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Pilot Study of Zonisamide (1,2-Benzisoxazole-3-methanesulfonamide) in Patients with Refractory Partial Seizures

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Summary: A new anticonvulsant compound, zonisamide (1,2 benzisoxazole-methanesulfonamide), was studied in 10 adults with medically refractory partial seizures. Following a single oral dose of 400 mg, peak plasma levels occurred an average of 2.8 h after dosing, and the mean clearance from plasma was 2.34 L/h. Whole blood concentrations were higher than plasma concentrations because of red blood cell binding. Steady-state plasma concentrations were higher than predicted from a linear kinetic model. In most patients, seizure frequency was reduced after zonisamide was substituted for a standard antiepileptic drug. Dose-related reversible side effects in the central nervous and gastrointestinal systems were observed. Most patients tolerated doses between 5.2 and 12.5 mg/kg/day. **Key Words:** AD-810—1,2-Benzisoxazole-3-methanesulfonamide—CI-912—Partial seizures—Zonisamide.

Currently available antiepileptic drugs such as carbamazepine, phenobarbital, phenytoin, and primidone are effective in controlling epileptic seizures in many patients. However, there remains a large group of people for whom seizures cannot be controlled with drugs. In adults, the partial seizures (simple partial, complex partial, and partial seizures evolving to generalized seizures) are among the most difficult to control with medical management. There is a need to develop and test new compounds that may be safe and effective in the treatment of partial seizures.

There is evidence that a new compound, zonisamide (1,2-benzisoxazole-3-methanesulfonamide), may be an effective antiepileptic drug. The anticonvulsant properties of zonisamide were discovered through extensive testing of numerous 3-substituted 1,2-benzisoxazole compounds (Masuda et al., 1980). These properties of zonisamide were demonstrated in several animal models, including maximal electroshock seizures, maximal pentylenetetrazole-induced seizures, and kindling (Masuda et al., 1979, 1980; Kamei et al., 1981). The compound has been shown to suppress focal spiking and spread of secondarily generalized seizures in experimental animals (Ito et al., 1980). These studies indicate that the anticonvulsant profile of zonisamide is similar to that of phenytoin or carbamazepine (Masuda et al., 1980; Kamei et al., 1981).

Masuda et al. (1979) studied the relationship of plasma concentrations of zonisamide, its anticonvulsant effects, and impaired motor function in several species. Based on comparisons with phenytoin, phenobarbital, and carbamazepine in these animal paradigms, the authors predicted that zonisamide would be effective clinically in plasma concentrations between 10 and 70 μg/ml.

The present protocol was designed to study the single- and multiple-dose pharmacokinetics of zonisamide in patients receiving other antiepileptic drugs, to evaluate the safety of zonisamide with chronic administration, and to provide preliminary evidence of the efficacy of zonisamide in controlling medically refractory partial seizures in humans.

PATIENTS AND METHODS

Six men and five women of nonchildbearing potential entered the study. All patients were between 19 and 50 years of age and had at least four partial seizures per month, in spite of therapeutic plasma levels of two or

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TABLE 1. *Outline of experimental protocol*

Study phase	Treatment	Duration
1. Eligibility screen		
2. Baseline	Two or three standard antiepileptic drugs	8 wk
3. Single-dose kinetic study	Single dose of 400 mg of zonisamide. Continue baseline drugs	1 wk
4. Multiple-dose study	Zonisamide every 12 h plus baseline drugs	1 wk
5. Hospitalization	Continue zonisamide. Withdraw one baseline drug	~10 days
6. Outpatient treatment	Zonisamide plus remaining baseline drug(s)	10 wk

three standard antiepileptic drugs. Patients with more than four generalized tonic-clonic seizures in the 3 months before the study were not entered. Patients with other significant medical or psychiatric illnesses, with progressive neurological disorders, or with a history of status epilepticus were not eligible for this study. Informed written consent was obtained in each case. On entering the study, each patient underwent complete neurological and general physical examinations, electrocardiograms, EEG, complete blood count, blood chemistry profile, measurement of plasma anticonvulsant levels, and urinalyses. Seizures were classified according to the Revised International Classification of Epileptic Seizures (Dreifuss et al., 1981). One patient withdrew from the study in the baseline period, before receiving zonisamide. The study protocol is outlined in Table 1.

Baseline

The protocol included an 8-week baseline period during which each patient continued receiving either two or three standard antiepileptic drugs. The baseline treatment for each patient had previously been determined, on clinical grounds, to be the most effective regimen for that individual. The baseline treatment for each patient is listed in Table 2. Patients kept daily seizure logs throughout the study and were evaluated every 4 weeks during the baseline period. This evaluation included a review of the seizure log, interval medical history, general physical and neurological examinations, electrocardiogram, EEG, complete blood count, blood chemistry profile, measurement of plasma anticonvulsant drug levels, and urinalyses. A neuropsychological test battery was performed at the end of the baseline period.

Single-dose pharmacokinetic study

Following the baseline period, a single-dose kinetic study was performed. A single oral dose of zonisamide was given on the first day. Blood samples were obtained at 0, 0.33, 0.67, 1, 2, 4, 8, 12, 24, 36, 48, 60, 72, 84, and 96 h. These samples were assayed to determine the plasma and whole blood concentrations of zonisamide, using a high-pressure liquid chromatography technique (Warner-Lambert). Red blood cell concentrations were calculated from the plasma and whole blood concentrations and the hematocrit. Formulas used for calculating kinetic parameters are given in the Appendix.

Multiple-dose pharmacokinetic study

After completion of the single-dose kinetic phase, zonisamide was administered orally every 12 h. The dose for each patient was based on estimation of pharmacokinetic parameters derived from the single-dose kinetic study. An oral clearance rate was calculated for each patient (see Appendix for formulas). Then, based on a linear kinetic model, the dose required to achieve an average steady-state concentration of 17.5 μg/ml was calculated. The actual dose given in each case was ~80% of the calculated dose. This dose was given daily in two divided doses (every 12 h) for 7 days. During this interval, trough blood samples were taken every 48 h for measurement of whole blood and plasma levels.

Withdrawal of one baseline drug

On the eighth treatment day, each patient was admitted to the University of Michigan Clinical Research Center for ~10 days. One baseline antiepileptic drug was withdrawn, and trough (8 a.m.) plasma levels of all antiepileptic drugs were sampled each day. Approximated peak levels (11 a.m.) were sampled every other day. Doses of zonisamide were adjusted to achieve a plasma level of 15–40 μg/ml or reduced to eliminate side effects.

Outpatient treatment period

Once the plasma level of the drug withdrawn fell below 15% of the initial level, the patient was discharged from the hospital and evaluated weekly for 4 weeks, and then every 2 weeks for the remainder of the 12-week treatment period. Evaluation procedures were identical to those done during the baseline period. Neuropsychological tests were administered on week 12 of treatment.

RESULTS

Pharmacokinetics of zonisamide

The mean concentrations of zonisamide in plasma, whole blood, and red blood cells, following a single oral dose of 400 mg, are shown in Figure 1. The mean time to reach peak concentration (t_{max}) following a single oral dose of 400 mg was 2.8 h [coefficient of variation (CV) 37%] for plasma and 5.8 (CV 46%) for whole blood. The mean maximum concentration was 5.48 μg/ml (CV

TABLE 2. *Concomitantly administered antiepileptic drugs*

Patient	Weight (kg)	Drug	Initial dose (mg/kg/day)	Plasma level (μg/ml)		
				Initial	Mean baseline	Mean treatment
1	80.0	Carbamazepine	25.0	5.7	6.0	7.2
		Phenytoin	5.0	16.8	19.4	22.5
		Phenobarbital[a]	2.5	42.5		
2	84.6	Phenytoin	5.3	12.3	14.4	16.8
		Carbamazepine[a]	7.1	5.6		
3	116.0	Carbamazepine	8.6	7.2	7.9	9.6
		Primidone[a]	3.2	6.4		
		Phenobarbital[b]	0.0	11.7		
4	80.3	Phenytoin	5.0	27.2	20.8	17.0
		Primidone	9.3	8.8	8.3	7.8
		Phenobarbital[b]	0.0	33.3	33.5	35.2
		Valproic acid[a]	18.7	55.1		
5	77.6	Carbamazepine	18.0	5.2	5.9	8.7
		Primidone	6.4	5.4	5.0	4.9
		Phenobarbital[b]	0.0	15.1	16.8	21.0
		Phenytoin[a]	5.9	10.5		
6	81.6	Phenobarbital	2.2	26.3	25.0	25.4
		Phenytoin[a]	5.5	21.4		
7	69.7	Carbamazepine	17.2	7.2	7.2	9.8
		Phenobarbital[a]	2.6	26.4		
8	56.7	Carbamazepine	17.6	7.9	9.3	14.2
		Phenytoin[a]	7.1	15.4		
9	47.6	Carbamazepine	21.0	5.4	5.4	20.0
		Phenytoin[a]	6.3	14.4		
10	77.1	Carbamazepine	15.6	9.1	9.4	12.5
		Phenytoin[a]	5.2	15.1		

[a]Withdrawn during treatment period.
[b]Derived from primidone.

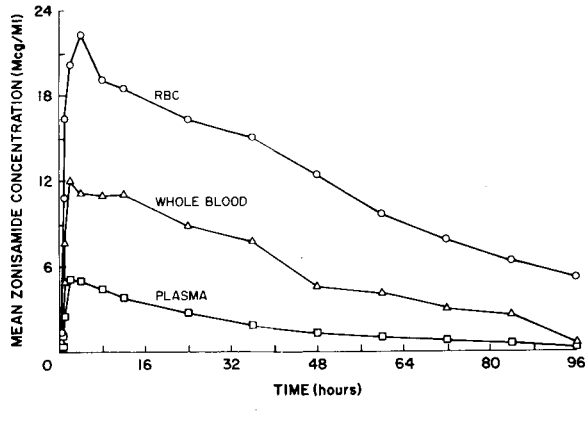

FIG. 1. Mean concentrations of zonisamide in plasma (squares), whole blood (triangles), and red blood cells (RBC; circles) following a single oral dose of 400 mg.

35.6%) for plasma and 13.4 μg/ml (CV 27.3%) for whole blood. The mean plasma clearance was 2.34 L/h (CV 36.6%). The mean plasma elimination rate constant was 0.0264 h^{-1} (CV 26.9%). The calculated half-life was 28.4 h (CV 33.9%). Although maintenance doses were chosen to reach a mean steady-state plasma concentration of 17.5 μg/ml, the actual steady-state levels tended to exceed the predicted value. The actual doses given every 12 h and the resultant average minimum steady-state concentrations in plasma are given in Table 3. In most cases, the minimum steady-state plasma concentration ($C_{ss,\,min}$) could be roughly estimated (± 28%) from the single-dose data using a simple formula: $C_{ss,min} = 1.81\ R/CL$, where CL is the plasma clearance and R is the daily dose. However, detailed analysis indicates that zonisamide follows Michaelis-Menten kinetics (Wagner et al., 1984).

Drug–drug interactions

The doses and plasma concentrations of concomitantly administered antiepileptic drugs are summarized in Table 2. For most drugs, the average plasma concentration during the baseline period was somewhat lower than the average concentration during treatment with zonisamide. There was a consistent rise in average carbamazepine concentrations following initiation of zonisamide therapy.

Seizure control

The effects on seizure control were measured in most cases by comparing the number of seizures during the 8-week baseline period to the number of seizures during

TABLE 3. *Average minimum steady-state concentrations of zonisamide as a function of dose*

Patient	Dose (mg/kg/day)	Treatment days	No. of values	Plasma minimum steady-state concentration (μg/ml)
1	10.00	8–20	12	26.1
1	20.00	45–59	3	41.3
2	9.46	9–115	13	25.1
3	3.44	9–44	14	19.6
3	5.18	72–215	7	39.9
4	14.94	8–12	5	49.6
4	12.46	17–166	10	36.3
5	7.72	9–13	5	19.6
7	11.48	3–9	3	22.9
7	5.74	38–87	5	36.2
8	10.58	8–31	9	25.0
8	8.82	52–166	5	30.2
9	12.60	8–16	9	35.0
10	14.70	23–74	6	35.9

the last 8 weeks of treatment (following substitution of zonisamide for one standard antiepileptic drug). These data are summarized in Table 4. Patient 5 was withdrawn from the study after 3 weeks because of a flurry of seizures. In retrospect, this flurry did not result from treatment with zonisamide, because similar flurries had occurred before the study and continued to occur following discontinuation of administration of the drug. In this case, seizure frequency (number of seizures per week) was used to calculate the percentage change in seizures. Patient 10 did not provide an accurate report of seizures during the first 4 weeks of baseline; in this case, the last 4 weeks of baseline were compared with the last 4 weeks of the treatment period. One patient experienced complete seizure control following treatment with zonisamide. Four others had >75% improvement. All but one of the remaining five patients had at least 50% reduction in seizure frequency. Patient 6 had no change in seizure frequency but reported a reduction in seizure severity. Frequencies of simple partial and complex partial seizures were reduced in most patients. However, generalized seizures occurred slightly more often during the treatment period in two patients.

Side effects and toxicity

All observed or reported side effects are listed in Table 5. No hematologic, hepatic, renal, cardiac, or other systemic toxic effects were observed. Side effects were observed or reported by all patients, but these were reversible or reduced to a tolerable level in each case. In

TABLE 4. *Comparison of seizure frequency during an 8-wk baseline period to seizure frequency in the last 8 wk of the treatment period*

	No. of seizures												
	Baseline						Treatment						Percentage change
Patient	SP	CP	PG	U	Total		SP	CP	PG	U	Total		
1		30	1		31		3	5	5	2	15		−52
2		23			23			1			1		−96
3	196	9			205		24	2			26		−87
4		38			38		14	4			18		−53
5	224				224	(28/wk)		38			38	(12.7/wk)[a]	−55
6	1	7			8		2	1	2	3	8		0
7	173	26			199						0		−100
8	30[b]				30			1			1		−97
9				252[c]	252		17	20			37		−85
10	6				6	(1.5/wk)	3				3	(0.75/wk)	−50[d]

SP, simple partial seizures; CP, complex partial seizures; PG, partial evolving to generalized seizures; U, unclassified because of incomplete description.

[a]This patient was withdrawn from study after 3 weeks of zonisamide treatment.

[b]Estimated minimum. Simple partial seizures were too numerous to count accurately.

[c]The patient was not able to differentiate between simple and complex partial seizures because of the high seizure frequency.

[d]Number based on last 4 weeks of baseline and last 4 weeks of zonisamide treatment.

TABLE 5. *Observed or reported side effects*

Side effect	No. of patients
Dizziness	3
Ataxia	7
Nystagmus	8
Diplopia	4
Tremor	3
Asterixis	1
Dysarthria	5
Drowsiness	7
Confusion	7
Nausea	2
Vomiting	1
Loss of appetite	5
Weight loss	8
Gustatory symptoms[a]	2
Cold chills[a]	2
Numbness[a]	1

[a]Reported by patients, but probably not drug related.

no case did side effects necessitate withdrawal from the study. The most common side effects were weight loss, nystagmus, mild ataxia, drowsiness, and mild mental confusion. In one patient who exhibited paranoid ideation and withdrawn behavior, zonisamide was withdrawn briefly, and these problems resolved. However, the behavior did not occur following reinstitution of the drug, and she continued taking the drug without side effects. Although symptoms and signs of toxicity appeared to occur primarily when plasma concentrations exceeded 40 μg/ml, a clearly definable toxic plasma level could not be determined in this small number of patients. However, impaired performance on some of the formal measures of cognitive and psychomotor tasks appeared to be related to the plasma levels of zonisamide. The relationship between plasma levels and neuropsychological performance will be discussed in a subsequent publication.

Side effects were most frequent during the initial 2 weeks of treatment with zonisamide. In some cases, side effects were associated with a rise in the plasma level of carbamazepine (three cases) or phenytoin (one case) and were resolved or markedly reduced after the dose of that drug was lowered. In seven patients, side effects were resolved or markedly improved after the dose of zonisamide was reduced. The final maintenance dose, resulting in minimal or no side effects, ranged between 5.2 and 12.5 mg/kg/day (mean ± SD 8.5 ± 2.5). The resultant plasma level ranged from 16.5 to 49.6 μg/ml (mean ± SD 30.7 ± 10.2).

DISCUSSION

The results of this study suggest that zonisamide may be effective in controlling simple partial and complex partial seizures. In all but one case, the number of partial seizures was reduced after substitution of zonisamide for one of the baseline antiepileptic drugs. This observation must be interpreted cautiously. In an unblinded study with no control group, the possibilities of observer bias or placebo effects must be considered. It is conceivable that elimination of one of the baseline antiepileptic drugs could have improved seizure control. However, these preliminary observations indicate that a more definitive efficacy study, using a double-blind controlled protocol, is warranted. Clinically significant antiepileptic effects were observed with plasma levels between 16.5 and 49.6 μg/ml. Dose-related side effects in the central nervous and gastrointestinal systems were observed. These observations suggest that the therapeutic range predicted from animal studies, 10–70 μg/ml (Masuda et al., 1979), may represent a reasonable estimate, although toxicity may occur at levels well below 70 μg/ml. Further study will be required to achieve a more accurate estimation of the therapeutic range. Zonisamide is quickly absorbed from the gastrointestinal tract, having an average t_{max} of 2.8 h. The calculated average half-life in plasma is ~ 28 h. However, this value may not be meaningful if, as we suspect, the drug follows concentration-dependent kinetics (Wagner et al., 1984).

The single-dose pharmacokinetic parameters observed in these patients were different from those reported in normal human volunteers by Ito et al. (1982). In that study, a single oral dose of 400 mg resulted in a mean peak plasma concentration of 13.4 μg/ml, a mean t_{max} of 5.3 h, and a mean elimination half-life of 56.7 h. These differences suggest the possibility of drug–drug interactions affecting the pharmacokinetics of zonisamide in patients receiving other antiepileptic drugs. The observed rise in level of concomitantly administered antiepileptic drugs, particularly carbamazepine, suggests the possibility that zonisamide may alter the pharmacokinetics of other drugs.

The clearance from the plasma following a single oral dose provides a rough prediction of the doses required to achieve a given steady-state concentration. Doses between 4 and 10 mg/kg/day should result in plasma levels in the expected therapeutic range. Zonisamide is highly bound to the red blood cell, resulting in high whole blood concentrations relative to plasma concentrations. The pharmacological and clinical implications of this red blood cell binding require further study. Zonisamide holds promise as a clinically useful antiepileptic drug. Further, more definitive efficacy studies and long-term safety and efficacy studies are in progress.

APPENDIX

The following equations were used to calculate pharmacokinetic parameters:

$\ln C_p = \ln C_p^o - \beta t$ (applied to log-linear postpeak C_p and t data)

$\overline{CL}_{po}$ = dose/(AUC 0–∞)

$\overline{C}_{ss}$ = dose/$(\overline{CL}_{po})\tau$

$V_\beta = \overline{CL}_{po}/\beta$

$$C_{ss}^o = \frac{\text{dose}}{V_\beta}\left(\frac{e^{-\beta\tau}}{1 - e^{-\beta\tau}}\right)$$

RBC concentration = $\frac{1}{H}[C_B - (1 - H)C_p]$

where

$\overline{CL}_{po}$ = plasma clearance after the single dose of 400 mg
β = elimination rate constant
$\overline{AUC}$ = area under the curve
$\overline{C}_{ss}$ = predicted average steady-state plasma concentration assuming linear kinetics
C_{ss}^{min} = predicted minimum steady-state concentration assuming linear kinetics
V_β = volume of distribution in the β phase
RBC = red blood cell
H = fractional hematocrit
C_B = whole blood concentration of zonisamide
C_p = plasma concentration of zonisamide
τ = dosage interval (12 h)

Note that after a 400-mg single dose, kinetics were essentially linear, and linearity was observed when postpeak C_p was plotted on semilogarithmic graph paper versus time. Hence, estimation of $\overline{CL}_{po}$, V_β, and β were perfectly valid.

When the patients were dosed to steady state, the plasma levels increased to a sufficient magnitude that kinetics became nonlinear, and steady-state clearance averaged only ~40% of single-dose $\overline{CL}_{po}$.

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REFERENCES

Dreifuss FE, Penry JK, Bancaud J, Henricksen O, Rubio-Donnadieu F, Seino M. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981;22:489–501.

Ito T, Hori M, Masuda Y, Yoshida K, Shimizu M. 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug: electroencephalographic profile. *Arzneimittelforsch* 1980;30:603–9.

Ito T, Yamaguchi H, Miyazaki H, Sekine Y, Shimizu M, Ishida S, Yagi K, Kakegawa N, Seino M, Wada T. Pharmacokinetic studies of AD-810, a new antiepileptic compound. Phase I trials. *Arzneimittelforsch* 1982;32:1581–6.

Kamei C, Oka M, Masuda Y,L Yoshida K, Shimizu M. Effects of 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810) and some antiepileptics on the kindled seizures in the neocortex, hippocampus and amygdala in rats. *Arch Int Pharmacodyn Ther* 1981;249:164–76.

Masuda Y, Karasawa T, Shiraishi Y, Hori M, Yoshida K, Shimizu M. 3-Sulfamoylmethyl-1,2-benzisoxazole, a new type of anticonvulsant drug. *Arzneimittelforsch* 1980;30:477–83.

Masuda Y, Utsui Y, Shiraishi Y, Karasawa T, Yoshida K, Shimizu M. Relationships between plasma concentrations of diphenylhydantoin, phenobarbital, carbamazepine, and 3-sulfamoylmethyl-1,2-benzisoxazole (AD-810), a new anticonvulsant agent, and their anticonvulsant or neurotoxic effects in experimental animals. *Epilepsia* 1979;20:623–33.

Wagner JG, Sackellares JC, Donofrio PD, Berent S, Samkar E. Nonlinear pharmacokinetics of CI-912 in adult epileptic patients. *Ther Drug Monit* 1984;6:277–83.

RÉSUMÉ

Un nouveau produit anticonvulsivant, le zonisamide (1,2 benzisoxazole-methylsulfonamide) a été administré à 10 adultes atteints de crises partielles non contrôlées par le traitement médical. Après une dose unique orale de 400 mg, le pic du taux plasmatique survient en moyenne 2 h 1/2 aprés l'ingestion, et la clairance plasmatique moyenne est de 2,34 litres par heure. Les concentrations sanguines totales sont plus élevées que les concentrations plasmatiques, en raison de la liaison aux globules rouges. Les concentrations plasmatiques à l'état d'equilibre sont plus élevées que celles que l'on peut déduire d'un modèle de cinétique linéaire. Chez la plupart des patients, la fréquence des crises a été réduite par la substitution du zonisamide au traitement antiépileptique standard. Des effets secondaires doses-dépendants et réversibles ont été observés au niveau du système nerveux central et du tube digestif. La plupart des patients ont toléré des doses entre 5,2 et 12,5 mg/kg de poids par jour.

(J. Roger, *Marseille*)

RESUMEN

En 10 adultos con ataques parciales refractarios al tratamiento médico, se ha estudiado la acción de un nuevo compuesto anticonvulsivo, la zonisamida (1,2 benzisoxazol-metanosulfonamida). Tras la ingestión de una sola dosis oral de 400 mg., se alcanzaron los niveles pico en plasma en un promedio de 2.8 horas después de la dosis y el aclaramiento medio del plasma fué de 2,34 litros/hora. Las concentraciones en sangre fueron más altas que las plasmáticas debido a que la medicación se ligaba a los hematies. Las concentraciones plasmáticas estables fueron más altas que las previsibles de un modelo cinético lineal. En la mayoría de los pacientes la frecuencia de los ataques se redujo después de cambiar la medicación antiepiléptica standard por la zonisamida. También se observaron los efectos colaterales sobre el tracto gastrointestinal y el sistema nervioso central que estaban relacionadas con la dosis y eran reversibles. La mayor parte de los pacientes toleró dosis que oscilaban entre 5.2 y 12.5 mg/kg/día.

(A. Portera Sanchez, *Madrid*)

ZUSAMMENFASSUNG

Ein neues Antikonvulsivum, Zonisamid (1,2 Benzisoxazol-Methansulfonamid) wurde bei 10 Erwachsenen mit therapieresistenten Partialanfällen gesucht. Nach einer oralen Einzeldosis von 400 mg wurden Plasmaspitzenwerte im Durchschnitt nach 2,8 Stunden erreicht. Die mittlere Clearance aus dem Plasma betrug 2,34 L/Stunde. Ganzblutkonzentrationen waren höher als Plasmakonzentrationen aufgrund der Bindung an die roten Blutkörperchen. Die steady-state Plasmakonzentrationen waren höher als bei einem linearen kinetischen Modell zu erwarten. Bei den meisten Patienten konnte die Anfallsfrequenz nach Substitution eines Standardantiepileptikums durch Zonisamid reduziert werden. Es bestanden dosisabhängige, reversible, zentral-nervöse und gastrointestinale Nebenwirkungen. Die meisten Patienten tolerierten Dosen zwischen 5,2 und 12,5 mg/kg/Tag.

(D. Scheffner, *Heidelberg*)