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Cinromide (3-bromo-*N*-ethylcinnanamide), a novel anticonvulsant agent

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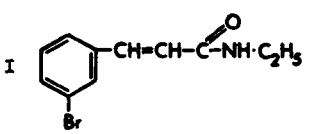
In a review article on antiepileptic drug development, Krall et al (1978) stated that despite optimal use of the 16 antiepileptic drugs marketed in the United States many patients with epilepsy fail to experience seizure control and others do so only at the expense of significant toxic side effects. In addition, multiple drug therapy, which has a number of obvious dangers such as drug interactions, is currently being practiced by many physicians in an attempt to control various types of seizures occurring within the same patient and also to control specific refractory seizure types in given patients.

We, therefore, have been seeking an agent that coupled a broad spectrum of anticonvulsant activity in a variety of animal models with low toxicity with the aim that such an agent might remove the need for multiple drug therapy. Cinromide appears to meet these efficacy and safety criteria and has the structure I.



The pharmacological properties of cinromide to date have been reported only in abstract form (Welch et al 1978; Soroko et al 1979). It appears to be a promising new antiepileptic drug as evidenced by suppression of highly refractory seizures of the Lennox-Gastaut syndrome in children (Lockman et al 1981). Two other open clinical studies suggest that cinromide is safe and has antiepileptic activity when used as adjunct therapy in patients with refractory partial seizures (Peck et al 1981) and in patients with uncontrolled primary and secondary generalized seizures (Ramsay et al 1981).

Anticonvulsant actions. In mice, cinromide afforded protection against maximal electroshock convulsions. The anticonvulsant activity was dose-related following both i.p. and oral administration (Fig. 1A). The ED50 values were 60 ± 11 mg kg^{-1} and 80 ± 15 mg kg^{-1} i.p. and orally, respectively. Similarly, cinromide afforded protection against maximal electroshock convulsions in the rat (Fig. 1B). The ED50 values were 58 ± 12 and 26 ± 6 mg kg^{-1}, i.p. and orally, respectively. In the rat following 50 mg kg^{-1} (ED84) orally the peak effect occurred at 60 min with a duration of 4–5 h. In addition, cinromide was 100% effective in blocking low-frequency (6 Hz) minimal electroshock seizures (Swinyard et al 1962) in mice at 400 mg kg^{-1} orally.

Cinromide afforded protection against leptazol (pentetrazol)-induced convulsions in mice. The i.p. and oral ED50 values were 90 ± 15 and 300 ± 61 mg kg^{-1}, respectively (Fig. 1C). In rats, cinromide administered i.p. produced a dose-related antileptazol activity with an ED50 value of 58 ± 11 mg kg^{-1} (Fig. 1D). Administered orally to rats, cinromide afforded protection to only 50% of the animals at doses as high as 600 mg kg^{-1}. In the intravenously infused leptazol-threshold test in rats, cinromide, at 75 mg kg^{-1} orally, significantly ($P = 0{\cdot}01$) elevated the amount of leptazol needed to induce clonic seizures.

Table 1 summarizes the oral ED50 values obtained 1 h post-administration for cinromide and a variety of clinically effective anticonvulsants. Against maximal electroshock seizures in the mouse, cinromide was more effective than either trimethadione, phensuximide or valproic acid and

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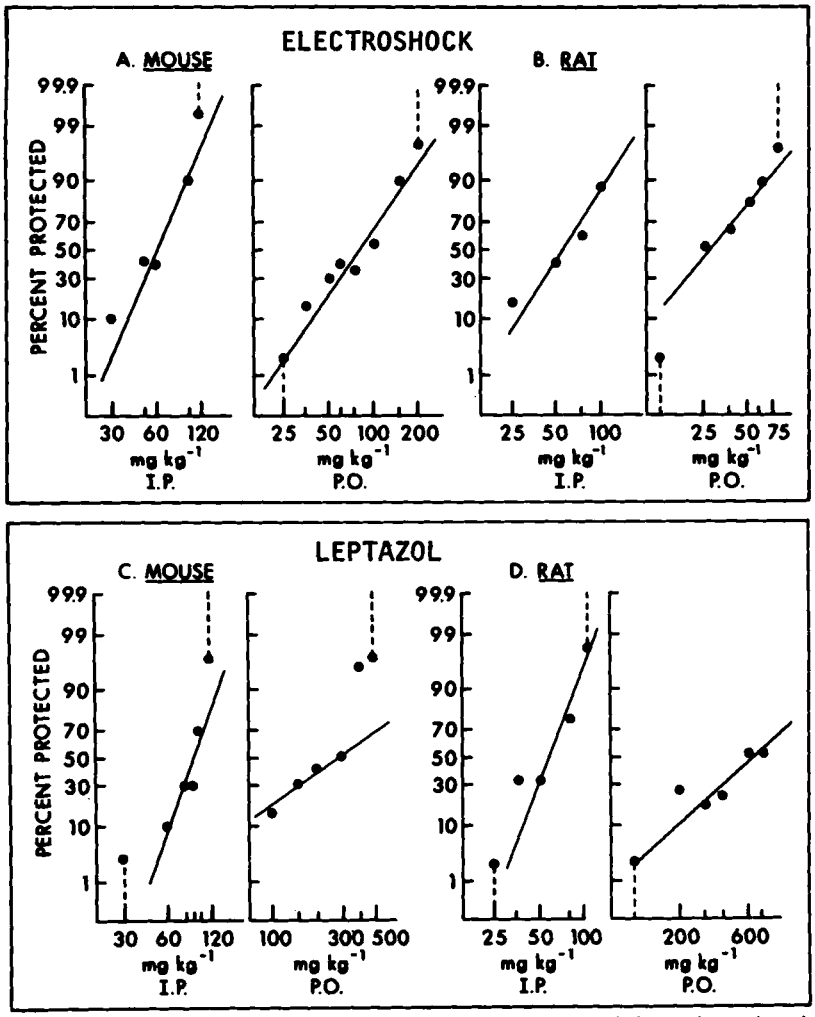

FIG. 1. The anticonvulsant activity of cinromide in mice and rats. The upper panel shows the antimaximal electroshock activity of cinromide in the mouse (A) and rat (B). Maximal electroshock treatment was administered using a Wahlquist Seizure Apparatus and corneal electrodes according to the method of Woodbury & Davenport (1952). Sprague Dawley male rats, 200–300 g, received 150 mA and Blue Spruce (ICR) male mice, 18–22 g, received 50 mA for 0·2 s. Compounds were administered i.p. or orally, 30 min and 1 h respectively, before electroshock treatment. Animals were considered protected if the hind-limb extensor component was blocked. Ten to 22 animals were used per dose level. The lower panel shows the antileptazol activity of cinromide in the mouse (C) and rat (D). Leptazol convulsions were induced in mice and rats using the method of Swinyard et al (1952). Animals were pretreated with the test compound i.p. or orally, 30 min and 1 h, respectively. Controls received diluent. All animals then received leptazol 90 mg kg^{-1} i.p. and were observed for 15 min. An animal was considered protected if the test compound prevented clonic seizure activity. Six to 20 animals per dose of compound were used. All ED50 values were calculated according to the method of Miller & Tainter (1944).

approximately equipotent with phenacemide and less potent than either diphenylhydantoin or phenobarbitone sodium. In the rat, cinromide compared favourably with all four standard agents in antagonizing maximal electroshock seizures. Against leptazol in the mouse, cinromide was similar in potency to trimethadione, less potent than either phenacemide or phensuximide and considerably weaker than phenobarbitone. In the rat, cinromide was equipotent with trimethadione and phenacemide and less potent than phensuximide against leptazol-induced seizures. In both species diphenylhydantoin potentiated leptazol-induced convulsions. Cinromide did not exhibit sedative effect at any of the doses studied in either species.

General pharmacologic effects. In mice at doses starting at 100 mg kg^{-1} (i.p.) and 500 mg kg^{-1} (oral) hypoactivity, muscle tone decrease and hypothermia were observed. Intensity gradually increased with increasing doses. LD50 values in male mice were 660 ± 28 mg kg^{-1} (i.p.) and 2277 ± 250 mg kg^{-1} (oral). In male rats the oral LD50 was 4437 ± 165 mg kg^{-1} and the same signs as seen in the mouse were observed starting at 1500 mg kg^{-1}.

Cardiovascular and autonomic actions. In two anaesthe-

Table 1. A comparison of the anticonvulsant ED50 values of cinromide and standard anticonvulsants.

Test	Species	Cinromide	Standards	
Electroshock	Mouse	80 ± 15	Trimethadione	1000 ± 180
			Diphenylhydantoin	7·9 ± 0·7
			Phenobarbitone Na	15 ± 2
			Phenacemide	64 ± 8
			Phensuximide	330 ± 12
			Valproic acid	850 ± 27
Electroshock	Rat	26 ± 6	Diphenylhydantoin	20 ± 4
			Phenobarbitone Na	15 ± 4
			Phenacemide	10 ± 1
			Valproic acid	206 ± 19
Leptazol	Mouse	300 ± 61	Trimethadione	400 ± 29
			Phenobarbitone Na	25 ± 4·5
			Phenacemide	115 ± 15
			Phensuximide	100 ± 9
			Diphenylhydantoin	—potentiation
Leptazol	Rat	600	Trimethadione	700 ± 52
			Phenacemide	600
			Phensuximide	175 ± 23
			Diphenylhydantoin	—potentiation

All drugs administered orally.

tized open-chested dogs no significant changes in arterial blood pressure, e.g.c., heart rate, cardiac output, coronary flow and dp/dt were observed for 4 h after cinromide given at 300 mg kg^{-1} i.p. In two conscious dogs no significant effects on arterial blood pressure or heart rate were observed over 5 h after receiving cinromide at 300 and 600 mg kg^{-1} orally.

In two spinal cats following cinromide at doses of 300 and 600 mg kg^{-1} i.p., the mean arterial blood pressure, heart rate and the responses of the nictitating membrane to both pre- and post-ganglionic stimulation were unaltered. The contractions of the nictitating membrane observed after i.v. injection of noradrenaline were also unaltered.

Cinromide was without direct effects in guinea-pig isolated ileum or the rabbit aortic strip at concentrations of 10^{-6} – 10^{-4} M. The responses induced by submaximal concentrations of acetylcholine and histamine in guinea-pig ileum were attenuated approximately 25% by cinromide but only at 10^{-4} M. In the rabbit aortic strip cinromide at concentration of 10^{-6} – 10^{-4} M failed to alter noradrenaline-induced contractions.

In spontaneously beating, guinea-pig atria cinromide caused a negative chronotropic effect of 25 and 60 beats min^{-1} at concentrations of 10^{-5} and 10^{-4} M, respectively. The responses elicited in this preparation by histamine and isoprenaline were unaffected by cinromide at 10^{-4} M.

Cinromide, at 10^{-5} M inhibited 5-HT-induced contractions in rat fundus strips by 46%. At 10^{-4} M it relaxed the rat fundus strip and completely inhibited 5-HT-induced contractions. For comparison, methysergide at 3×10^{-9} M inhibited 5-HT 47% in this same preparation.

Biochemical studies. Cinromide administered i.p. chronically twice daily for 13 days to mice at 60 and 95 mg kg^{-1} did not significantly affect dopamine concentrations in brain. The 60 mg kg^{-1} dose did not alter noradrenaline concentrations in either mouse brain or heart. However, noradrenaline was significantly elevated by 23% in brain and 14% in heart at the 95 mg kg^{-1} dose level.

In vitro, at 10^{-4} M, cinromide produced approximately 77% inhibition of monoamine oxidase prepared from both liver and brain of rats using tyramine as the substrate. Choline acetyltransferase, γ-aminobutyric acid transferase and glutamic acid decarboxylase were not inhibited by cinromide by 10^{-4} M.

It is concluded that cinromide can be described as a safe, broad-spectrum agent because it is active in protecting animals against maximal electroshock, maximal leptazol, leptazol infusion and in the low-frequency minimal seizure tests at doses well below the LD50 values. Recently, Lockard et al (1979) demonstrated that cinromide was also an effective agent in the alumina gel chronic epilepsy monkey model. Cinromide has exhibited indications of efficacy in the treatment of epilepsy in man in several controlled, 'add-on' studies.

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