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BRIEF COMMUNICATION

Therapeutic Effects of GABA-ergic Drugs in Affective Disorders. A Preliminary Report[1]

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EMRICH, H. M., H. ALTMANN, M. DOSE AND D. VON ZERSSEN. *Therapeutic effects of GABA-ergic drugs in affective disorders. A preliminary report.* PHARMACOL BIOCHEM BEHAV **19**(2)369–372, 1983.—A possible antimanic efficacy of the GABA-ergic anticonvulsant valproate was examined by use of a double-blind, placebo-controlled ABA design. A marked improvement was observed after valproate medication in a group of 5 acutely ill manic patients. Similar results were obtained in 7 trials examining the antimanic property of the keto-derivative of carbamazepine (oxcarbazepine) in 6 patients with acute mania, whereas no antimanic effect could be observed in a treatment with diazepam and with THIP. Combination of THIP and diazepam in another patient showed a slight antimanic effect. Additionally, a possible prophylactic effect of long-term treatment using valproate was examined. In 8 of 9 patients exhibiting a bipolar affective or schizoaffective psychosis, who did not properly respond to lithium treatment, a prophylactic effect of valproate medication could be demonstrated. The results point to the view that anticonvulsants, possibly due to GABA-ergic effects, may be beneficial in affective disorders.

GABA Mania Anticonvulsants Depression Valproate Oxcarbazepine Diazepam THIP

SINCE GABA represents one of the most important inhibitory transmitters in the CNS [14], not only anticonvulsant but also antimanic properties have been attributed to direct and indirect activation of GABA-ergic neurons. Several anticonvulsants have been used in the past as antimanic agents, which turned out to, at least partially, exert direct or indirect GABA-ergic effects; e.g., diphenylhydantoin (DPH), which is specifically GABA-ergic [6], has been used by Kubanek and Rowell [10] in 9 manic patients with great improvement in 5 and slight improvement in 2 of them. Carbamazepine, which exerts indirect GABA-ergic effects [4], has been used in acute mania as well as for prophylaxis [2, 3, 17, 18] and appears to be highly effective in both conditions. Similar reports have been documented about the amidation product of valproate, dipropylacetamide (DPA) [11, 12, 13], which, in a similar way as valproate, exerts indirect GABA-ergic actions [5].

The present investigation aimed at an evaluation of possible antimanic effects of valproate, oxcarbazepine (the keto-derivative of carbamazepine [20]), of diazepam, and of the specific GABA-agonist THIP [H_2O(4,5,6,7-tetrahydroisoxazolo) [5,4-C]pyridin-3-ol] [1]. Oxcarbazepine was used instead of carbamazepine, since this drug has less side effects than carbamazepine itself.

METHOD

Acute Treatments

Five patients treated with valproate displayed maniform psychoses (ICD-9-No. 296.3, 295.7) and were treated using a double-blind placebo-controlled variable ABA-design (A=placebo, B=valproate), the length of each treatment phase was unknown to the patient and to the psychiatrist performing the psychopathological evaluation (see also [9]). Informed consent was obtained from both the patients themselves and their close relatives, prior to commencement of the trial. Three hundred mg tablets of valproate were provided three times per day (at 7:45, 12:15, and 18:15) up to a dosage of, in one case, 3.8 g/day. Psychopathological evaluation was performed by a physician using the Inpatient Multidimensional Psychiatric Scale (IMPS; [16]). Five of the twelve IMPS-subscales (EXC, HOS, GRN, MTR, CNP) were summed up to form a score reflecting the patient's manic symptomatology (cf. [22]). An extensive physical and neurological examination was performed in all patients prior to the initiation of the trial. X-ray examination of the chest, ECG, EEG, and routine chemical measurements were performed prior to the onset of valproate medication. Thrombocyte count and bleeding time, in particular, were controlled

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TABLE 1

ACUTE EFFECTS OF VALPROATE, OXCARBAZEPINE, DIAZEPAM AND THIP IN MANIC PATIENTS

Case	Age	Sex	Diagnosis (ICD-9)	Medication	Maximal dosage (mg/day)	Initial IMPS value (%)	Mean IMPS value at maximal dosage (%)	Change (Δ%)
1	21	f	295.7	valproate	1,800	27.1	3.4	87.5
2	23	m	296.3	valproate	3,800	40.7	19.8	51.4
3	31	f	296.3	valproate	2,700	23.1	13.6	41.1
4	18	f	296.3	valproate	1,800	24.6	6.2	74.8
5	53	f	296.3	valproate	3,000	15.7	16.8	−7.0
6	28	f	295.7	oxcarbazepine	1,800	36.9	27.6	25.2
7	17	m	296.2	oxcarbazepine	1,800	44.6	16.6	62.8
8	34	f	296.3	oxcarbazepine	1,800	13.6	9.5	30.2
9	32	f	296.3	oxcarbazepine	1,800	26.1	11.3	56.7
10	28	m	295.7	oxcarbazepine	1,800	35.0	28.1	19.7
11a	33	f	295.7	oxcarbazepine	1,800	37.0	2.8	92.4
11b	34	f	295.7	oxcarbazepine	2,100	40.0	15.0	62.5
12	51	f	296.3	diazepam	60	23.0	28.8	−25.2*
13	56	f	296.3	THIP	70	31.1	43.6	−40.2
14	28	f	295.7	THIP+ diazepam	80 20	58.2	45.4	22.0

*MS-M data: slight improvement.

both before and during valproate medication. The serum concentration of valproate (venous puncture at 7:15, i.e., 13 hours after the last medication) was measured by use of gel-chromatography (detection limit 2 μg/ml [15]) in a double-blind design.

A similar type of variable double-blind placebo-controlled ABA investigation was performed in six patients (seven trials) displaying maniform psychoses (ICD-9-No. 295.7, 296.2, 296.5) employing the keto-derivative of carbamazepine, oxcarbazepine. Clinical and laboratory investigations were as described for the valproate studies. The oxcarbazepine dosage was increased in phase B to, maximally, 2100 mg/day.

In another patient with acute mania (ICD-9-No. 296.2) an acute trial was performed in the same fashion as described above using diazepam in a dosage ranging up to 60 mg/day.

In a further patient with acute mania (ICD-9-No. 296.3) a trial was performed using the same method as above, applying the specific GABA-agonist THIP in a dosage ranging up to 70 mg/day. In a further trial a combination of THIP (80 mg/day) and diazepam (20 mg/day) was applied.

Long-Term Prophylactic Treatments Using Sodium-Valproate

The prophylactic medication with valproate was performed in nine lithium non-responders, ICD-9-No. 296.3 (3), 295.7 (5), 296.0 (1); in 8 of them in combination with low doses of lithium (serum levels 0.4–0.8 mval/l) and in one case discontinuing the lithium treatment for some time, owing to the presence of severe lithium side effects. The clinical course of these outpatients was evaluated by a trained psychiatrist (open study) using the VBS (=Verlaufs-Beurteilungs-Skala, i.e., course-assessment-scale), a self-constructed scale [8] with 8 degrees of intensity, adapted here to reflect the global impression of "manic behavior" and "depression."

RESULTS

In Table 1 the clinical data of the patients evaluated during this study and the therapeutic effects are summarized. Valproate medication induces a mean therapeutic effect in the 50% range. This change occurs after a medication of 4–7 days. The therapeutic effect of oxcarbazepine, in a dosage of maximally (in 6 trials) 1800 mg/d, and in 1 trial 2100 mg/day, is comparable in its order of magnitude with that of valproate. One patient, treated with THIP in a maximal dosage of 70 mg/day, showed no therapeutic effect. The same is true for a patient treated with diazepam (in a dosage up to 60 mg/day). In this case, however, the MS-M data showed a slight improvement. A further patient treated with a combination of THIP (up to 80 mg/day) and diazepam (up to 20 mg/day) showed a small therapeutic effect (Table 1). The long-term application of sodium-valproate in combination with low doses of lithium was performed by use of a dose range from 800–1,800 mg/day, leading to plasma levels of 48–102 μg/ml. The duration of this prophylactic treatment is, as of presently, 1.5–5.5 years in 8 patients with bipolar affective or schizoaffective psychosis and one patient with monopolar depression (cf., Table 2). The average intervals between phases during the last 5 years before valproate therapy range from 5–19 months. During the observation period, as yet evaluated, only one case with a very severe schizoaffective psychosis has turned out to be not only a lithium- but also a valproate-non-responder, and another patient with schizoaffective psychosis exhibited two relapses of only the schizophrenic symptoms (cf., Table 2).

DISCUSSION

The present data, in addition to the evidence derived from studies in the literature (see Introduction above), are collectively strongly indicative of a positive therapeutical role of

TABLE 2

CLINICAL COURSE OF PATIENTS UNDER LONG-TERM VALPROATE THERAPY (IN COMBINATION WITH LOW DOSAGE LITHIUM PROPHYLAXIS)

Case	Age	Sex	Diagnosis (ICD-9)	Average interval between phases during the last 5 years before valproate treatment (months)	Duration of valproate therapy (years)	Number of relapses of the affective disorder during valproate therapy
S.W.	50	m	296.3	9	5.5	0
S.A.	36	m	295.7	10	5	2*
H.W.	41	m	295.7	5	4.5	0
B.W.	58	m	296.3	10	3.5	0
R.R.	35	f	295.7	19	3	2
S.M.	26	f	295.7	12	3	0
S.I.	62	f	296.1	7	2.5	0
H.H.	35	f	296.3	11	1.5	0
L.H.-P.	27	m	295.7	12	1.5	0

*Relapses of only schizophrenic symptoms.

different types of anticonvulsants in the therapy of manic syndromes and also, possibly, in depression. Both oxcarbazepine and sodium-valproate exerted a mild, but highly significant therapeutic action in acutely ill manic patients, whereas no positive effect of diazepam and of THIP alone was observed. It should be mentioned that the magnitude of the effects of valproate and of oxcarbazepine is comparable to that observed with acute lithium treatment [7]. Interestingly, there is also, from a clinical point of view, an apparent similarity between the mode of action of anticonvulsants in acute mania and the action of acute lithium treatment which is known to possess non-sedative, specific, mild antimanic properties. These similarities in the clinical profile of action may give rise to speculations as to a possible common mode of action of these therapeutic agents. One possibility of interest lies in the indirect GABA-ergic properties of these drugs [4,7].

The data concerning the action of THIP and of diazepam are not easily interpreted due to the low number of observations. Possibly, a combination of both compounds is more effective, since direct and indirect activation of GABA-ergic transmission is activated by this combined treatment.

Concerning the toxic effects of valproate on the liver, documented previously [19,21], it should be emphasized that these effects were observed primarily in epileptic children. Further, a strict routine evaluation of liver function was performed in our study and never revealed abnormal clinicochemcial findings.

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