CURRENT LITERATURE

DIURETICS AS ANTIEPILEPTIC DRUGS

Are Certain Diuretics Also Anticonvulsants?

Hesdorffer DC, Stables JP, Hauser WA, Annegers JF, Cascino G

Ann Neurol 2001;50:458–462

A history of diuretic use has been shown to be protective for first unprovoked seizure in adult patients. Recent animal studies suggest that certain diuretics have anticonvulsant activity. We evaluated the potential for the anticonvulsant activity of current diuretic use in a population-based, case-control study in older adults. We also tested chlorthiazide and furosemide for seizure protection in animal models of epilepsy. Concurrent medical prescription of any diuretic was protective for the development of epilepsy [odds ratio (OR) = 0.62, 95% confidence interval (CI) = 0.39–0.99]. A protective effect for current thiazide use was observed (OR = 0.53, CI = 0.31–0.90), and a protective effect for furosemide was suggested (OR = 0.44, CI = 0.1–1.9). In mice, both chlorthiazide and furosemide suppressed the occurrence of maximal electroshock-induced seizures in a dose-dependent manner. Chlorthiazide's toxic dose for 50% of animals tested (TD50) could not be achieved even with dosing as high as 1,500 mg/kg for furosemide; TD50 was 549 mg/kg. Results were similar in rats. Furosemide and chlorthiazide are protective for unprovoked seizures in an epidemiological study and in animal models. Given the potential therapeutic value for seizure control, low toxicity, and low cost, therapeutic efficacy should be explored in clinical studies.

COMMENTARY

When neurologists talk of diuretics as antiepileptic drugs (AEDs), they usually refer to acetazolamide (Diamox®), a carbonic anhydrase inhibitor in which an antiepileptic effect has been attributed to the accumulation of CO_2 in the brain (1). In this manuscript, Hersdorffer et al. expanded on observations made in a 1996 case-control study on the impact of loop diuretics (such as thiazides and furosemide) that were used for the treatment of uncontrolled hypertension. These diuretics protected patients against an 11-fold higher risk of seizures identified in patients with left ventricular hypertrophy not treated with diuretics (2). In this study, these authors demonstrated that past or present use of any diuretic was protective for the development of a first unprovoked seizure in adults aged 55 or older, with the effect being more obvious for a present use of thiazide and furosemide. Antiepileptic effects of these two diuretics were also demonstrated in the maximal electroshock seizure (MES) model.

This is not the first time that diuretics other than acetazolamide are found to display antiepileptic effects in in vitro and animal models of epilepsy studies (3,4). Reid et al. have suggested that loop diuretics prevent seizures by blocking the KCC_2 potassium-chloride transporter in neuronal membranes (3), whereas Hochman et al. suggested that furosemide prevents seizures through nonsynaptic mechanisms by blocking the synchronization of neuronal activity necessary to generate seizures (4).

The evidence from these experimental studies and now from this population-based, case-controlled study suggesting a protective effect of diuretics (other than acetazolamide) is compelling enough to warrant controlled studies of loop diuretics in patients with epilepsy. Antiepileptic efficacy of acetazolamide has been suggested in absence, myoclonic, and generalized tonic-clonic seizures, as well as in complex partial seizures (1), but most of these data were derived from uncontrolled studies. There is agreement, however, on its time-limited efficacy, as patients tend to develop tolerance after a few months. Whether loop diuretics share these properties is yet to be established. A different spectrum of efficacy and antiepileptic efficacy is possible in loop diuretics, given their different mechanisms of action in the brain. One wonders why the potential antiepileptic effect of this class of drugs has not yet been evaluated in clinical placebo-controlled trials. After all, loop diuretics are usually well tolerated and inexpensive, and their long-term safety and tolerability has been established.

References

1. Resor SR, Resor LD, Woodbury DM, Kemp JW. Acetazolamide. In: Levy RH, Mattson RH, Meldrum BS, eds. Antiepileptic drugs, 4th ed. New York: Raven Press, 1995:969–985.
2. Hersdorffer DC, Hauser WA, Annegers JF, Rocca WA. Severe, uncontrolled hypertension and adult-onset seizures: a case-control study in Rochester, Minnesota. Epilepsia 1996;37:736–741.

3. Reid KH, Shang ZG, Vasudeva GI. Agents which block potassium-chloride cotransport prevent sound-triggered seizures in post-ischemic audiogenic seizure-prone rats. Brain Res 2000;864:134–137.
4. Hochman DW, Baraban SC, Owens JWM, Schwartzkroin PA. Dissociation of synchronization and excitability in furosemide blockade of epileptiform activity. Science 1995;270:99–101.

by Andres M. Kanner, M.D.