

Anticonvulsive activity of duloxetine: A new choice for the epileptic patients with depression.

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Abstract: The aim of this study was to investigate the antiepileptic effects of duloxetine in the maximal electroshock test and convulsions induced by four compounds: Pentylenetetrazole, 3-mercaptopropionic acid, thiosemicarbazide, and bicuculline. Duloxetine exhibited moderate anticonvulsive activity with an ED₅₀ (median effective dose) of 48.21 mg/kg in the maximal electroshock test in mice. The anticonvulsive action of duloxetine was also confirmed in chemical-induced seizure tests, where this drug decreased tonic convulsions. Single administration of duloxetine (6.25-25 mg/kg) significantly increased the anticonvulsant effects of valproate, carbamazepine, and oxcarbazepine in the maximal electroshock test. Furthermore, pretreatment with thiosemicarbazide (an inhibitor of GABA synthesis enzyme) significantly increased the ED₅₀ of duloxetine, suggesting the GABAergic system may contribute to the anticonvulsive action of duloxetine. These results support the use of duloxetine in the treatment of coexisting depression and epilepsy.

Keywords: Duloxetine; anticonvulsive; electroshock maximal.

INTRODUCTION

Epilepsy and depression are common diseases affecting the global population. It has been recently reported that the two conditions coexist in a large number of patients (Jackson *et al.*, 2005; Dutt *et al.*, 2014), with the lifetime prevalence of depression with epilepsy being estimated to be as high as 50% (Kanner, 2005). Insomnia associated with depression can also increase seizure frequency and epilepsy will aggravate depression owing to the shame it brings upon patients (Jackson *et al.*, 2005; Błaszczyk *et al.*, 2016). An increasing number of patients with epilepsy require some form of antidepressant or anxiolytic medication.

It is widely accepted that improper treatment of patients with both depression and epilepsy will worsen both the diseases (Mehndiratta *et al.*, 2013; Salpekar *et al.*, 2015). Information in the British National Formulary (BNF) and in patient leaflets for all classes of antidepressant state that they are contraindicated or should be used with caution in people with epilepsy. As a result, most physicians are reluctant to prescribe antidepressants for people with epilepsy and patients are unsure as to whether they should take them. Therefore, the choice of antidepressants for patients with epilepsy is very important. More information on the safety of treating epileptic patients with antidepressants and effects of these drugs on seizures is required.

To date, many antidepressant drugs have been reported to have positive or negative effects for patients with epilepsy, depending on their mechanism of action (Kanner *et al.*, 2016; Hill *et al.*, 2015; Sun *et al.*, 2009; Ago *et al.*, 2007;

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Favale *et al.*, 2003; Schmitz, 2002). Ojemann *et al.* performed a retrospective study on the use of the tricyclic antidepressant doxepin in patients with epilepsy, and found that while the depressive symptoms of the patients had been reduced by 89%, the frequency of their seizures had increased by 79% (Ojemann *et al.*, 1982), thus suggesting that this drug is inappropriate for people with epilepsy. In contrast, many experimental and clinical studies show that selective 5-HT reuptake inhibitors (SSRIs) are an appropriate treatment strategy for patients with this condition. In open trials, in patients with epilepsy that are resistant to treatment, a significant drop in seizure frequency following treatment with SSRIs was reported (Favale *et al.*, 1995; Specchio *et al.*, 2004). Indeed, several experimental studies have confirmed that increasing serotonergic and/or noradrenergic neurotransmission potentiates both the anticonvulsive and antidepressant effects of SSRIs (Mostert *et al.*, 2008; Mula, 2013; Seethalakshmi and Krishnamoorthy, 2007).

Duloxetine is a serotonin-norepinephrine reuptake inhibitor (SNRI) marketed by Eli Lilly with the trade name Cymbalta. It is the most widely prescribed antidepressant and is primarily administered to treat major depressive and general anxiety disorder (Wong and Bymaster, 2002). There are limited reports on whether duloxetine can worsen the seizures patients with epilepsy, although one study reported a small number of cases of generalized tonic-clonic seizure following very high doses of this drug (Pellicciari *et al.*, 2012). There are no experimental studies on the anticonvulsive effects of duloxetine.

In the present study we investigated the anticonvulsive ability and neurotoxicity of duloxetine hydrochloride (DH)

in several screening models of seizures in mice. When prescribing antidepressants for those with epilepsy, interactions between these drugs and common antiepileptic drugs (AEDs) are an important consideration for physicians. The effects of acute DH treatment on the antiepileptic effects of three classical AEDs were also studied in the maximal electroshock (MES) test in mice. The aim of this work was to investigate the safety and effects of duloxetine in treating coexisting depression and epilepsy.

MATERIALS AND METHODS

Animals and experimental conditions

All experiments were performed on adult male KunMing mice weighing 20–24g. The mice were kept in colony cages with free access to food and water under standardized housing conditions (natural light–dark cycle, temperature of 22±2°C). After 3 days of adaptation to laboratory conditions, the animals were subjected to experimental. Each mouse was used only once. Procedures involving animals and their care were conducted in accordance with the Guide for the Care and Use of Laboratory Animals, 8th Edition, National Academies Press, Washington, DC. Local ethical committee approval was also obtained. Additionally, all efforts were made to minimize animal suffering and to use only the number of animals necessary to produce reliable scientific data.

Drugs

The following drugs were used in this study: pentylenetetrazole (PTZ), 3-mercaptopropionic acid (3-MP), thiosemicarbazide (TSC), bicuculline (BIC), and para-chlorophenylalanine (PCPA) (these drugs from Aladdin Industrial Inc., Shanghai, China), duloxetine hydrochloride (DH), valproate sodium (VPA), carbamazepine (CBZ), oxcarbazepine (OXC) (these drugs from melongpharma, Dalian, China). PTZ, 3-MP, TSC, DH, and VPA were dissolved in saline, while CBZ and OXC were dissolved in dimethyl sulfoxide (DMSO). BIC was dissolved in 0.1N HCl, diluted with saline to the final volume (the final pH was about 6) and used within 30 min. PCPA was dissolved in 1N NaOH solution, and neutralized with 1N HCl to dregs just emerging, then diluted with saline to the final volume. All drugs were prepared each day as fresh solutions and administered in a volume of 5 ml/kg body weight. DH was administered in a single injection at 30 min before tests.

The maximal electroshock test

The MES test in rodents is a well known animal model of tonic-clonic convulsions, which was adopted by National Institutes of Health (USA) to screening antiepileptic drugs (White *et al.*, 2003; Levy *et al.*, 1995). In the MES test, seizures were elicited with a 60 Hz alternating current of 50 mA intensity in mice. The current was applied via ear-clip electrodes for 0.2 s. The protection against the spread

of MES-induced seizures was defined as the abolition of the hind limb tonic extension spasm. Drugs were administered intraperitoneally (i.p.) at the dose levels of 30, 100 and 300mg/kg for evaluating preliminarily anticonvulsant activity at 30min interval after administration. After the rough effective dose obtained, the tests for determination of the median effective dose (ED₅₀) were carried out. Groups of ten (six in each group for the determination of ED₅₀ value of three antiepileptic drugs) mice were given a range of intraperitoneal doses of the tested compound until at least three points were established in the range of 10–90% seizure protection (each mouse administered only one dose and have one seizure induced). From these data, the respective ED₅₀ values, and 95% confidence intervals were calculated by computer from an equation of a dose-response curve (Litchfield *et al.*, 1949).

Chemical-induced seizures tests

In chemical induced seizures test, mice were given doses of convulsant drugs that could induce seizures at a certain proportion (bigger than 90%). The doses used were: PTZ, 100 mg/kg; 3-MP, 60 mg/kg; TSC, 50mg/kg; BIC, 5.4 mg/kg. The vehicle and DH (50mg/kg) were administered i.p. to groups of ten mice at 30 min before injection of PTZ (subcutaneously, s.c.), 3-MP (i.p.), TSC (i.p.) and BIC (s.c.). The mice were placed in individual cages and observed for 60 min, the numbers of clonic seizure (range from exaggerated twitches of the limbs to violent shaking or vibrating of the stiffened extremities) and tonic seizure (the extremities pull towards the body or rigidly push away from it, usually maximal extension of the hind leg), as well as the number of deaths were noted (Bernasconi *et al.*, 1988; Arnoldi *et al.*, 1990).

Test for the effects of PCPA and TSC on the anti-MES action of DH

Pretreatment of PCPA or TSC will significantly decrease the 5-HT or GABA levels in the brain of mice, respectively (Kilian *et al.*, 1973). In this study, forty mice were pretreated with PCPA at a dose of 150 mg/kg/day (or TSC at a dose of 25 mg/kg/day) for 3 days. On the last day, the treated mice were used for the determination of the ED₅₀ value of DH in the MES test. The ED₅₀ value of DH interfered by PCPA and TSC were obtained and compared to the previous ED₅₀ value of DH achieved in the MES test.

Test for the effects of DH on the anti-MES action of three antiepileptics

Vehicle and DH (50, 25, 12.5 mg/kg) were administered i.p. in a single injection. Then the antiepileptics VPA, CBZ and OXC were administered i.p. immediately. Thirty minutes later, the mice were subjected to electroconvulsion. The ED₅₀ values (including the antiepileptics alone and DH combined) were obtained according to the above description in the MES test.

Neurotoxicity (NT) evaluation of DH

The neurotoxicity of the DH was measured in mice by the rotarod test (White *et al.*, 2003; Levy *et al.*, 1995). Mice were trained to stay on a rotarod of diameter 3.2cm which rotates at 10 rpm. Trained animals were given i.p. injection of the DH. Neurotoxicity was indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of the trials.

Table 1: Effects of duloxetine hydrobromide (DH) in maximal electroshock test (preliminary evaluation).

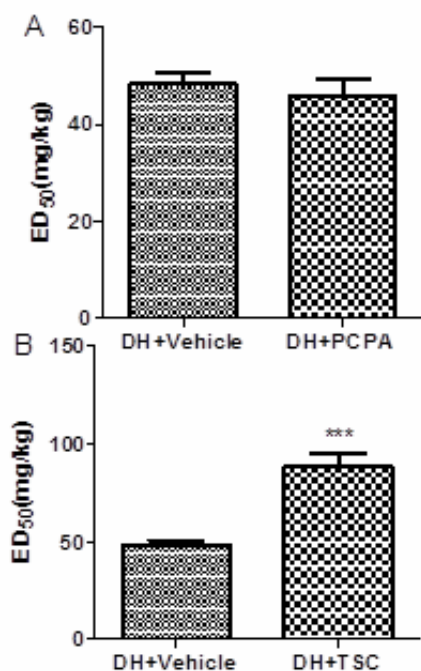
Dose (mg/kg)	30	100	300
Seizures recorded	0/3	3/3	-

Seizure activity was recorded 30 minutes after intraperitoneal drug treatment. All animals in the 300 mg/kg condition had clonic seizures and died.

Table 2: Effects of duloxetine hydrobromide (DH) in maximal electroshock test (quantitative evaluation).

Dose (mg/kg)	Protection	ED ₅₀ (mg/kg)
42	3/10	48.21 (43.93-52.91)
50	6/10	
60	8/10	
72	10/10	

Protection refers to the number of animals protected from seizures /number of animals tested.



All data are presented as median effective dose (ED₅₀) + SEM. All drugs were administered i.p. in a single injection, 30 minutes before maximal electroshock-induced seizures; ****p*<0.001 vs. control group (pretreatment with saline).

Fig. 1: Effect of para-chlorophenylalanine (PCPA) (A) and thiosemicarbazide (TSC) (B) on the anticonvulsant action of duloxetine hydrobromide (DH) in electroshock-

induced seizures in mice.

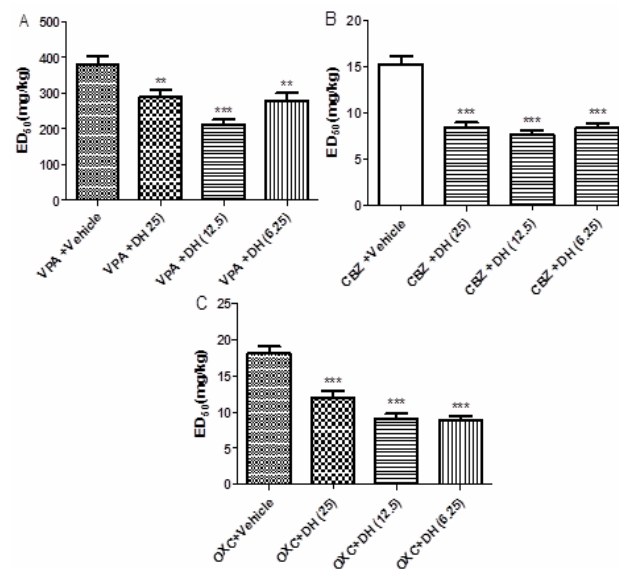
STATISTICS ANALYSIS

ED₅₀ values with their respective 95% confidence intervals were calculated using log-probit analysis. In order to compare ED₅₀ value, standard error (SEM) of the mean values were transformed from 95% confidence limits and the ED₅₀ with the SEM were compared using the One-way analysis of variance (ANOVA) followed by Dunnett's test. The seizures number and lethality from the chemical induced seizures models were compared by the Fisher's exact test. Differences among values were considered statistically significant if *P*≤0.05. All statistical tests were performed using commercially available GraphPad Prism version 5.0 for Windows.

RESULTS

The maximal electroshock test

DH was initially administered at doses of 30, 100 and 300 mg/kg. As shown in table 1, DH prevented seizures at the dose of 100mg/kg in the MES test. However, all animals died when a dose of 300mg/kg was administered. The ED₅₀ of DH in MES test was calculated as 48.21 mg/kg (table 2).



Data are presented as median effective doses (ED₅₀ with SEM values), where antiepileptic drugs protected 50% of animals against seizures. All drugs were administered i.p. in a single injection 30 min before maximal electroshock-induced seizures; ***p*<0.01, ****p*<0.001 vs. control (animals treated with an antiepileptic plus saline).

Fig. 2: Effect of acute treatment with duloxetine hydrobromide (DH) on the anticonvulsant action of valproate VPA (A), carbamazepine CBZ (B), and Oxcarbazepine OXC (C) in maximal electroshock-induced seizures in mice.

Table 3: Effects of acute treatment with duloxetine hydro bromide (DH) on convulsions and death induced by pentetrazol (PTZ) in mice.

Groups	Clonic convulsions	Tonic convulsions	Death
PTZ (100 mg/kg)	100%	100%	90%
PTZ (100 mg/kg) + DH (50 mg/kg)	90%	0%***	90%

Table 4: Effects of acute treatment with duloxetine hydro bromide (DH) on convulsions and death induced by 3-mercaptopropionic acid (3-MP) in mice.

Groups	Clonic convulsions	Tonic convulsions	Death
3-MP (60 mg/kg)	100%	90%	100%
3-MP (60 mg/kg) + DH (50 mg/kg)	100%	20%**	30%**

Table 5: Effects of acute treatment with duloxetine hydrobromide (DH) on convulsions and death induced by thiosemicarbazide (TSC) in mice.

Groups	Clonic convulsions	Tonic convulsions	Death
TSC (50 mg/kg)	100%	90%	90%
TSC (50 mg/kg) + DH (50 mg/kg)	100%	0%***	80%

Table 6: Effects of acute treatment with Duloxetine hydrobromide (DH) on convulsions and death induced by bicuculline (BIC) in mice.

Groups	Clonic convulsions	Tonic convulsions	Death
BIC (2.7 mg/kg)	100%	100%	100%
BIC (2.7 mg/kg) + DH (50 mg/kg)	100%	40%**	90%

Results are expressed as a percentage of animals that showing clonic and tonic convulsions and death among all animals tested. The number of animals tested in each group was ten. Significance determined with Fisher's exact test. ** $p < 0.05$ vs group of BIC (2.7 mg/kg).

Table 7: Assessment of the neurotoxicity of duloxetine hydrobromide (DH) with the rotarod test.

Dose (mg/kg)	Neurotoxicity	TD ₅₀ (mg/kg)
6.25	0/3	58.24 (53.17-64.40)
12.5	0/3	
25	0/3	

Neurotoxicity refers to the number of animals falling off the rotarod /number of animals tested.

Chemical-induced convulsions tests

To further evaluate the anticonvulsive ability of DH, four compound-induced convulsions tests were carried out. It is known that pentylenetetrazole (PTZ) can induce seizures through inhibition of γ -aminobutyric acid (GABA) neurotransmission. In PTZ-induced convulsion tests, 100mg/kg of PTZ resulted in seizures in over 90% of mice. As shown in table 3, treatment with DH led to a significant decrease in PTZ-induced tonic convulsions when compared to only PTZ administered (from 100% to 0%, $p < 0.001$).

3-Mercaptopropionic acid (3-MP) is a competitive inhibitors of glutamate decarboxylase (GAD) which can inhibit the synthesis of GABA, decreasing the levels of this neurotransmitter in the brain. 3-MP at a dose of 60 mg/kg induced convulsions in 90% of mice (table 4). Combined treatment with 3-MP and DH led to a

significant decrease in tonic convulsions and death when compared to administration of 3-MP alone (from 90% to 20%, $p < 0.01$ and from 100% to 30%, $p < 0.01$).

Thiosemicarbazide (TSC) is a competitive inhibitors of glutamic acid decarboxylase required for GABA synthesis, which induces convulsions through its action to decrease GABA concentration in the brain. TSC induced convulsions in over 90% of mice when administered at a dose of 50 mg/kg (table 5). Combined treatment of TSC and DH led to a significant decrease for the number of tonic convulsion when compared to administration of TSC alone (from 90% to 0%, $p < 0.001$).

Bicuculline (BIC) is a competitive GABA_A receptor antagonist, known to produce seizures in mice. BIC induced convulsions in more than 90% of mice at the 2.7 mg/kg dose (table 6). Combined treatment of BIC and DH

led to a significant decrease in tonic convulsions when compared to administration of BIC alone (from 100% to 40%, $p < 0.01$).

The effects of PCPA and TSC on the anti-MES action of DH in MES test.

To determine the anticonvulsant mechanism of DH, the effects of treatment with PCPA (an inhibitor of 5-HT synthesis enzyme) and TSC (an inhibitor of GABA synthesis enzyme) on the anticonvulsant action of duloxetine were determined. PCPA (150mg/kg/day for 3 days) did not markedly affect the anti-MES action of DH, although the ED₅₀ value showed a slight decrease from 48.21 to 45.73 mg/kg. However, TSC (25mg/kg/day for 3 days) significantly decreased the anti-MES action of DH with an ED₅₀ value increase from 48.21 to 88.00 mg/kg ($p < 0.001$) (fig. 1). These results suggest the GABAergic system may contribute to the anticonvulsive action of duloxetine.

The effects of DH on the anti-MES action of three antiepileptics in MES test

The effects of DH on the anticonvulsive activity of three classical antiepileptics were also evaluated. Single administration of the antidepressant DH was ineffective in the maximal electroshock test in mice at doses of 6.25 to 25mg/kg. DH applied at 25, 12.5 and 6.25mg/kg significantly potentiated the seizure-preventing activity of VPA, decreasing its ED₅₀ value from 380.36±21.82 to 291.02±19.76, 212.53±14.08, and 279.70±20.76mg/kg, respectively. DH also significantly increased the ability of CBZ to prevent seizures at doses of 25, 12.5 and 6.25 mg/kg, decreasing its ED₅₀ value from 15.21±0.87 to 8.33±0.61, 7.61±0.52, and 8.33±0.52 mg/kg, respectively. A similar pattern of results was observed for the antiepileptic OXC, DH at 25, 12.5, and 6.25mg/kg doses significantly potentiated the anticonvulsant action of OXC, decreasing its ED₅₀ value from 18.07±1.00 to 12.00 ±0.87, 9.13±0.62 and 8.86±0.59 mg/kg, respectively (fig. 2).

Neurotoxicity (NT) evaluation of DH

Neurotoxicity of DH was evaluated with the rotarod test to determine its safety. Single administration of the antidepressant DH at doses ranging from 6.25 to 25 mg/kg did not have neurotoxic effects. To determine the median toxic dose (TD₅₀) of DH, higher doses of DH were also administered. The TD₅₀ of DH was determined to be 58.24 mg/kg (table 7).

DISCUSSION

The present study suggests that acute DH treatment protects against electroshock-induced convulsions in mice. However, administration of this antidepressant at 300 mg/kg was lethal. DH is also effective at preventing compound-induced convulsions, markedly inhibiting tonic convulsions induced by PTZ, 3-MP, TSC, and BIC.

These findings further support the view that DH can act as an anticonvulsive.

The anticonvulsant action of antidepressant drugs is likely related to their ability to increase serotonergic and/or noradrenergic neurotransmission (Jobe, 2003; Jobe *et al.*, 2005). 5-Hydroxy-tryptophan (5-HTP), the precursor of 5-HT, has anticonvulsant effects in experimental animals (Scudder *et al.*, 1966). Patients with epilepsy have lower plasma concentrations of 5-HTP than healthy controls (Filippini *et al.*, 1996). However, the results of this study are inconsistent with these reports. PCPA is a selective and irreversible inhibitor of tryptophan hydroxylase, which decreases levels of 5-HT via inhibition its biosynthesis (Jouvet, 1999). In the present study, treatment with PCPA did not markedly affect the anti-MES action of DH, suggesting that 5-HT neurotransmission is not directly implicated in the anticonvulsive action of DH. In contrast, treatment with TSC significantly increased the ED₅₀ of DH in the MES test. TSC is a competitive inhibitor of GAD required for GABA synthesis which induces convulsions via decreasing neural GABA concentrations (Collins, 1973). The anticonvulsive action of DH suggested that the GABAergic system might contribute to the anticonvulsive action of DH. This point also coincides with the findings that DH markedly inhibits tonic convulsions induced by PTZ, 3-MP, TSC, and BIC, given that these convulsants all target the GABAergic system.

Previous studies have also shown that the anticonvulsant action of antidepressants may not be through modulation of the serotonergic system. The antidepressant tianeptine has been reported to protect against pentylenetetrazole-induced convulsions, despite the fact that it decreases 5-HT concentration in the synaptic cleft (Ceyhan *et al.*, 2005). Mirtazapine, which blocks α_2 , 5-HT₂ and 5-HT₃ receptors, does not affect PTZ- or MES-induced seizures in mice (Yilmaz *et al.*, 2007). The anticonvulsive effect of 5-HT may be mediated through indirect mechanisms such as inhibition of voltage-gated ion channels (e.g., Na⁺, K⁺, Ca²⁺, Cl⁻), on excitatory neurotransmitter receptors (e.g., N-methyl-D-aspartic acid receptors), inhibitory neurotransmitter receptors (e.g., GABAA), and neurosteroid synthesis (Robinson *et al.*, 2003; Ye *et al.*, 2008). The mechanisms by which antidepressant drugs exert their anticonvulsant activity are unclear.

When prescribing antidepressant drugs for patients with epilepsy, physicians should not only consider the effects of these drugs on seizures, but also the interactions of these drugs with AEDs. More antidepressants increase the anticonvulsive action of AEDs than can inhibit convulsions at doses used clinically. Because of the paucity of clinical data on this subject, details about such interactions are often gleaned from experimental studies. In the present study, the MES model was used in mice.

DH significantly increased the anticonvulsive action of the AEDs used (VPA, CBZ and OXC) at doses ranging between 6.25 and 25 mg/kg. It is worth mentioning that the moderate dose of DH (12.5mg/kg) potentiated the anticonvulsive action of the AEDs to the greatest extent. This dose in mice is equivalent to 1mg/kg in humans (Raegan-Shaw, *et al.*, 2007), which is similar to the clinical dose of duloxetine used (60mg/day). Clinical doses of DH may markedly improve the therapeutic effect of the AEDs and this may also be true of lower doses.

In summary, the protective effects of DH on several kinds of seizures were investigated. DH may be used in the future as an anticonvulsant. Interestingly, DH (applied at a clinical dose or lower) significantly enhanced the anticonvulsive activity of three widely prescribed AEDs. There was no evidence of neurotoxicity at the doses used, which supports the use of DH alongside AEDs in the treatment of coexisting depression and epilepsy.

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