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Effect of hydrochlorothiazide on the anticonvulsant action of antiepileptic drugs against maximal electroshock-induced seizures in mice

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Abstract:
Background: The purpose of this study was to evaluate the effect of hydrochlorothiazide (HCTZ), a thiazide-type diuretic and an antihypertensive drug, on the anticonvulsant activity of numerous antiepileptic drugs (AEDs: carbamazepine – CBZ, phenytoin – PHT, valproate – VPA, phenobarbital – PB, oxcarbazepine – OXC, lamotrigine – LTG and topiramate – TPM).
Methods: The effects of HCTZ and AEDs on convulsions were examined in the maximal electroshock seizure (MES) test in mice. Additionally, adverse effects of combined treatment with HCTZ and the AEDs in the passive avoidance task and chimney test were assessed. All drugs were injected intraperitoneally (*ip*) at single doses.
Results: The data obtained indicate that HCTZ (100 mg *ip*) enhanced the anticonvulsant action of CBZ, decreasing its ED_{50} value from 11.9 to 7.7 mg/kg ($p < 0.05$), and had no impact on the antielectroshock activity of the other AEDs. The observed interaction between HCTZ and CBZ was not pharmacokinetic in nature as HCTZ did not alter free plasma (non-protein-bound) and total brain concentrations of CBZ. The combined treatment with HCTZ and the AEDs was free from side-effects on motor performance and long-term memory in mice.
Conclusions: To the degree, the experimental data can be transferred to clinical conditions, the use of a single dose of HCTZ in patients receiving VPA, PHT, PB, OXC, LTG or TPM, seems neutral regarding their anticonvulsant potency. Acute HCTZ may positively influence the anticonvulsant action of CBZ in epileptic patients.

Key words:
hydrochlorothiazide, antiepileptic drugs, maximal electroshock, seizures

Introduction

Epidemiological studies have indicated the higher risk for hypertension in persons with epilepsy [8]. Such a co-morbidity will require using simultaneously antiepileptics and antihypertensive drugs in the treatment that can lead to pharmacokinetic and/or pharmacodynamic interactions. Thiazide diuretics are moderately potent diuretics and are widely used as first-line drugs for the treatment of hypertension [3, 6]. During the first days of therapy, they reduce blood pressure by decreasing plasma volume and extracellular fluids, while in the long term the decrease in total peripheral vascular resistance is the mechanism of the antihyper-

tensive effect of thiazides [1]. It is noteworthy that hydrochlorothiazide (6-chloro-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide) (HCTZ), a thiazide-type diuretic, is the most commonly prescribed antihypertensive drug worldwide [20]. Thiazides have also uses in the treatment of edematous disorders, diabetes insipidus or hypercalciuria [3]. In the kidney, thiazide diuretics primarily inhibit the process of sodium and chloride reabsorption in the distal tubule [11]. In sufficient concentrations, thiazides have also inhibitory activity toward carbonic anhydrase [3].

Recent epidemiological data have shown that thiazides can be protective for first unprovoked seizure in adult patients [9]. In animal studies, chlorothiazide dose-dependently suppressed convulsions in the maximal electroshock seizure (MES) model, which is used to evaluate a compound's protective effects against generalized tonic-clonic seizures [9, 14]. However, little is known about pharmacological interactions between thiazide diuretics and antiepileptic drugs (AEDs) in animal models of seizures. So far, it has been documented that HCTZ did not affect the convulsive threshold for tiagabine [16]. According to our knowledge, HCTZ has not been tested in combinations with AEDs in other models of seizures. In contrast, the interactions between loop diuretics and AEDs have been well studied [15, 17, 19]. Furosemide and ethacrynic acid, two potent loop diuretics, have been found to enhance the anticonvulsant action of valproate (VPA) in the MES test [17, 19]. Ethacrynic acid also potentiated the antiseizure action of topiramate (TPM) [15]. In the current study, the effect of HCTZ on the anticonvulsant activity of numerous AEDs in the MES model was evaluated. We examined the combinations of HCTZ with classical (carbamazepine – CBZ, phenytoin – PHT, phenobarbital – PB and VPA), and some second-generation AEDs (oxcarbazepine – OXC, lamotrigine – LTG and TPM).

Materials and Methods

Animals

The experiments were conducted on adult male Swiss mice weighing 22–27 g. The animals were housed in colony cages with free access to food (chow pellets) and tap water *ad libitum*. They were kept under standardized laboratory conditions (a 12-h light-dark cycle and a temperature of 21 ± 1°C). The experimental groups, consisting of eight animals, were made up at random. The experimental protocols and procedures described in this manuscript were approved by the Local Ethics Committee for Animal Experiments at the University of Life Sciences in Lublin and complied with the European Communities Council Directive of 24 November 1986 (86/609/EEC).

Drugs

Hydrochlorothiazide (Hydrochlorothiazidum, Polpharma S.A., Starogard Gdański, Poland), carbamazepine (Amizepin, Polpharma S.A., Starogard Gdański, Poland), valproate magnesium (Dipromal, ICN Polfa S.A., Rzeszów, Poland), phenytoin (Phenytoinum, Polfa, Warszawa, Poland), phenobarbital (Luminalum, Unia, Warszawa, Poland), oxcarbazepine (Trileptal, Novartis Pharma GmbH, Nürnberg, Germany), lamotrigine (Lamitrin, GlaxoSmithKline, Brentford, UK) and topiramate (Topamax, Janssen-Cilag International N.V., Beerse, Belgium) were used in this study. VPA was directly dissolved in distilled water. HCTZ, CBZ, PHT, PB, OXC, LTG and TPM were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA) in distilled water. The studied drugs were injected intraperitoneally (*ip*) at a volume of 5 ml/kg body weight and administered 120 min (HCTZ and PHT), 60 min (PB, LTG and TPM), or 30 min (CBZ, VPA and OXC) before the tests; control animals received injections of the vehicle. Treatment times to provide maximum anticonvulsant effects were based on previous reports [9, 19].

Electroconvulsions

Electroconvulsions were produced with the use of auricular electrodes and an alternating current (50 Hz, 500 V, 0.2 s stimulus duration) delivered by a generator (Rodent Shocker, Type 221, Hugo Sachs, Freiburg, Germany). The criterion for the occurrence of seizure activity was the full tonic extension of both hind limbs. The convulsive threshold was evaluated as CS_{50}, which is the current strength (in mA) required to produce tonic hindlimb extension in 50% of the animals tested. To calculate the convulsive threshold, at least three groups of mice (eight animals per group) were challenged with electroshocks of various intensities. An intensity-response curve was calculated with a computer, based on a percentage of ani-