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Zonisamide in Epilepsy: A Pilot Study

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Summary: We compared zonisamide monotherapy (12 weeks) to carbamazepine monotherapy (12 weeks) after phenytoin baseline monotherapy (8 weeks) in an open crossover pilot study of eight adults with uncontrolled partial seizures. Zonisamide had definite antiepileptic activity in five subjects. In two of these, response to zonisamide was superior to that to either phenytoin or carbamazepine. A third subject became seizure free on zonisamide, but had to be withdrawn after 18 days because of mild Stevens-Johnson syndrome. The other three subjects were withdrawn from the study because of drug toxicity, manifested mainly by impaired higher mental function and increased seizures. The best response to zonisamide was at doses approximating 6 mg/kg/day, with plasma levels of 20–30 mg/L. Plasma levels of >30 mg/L usually were associated with toxicity. The pharmacokinetics of zonisamide are complex and nonlinear, with steady-state plasma levels being approximately three times higher than those predicted from a single-dose study. **Key Words:** AD-810—CI-912—Clinical trial—Epilepsy—Partial seizures—Zonisamide.

Epilepsy is a common chronic neurological disorder affecting ~1% of the population. In most patients, seizures are controlled with currently available medications, but a substantial minority of patients does not benefit from standard medical treatment or does so only at the price of disabling drug toxicity. Thus there is a need for new, more effective, and less toxic antiepileptic drugs (Porter, 1983).

Zonisamide [3-sulfamoylmethyl-1,2-benzisoxazole (AD-810 or CI-912)] is a new experimental antiepileptic agent developed by Dainippon Pharmaceutical Co. and being evaluated by Warner Lambert Co. in the United States. It is chemically distinct from the commonly used antiepileptic agents. Its antiepileptic spectrum in rodents resembles closely that of phenytoin, and it is most effective against seizures arising in the cerebral cortex (Ito et al., 1980; Masuda et al., 1980; Kamei et al., 1981). A particularly promising aspect of the animal pharmacology of zonisamide is that the drug's therapeutic index is quite high in rodents, with antiepileptic activity manifested at plasma concentrations of 10 mg/L, whereas toxicity is not observed until levels ≥70 mg/L are reached (Masuda et al., 1979).

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Zonisamide is adequately absorbed and has a long plasma half-life, ~60 h in normal subjects and 27 h in patients (Ito et al., 1982; Matsumoto et al., 1983; Wilensky et al., 1984). However, its disposition is complicated by saturable binding to erythrocytes, probably to carbonic anhydrase (Maren et al., 1960), and observations on plasma and erythrocyte concentrations of zonisamide after single doses cannot be extrapolated to the multiple-dose situation (Wilensky et al., 1984).

Zonisamide was studied as a single medication in a group of adult epileptics whose seizures were uncontrolled by conventional medications. The study design chosen (see Patients and Methods) is a severe test of a new antiepileptic agent; only drugs with efficacy comparable to phenytoin and carbamazepine will perform favorably when tested in this way (Wilensky and Ojemann, 1980). The purpose of this pilot study was to make a rapid preliminary assessment of the antiepileptic efficacy, toxicity, and safety of zonisamide, uncomplicated by drug interactions, and to test the feasibility of a large double-blind study of zonisamide using the same design. The subsidiary goals of the study were to learn whether the provisional therapeutic range of zonisamide plasma levels (10–70 mg/L) found in animal experiments could be extrapolated to humans and to compare the pharmacokinetic behavior of zonisamide after chronic dosing to that observed after single doses.

PATIENTS AND METHODS

Subjects receiving stable phenytoin monotherapy were followed initially for an 8-week baseline. Two 12-week blocks (the first 10 days in the hospital for drug crossover), first receiving zonisamide then receiving carbamazepine or vice versa, then followed. At the end of the second drug treatment period, subject and physician reviewed the study records and made a joint decision of drug preference. Subjects continued to receive the preferred drug during the 8-week follow-up period.

Subjects

Eight ambulatory adult epileptic patients entered the study (Table 1). Each had four or more partial seizures per month, with or without secondary generalization, despite therapeutic plasma levels of phenytoin. The revised International Classification of Seizures was used (Dreifuss et al., 1981). Each patient had previously received extensive trials of standard antiepileptic medications. Women were of nonchildbearing potential. Informed consent was obtained according to the regulations of the University of Washington.

Study schedule

The study schedule is detailed in Table 2. Subjects were seen in the outpatient clinic of the University of Washington Epilepsy Center for clinical and laboratory evaluations and were hospitalized on the Center In-Patient Unit for drug crossover. In addition, subjects were contacted by telephone during the interval between hospital discharge and the next (third week) clinic visit, as a safety precaution. Provisions for emergency contact with physicians, clinic visits, and hospitalizations were explained in written instructions given to the subjects at the time they entered the study.

Laboratory tests

Plasma levels of phenytoin and carbamazepine were analyzed by high-performance liquid chromatography (Sawchuck and Cartier, 1980, 1982). Plasma and erythrocyte levels of zonisamide were also analyzed by high-performance liquid chromatography (Ito et al., 1982). Spiked control samples were processed along with each analytical analysis. The day-to-day coefficient of variation (CV) was 4% for phenytoin at a concentration of 14.0 mg/L and 5% for carbamazepine at a concentration of 6.9 mg/L (n = 53 for each compound). The CV for zonisamide in plasma was 3% at a concentration of 2.0 mg/L (n = 12) and 4% at a concentration of 15.0 mg/L (n = 17). The CV for zonisamide in erythrocytes was 8% at a concentration of 22.5 mg/L (n = 11). Recovery relative to spiked concentration for zonisamide was 100% in plasma and 90% in erythrocytes. The lower limits of detection for zonisamide were 0.2 mg/L in plasma and 0.5 mg/L in erythrocytes. Whole blood concentrations of zonisamide were calculated using the following equation: blood concentration = [(1 − hematocrit) × plasma concentration] + (hematocrit × erythrocyte concentration).

At the end of each drug period, a complete neuropsychological evaluation, the Neuropsychological Battery for Epilepsy, was administered (Dodrill, 1978). To evaluate emotional and psychosocial functioning, the Minnesota Multiphasic Personality Inventory and the Washington Psychosocial Seizure Inventory were given (Dodrill et al., 1980).

TABLE 1. *Subject characteristics*

Patient/age (yr)/sex	Presumed etiology	Seizure type; EEG (age in yr at onset)
1/45/F	Febrile seizure at 9 mo; head injury at 11 yr	CPS; left temporal epileptiform discharges (29)
2/30/M	Unknown	CPS, SG; moderate diffuse disturbance of brain function with temporal epileptiform discharges (1)
3[a]/48/F	?Meningitis	CPS, SG; multifocal left-sided epileptiform discharges (3)
4/50/F	Unknown	SPS, CPS; right frontal and temporal epileptiform discharges (28)
5[a]/32/M	Unknown	SPS, CPS, SG; midline and left frontal epileptiform discharges (<1)
6[a]/36/F	Unknown	CPS; slight diffuse disturbance of brain function (27)
7/18/M	?Premature birth	SPS, CPS, GTC; left frontal and temporal epileptiform discharges (9)
8[a]/36/F	Near drowning at 15 yr	CPS, SG; slight diffuse disturbance of brain function (15)

CPS, complex partial seizures; SG, secondarily generalized; SPS, simple partial seizures; GTC, generalized tonic-clonic.

[a]Withdrew from study during first mo of zonisamide administration.

TABLE 2. *Overall study schedule*

Event	Baseline (wk)		Hospital crossover (10 days)	Treatment period I (wk)						Hospital crossover (10 days)	Treatment period II (wk)						Follow-up (wk)	
	4	8		3	4	6	8	10	12		3	4	6	8	10	12	4	8
Physical examination	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	X	X	X
Vital signs	X	X	Daily	X	X	X	X	X	X	Daily	X	X	X	X	X	X		X
Symptoms	X	X	Daily	X	X	X	X	X	X	Daily	X	X	X	X	X	X		X
Seizure calendar	X	X	Daily	X	X		X		X	Daily	X	X		X		X		X
Hematology		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Blood chemistry		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Urinalysis		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Drug plasma levels	X	X	Daily	X	X	X	X	X	X	Daily	X	X	X	X	X	X	X	X
Electrocardiogram		X		X					X		X					X		X
Electroencephalogram		X							X							X		
Neuropsychological examination		X							X							X		

Drug administration

Phenytoin was dispensed in standard 100-mg capsules (Parke-Davis), carbamazepine in standard 200-mg tablets (Geigy), and zonisamide in 100-mg capsules prepared by Warner Lambert/Parke-Davis. Drugs were administered b.i.d. Based on data from our single-dose study of zonisamide (Wilensky et al., 1984) and previous experience with phenytoin and carbamazepine, the estimated dose equivalency for the three medications at the beginning of the study was 100 mg of phenytoin = 200 mg of carbamazepine = 200 mg of zonisamide. Doses were adjusted as necessary to minimize toxicity and maximize seizure control.

Treatment orders were phenytoin, zonisamide, and carbamazepine for patients 1, 2, 3, and 5 and phenytoin, carbamazepine, and zonisamide for patients 4, 6, 7, and 8.

RESULTS

Clinical course

Four subjects completed the study, and four were withdrawn before completion for various reasons. Table 3 outlines the clinical course of each subject during the study.

Of the four subjects completing the study, two (subjects 1 and 2) had the best overall response to carbamazepine, an intermediate response to zonisamide, and the poorest response during phenytoin baseline. The remaining two (subjects 4 and 7) responded best to zonisamide and have continued to receive it since the study was completed.

Side effects

Mild toxicity occurred in three of the eight subjects while they were taking phenytoin and in four of the six who received carbamazepine; however, toxicity was a major problem with zonisamide (Table 4). The side effects of zonisamide appeared to be largely dose related, increasing when plasma levels exceeded 30 mg/L (Table 4).

Neuropsychology

Table 5 summarizes the results of neuropsychological testing for the four patients who completed the study. All four patients had higher Verbal IQ scores and higher Full Scale IQ scores while receiving carbamazepine than while receiving zonisamide, with statistical significance achieved despite the small number of observations. There was a similar trend for poorer performance with zonisamide on Performance IQ and Halstead Impairment Index scores. These findings, although clearly preliminary, suggest that zonisamide, at the doses and high plasma levels attained in this study, may be associated with decreased mental skills.

Drug doses and levels

Figure 1 illustrates the accumulation of zonisamide in plasma and red blood cells on initiation of drug treatment in subject 7. Equivalent doses of the three antiepileptic agents used in this study were originally predicted to be in the ratio of 100 mg of phenytoin to 200 mg of carbamazepine to 200 mg of zonisamide; however, for subjects completing the study, they were 100 mg of phenytoin to 296 mg of carbamazepine to 141 mg of zonisamide (Table 6). Our cautious approach, designed to minimize side effects in initial administration of carbamazepine, probably accounts for the underestimation in carbamazepine dosage. More striking was the overestimation of required zonisamide dosage. Dosages of 500 mg/day were expected to result in plasma levels of ~9 mg/L, yet a mean dose of 475 mg/day (7.0 mg/kg) resulted in a mean plasma level of 32 mg/L. For example, subject 7 (Fig. 1) achieved this level with a dose of only 400

TABLE 3. *Clinical course during study*

Subject[a]	Seizure type	Mean monthly seizure frequencies[b] On PHT	On ZNA	On CBZ	Clinical details
1	CPS	20	9	5.7	Initial ZNA dose 600 mg/day raised to 800 mg/day at 10 days. Increasing toxicity at 4 wk (level 40 mg/L); toxicity eased with decrease in dose. CBZ preferred because of fewer seizures
2	CPS	17.5	11.3	12.7	ZNA at 500 mg/day (level 33 mg/L) produced some toxicity.
	SG	8.5	1	0.7	Seizures were fewer than on PHT with both ZNA and CBZ. CBZ preferred because of fewer side effects
3	CPS	15	>60	—	ZNA at 600 mg/day (level 37 mg/L) produced mild toxicity and
	SG	2	6	—	increased seizures. At 700 mg/day (level 50 mg/L), seizure incidence continued increased and toxicity was severe. Dropped from study. PHT restarted; toxicity cleared
4	SPS	28	1.7	≥27	Initial toxicity with high dose of ZNA on days 1 (1,200 mg, a
	CPS	3	8.3	2.3	medication error) and 2 (600 mg); cleared with lower dose. Levels 20–30 mg/L at 400 mg/day. Continued on ZNA because of fewer seizures
5	SPS	8.5	64	—	ZNA at 800 mg/day (level 33 mg/L) associated with toxicity and
	CPS	4	1	—	increased partial seizures. At 400 mg/day (level 19 mg/L)
	SG	2.5	5	—	toxicity and partial seizures cleared but GTC occurred excessively. Subject withdrawn from study and placed on CBZ
6	CPS	16	9	18	ZNA at 500 mg/day produced mild toxicity but seizures controlled. Toxicity cleared at 400 mg/day. On day 18 an allergic reaction (mild Stevens-Johnson) occurred. ZNA stopped and CBZ restarted. Allergic symptoms cleared but seizures recurred.
7	SPS	7	7.7	5	ZNA at 400 mg/day (level 27–31 mg/L) produced best seizure
	CPS	8.5	5	15.7	control. Mild initial side effects cleared spontaneously.
	SG	1.5	0	0	Continued on ZNA
8	CPS	0	Many	2.3	ZNA at 400 mg/day (level 35 mg/L) associated with toxicity and
	SG	1	>10	0	increased seizures. Toxicity improved but seizures, especially GTC, continued increased with lower ZNA dose (level 24–18 mg/L). Subject withdrawn from study and placed on CBZ

PHT, phenytoin; ZNA, zonisamide; CBZ, carbamazepine; CPS, complex partial seizures; SG, secondarily generalized; SPS, simple partial seizures; GTC, generalized tonic-clonic.

See Table 4 for details of toxicity.

[a]Drug order: PHT, ZNA, and CBZ for subjects 1–3 and 5; PHT, CBZ, and ZNA for subjects 4 and 6–8.

[b]One mo was defined as 28 days.

mg/day. Thus, as shown in Figure 2, observed steady-state plasma levels of zonisamide were on the order of three times those predicted, based on our single-dose study (Wilensky et al., 1984). Figure 3 depicts observed erythrocyte concentrations compared with those extrapolated from the single-dose study. The observed steady-state concentrations are lower than those predicted. This is consistent with saturation of erythrocyte binding of zonisamide at therapeutic concentrations (Ito et al., 1982; Wilensky et al., 1984). Finally, Figure 4 shows observed

TABLE 4. *Dose-related toxicity of zonisamide*

Subject	Dose (mg/day)	Plasma level (mg/L)	Toxic effects
1	600	34	Anomia, increased speech slurring
2	500	33	Speech slowed, decreased short-term memory
3	700, 500	50, 42[a]	Mental slowing, moderate ataxia, dysarthria, lethargy, increased seizure frequency (?)
4	1,200/600	29[a]	At start of crossover to zonisamide nausea, vomiting, perseveration in speech and writing, slowness. Cleared at 300 mg/day
5	800	33[a]	Dizziness, lethargy, mental slowing
6	500	Not done	Mental slowing, inability to concentrate and add a bowling score card
7	400	31	Speech slowed, decreased activity; tended to improve with time without a change in dose or plasma level
8	400	35	Dysphasia[b], difficulty in concentrating, mental slowness

[a]Not at steady-state.

[b]Possibly a postictal effect.

TABLE 5. *Comparison of carbamazepine and zonisamide on summary measures of performance*

Test variable	Carbamazepine Mean	Carbamazepine SD	Zonisamide Mean	Zonisamide SD	Significance
WAIS Verbal IQ	98.50	21.24	93.00	19.88	$p < 0.05$
WAIS Performance IQ	103.25	21.61	99.25	25.00	NS
WAIS Full Scale IQ	100.00	22.76	95.75	22.77	$p < 0.01$
Halstead Impairment Index	0.38	0.21	0.60	0.42	NS
MMPI average profile elevation	60.83	10.91	59.56	10.15	NS
WPSI overall psychosocial function	17.00	15.47	19.75	14.66	NS

WAIS, Wechsler Adult Intelligence Scales; MMPI, Minnesota Multiphasic Personality Inventory; WPSI, Washington Psychosocial Seizure Inventory.

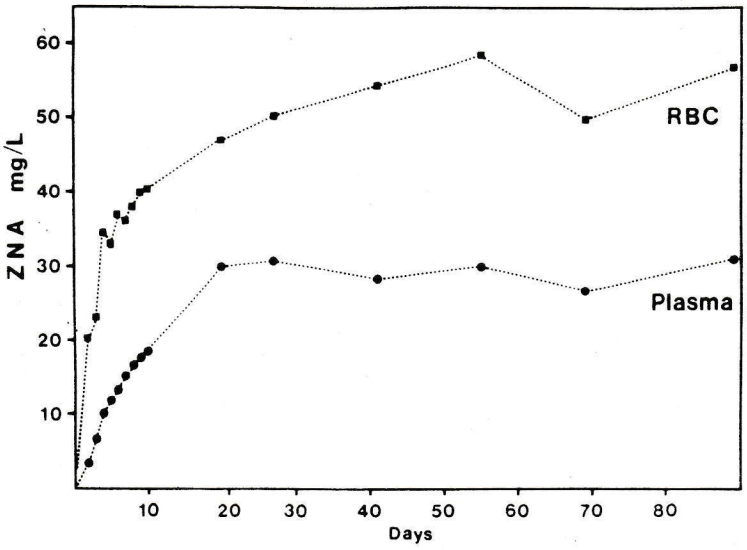

FIG. 1. Plasma and erythrocyte concentrations of zonisamide (ZNA) for subject 7 during administration of ZNA, 400 mg/day. Note the prolonged time (2–3 weeks) to reach steady-state plasma concentrations. RBC, red blood cell.

TABLE 6. *Final drug doses and concentrations*

Drug	Mean[a] ± SEM
Phenytoin	
Dose (mg/day)	338 ± 32
Dose (mg/kg/day)	5.1 ± 0.6
Plasma level[b] (mg/L)	19.9 ± 4.1
Zonisamide	
Dose (mg/day)	475 ± 48
Dose (mg/kg/day)	7.0 ± 0.7
Plasma level[b] (mg/L)	32.0 ± 0.9
Erythrocyte level[b] (mg/L)	62.4 ± 6.9
Carbamazepine	
Dose (mg/day)	1000 ± 82
Dose (mg/kg/day)	15.1 ± 2.2
Plasma level[b] (mg/L)	8.3 ± 0.6

[a]Observations are for the last month of each treatment period for the four patients who completed the study.
[b]Trough levels.

vs. predicted whole blood steady-state levels of zonisamide. Here there is reasonable agreement; further study is needed to determine whether this represents a true property of the drug—i.e., linear kinetics in blood—or merely a fortuitous combination of opposing effects.

The plasma levels of phenytoin in this study (19.9 ± 4.1 mg/L) were at the upper end of its therapeutic range, which is consistent with the patients' highly refractory seizures (Table 6). Carbamazepine levels (8.3 ± 0.6 mg/L) were in midtherapeutic range (Table 6). A provisional therapeutic range for zonisamide might be 20–30 mg/L. The upper limit of 30 mg/L is supported by the increasing frequency of adverse speech and cognitive effects observed at levels of >30 mg/L (Table 4). It is probable that poorer neuropsychological performance seen at a mean zonisamide level of 32 mg/L is dose related and that better performance would have been achieved at lower levels. The lower limit of the provisional therapeutic range is not so clearly defined. However, patients 5 and 8 had increases in generalized tonicoclonic seizure frequency at levels of ~20 mg/L or slightly below.

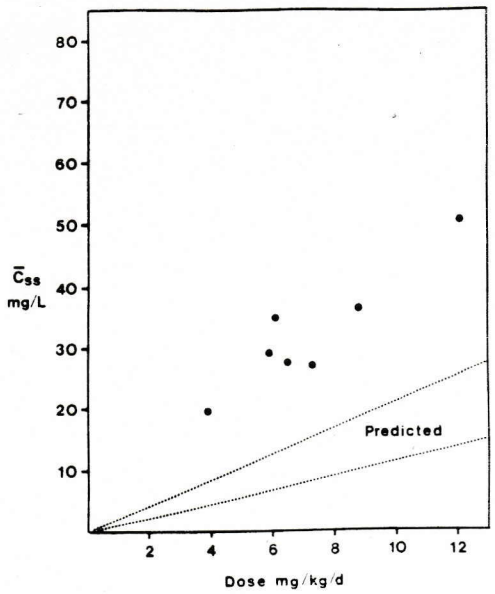

FIG. 2. Mean steady-state concentrations ($\bar{C}_{ss}$) of zonisamide (ZNA) in plasma for subjects 1–5, 7, and 8 compared with the range of concentrations predicted from our single-dose study in subjects treated with phenytoin (Wilensky et al., 1984). The dotted lines depicting the minimum and maximum predicted concentrations are the expected concentrations, assuming first-order kinetics, for the patients with the highest and lowest clearance values, respectively, found in the single-dose study. (Subject 6 withdrew from the study abruptly because of an allergic reaction to ZNA, so steady-state concentrations were not obtained.)

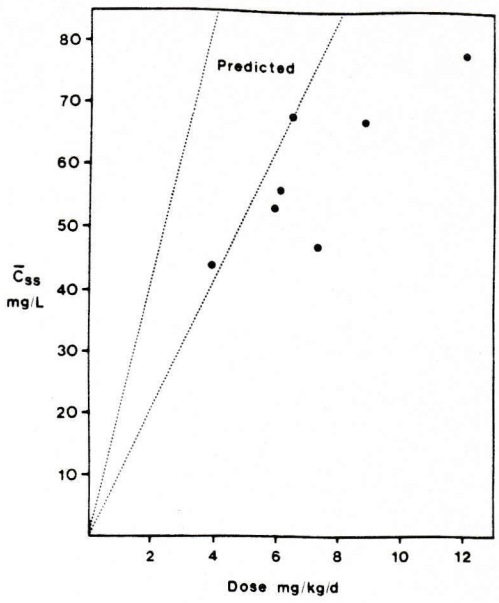

FIG. 3. Mean steady-state concentrations ($\bar{C}_{ss}$) of zonisamide (ZNA) in erythrocytes for the same subjects and sampling times shown in Figure 2 compared with the range of predicted values extrapolated from our single-dose study (Wilensky et al., 1984). Erythrocyte ZNA concentrations were lower than predicted values because of saturation of their binding capacity for ZNA.

Clinical laboratory tests

Few significant abnormalities were detected with blood chemistry, hematology, and urinalysis. Subject 2 had a transient increase in levels of serum glutamic-oxaloacetic transaminase (to 81 IU) and serum glutamic-pyruvic transaminase (to 97 IU) during week 3 of carbamazepine treatment, but these returned to normal spontaneously. Subject 4 had bacteria present in urine during a urinary tract infection in week 4 of zonisamide administration and transient leukopenia (white blood cell count 2,800/mm^3) during week 6 of zonisamide administration.

DISCUSSION

In five of the eight subjects, zonisamide showed definite antiepileptic activity. Two individuals had better seizure control with zonisamide monotherapy than with either phenytoin or carbamazepine. In two others, zonisamide was more effective than phenytoin but not as good as carbamazepine. The fifth individual (subject 6) was experiencing excellent seizure control with zonisamide when she developed an allergic reaction and the drug had to be withdrawn. The remaining three patients (subjects 3, 5, and 8) did very poorly while receiving zonisamide. In each case there was a significant deterioration in seizure control with toxicity. Once this syndrome occurred, it persisted despite reduction of zonisamide dose. These poor results with zonisamide may have been caused by one or more of the following factors: (a) too high an initial dose of zonisamide, (b) too abrupt a withdrawal of the previous anticonvulsant medication, and (c) seizure disorders refractory to zonisamide.

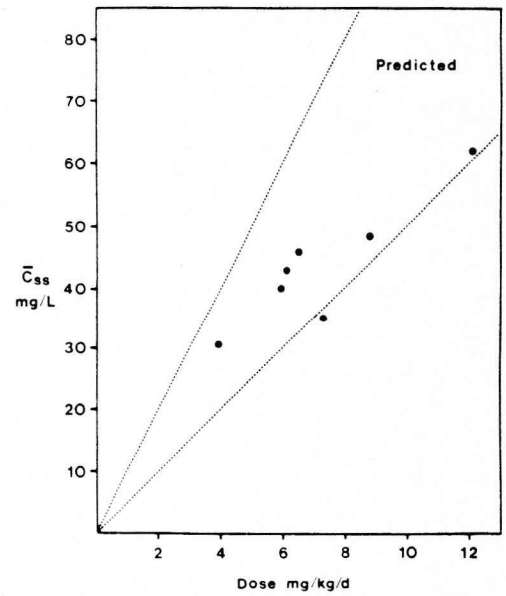

FIG. 4. Mean steady-state concentrations ($\bar{C}_{ss}$) of zonisamide (ZNA) in whole blood for the same subjects and sampling times shown in Figures 2 and 3 compared with those predicted from our single-dose study (Wilensky et al., 1984). In contrast to the plasma and erythrocyte data, observed concentrations in whole blood agreed reasonably well with predicted values.

The five subjects who showed a definite response to zonisamide were started at a mean dose of 460 mg/day (6.8 mg/kg), whereas the three nonresponders were started at a mean dose of 600 mg/day (8.1 mg/kg). Although there is considerable overlap in starting doses, these data suggest that a more cautious initiation of zonisamide treatment would result in fewer side effects. Although it is tempting to postulate that higher plasma levels of zonisamide actually caused the increased seizure frequency seen in subjects 3, 5, and 8, there is little evidence to support this. In fact, doses were lowered in each case after the deterioration in seizure control/toxicity syndrome developed, but seizures did not then come under control. Also, in animal studies, very high and lethal (604 mg/kg) doses of zonisamide given to mice failed to elicit convulsions (Masuda et al., 1980).

It may be that the dosages of previous anticonvulsant agents were reduced too rapidly while zonisamide therapy was initiated. Although rapid crossovers have been quite successful when going from phenytoin to carbamazepine or vice versa, the approach worked poorly when crossing from phenytoin to zonisamide in subjects 3 and 5 and from carbamazepine to zonisamide in subject 8. Because seizures tend to beget more seizures, in these patients the withdrawal convulsions may have led to deteriorating overall seizure control. Subtle postictal neuropsychological deficits may then have been compounded by drug toxicity, leading to the syndrome we observed. It is, of course, possible that subjects 3, 5, and 8 simply were nonresponders to zonisamide and that no changes in protocol could have prevented their problems. However, by extending the duration of crossovers onto zonisamide, with a more gradual reduction in previous drug dosage, the risk to subjects of deteriorating seizure contol may be reduced.

Zonisamide toxicity appeared to be qualitatively different from that observed with either phenytoin or carbamazepine, with impairments in speech and higher mental function more troublesome than cerebellar dysfunction. Neuropsychological tests confirm the subjects' complaints. Dizziness, confusion, inebriation, and decreased mental acuity were also common side effects with the prototype unsubstituted antibiotic sulfonamide, sulfanilamide (Goodman and Gilman, 1941). Similar negative cognitive effects were also noted in a previous study of another sulfonamide, sulthiame (Dodrill, 1975). Thus, the pattern of zonisamide toxicity in the central nervous system resembles most closely that of the early prototype unsubstituted sulfonamides, rather than that of the conventional antiepileptic agents. The relatively wide therapeutic window of zonisamide in rodents, based on the ratio of dosage causing gait disturbance to that blocking maximal electroshock seizures, may be misleading, in that decreased mental acuity occurred at doses that did not cause ataxia in our subjects. A dose-response study of the effects of zonisamide on some measure of learning or activity level in rodents might be appropriate at this time.

The expected neurotoxic plasma concentration of zonisamide of ≥ 70 mg/L, based on animal studies, was too high. In fact, slowed speech, lethargy, and mental slowing occurred in most of our patients at levels of >30 mg/L (Table 4). Although we are not able to specify precisely the lower limit of antiepileptic plasma concentration of zonisamide, a tentative therapeutic range is 20–30 mg/L. Thus, zonisamide appears to have a narrow therapeutic window, and dosing will require careful, individualized titration, with plasma level monitoring.

Difficulties in achieving desired plasma concentrations of zonisamide are compounded by the drug's complex pharmacokinetics. The initial kinetic study in normal subjects suggested that plasma levels achieved after chronic dosing would be higher than those predicted from single-dose studies (Ito et al., 1982). Our findings confirm this. Plasma levels were approximately three times higher than we predicted from a single-dose study in epileptic subjects (Fig. 2) (Wilensky et al., 1984). Regardless of the mechanism for this nonlinear kinetic behavior, its existence, coupled with the drug's narrow therapeutic window, underlines the need for careful individualization of zonisamide dosage. Based on our experience, a target dose of 6 mg/kg is appropriate, and steady-state plasma concentrations will be achieved in 2–3 weeks. At this time, plasma levels can be checked, and the subject can be examined with special attention to mental status. Whether side effects might be minimized by building up to the target dose of zonisamide gradually is unknown.

In conclusion, zonisamide monotherapy showed definite antiepileptic activity in five of eight adults with long-term refractory partial seizure disorders. In two subjects, response to zonisamide was superior to that with either phenytoin or carbamazepine monotherapy. Zonisamide toxicity was qualitatively different from that of standard antiepileptic agents in that impairment of speech and higher mental functions was more common than cerebellar dysfunction. Zonisamide appears to have a low therapeutic index, with a tentative therapeutic range of 20–30 mg/L in plasma, which should be achieved with doses on the order of 6 mg/kg. The drug's kinetics are complex and nonlinear, with plasma levels after chronic dosing approximately three times higher than those predicted from single-dose studies. The combination of low therapeutic index and nonlinear kinetics necessitates careful individualization of dosing, with plasma level monitoring. Further neuropsychological studies are required to delineate precisely the effects of zonisamide on higher nervous system function; further pharmacokinetic studies are needed to determine the mechanisms of the drug's nonlinear disposition and to establish dosing guidelines. A double-blind comparison of monotherapy

with zonisamide vs. carbamazepine, patterned after this open study, appears to be feasible, but the duration of drug crossovers will have to be increased and initial zonisamide doses decreased, to avoid the deterioration in seizure control combined with severe toxicity experienced during the first month of zonisamide therapy in three of the eight patients studied.

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RÉSUMÉ

Les auteurs ont comparé la monothérapie au zonisamide (pendant 12 semaines) à la monothérapie à la carbamazépine (pendant 12 semaines) après une médication de base par la phénytoïne (pendant 8 semaines). Cette étude a été un cross-over ouvert et a été faite chez 8 adultes ayant des crises partielles non contrôlées par le traitement. le zonisamide a une activité antiépileptique nette chez 5 sujets et chez 2 d'entre eux, la réponse a été meilleures qu'avec la phénytoïne et la carbamazépine. Une 3e sujet est devenu libre de crises sous zonisamide, mais le médicament a dû être arrêté au bout de 18 jours en raison d'un syndrome de Stevens-Johnson léger. Les 3 autres patients sont sortis de l'étude à cause d'une toxicité médicamenteuse se traduisant surtout par une atteinte des fonctions mentales supérieurs et une recrudescence des crises. Les meilleurs résultats ont été obtenus avec des doses d'environ 6 mg/kg par jour, avec des taux plasmatiques de 20–30 mg/litre. La pharmacocinétique du zonisamide est complexe et non linéaire, les taux plasmatiques à l'état d'équilibre étant à peu prés 3 fois plus élevés que ceux prédits par l'étude de l'administration de doses uniques.

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RESUMEN

En 8 adultos con epilepsía parcial no controlada se ha realizado un estudio piloto abierto y cruzado comparando 12 semanas de monoterapia con zonisamida con monoterapia con carbamazepina (12 semanas) después de una monoterapia básica con fenitoina (8 semanas). La zonisamida mostró una clara actividad antiepiléptica en 5 sujetos. En dos de estos la respuesta de la zonisamida fué superior a la que se había alcanzado con fenitoina o con carbamazepina. Un tercer enfermo no tuvo ningún ataque con zonisamida pero la tuvo que interrumpir después de 18 días debido a un síndrome moderado de Stevens-Johnson. Los otros 3 individuos fueron excluídos del estudio porque la toxicidad medicamentosa se manifestaba fundamentalmente con trastorno de las funciones mentales superiores y un incremento de los ataques. Las mejores respuestas a la zonisamida se obtuvieron con dosis que se aproximaban a ómg/kg/d, con niveles plasmáticos de 20–30 mg/L. Los niveles plasmáticos superiores a 30 mg/L se asociaron generalmente con toxicidad. La farmacocinética de la zonisamida es compleja y no lineal con niveles plasmáticos estables de aproximádamente 3 veces más altos que los previsibles para un estudio de dosis única.

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ZUSAMMENFASSUNG

Bei 8 Erwachsenen mit therapieresistenten Partialanfällen wurden die Ergebnisse von 12 Wochen Zonisamid Monotherapie, mit 12 Wochen Carbamazepin Monotherapie nach 8 Wochen Phenytoin Basismonotherapie in einer offenen crossover Pilotstudie verglichen. Zonisamid zeigte eindeutige antiepileptische Aktivität bei 5 Patienten. Bei 2 von ihnen überstieg die Wirkung auf Zonisamid die von Phenytoin bzw. Carbamazepin. Der dritte Patient wurde unter Zonisamid anfallslfrei,

die Therapie mußte aber 18 Tage später wegen eines leichten Stevens-Johnson-Syndroms abgesetzt werden. Die anderen 3 Patienten vollendeten die Studie nicht, da bei ihnen toxische Nebenwirkungen in Form einer Beeinträchtigung höherer geistiger Leistungen und einer Anfallszunahme auftraten. Die besten Ergebnisse auf Zonisamid brachten Dosen um 6 mg/kg/Tag mit Plasmaspiegeln von 20 bis 30 mg/1. Plasmaspiegel über 30 mg/l waren gewöhnlich mit toxischen Symptomen vergesellschaftet. Die Pharmakokinetik des Zonisamid ist komplex und nicht linear; steady state Plasmaspiegel liegen annähernd dreimal höher als von einer Monotherapie zu erwarten.

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