshock- [15–17], pentetrazole- [17], lidocaine- [18], focal penicillin- [19], strychnine- [20], picrotoxin- [21], isoniazid- [22], and sound-induced seizures in mice [23,24]. Similar properties proved also metoprolol and acebutolol in the test of maximal electroshock in mice [16] and sound-induced convulsions in DBA2 mice [24]. In contrast, hydrophilic atenolol, not penetrating to the brain, remained inactive in both models. Timolol occurred effective in *icv* pentetrazole-induced seizures [25], but ineffective in maximal electroshock in mice [15].

On the other hand, the only data on anticonvulsant action of class III antiarrhythmic concerns amiodarone that inhibited pentetrazole- and caffeine-induced convulsions in mice [26].

Since there are no available data on interactions between sotalol and antiepileptic drugs, we decided in this study to evaluate the effect of sotalol on the anticonvulsant action of conventional antiepileptics in the widely used mouse model of tonic-clonic convulsions.

Materials and methods

Animals

The experiments were carried out on 20–25 g female Swiss mice, which were kept in colony cages with free access to tap water and food. Standard laboratory conditions with a natural dark-light cycle were maintained during experiments. All procedures were conducted between 9 a.m. and 2 p.m. and experimental groups consisted of 8–10 animals. All experiments conducted in this study were approved by the Local Ethical Committee for the Animal Experiments.

Drugs

Sotalol (SOT), an antiarrhythmic drugs, and four antiepileptic drugs were used in the study: phenobarbital (PB), valproate (VPA), carbamazepine (CBZ) and phenytoin (PHT). Phenobarbital was purchased from UNIA Pharmaceutical Department, Warsaw, Poland, while all remaining medications from Sigma, St. Louis, MO, USA. Valproate was dissolved in sterile saline, whereas phenobarbital, phenytoin, carbamazepine and sotalol were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in saline. All drugs were administered in a volume of 10 ml/kg intraperitoneally (*ip*) phenytoin – 120 min, phenobarbital and sotalol – 60 min, valproate, and carbamazepine – 30 min before the tests.

Maximal electroshock seizure test in mice

Maximal electroshock test (MES) is a commonly used standard preclinical model of tonic-clonic seizures [27]. Detailed experimental procedures were previously described by Borowicz et al. [28]. The anticonvulsant activity of antiepileptic drugs and their combinations with sotalol was determined as their ability to protect 50% of the mice against tonic hindlimb extension induced by electroconvulsions. Dose-response curves were constructed based on the percentage of mice protected [29]. The respective median effective doses (ED_{50} values in mg/kg) were evaluated according to Litchfield and Wilcoxon [29].

Chimney test

To determine the effects of sotalol and its combinations with classical antiepileptic drugs on motor coordination, we used the chimney test of Boissier et al. [30]. The test was thoroughly described in previous articles [28]. Antiepileptics were administered alone, at doses equal to their ED_{50} values, or in combinations with sotalol (60 and 80 mg/kg).

Step-through passive avoidance task

The step-through passive avoidance test is based on natural aversion of rodents to bright places and was used as a measure of long-term memory. Mice were tested according to description provided previously [28]. Control animals did not enter the dark compartment within 180 s. Like in the chimney test, antiepileptics were applied alone at their ED_{50}s or in combinations with sotalol (60 and 80 mg/kg).

Measurement of brain concentrations of antiepileptic drugs

Brain concentrations of classical antiepileptic drugs (phenobarbital, carbamazepine, valproate and phenytoin) were determined by fluorescence polarization immunoassay. Control animals were administered with one of the antiepileptic drugs and saline. The examined groups were administered with the respective antiepileptic drug and sotalol at the dose of 80 mg/kg. According to the procedure, the mice were killed by decapitation at times scheduled for the MES test. Then the brains were removed, weighed and homogenized (Ultra Turax T8 homogenizer, IKA, Staufen, Germany) with Abbott buffer (2:1 vol/weight). Homogenates were centrifuged at 10,000*g* for 15 min and supernatants (75 μl) were analyzed for AED content using an Abbott TDx analyzer (Irvine, TX, USA). Drug concentrations were automatically calculated by the

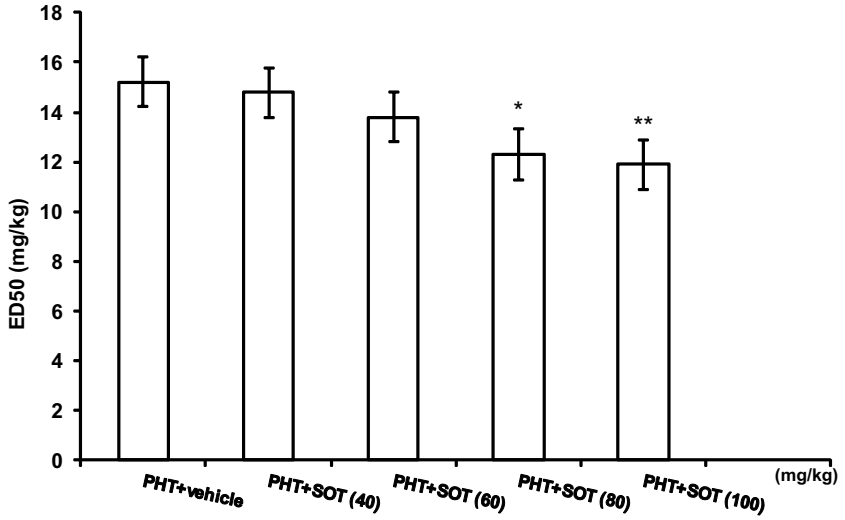

Fig. 1. Effect of sotalol (SOT) on the on the anticonvulsant action of valproate (VPA) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which VPA alone and in combinations with SOT protected 50% of animals against seizures. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* control (animals treated with VPA plus saline).

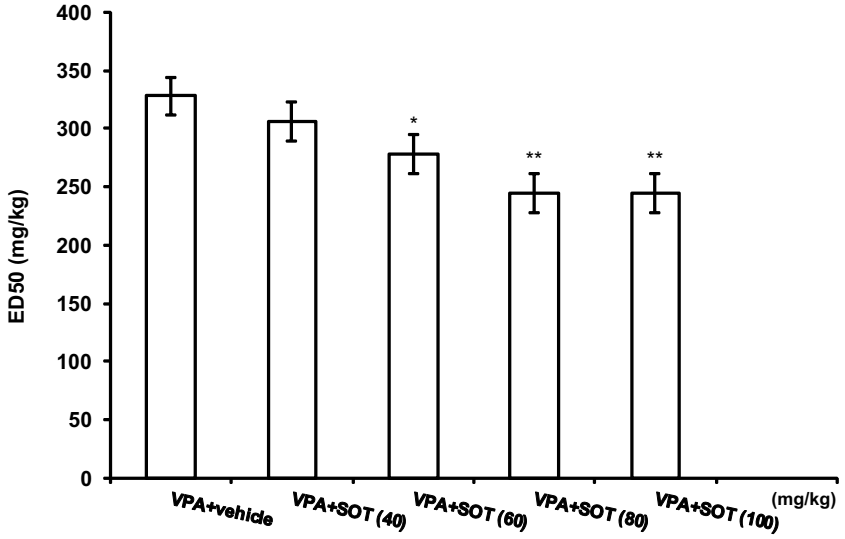

Fig. 2. Effect of sotalol (SOT) on the on the anticonvulsant action of phenytoin (PHT) against maximal electroshock-induced seizures in mice. Data are presented as median effective doses (ED_{50} dose with SEM values), at which PHT alone and in combinations with SOT protected 50% of animals against seizures. $^{*}p < 0.05$, $^{**}p < 0.01$ *vs.* control (animals treated with PHT plus saline).

analyzer and expressed in micrograms per milliliter. Data were subsequently computed as means ± SD of at least eight determinations.

Statistics

ED_{50} values with their respective 95% confidence limits were calculated in computer log-probit analysis according to Litchfield and Wilcoxon [29]. Then, standard errors (SEMs) of the mean values were assessed on the basis of confidence limits and ED_{50} values were compared with the Student's *t* test.

Fisher's exact probability test was used to analyze qualitative variables from the chimney test and passive-avoidance task.

Brain concentrations of antiepileptic drugs were evaluated by the use of the unpaired Student's *t* test. The significance level was set at $p \leq 0.05$.

Results

Electroconvulsive threshold

Sotalol administered at the wide dose range of 20–100 mg/kg did not significantly influenced the electroconvulsive threshold. The control value was 5.8 ± 0.50 mA (data not shown in Tables).

Maximal electroshock test

Since sotalol was ineffective in the electroconvulsive threshold test, it was combined with classical antiepileptic drugs at the whole dose range of 20–100 mg/kg. The antiarrhythmic drug applied at 60, 80 and 100 mg/kg potentiated the antielectroshock of valproate, reducing its ED_{50} value from 327.8 ± 9.78 to

278.1 ± 7.64, 244.6 ± 9.40, and 244.6 ± 9.40, respectively (Fig. 1). Moreover, sotalol applied at 80 and 100 mg/kg decreased ED_{50} values of phenytoin from 15.2 ± 0.96 to 12.3 ± 0.85 and 11.9 ± 0.66, respectively (Fig. 2). The action of carbamazepine (ED_{50} = 14.8 ± 1.06) and phenobarbital (ED_{50} = 24.8 ± 2.18) was not affected by sotalol (Table 1).

Chimney test and passive-avoidance task

Classical antiepileptic drugs administered alone or in combinations with sotalol at the dose range of 60–100 mg/kg did not affect either motor performance or long-term memory of tested mice (Table 2).

Plasma and brain concentrations of antiepileptic drugs

Sotalol (80 mg/kg) did not significantly affect brain concentrations of antiepileptic drugs used in this study (Table 3).

Discussion

Results presented in this study show that single administration of sotalol potentiated the antielectroshock effect of valproate and phenytoin, remaining without significant effect on the action of carbamazepine and phenobarbital. All revealed interactions seem to be pharmacodynamic, since sotalol did not change brain concentrations of antiepileptic drugs used in this study.

Sotalol is above all a β-blocker exhibiting properties of class III antiarrhythmic drug, which seems to be beneficial from clinical point of view. According to some recommendations, β-blockers should be applied in all patients treated with antiarrhythmic drugs [31], so drugs combining the two properties may be of special value. The second drug meeting these criteria is propafenone that belongs to class 1C antiarrhythmic drugs and exhibits a moderate β-adrenolytic activity.

Since β-blockers show antiseizure efficacy, their use or use of antiarrhythmics blocking β-receptors seems to be an advantageous choice in epileptic patients with arrhythmias and/or hypertension.

According to available medical literature, β-blockers not only present antiseizure activity in various animal models, but also potentiate the anticonvulsant action of some antiepileptic drugs in these models. Propranolol and metoprolol enhanced the action of valproate and diazepam, and acebutolol the action of valproate against the maximal electroshock in mice [16]. Carvedilol potentiated the effect of gabapentin against increasing current electroshock- and pentetrazole-induced seizures in mice [32]. Finally, atenolol combined with diazepam gave total protection against aminophylline-induced convulsions and death in mice [33]. Furthermore, β-blockers enhance also the anticonvulsant effect of other drugs in animal models of epilepsy. For instance, pindolol increased the action of fluoxetine in focal hippocampal seizures induced by electrical stimulation in rats [34], while propranolol enhanced the protective action of nifedipine against maximal electroshock in mice [35].

Knowledge about the action of β-blockers in epileptic patients is, however, very scarce. The only available data concern the action of propranolol and were published more than 20 years ago. It was reported that propranolol (20–40 mg/kg) significantly reduced seizures in patients with drug-resistant chronically unstable generalized epilepsy [36]. Additionally, propranolol (80–160 mg/kg) decreased by at least 50% frequency of startle induced epileptic seizures in 3 of 11 patients [37].

In our previous work we showed that propafenone increases the electroconvulsive threshold and potentiates the action of valproate, carbamazepine, phenytoin and phenobarbital against maximal electroshock in mice [38]. So, despite similar mechanisms of action, propafenone and sotalol differently affect electrical seizures and the antiseizure action of classical antiepileptic drugs. No characteristic pattern was also found among pure β-blockers. These drugs differently affect seizures and the action of

Table 1
Effects of sotalol administration on the antielectroshock action of phenobarbital and carbamazepine

Treatment (mg/kg)	ED_{50} (mg/kg)
PB + vehicle	24.8 ± 2.18
PB + SOT (40)	24.7 ± 1.32
PB + SOT (60)	22.4 ± 2.18
PB + SOT (80)	22.8 ± 2.32
PB + SOT (100)	19.9 ± 1.54
CBZ + vehicle	14.8 ± 1.06
CBZ + SOT (40)	14.0 ± 0.44
CBZ + SOT (60)	13.8 ± 0.77
CBZ + SOT (80)	13.4 ± 0.60
CBZ + SOT (100)	13.5 ± 0.56

Results are expressed as a current strength inducing tonic-clonic convulsions in 50% of tested mice (CS_{50}) ± SEM. SOT, sotalol.

Table 2
Effects of conventional antiepileptic drugs administered alone or in combinations with sotalol on long-term memory and motor coordination.

Drug administered (mg/kg)	Median (25, 75 percentiles)	Mice impaired (%)
Vehicle	180 (180, 180)	0
SOT (40.0)	180 (180, 180)	0
SOT (60.0)	180 (180, 180)	0
SOT (80.0)	180 (180, 180)	10
SOT (100.0)	180 (180, 180)	20
VPA (327.8) – ED_{50}	180 (167, 180)	10
VPA (278.1) + SOT (60)	180 (120, 180)	20
VPA (244.6) + SOT (80)	180 (112, 180)	20
VPA (244.6) + SOT (100)	178 (96, 180)	30
PHT (15.2) – ED_{50}	180 (180, 180)	10
PHT (13.8) + SOT (60.0)	180 (180, 180)	0
PHT (12.3) + SOT (80)	180 (180, 180)	0
PHT (11.9) + SOT (100)	180 (162, 180)	10
CBZ (14.8) – ED_{50}	180 (180, 180)	0
CBZ (13.8) + SOT (60.0)	180 (180, 180)	0
CBZ (13.4) + SOT (80.0)	180 (165, 180)	0
VPA (294.5)	168 (126, 180)	10
VPA (197.1) + PROP (50.0)	180 (157, 180)	20
PB (24.6)	180 (180, 180)	10
PB (18.0) + PROP (50.0)	180 (180, 180)	10

Results are shown as percentage of animals showing motor deficits in the chimney test and as median retention times (with 25th and 75th percentiles in parentheses) observed in the step-through passive-avoidance task. Statistical analysis of data from the chimney test was performed with Fisher's exact probability test, whilst data from the passive-avoidance test were evaluated by use of the Kruskal-Wallis nonparametric ANOVA test followed by the *post-hoc* Dunn's test. SOT, sotalol; CBZ, carbamazepine; VPA, valproate; PB, phenobarbital; PHT, phenytoin.

Table 3
Brain concentrations of conventional antiepileptic drugs applied alone and in combinations with sotalol.

Treatment (mg/kg)	Brain concentration (μg/ml)
CBZ (13.4) + vehicle	2.04 ± 0.53
CBZ (13.4) + SOT (40.0)	1.58 ± 0.54
VPA (306.4) + vehicle	85.12 ± 3.94
VPA (306.4) + SOT (40.0)	87.32 ± 4.58
PHT (12.3) + vehicle	0.95 ± 0.16
PHT (12.3) + SOT (80.0)	0.86 ± 0.16
PB (19.9) + vehicle	6.42 ± 0.18
PB (19.9) + SOT (80.0)	6.54 ± 0.13

Data are presented as means ± SD of at least eight determinations. Statistical analysis of the brain concentrations of antiepileptic drugs was performed using the unpaired Student's *t*-test. SOT, sotalol; CBZ, carbamazepine; VPA, valproate; PHT, phenytoin; PB, phenobarbital.

antiepileptic drugs. Experimental studies remain the only way to establish the effect of antiarrhythmic drugs in animal models of epilepsy.

Summing up, in the present study we revealed that sotalol, despite blocking potassium channels and potential proconvulsant effects, can be potentially co-administered with conventional antiepileptic drugs. This antiarrhytmic drug enhanced the anti-electroshock action of two examined antiepileptics and, alone or in combinations with all four antiepileptics, produced no motor or memory impairment in mice. It should be underlined that the maximal dose of sotalol used in the present study (100 mg/kg) reflects the dose of 8 mg/kg in humans [39], which is in the single dose range used in clinical conditions. To draw wider conclusions, our results should be confirmed in other animal models of epilepsy and clinical conditions.

Conflict of interest

Authors do not have any conflict of interest to declare.

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