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Cinromide in Epilepsy: A Pilot Study

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Summary: Monotherapy with the experimental antiepileptic drug cinromide was evaluated in 11 adult outpatients with uncontrolled partial epilepsy. They were treated with phenytoin for 2 months, cinromide for 4 months, and carbamazepine for 4 months. Four patients withdrew from the study during or shortly after crossover to cinromide due to increased seizure frequency or severity. Of the remainder, three preferred carbamazepine, two cinromide, and two phenytoin, based on both seizure control and degree of toxicity. Overall seizure control was not significantly different with any of the three agents, but during cinromide administration secondarily generalized seizure control was uniformly worst and there was also a tendency toward decreased performance on neuropsychological tests. CNS toxicity and gastrointestinal toxicity were prominent during the first month of cinromide treatment, but subsided with time or dose reduction. No abnormalities requiring drug withdrawal were found with laboratory testing. The results suggested, at best, a very limited clinical usefulness for cinromide, and it has been withdrawn from testing by its manufacturer.

Cinromide (3-bromo-*N*-ethylcinnamamide) is an experimental antiepileptic drug with a novel chemical structure (Fig. 1). It is active against both maximal electroshock- and pentylenetetrazol-induced seizures in rodents at nontoxic doses (Soroko et al., 1981). The compound also exhibits anticonvulsant activity in epileptic monkeys (Lockard et al., 1979, 1980). The primate studies revealed that cinromide was extensively metabolized to amide and acid metabolites, and that the anticonvulsant effects of the drug were probably due to its amide metabolite (Fig. 1) (Lockard et al., 1979; Levy et al., 1981).

Open studies in epileptic patients in which cinromide (1.2–4.8 g/day) was added to standard antiepileptic treatment regimens resulted in reduced seizure frequency in approximately one-half the patients studied (Perchalski et al., 1982). However, it was unclear how much of the improvement in seizure control was due to drug interactions or placebo effect, and how much was at-

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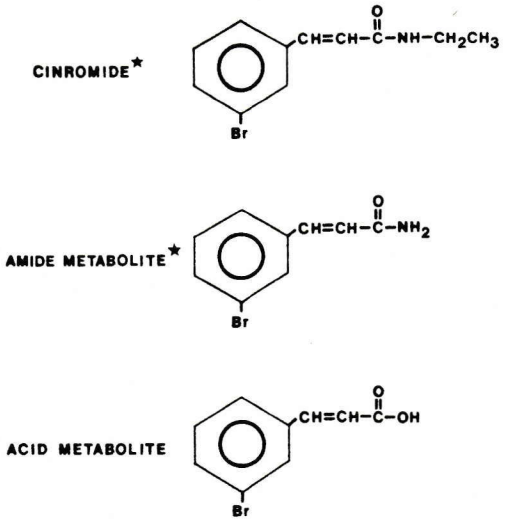

FIG. 1. Chemical structures of cinromide and its amide and acid metabolites. A star indicates anticonvulsant activity in animal models.

tributable to the direct effects of cinromide. The present open pilot study was undertaken in an attempt to establish the independent antiepileptic efficacy, toxicity, and safety of the drug.

METHODS

Chronology

The basic study design is shown in Fig. 2 (Wilensky and Ojemann, 1980). Each patient entered the trial while receiving stable phenytoin monotherapy, and continued receiving phenytoin for an 8-week base-line period. At the beginning of the ninth study week, patients were hospitalized on the Epilepsy Center Diagnostic Treatment and Rehabilitation Unit for a 1-week drug crossover to either cinromide (seven patients) or carbamazepine (four patients). They were then followed as outpatients for the next 15 weeks while receiving their new medication. At the beginning of the 25th study week, the patients were again hospitalized for 1 week for crossover from cinromide to carbamazepine (five patients) or carbamazepine to cinromide (four patients), discharged, and again followed as outpatients

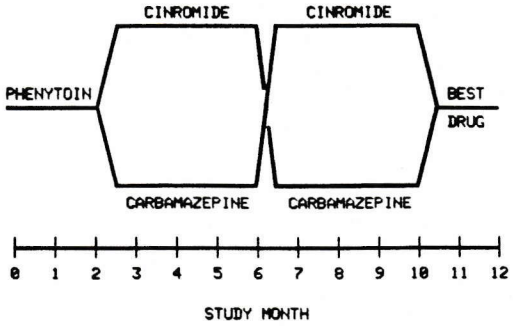

FIG. 2. Study chronology.

for 15 weeks. At the end of the second study period, physician and patient reviewed the study records and determined whether cinromide or carbamazepine had provided the best combination of seizure control and freedom from toxicity. Patients then entered an 8-week follow-up period in which they were treated with either carbamazepine or phenytoin. (Authorization for cinromide treatment longer than 16 weeks was not available from its manufacturer.)

Subjects

Eleven ambulatory adult epileptic patients entered the study, each with four or more partial seizures per month (with or without secondary generalization) despite therapeutic doses and levels of standard antiepileptic drugs (Table 1). Informed consent was obtained.

Clinical and Laboratory Data

The overall time and event schedule for the outpatient and inpatient phases of the study is shown in Table 2. In brief, patients were seen in the outpatient clinic of the Epilepsy Center of the University of Washington for clinical and laboratory evaluations during an initial screening and then during the weeks indicated. Two weeks were spent as inpatients during drug crossovers.

Plasma levels of phenytoin and carbamazepine were measured by gas-liquid chromatography (Friel and Green, 1973;

TABLE 1. *Patient characteristics*

Patient	Age	Sex	Presumed etiology	Seizure type (age in years at onset)[b]
1	35	F	Skull fracture	PC (13)
2	22	M	Skull fracture	PC (<10)
3	25	F	Febrile seizures	PE (8)
4[a]	44	M	Head injury	PC (21)
5	38	F	Loss of consciousness from fall	PC (18)
6	33	M	Premature birth	PE (20)
7	29	M	Tuberous sclerosis	PE (?), SG (0.8)
8[a]	41	F	?	PE (19), PC (39)
9[a]	30	M	Calcified lesion	PE (1), SG (1)
10	29	M	?	PC (10), SG (10)
11[a]	34	F	Near drowning	PC (17), SG (15)

[a] Withdrew from study during first month of cinromide administration.
[b] Based on history: PE, partial elementary; PC, partial complex; SG, partial secondarily generalized.

Friel and Troupin, 1975). Our laboratory is a participant in the American Association for Clinical Chemistry Therapeutic Drug Monitoring Quality Control Program. Plasma levels of cinromide and metabolites were determined by a modification of the high-performance liquid chromatographic method described previously (Wilensky et al., 1981).

At the end of each drug period, a brief neuropsychological evaluation was completed which included the administration of portions of the Neuropsychological Battery for Epilepsy (Dodrill, 1978). To evaluate psychosocial functioning, the Washington Psychosocial Seizure Inventory (Dodrill et al., 1980) was given.

Drug Administration

Phenytoin was dispensed in standard 100-mg capsules (Parke-Davis), carbamazepine in standard 200-mg tablets (Geigy), and cinromide in 300-mg tablets supplied by the manufacturer (Burroughs Wellcome). Drugs were packaged in individual envelopes with each envelope containing a single dose of the drug being administered. Phenytoin was administered twice daily, at 0700 and 2200 hours. Carbamazepine and cinromide were administered four times daily, at 0700, 1200, 1700, and 2200 hours, with doses divided as evenly as possible among the four daily envelopes. Outpatient medication compliance was monitored by pill counts and measurements of plasma antiepileptic drug levels.

Inpatient drug crossovers were performed rapidly for patients 1–7. When crossing from either phenytoin or carbamazepine, cinromide dosing was initiated at 2,400 mg/day for the first 3 days and then raised to 3,600 mg/day for the remainder of the week. Phenytoin and carbamazepine doses were tapered over the first 3 days of crossover and stopped on day 4. Crossovers from either phenytoin or cinromide to carbamazepine were performed by initiating carbamazepine dosing at 400 mg/day and gradually raising the dose to 800 mg/day during the first week. Phenytoin and cinromide doses were tapered and discontinued on the fourth crossover day.

Patients 1–7 experienced pronounced cinromide side effects during and following the crossovers described above. Because of this, the crossover protocols were modified for patients 8–11. Patients 8 and 9 underwent crossover from carbamazepine to cinromide with the carbamazepine dose unchanged for the first 5 days, halved for days 6 and 7, and then stopped. Cinromide was begun at 2,400 mg/day, raised to 3,000 mg/day on day 4, and then continued at that dose. Patients 10 and 11 underwent cross-

TABLE 2. *Overall study time and event schedule*

Event	Base-line (weeks)		Hospital crossover	Treatment I (weeks)					Hospital crossover	Treatment II (weeks)					Follow-up (week)
	4	8		10	12	16	20	24		26	28	32	36	40	48
Physical examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Brief neurological examination	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Vital signs	x	x	x[a]	x	x	x	x	x	x[a]	x	x	x	x	x	x
Symptoms	x	x	x[a]	x	x	x	x	x	x[a]	x	x	x	x	x	x
Seizure calendar	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Ophthalmologic examination		x						x						x	
Blood chemistry		x		x		x		x		x		x		x	x
Hematology		x		x		x		x		x		x		x	x
Urinalysis		x		x		x		x		x		x		x	x
Electrocardiogram		x		x				x		x				x	x
Antiepileptic drug plasma levels	x	x	x[a]	x	x	x	x	x	x[a]	x	x	x	x	x	x
Neuropsychological examination		x						x						x	

[a] Daily.

over from phenytoin to cinromide with the phenytoin dose tapered very gradually over 7 days and the cinromide dose initiated at 1,800 mg/day and gradually raised to 3,000 mg/day over 6 days.

Reporting on an earlier single dose study in epileptic patients (Wilensky et al., 1981), we predicted that at steady state the molar concentration ratio of acid metabolite: amide metabolite:cinromide would be approximately 36:4:1. Median plasma half-lives were: cinromide, 0.7 h; amide metabolite, 1.7 h; and acid metabolite, 4.9 h. Thus, even with cinromide administered four times daily, the parent drug was not expected to accumulate during chronic dosing. Based on this experience and information in the literature (Perchalski et al., 1982), we estimated that chronic dose equivalents for the three agents in the study would be approximately: 100 mg phenytoin = 200 mg carbamazepine = 600 mg cinromide. However, every effort was made to titrate individual patients' doses of each drug for optimum seizure control and minimum side effects, and frequent dose adjustments were made.

Analysis

Standardized 30-day seizure frequencies were calculated for only the last 3 months of each study block to exclude any increase in seizures during the first month of treatment with a new drug related to withdrawal of the previous agent. Two months of baseline data during phenytoin administration and following study entry were used for statistical comparisons.

Analyses were carried out only on the data from patients completing the entire protocol, except when otherwise noted.

The Friedman test, a nonparametric analog of two-way analysis of variance, was used to evaluate the difference in seizure frequencies across treatments with patients as the blocking factor. Repeated measures analysis of variance was used to test for treatment differences in mean laboratory values and all neuropsychological and psychosocial variables. The chi-square test of equal proportions was used to examine treatment differences in the fractions of patients presenting abnormal symptoms and neurological exams.

RESULTS

Dropouts

Four patients were withdrawn from the study during or shortly after crossover to cinromide. Patient 4 began having serial partial seizures during the first day of cinromide monotherapy and was withdrawn from the study, and phenytoin administration was reinstituted. Patient 8 suffered the first generalized tonic-clonic seizures (four) in her life during the second week of cinromide monotherapy and was withdrawn from the study, and carbamazepine administration was reinstituted. Patient 9 developed generalized tonic-clonic status epilepticus during the second week of cinromide administration, required emergency treatment, was withdrawn from the study, and restabilized by taking carbamazepine. Patient 11 experienced toxicity and increased generalized tonic-clonic seizures during the first 2 weeks of cinromide therapy, stopped taking cinromide, and restarted phenytoin without contacting her physician. (This patient may not have taken cinromide according to directions during this period.)

Seizure Control

No significant differences were found among total or partial seizure frequencies during phenytoin, cinromide, and carbamazepine administration for the seven completing patients (Table 3). However, generalized tonic-clonic seizure control was uniformly poorest with cinromide in the patients with this seizure type (Fig. 3). This observation includes patients 7 and 10, who completed the study, as well as patients 8, 9, and 11, who were withdrawn from the

TABLE 3. *Mean total 30-day seizure frequencies for patients completing study*[a]

Patient no.	Phenytoin	Cinromide	Carbamazepine
1	48	53	7
2	13	14	16
3	7	16	8
5	45	7	17
6[b]	4	1	3
7[b]	10 (9)	19 (19)	10 (10)
10	41 (10)	14 (14)	11 (2)

[a] Crossover months excluded.
[b] Carbamazepine treatment preceded cinromide treatment.
Numbers in parentheses are numbers of generalized tonic-clonic seizures.

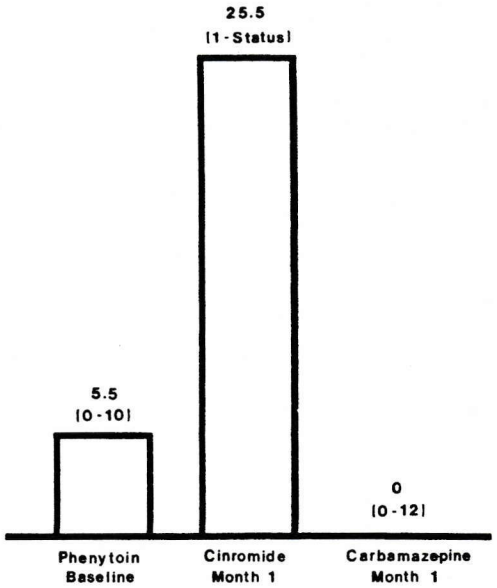

FIG. 3. Median monthly frequency of secondarily generalized seizures.

study. Thus, while overall seizure counts were not significantly different during treatment with phenytoin, cinromide, and carbamazepine, generalized seizures were more common with cinromide, particularly during the first 2 weeks of administration.

Side Effects and Toxicity

During the first month of treatment with cinromide, toxicity was prominent. The fraction of patients presenting drug-related toxic symptoms and abnormal neurological examinations did not differ significantly across treatment periods during either crossover or the study periods, but the number of complaints per patient differed dramatically (Fig. 4). Toxic symptoms of cinromide (especially drowsiness, lethargy, dizziness, and gastric disturbance) were qualitatively similar to those observed during phenytoin and carbamazepine therapy, but several patients reported insomnia during cinromide therapy. Toxic symptoms subsided with time or after reduction in dosage, and several patients were able to tolerate a gradual increase in dose over the final 12 weeks of cinromide administration without further toxicity problems.

There were no statistically significant differences across the drug treatment periods on the neuropsychological tests that could not be accounted for on the basis of repeated exposure to the testing materials or practice effects. When performance during cinromide administration was compared with that during carbamazepine administration, it was noted that on eight of 12 variables performance was better with carbamazepine and on only three variables was performance better with cinromide. (Performance was identical on one variable.) There were no differences in psychosocial functioning.

There were no clinically or statistically significant differences across the phenytoin, cinromide, and carbamazepine treatment periods with respect to any of the laboratory test results. None of the patients had any laboratory test results that were deemed dangerous enough to require discontinuation of drug administration at any time during the study.

Drug Doses and Plasma Levels

The eventual cinromide doses used were somewhat higher than the initial estimates, and the actual mean dose equivalency in the study was: 100 mg phenytoin = 209 mg carbamazepine = 705 mg cinromide. Mean (trough) ± SEM carbamazepine levels (7.9

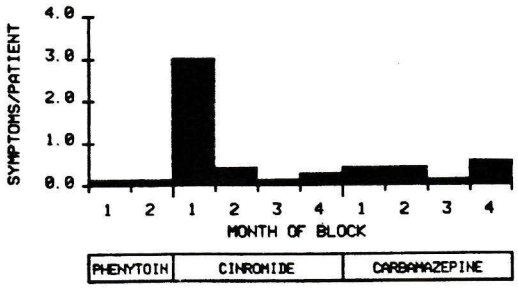

FIG. 4. Mean number of toxic symptoms reported per patient.

± 0.3 mg/L) were therapeutic, while phenytoin levels (27 ± 3 mg/L) were above the usual therapeutic range (Table 4). As expected, cinromide levels were barely detectable (mean 0.4 mg/L), while the amide metabolite (mean 2.9 mg/L) and acid metabolite (mean 31 mg/L) reached levels similar to those predicted from the single dose study (Wilensky et al., 1981).

Mean plasma levels of the amide and acid metabolites at the time of withdrawal from the study for the four patients who were withdrawn were 2.5 and 21 mg/L, respectively. These mean levels are within 1 SE of those found at the time of discharge in the patients who completed the cinromide trial, suggesting that inadequate dose was probably not the cause of the poor response to cinromide in the dropouts.

Drug Preference

Although there was no discernible treatment effect on total seizure frequency, striking differences did occur in individual patients. Four of the seven patients who completed the study preferred cinromide to carbamazepine treatment, because of better seizure control in three (2, 5, and 6) and due to a drop in seizure frequency during the last month of cinromide administration in patient 7. Two of the patients who preferred cinromide over carbamazepine (2 and 7) actually had the best clinical response during the phenytoin base-line period and received phenytoin during the follow-up period. Thus, the overall results of the study were that two patients preferred cinromide, two phenytoin, and three carbamazepine, while four patients receiving cinromide and none receiving phenytoin or carbamazepine dropped out of the study.

TABLE 4. *Drug plasma levels and doses (mean ± SEM)*

Drug	Mean values	Last month of treatment
Cinromide[a]		
Plasma level (mg/L)	0.4 ± 0.2	0.2 ± 0.1
Amide metabolite	2.9 ± 0.6	3.2 ± 0.9
Acid metabolite	31 ± 3	33 ± 4
Dose (mg/day)	3,100 ± 160	3,500 ± 230
Dose (mg/kg/day)	43 ± 4	45 ± 5
Phenytoin		
Plasma level (mg/L)	27 ± 3	24 ± 3
Dose (mg/day)	440 ± 40	430 ± 40
Dose (mg/kg/day)	5.9 ± 0.5	5.8 ± 0.4
Carbamazepine		
Plasma level (mg/L)	7.9 ± 0.3	8 ± 1
Dose (mg/day)	920 ± 40	1,100 ± 80
Dose (mg/kg/day)	12 ± 1	14 ± 2

[a] Last month values for patient 1 omitted.

DISCUSSION

Three problems were encountered during crossover to cinromide: the necessity for dosing four times daily because of the short plasma half-lives of cinromide and its metabolites, extensive initial toxicity, and poor control of secondarily generalized seizures. The four patients who were withdrawn from the study were receiving maximal tolerable doses of cinromide (with significant toxic symptoms), yet each had a substantial increase in seizure frequency or severity. This could be attributed to the rapid withdrawal of the predecessor drug, but no corresponding problems were observed during crossovers to carbamazepine, suggesting that the difficulty lay more in the inadequate buildup or delayed efficacy of cinromide.

Overall seizure control was not significantly different with phenytoin, cinromide, or carbamazepine for the seven patients who completed the study, but secondarily generalized seizure control was uniformly worst with cinromide. It is likely that toxicity pre-

vented us from administering full antiepileptic doses of cinromide. Primate studies showed that amide metabolite levels of 5 mg/L or higher were required for antiepileptic effects (Levy et al., 1981). We were unable to maintain amide metabolite levels in this range in our patients because of unacceptable toxicity. When used as a single drug, cinromide had an unfavorable therapeutic index and few, if any, advantages over standard antiepileptic therapy. Open add-on trials suggested that cinromide had promise as an adjuvant drug in the management of partial and generalized tonic-clonic seizures and for Lennox-Gastaut syndrome (Perchalski et al., 1982). However, placebo-controlled double-blind studies of cinromide as an add-on medication failed to demonstrate efficacy, and the drug has been withdrawn from testing by its manufacturer.

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RÉSUMÉ

On a évalué les résultats d'une monothérapie par le cinromide, drogue antiépileptique expérimentale, chez 11 adultes ayant une épilepsie partielle non contrôlée, suivis en consultation externe. Ces malades ont été traités par phénytoïne pendant 2 mois, cinromide pendant 4 mois et carbamazepine pendant 4 mois. Quatre patients ont été exclus de l'étude pendant ou peu après le passage au cinromide en raison d'une augmentation de la fréquence ou de la sévérité des crises. Parmi les patients restants, trois préféraient la carbamazepine, deux le cinromide et deux la phénytoïne, à la fois en ce qui concerne le contrôle des crises et le degré de toxicité. Le contrôle des crises n'était significativement différent pour aucun des trois produits, mais le contrôle des crises secondairement généralisées était invariablement plus mauvais avec le cinromide, et l'on observait aussi une tendance à la diminution des performances aux tests neuropsychologiques pendant le traitement par cinromide. Des effets toxiques neurologiques et gastro-intestinaux survenaient pendant le premier mois de ce traitement mais s'atténuaient avec le temps ou la réduction de la dose. Les tests biologiques ne montraient aucune anomalie nécessitant l'arrêt du médicament. Ces résultats suggéraient, au mieux, une utilité clinique très limitée de ce médicament et il a été retiré des essais par le fabricant.

(Charlotte Dravet, *Marseille*)

RESUMEN

Se ha evaluado la monoterapia con cinromida (antiepiléptico experimental) en 11 adultos con epilepsía parcial no controlada. Recibieron fenitoina dos meses, cinromida cuatro meses y carbamazepina cuatro meses. Cuatro pacientes fueron excluídos durante o a los pocos días del comienzo del crossover, por haberse in-

crementado la frecuencia y severidad de los ataques. De los restantes, tres prefirieron la carbamazepina, dos la cinromida y dos la fenitoina, basándose en el control de los ataques y grado de toxicidad. En general no se observaron diferencias significativas entre los tres medicamentos pero el control de las crisis generalizadas secundarias fué uniformemente peor durante la administración de la cinromida y también se observó una tendencia hacia el decremento de los resultados de los tests neuropsicológicos. La toxicidad gastrointestinal y de sistema nervioso central fueron prominentes durante el primer mes de tratamiento con cinromida pero se redujeron con el tiempo o con la disminución de la dosis. En los tests de laboratorio no se observaron anormalidades que aconsejaran una interrupción del fármaco. Los resultados sugieren, en sus mejores aspectos, una muy limitada utilidad clínica de esta medicación por lo que ha sido eliminada, por el fabricante, de ensayos terapeúticos.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

Die Monotherapie mit dem zu prüfenden antiepileptischen Medikament Cindromid wurde bei 11 erwachsenen ambulanten Patienten mit unbeherrschter Partialepilepsie durchgeführt. Diese wurden 2 Monate lang mit Phenytoin, 4 Monate lang mit Cindromid und 4 Monate mit Carbamazepin behandelt. Vier Patienten verließen die Untersuchung während oder kurz nach der Einführung von Cindromid wegen einer zunehmenden Frequenz oder Schwere der Anfälle. Von den verbleibenden favorisierten 3 des Carbamazepin, 2 das Phenytoin aufgrund der Anfallskontrolle und der etwaigen Toxizität. Das Ausmaß der Anfallskontrolle unterschied sich nicht signifikant zwischen den 3 Medikamenten, aber sekundär generalisierte Anfälle waren insgesamt am schlechtesten zu kontrollieren und es bestand daneben eine Tendenz zum schlechteren Abschneiden bei neuropsychologischen Tests während der Cindromidverabfolgung. Die Toxizität auf das ZNS und den gastrointestinalen Apparat zeigte sich während des ersten Monats der Cindromidbehandlung verschwand aber allmählich, vor allem bei Dosisreduktion. Bei Laboruntersuchungen zeigten sich keine Auffälligkeiten, die ein Absetzen des Medikaments erforderlich machten. Die Ergebnisse lassen höchstens eine sehr begrenzte klinische Verwendbarkeit für dieses Medikament vermuten, das Präparat wurde während des Tests vom Hersteller zurückgezogen.

(D. Scheffner, *Heidelberg*)