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Oxcarbazepine (GP 47 680) in the treatment of intractable seizures

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A single blind, within-patient clinical study was carried out on sixteen profoundly mentally retarded in-patients. Five of them had primary generalized, four had partial, six secondary generalized and one had mixed epileptic seizures. With the exception of two patients, all had for months or years been on CBZ combined with other anticonvulsive drugs. Eleven cases had received diphenylhydantoin, eight valproate, six had been given phenobarbital and five nitrazepam. Without changing other anticonvulsive therapy, CBZ was replaced by ox-CBZ up to a dosage of 30 mg/kg b.w. in two or three daily doses.

The anticonvulsive efficacy of ox-CBZ was considered better than that of CBZ in eight patients. In three cases, CBZ was preferred and in the remaining five no preference could be stated. A desirable psychotropic effect was found in three patients on ox-CBZ. Unwanted side effects occurred in seven patients. Two of them had their first episode of status epilepticus during the trial. Two out of sixteen patients had to discontinue the therapy. One of them experienced several episodes of status epilepticus, and the other patient lost appetite and had to be fed by tube. No signs of hepatitis occurred in any patient. Three patients are still on ox-CBZ, three and a half years from the start of the trial.

A knowledge of metabolic pathways and intermediate compounds has been proven useful for the development of new drugs with a clinical effect. Several derivatives of carbamazepine (CBZ) have also been studied for anticonvulsive purposes. One of them, oxcarbazepine (10, 11-dihydro-10-oxo-5H-dibenz(b, f)-azepine-5-carboxamide, GP 47 680) (Fig. 1) has been shown to have an anticonvulsive effect in both animals [1, 3] and in men [4, 5, 6]. Its pharmacokinetics and metabolism [2], and remarkably few untoward side effects in humans in comparison with CBZ have been re-

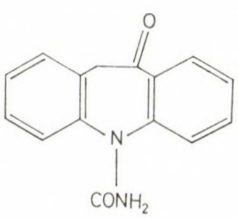

FIG. 1. Oxcarbazepine

ported [1, 4, 6]. Oxcarbazepine (ox-CBZ) is not a biological metabolite of CBZ but may be characterized as its 10-keto-derivative, which is rapidly converted to mono-hydroxy-CBZ and may be determined in plasma and other body fluids.

The purpose of the present study was to compare ox-CBZ with CBZ (Tegretol®) in profoundly retarded drug-resistant epileptic children and young adults in an institution for mentally retarded. In particular, clinical effect, unwanted side effects, effect on EEG, and association between oral dose, blood concentration and, on the other hand, clinical effect was compared.

Subjects and Methods

The patients were selected from 90 cases institutionalized for profound mental retardation and drug-resistant seizures. Sixteen out of the cases fulfilled the inclusion criteria: in-patients aged 5—25 years who had drug-resistant epileptic seizures when on CBZ. The age of six patients was 5—14 years, and the mean age of the remaining ten patients was 20 years. There were eleven males and five females.

In accordance with the informed consent of the parent or legal guardian the patients were accepted for the study, which was a singleblind, within-patient clinical trial.

Out of the 16 patients with various seizure types (Table I), all but two had been on CBZ combined with other anticonvulsive drugs for months or years. Eleven cases had received diphenylhydantoin, eight valproate, six had been given phenobarbital and five nitrazepam. The sixteenth patient had also received sultiam. The dosages of combined drugs were maintained unchanged during the trial.

Before the trial the patients were followed prospectively for seizures for a month. The frequency of seizures found during that period were compared with the frequency of fits during another, retrospective period of 12 months, which preceded the prospective period. Between the two frequencies, no statistically significant difference was found in X^2 test.

Table I

Seizure diagnoses prior to the trial

Types of seizures	N
Primary generalized	5
Partial, no secondary generalization	4
Partial with secondary generalization	6
Mixed	1
Total	16

CBZ was then gradually during 4—6 weeks replaced by 30 mg/kg b.w. of ox-CBZ in two or three doses. The titration phase was followed by a maintenance period of 12 weeks and ox-CBZ was again replaced by CBZ in all but three cases.

During the run-in, maintenance and post-trial periods clinical effects, function of bone marrow, liver and kidney, and serum levels of monohydroxy-CBZ were frequently monitored. The EEG was examined before and after the trial. The serum drug levels were determined by high pressure liquid chromatography. The clinical effects were judged by both the doctor and the ward staff.

The study was conducted in accordance with the ethical guidelines presented in the Declaration of Helsinki and after the approvement of the study design of the local ethical committee.

Results

The anticonvulsive efficacy of ox-CBZ was considered better than that of CBZ in eight patients. In three of

TABLE II

Anticonvulsive effect of oxcarbazepine in comparison with carbamazepine according to occurrence of fits and oxcarbazepine blood levels

Patient No.	Anticonvulsive effect	No. of fits during CBZ	No. of fits during ox-CBZ	Blood level of ox-CBZ (μmol/l)
1.	ox-CBZ > CBZ	7	0	66
2.	ox-CBZ = CBZ	5	4	73
3.	ox-CBZ > CBZ	110	37	61
4.	ox-CBZ > CBZ	28	4	80
5.	ox-CBZ > CBZ	24	15	57
6.	ox-CBZ < CBZ	103	124	38
7.	ox-CBZ > CBZ	180	83	48
8.	ox-CBZ > CBZ	12	4	50
9.	ox-CBZ = CBZ	7	13	73
10.	ox-CBZ > CBZ	6	4	58
11.	ox-CBZ < CBZ	4	8	20
12.	ox-CBZ = CBZ	1	1	52
13.	ox-CBZ = CBZ	10	5	73
14.	ox-CBZ < CBZ	11	18	63
15.	ox-CBZ > CBZ	12	9	48
16.	ox-CBZ = CBZ	2	1	

> means "better than", = means "equal", < means "poorer than"

them, the number of seizures when on ox-CBZ, decreased 75—100% and in five 50—74% of that found during the CBZ treatment. In three more cases, CBZ was preferred, and in the remaining five patients, no preference could be stated. In Table II, the mean blood values of the last four ox-CBZ specimens of each patient are shown. The clinical effect does not appear to be in any direct correlation to these values. Patients with a better ox-CBZ effect than CBZ effect had a mean concentration of 59 μmol/l of ox-CBZ and those with a better effect when on CBZ a mean level of 41 μmol/l. The value of ox-CBU was 67 μmol/l in cases with no difference in the anticonvulsant effect whether on ox-CBZ or CBZ.

A wanted psychotropic effect — improved attentiveness and frustration tolerance, decreased hyperkinesia, aggressiveness, anxiety and impulsiveness etc. — was found in three patients on ox-CBZ, in two of them without any good anticonvulsive effect. On the other hand, CBZ had a similar psychotropic effect in three other cases.

Unwanted side effects occurred in three out of eight patients with a good efficacy when on ox-CBZ treatment (Table III). A transient rise of SGOT and SGPT blood levels up to 223 and 249 units respectively (normal < 40) was found in one patient. No signs of hepatitis occurred, neither were any haematological complications. During the first replacement period, one pa-

TABLE III

Unwanted side effects of ox-CBZ treatment

Good ox-CBZ efficacy compared with CBZ (8 patients)	
— poor appetite, temporarily a slight disturbance of liver function	1 patient
— temporary hypothermia initially	1 patient
— anorexia, discontinuation of therapy	1 patient
Poor or equal efficacy, compared with CBZ (8 patients)	
— episodes of status epilepticus, discontinuation of ox-CBZ	1 patient
— increase of body weight of 3 kg/3 months	1 patient
— loss of appetite, more autistic	1 patient
— one episode of status epilepticus	1 patient

tient showed signs of hypothermia and another an increasing frequency of seizures. Both these side effects could be overcome by a renewed and slower run-in period.

Two of the sixteen patients had to discontinue the therapy. One of them experienced several episodes of status epilepticus, and the other lost appetite and had to be fed by tube.

In the present drug-resistant series of patients, there were four cases who experienced episodes of status epilepticus during the follow-up period. One of them had had these episodes both before, during and after the trial. Ox-CBZ didn't affect their occurrence. Another patient presented with a status epilepticus only in association with any change of the anticonvulsive therapy. This also occurred when CBZ was replaced by ox-CBZ.

The remaining two patients had their first episode of status epilepticus during the trial. One of them, a 13-year-old girl with a profound mental retardation and grand mal as well as psychomotor epileptic seizures, developed a status epilepticus when ox-CBZ had reached the blood level of 33 μmol/l. The status lasted for forty minutes in contrast to her habitual fits of one to five minutes. Ox-CBZ was continued for several more weeks without further episodes of status epilepticus. The co-medication comprised sodium valproate 41 mg/kg b.w. per day. Her EEG showed a moderate background slowing without irritative findings, but computerized tomography of the brain was normal.

In a male patient, aged 19 years, who had profound mental retardation and preceding short psychomotor fits, several episodes of status epilepticus were provoked during ox-CBZ therapy combined with diphenylhydantoin 4.3 mg/kg b.w. per day and nitrazepam 0.25 mg/kg b.w. per day. There was a grave background slowing and spike-and-wave bursts in the EEG. Status epilepticus did not reoccur when his ox-CBZ therapy was discontinued. The EEG was abnormal in all the cases (Table IV).

Three patients have now for 3 1/2 years received ox-CBZ, and it is highly preferred to CBZ by the staff. In all of them the seizure frequency has diminished by more than 50%, and in two cases it has been possible to discontinue diphenylhydantoin. A general observation of the remaining thirteen patients was that disconti-

TABLE IV

Changes in EEG during oxcarbazepine trial

Variable	Better or disappeared N	Unchanged N	Worse or increased N	Total N
General disturbance	4	11	1	16
Amount of theta and delta activity	4	11	1	16
Asymmetry	3	12	1	16
Irritative activity	2	14	—	16

nuation of ox-CBZ made the patients less bright and alert. One patient became autistic and had more seizures than before or during ox-CBZ.

DISCUSSION AND CONCLUSIONS

The present series comprised in-patients of an institution for mentally retarded who all had both a profound mental retardation and an intractable epilepsy. Situated relatively close to the University Hospital in Turku, the institution had, in addition to micro-laboratory, endocrinological and neurophysiological laboratory facilities, and it had access to a highly qualified academic neurological unit. In spite of that, the pre-trial anticonvulsive treatments had been unsuccessful.

Out of the sixteen patients, eight benefited by ox-CBZ, but only in three the beneficial effect was persistent and good enough to justify continued therapy with ox-CBZ instead of CBZ. Every fifth patient can be considered significantly benefited by ox-CBZ.

The present results support those earlier reported [5].

There were fewer unwanted side effects in patients with a favourable result of treatment than in those with a poor effect. Episodes of status epilepticus in association with ox-CBZ therapy have not been reported earlier. These cases had a profound mental retardation and intractable seizures but no common causative factors could be demonstrated.

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