Fluctuation of Plasma Cortisol Levels in Multiple Sclerosis

F. M. Butterworth, G. E. Ristow, E. Collarini

SUMMARY: *Using radioimmunoassay, the levels of plasma cortisol of 23 patients with multiple sclerosis and 10 control subjects were determined at three or more times over a one-year period. The status of the disease was ascertained by neurological examination at the same time. Twelve of the patients were considered stable because they showed no changes in their disease status during the year. The remaining 11 patients were designated active since each had one or more relapses. The levels of cortisol of the control and stable groups remained relatively constant during the one-year period, but the levels of the active group fluctuated significantly more than either of the other two groups. Furthermore the active patients who had more than one episode had the greatest fluctuation in their cortisol levels. The fluctuations could indicate some endocrinological aberration in patients with active multiple sclerosis or may be secondary to the influence of the disease.*

RÉSUMÉ: *Nous avons déterminé, par radioimmunoessai, les taux de cortisol plasmatique chez 23 patients atteints de sclérose en plaques et 10 sujets contrôles, et ce trois fois ou plus au cours d'une année. L'état de la maladie fut simultanément évalué par examen neurologique. Douze de ces patients furent considérés stables, n'ayant subi aucune modification de leur état au cours de l'année. Les onze autres furent considérés comme actifs, car ils eurent un ou plusieurs épisodes au cours de l'année. Le taux de cortisol demeura relativement constant durant l'année chez les deux groupes étudiés, mais les niveaux fluctuaient significativement plus dans le groupe actif. Les patients actifs ayant subi plus d'une rechute avaient le plus de fluctuations dans leur niveau de cortisol. Ces variations pourraient traduire une anomalie endocrinienne chez les patients sclérosés en phase active, mais elles pourraient aussi être secondaires au processus morbide lui-même.*

INTRODUCTION

The cause of multiple sclerosis (MS) is unknown, but the immune system is clearly involved. For example, a significant number of MS patients have subpopulations of abnormal T lymphocytes (Goust et al., 1978; Knight et al., 1975). Further, it has been documented that MS patients may have an immunological response to white matter preceding a relapse (Myers and Ellison, 1975). In addition, immunosuppressive drugs including adrenocorticosteroids and ACTH have been reported to cause some improvement in treated patients (Cendrowski, 1975; Hommes et al., 1975; but see Millar et al., 1967).

There have been several studies of adrenocortical activity and of the behavior of the adrenocortex-pituitary axis in MS patients (Garcia-Reyes et al., 1952; Teasdale et al., 1967; and Millac et al., 1969). Although the studies showed the MS patients to be normal in this respect, the studies were of an immediate and short-term nature. Approximately half of the patients in each of the studies were having a relapse; the other half were classified as stable. However, because the study was a one-time situation, no information could be provided relating changes of the disease status to the adrenocortical activity of the patients over an interval long enough to include several periods of stability and relapse for each of the patients.

In order to pursue the extended-term nature of the problem, the present study was carried out over a period of one year with a group of patients, where some had relapses and others were stable. As the paper will show, it was found that people suffering relapses had levels of plasma

cortisol that fluctuated more than those whose disease status was stable.

MATERIALS & METHODS

The patients who participated in the study attended a regularly scheduled MS clinic at a large metropolitan hospital in the Detroit area. Only patients with clinically definite MS (Schumacher et al., 1965; Rose et al., 1976) were considered, as judged by one of the authors (G.E.R.). Control subjects, who were asymptomatic were either friends or relatives of the patients or were from the clinic staff. Only those patients (and control subjects) who visited the clinic three or more times throughout a one-year period were used for this report.

Clinical data were obtained from the patients' records and by direct examination by one of the authors (G.E.R.). MS has a variable course and, therefore, at any given time any patient will be in one of the four disease states. The states are: *stable*, where the patient shows no change from the previous clinical evaluation; *progressive*, where the patient's condition become slightly worse than in the previous visit; *remission*, where the symptoms and signs of the previous evaluation improve; and *exacerbation*, where the patient's condition becomes slightly worse than worse. Patients who showed a change in disease state (CDS) from the previous visit were classified as *active*. The period of time between visits averaged three months and ranged from three weeks to six months. Those who throughout the year remained the same neurologically were classified as *stable*. Control subjects had no known MS history. There were comparable distributions of ages and sexes in each of the three groups of individuals. Subjects did not receive adrenocorticosteroid or ACTH therapy while participating in the study.

During the clinic, blood was drawn from each subject participating in the study. Using Vacu-Tainers containing dry EDTA, blood was drawn during a one-hour interval (1:30-2:30 p.m.) and immediately stored on ice. About two hours later, plasma was prepared by centrifugation at 4°C, aliquoted, quick-frozen in dry ice and ethanol, and stored in air-tight tubes at -20°C.

Cortisol levels were determined using the radioimmunoassay (RIA) method of Abraham et al. (1972) and Abraham (1975, personal communication). The cortisol antiserum was produced by Endocrine Sciences (Tarzana, California), ^{3}H-cortisol (spec. act. = 40 Ci/m mol) was obtained from New England Nuclear Corporation and unlabeled cortisol was purchased from Steraloids, Incorporated (Wilton, New Hampshire). Tritiated cortisol was purified by chromatography on Sephadex LH20 (Pharmacia) just prior to use. The heat inactivation method was always employed on the plasma samples. A standard curve and plasmas containing known amounts of cortisol were used in each RIA run. In all RIA runs used, the coefficient of variation of the known plasmas was less than 10%, and never greater than 10% of the expected value. Cortisol values were extrapolated and expressed as ng/ml of plasma from a hand-drawn standard curve and later verified by computation. The RIAs were done without any knowledge of the clinical results. Statistical comparisons of variations expressed as standard deviation of cortisol levels were carried out using Student's t-test and pooled estimate method.

RESULTS & DISCUSSION

A one-year longitudinal study was carried out on MS patients in regard to their level of plasma cortisol and their disease course. The patients with clinically definite MS were assayed at least three separate times over a one-year period for plasma cortisol levels. At the same time their disease course was ascertained by neurological exam. In addition, the plasma cortisol levels were determined in a group of control subjects who were asymptomatic. The results of this study are illustrated in Table 1.

There were three groups of subjects: Control, who were asymptomatic; MS-Stable, whose neurological condition remained constant for the year; and MS-Active, who experienced at least one relapse. Each group had comparable distributions of sexes and ages. There were about three times as many females as males in all these groups, and the age means and distributions were similar. Note that the distribution of ages in the control group was larger because the range was larger. The age at onset of the disease (AAO) was slightly higher in the MS-Active group (33 yrs as opposed to 29 yrs), which may be due to the fact that those patients in the MS-Active groups (E, G, and J) have the same date of diagnosis as that of the AAO, suggesting that earlier symptoms went unnoticed. The duration of the disease had a similar mean and distribution for both MS groups. The average number of visits to the clinic were slightly greater for the MS patients than the control subjects.

In the final two columns on the far right of Table 1, the average cortisol level for the year and corresponding standard deviation for each patient are presented. The level of plasma cortisol, expressed in ng/ml, was determined for each patient's, visit to the clinic. The average of all of the visits is in column six of the table, and the corresponding standard deviation is in the seventh column. This standard deviation is the principal measure of cortisol fluctuation (CF) or variability in cortisol level and is, as will be shown below, related to the disease status of the patient.

The individual standard deviations or CF's (column 7, Table 1) were averaged for each of the three patient groups to produce a measure of the average cortisol fluctuation (ACF) of the patient group. When the ACF's of each of the groups were compared, statistically significant differences between certain groups were demonstrated. The ACF's of the control and MS-Stable groups are statistically the same when compared using Student's t-test (P = 0.7) and the pooled estimate method. However, when the ACF of the MS-Active is compared with that of the control or the MS-Stable group, the MS-Active average cortisol fluctuation is significantly greater at the 95 percent level than either of the other two groups, using Student's t-test or the pooled estimate test.

The significant difference between the MS-Active and the other two

groups is due largely to the CF's of the patients who have experienced more than one relapse during the year. These patients are indicated with a "V" (very active) in the first column of Table 1. The average cortisol fluctuation (ACF) of the very active group is 76 (23). If this ACF is compared with that of the control or the MS-Stable groups, the differences are highly significant at the 99 percent level using either statistical test. The difference between the ACF's of the slightly active and very active groups is not significant (P=0.15). However, if these ACF's are compared with those of the stable group, one sees a definite, increasing trend: stable, 42 (25); slightly active, 53(25); and very active, 76 (23). Although this trend is intriguing, more patient data is needed.

TABLE 1

Cortisol fluctuations in control, MS-Stable and MS-Active patients as depicted by the standard deviation (S.D.) derived from the average of cortisol determinations made over a one-year period.

PATIENT GROUP	SEX	AGE	AGE AT ONSET	NUMBER OF VISITS	CORTISOL LEVEL FOR YEAR AVERAGE	S.D.
CONTROL						
A	F	46		3	150	62
B	F	60		4	126	56
C	M	70		4	85	20
D	F	56		3	96	34
E	F	28		3	203	64
F	F	12		3	111	54
G	M	52		3	135	49
H	M	48		4	173	44
I	F	52		3	152	16
J	F	22		3	184	56
10		45 (18)		3.3	142 (38)	46 (17)*
MS-STABLE						
A	M	44	34	3	143	25
B	F	45	28	5	236	73
C	F	26	22	4	111	14
D	M	36	30	3	173	9
E	F	49	34	3	142	11
F	F	44	20	3	218	29
G	M	57	34	4	196	36
H	F	49	27	3	167	59
I	F	47	34	4	189	82
J	F	28	20	3	156	63
K	F	63	36	4	167	63
L	M	38	29	4	157	36
12		44 (11)	29 (6)	3.6	171 (34)	42 (25)*
MS-ACTIVE						
A	F	30	19	3	197	50
B	M	51	37	3	120	25
C-V**	F	48	19	3	294	113
D-V	M	27	26	6	202	53
E-V	F	47	41	3	149	71
F-V	F	47	32	3	133	88
G	F	59	49	4	110	41
H	F	40	29	3	131	56
I-V	M	45	32	4	123	78
J-V	F	62	47	4	201	51
K	F	54	29	3	182	93
11		46 (11)	33 (10)	3.6	167 (55)	65 (26)*

*Average cortisol fluctuation (ACF)=average standard deviation of cortisol for each patient group. The number in parentheses is the corresponding standard deviation.

**V = very active (see text)

An attempt was made to depict a causal relationship between the cortisol fluctuation and the active disease course. By graphing the cortisol levels and clinical evaluation for each visit for the active patients, one can see no obvious relationship exists. It must be borne in mind that in this graph the lines connecting the points are drawn solely for visual continuity. Although a relapse occurred between two visits, it was often difficult to ascertain from the records or the patient exactly when the relapse occurred. Of course, the cortisol levels during the interval were not known. Inspecting the graph, one can see some large cortisol fluctuations (CF) preceded the change in disease state (CDS); some CF occurred simultaneously with the

CDS, and other CF's followed the CDS. Clearly the intervals are large and a cause and effect analysis will have to await a study which includes more frequent clinic visits.

Although the difference in the magnitude of the fluctuations is statistically significant, the possibility that the MS-Active group's wide fluctuations are due simply to chance or other physiological parameters must be considered. It is known, for example, that the plasma cortisol levels of women fluctuate as a function of the monthly menstrual cycle. However, analysis of our data shows that although the females have greater average fluctuations than the men, the differences between the fluctuations in men and women of each of the groups

and also between those of men and women as a whole are not significant. Furthermore, a study of Abraham et al. (1972), where plasma cortisol was measured daily through a menstrual cycle, demonstrates the differences are small. Five values gave a standard deviation of less than 40 ng/ml. Although the selected data were intentionally biased to inflate the standard deviation, the fluctuation is similar to that of the stable and control groups reported in this paper. In addition, Genazzini et al. (1975), using fluorometric analysis, also measured daily cortisol levels in 5 female subjects through 15 cycles. Again, a non-random averaging of 5 values of their data intentionally selected to yield the widest fluctuation gave an average standard deviation (ACF) of less than that found in our control or stable groups. Therefore, it is highly unlikely that variations due to changes in the menstrual cycle have had a significant effect on our results.

Elegant studies by Weitzman et al. (1971) have shown that the level of plasma cortisol varies cyclically throughout the course of a day. Blood samples collected every 20 minutes throughout 24 hours indicated the plasma cortisol levels of seven normal subjects reached peaks of nearly 200 ng/ml early in the morning and moved downward to almost a zero level in the evening. During the downward movement, all individuals displayed episodic cortisol secretion. Although we chose to collect our samples at a fixed time in order to achieve optimal uniformity, there was a possibility that there were episodic secretions at the time the blood was drawn. However, analysis of the combined data of Weitzman et al. (1971) and Czeisler et al. (1976) shows that these episodic variations are relatively small and insignificant in terms of the magnitude of the fluctuations found. For example, we selected non-randomly to inflate the standard deviations 5 values per patient from their data (12 patients each with 10 samples taken from noon to 3 p.m.). Averaging the individual standard deviations yielded a variability that was smaller than that found in our control and MS-Stable groups.
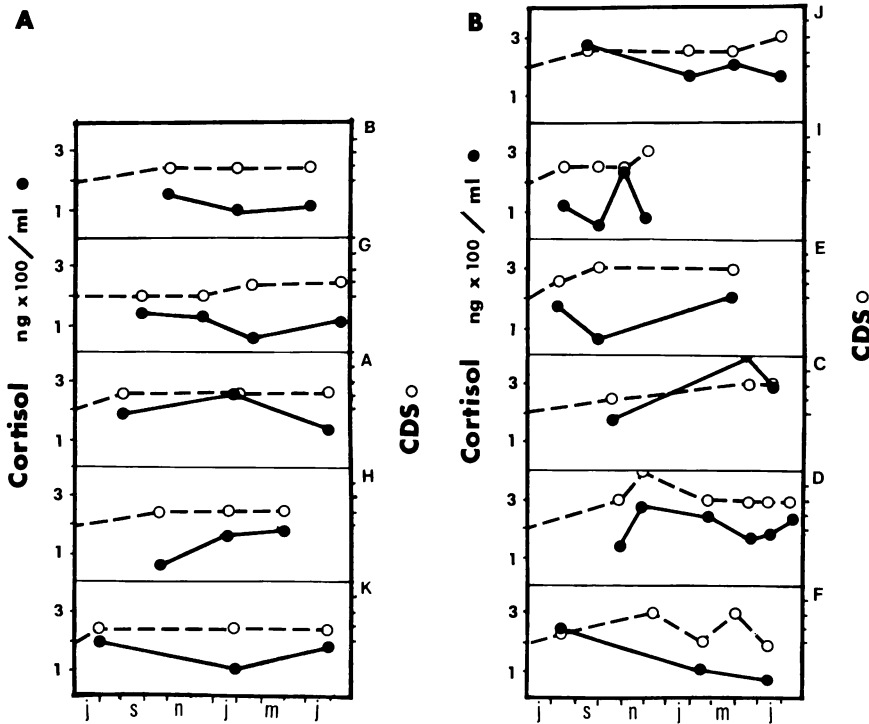

Figure 1 — Graphic representation of the cortisol levels (•——•) and disease state (o----o) of the eleven MS-Active patients. The left-hand ordinate is plasma cortisol in ng/ml. The right-hand ordinate represents the disease status in arbitrarily-chosen units. When the line is parallel to the abscissa, the condition was stable. When the line rises one unit, the disease state was progressive since the previous visit. A two-unit rise depicts an exacerbation. A lowering of the line is a remission. The lines connecting points are for visualization purposes only. To the right of each curve are the patients' reference letters (see Table 1). The abscissa is time in months. Note that the patients in part A experienced only one progressive episode during the year. The patients in part B experienced at least two episodes. Also note that occasionally only the disease state of a patient was assessed, but the blood was not drawn.

The Weitzman studies (1971) demonstrated two phases of cortisol secretory cycle: the major phase, in the early morning, which influenced the overall amplitude of the daily cycle, and the episodic phase, in the afternoon, which influenced the rate of cortisol decay. It is not known whether the same control mechanism regulates both phases. The large range of variability in the MS-Active patients may be due to variability in either of the two phases, because the plasma was collected during the middle of the episodic phase. In order to decide between the two alternatives, plasma would have to be collected earlier in the day. Secretion may not be the sole cause of the fluctuations, since the level of plasma cortisol is due also to the rate of degradation.

The wide fluctuations of plasma cortisol in the MS-Active patients may be induced by the pathophysiological effects of the disease. But perhaps the variability is due to effects secondarily related to the disease. For example, the fluctuations may be induced by changes in daily routines peculiar to one suffering a relapse (for example, see Weitzman, 1975); induced by depression (Sachar, 1975); or perhaps simply the MS-Active patient may be more susceptible to the psychological stress of venapuncture itself (Czeisler et al., 1976). On the other hand, there is a possibility that a defect exists in the hypothalamus-pituitary-adrenal-cortex (HPAC) axis in the MS-Active subjects. Studies of Garcia-Reyes et al. (1952), Teasdale et al. (1967), and Millac et al. (1969) have shown that the HPAC axis performs normally in MS-Active patients in response to specific pharmacological stimuli. However, because of the short-term nature of these studies, one cannot rule out the possibility of sporadic malfunctions in the HPAC axis in active patients over extended periods of time.

In conclusion, the results of a longitudinal study of MS patients showed that patients having an active disease course over a one-year period had plasma cortisol levels that fluctuated significantly more than patients whose disease course was stable and also asymptomatic control subjects. The data suggest that the more active the disease course, the more widely fluctuating the plasma cortisol levels.
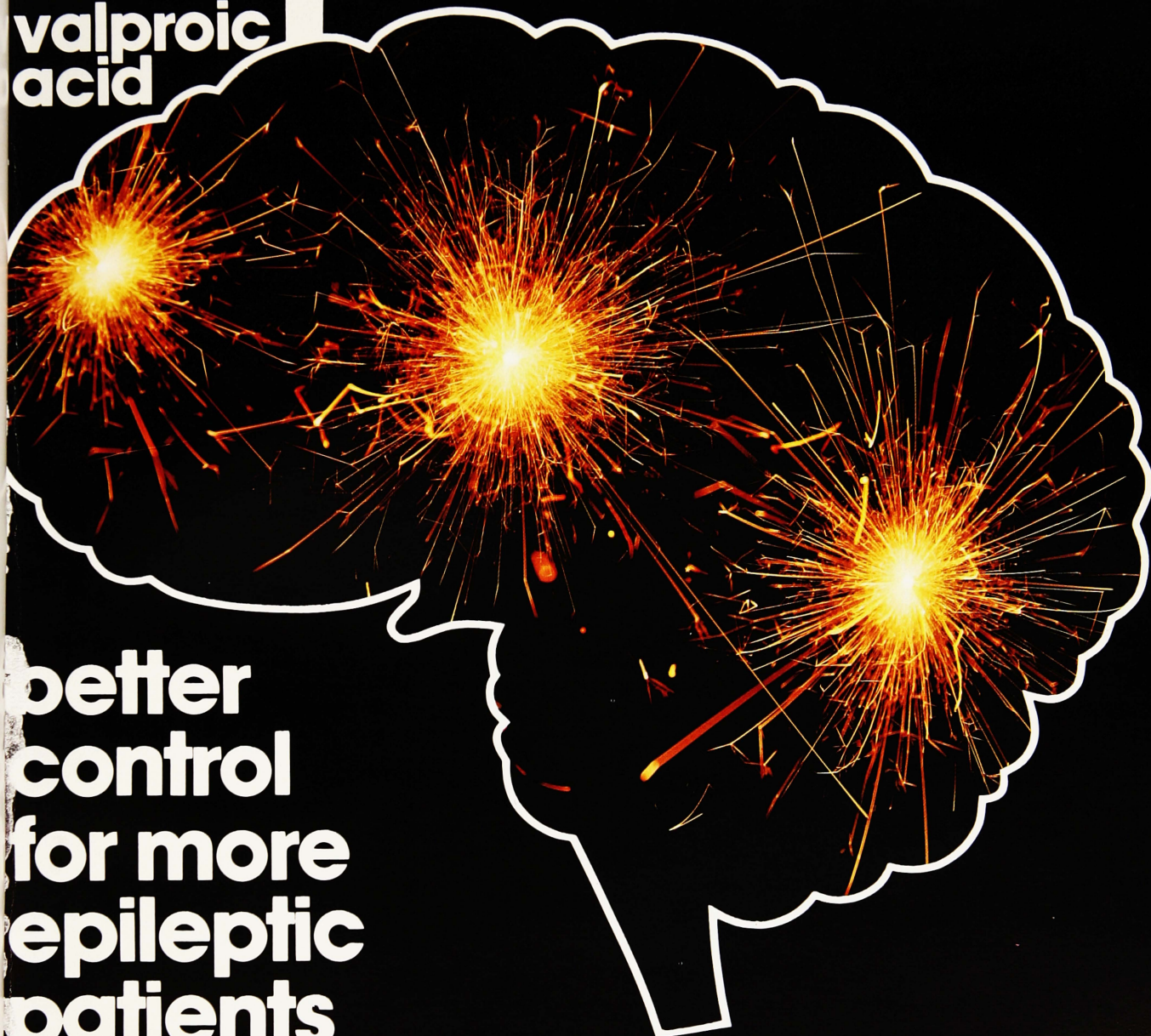
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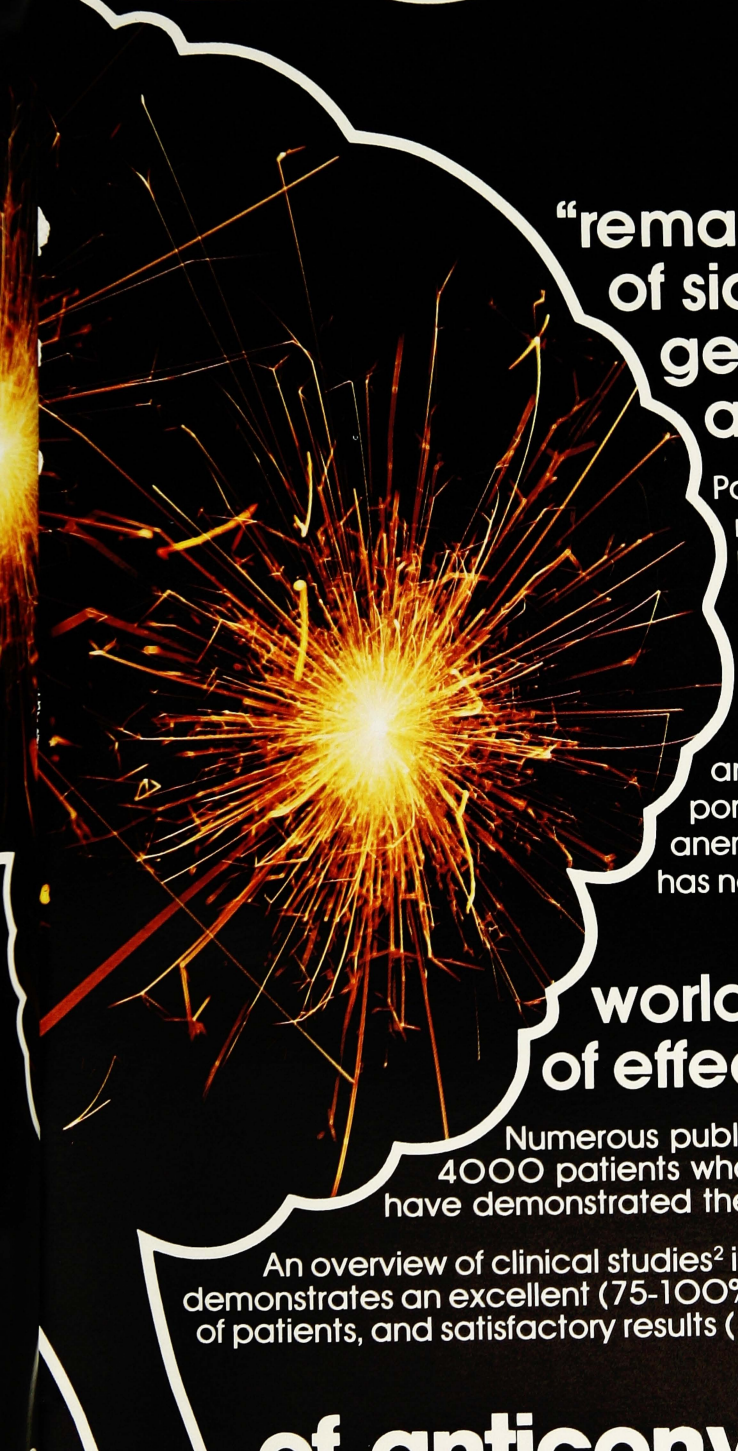$$O$$
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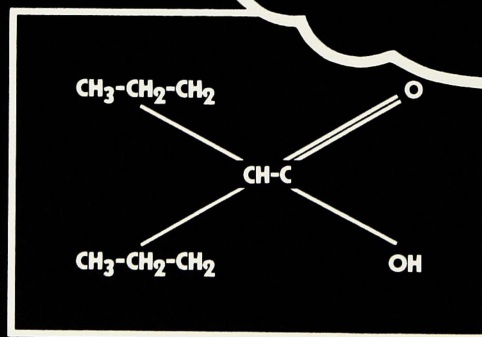
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Depakene
valproic acid

Prescribing Information

CLINICAL PHARMACOLOGY

Depakene (valproic acid) has anticonvulsant properties. Although its mechanism of action has not yet been established, it has been suggested that its activity is related to increased brain levels of gamma-aminobutyric acid (GABA).

Valproic acid is rapidly absorbed after oral administration. Peak serum levels occur approximately one to four hours after a single oral dose. The serum half-life ($t_{0.5}$) of valproic acid is approximately 8 to 12 hours. Valproic acid is rapidly distributed throughout the body and the drug is strongly bound (90%) to human plasma proteins. The therapeutic plasma concentration range is believed to be from 43 to 86 μg/mL.

Excretion of valproic acid and its metabolites occurs principally in the urine, with minor amounts in the feces and expired air. Very little unmetabolized parent drug is excreted in the urine. The principal metabolite formed in the liver is the glucuronide conjugate.

INDICATIONS AND CLINICAL USE

Depakene (valproic acid) is indicated for use as sole and adjunctive therapy in the treatment of simple and complex absence seizures, including petit mal. Valproic acid may also be used adjunctively in patients with multiple seizure types which include absence.

In accordance with the International Classification of Seizures, simple absence is defined as a very brief clouding of the sensorium or loss of consciousness (lasting usually 2-15 seconds), accompanied by certain generalized epileptic discharges without other detectable clinical signs. Complex absence is the term used when other signs are also present.

CONTRAINDICATIONS

Depakene (valproic acid) is contraindicated in patients with known hypersensitivity to the drug.

WARNINGS

Liver dysfunction, including hepatic failure resulting in fatalities, has occurred in a few patients receiving Depakene (valproic acid) and concomitant anticonvulsant drugs. These events have occurred during the first six months of treatment with valproic acid. Although a causal relationship has not been established, caution should be observed when administering Depakene to patients with pre-existing liver disease. Liver function tests should be performed prior to therapy and every two months thereafter.

Use in pregnancy

The safety of Depakene (valproic acid) during pregnancy has not been established, however, animal studies have demonstrated teratogenicity. Therefore, the physician should weigh the potential benefits against the possible risks in treating or counselling women of childbearing age who have epilepsy.

Recent reports indicate an association between the use of anticonvulsant drugs and an elevated incidence of birth defects in children born to epileptic women taking such medication during pregnancy. The incidence of congenital malformations in the general population is regarded to be approximately 2%; in children of treated epileptic women this incidence may be increased two to threefold. The increase is largely due to specific defects, e.g. congenital malformations of the heart, and cleft lip and/or palate. Nevertheless, the great majority of mothers receiving anticonvulsant medications deliver normal infants.

Data are more extensive with respect to diphenylhydantoin and phenobarbital, but these drugs are also the most commonly prescribed anticonvulsants. Some reports indicate a possible similar association with the use of other anticonvulsant drugs, including trimethadione and paramethadione. However, the possibility also exists that other factors, e.g. genetic predisposition or the epileptic condition itself may contribute to or may be mainly responsible for the higher incidence of birth defects.

Anticonvulsant drugs should not be discontinued in patients in whom the drug is administered to prevent major seizures, because of the strong possibility of precipitating status epilepticus with attendant hypoxia and risk to both the mother and the unborn child. With regard to drugs given for minor seizures, the risks of discontinuing medication prior to or during pregnancy should be weighed against the risk of congenital defects in the particular case and with the particular family history.

Epileptic women of child-bearing age should be encouraged to seek the counsel of their physician and should report the onset of pregnancy promptly to him. Where the necessity for continued use of antiepileptic medication is in doubt, appropriate consultation might be indicated.

Nursing Mothers

Depakene is secreted in breast milk. As a general rule, nursing should not be undertaken while a patient is receiving Depakene.

Fertility

Chronic toxicity studies in juvenile and adult rats and dogs demonstrated reduced spermatogenesis and testicular atrophy at doses greater than 350 mg/kg/day in rats and 90 mg/kg/day in dogs. The effect of Depakene (valproic acid) on the development of the testis and on sperm production and fertility in humans is unknown.

PRECAUTIONS

General

Because of rare reports of platelet aggregation dysfunction, thrombocytopenia and elevated liver enzymes, it is recommended that liver function tests, platelet counts and bleeding time determinations be performed before initiation of therapy and at periodic intervals.

Because valproic acid may interact with other anticonvulsant drugs, periodic serum level determinations of such other anticonvulsants are recommended during the early part of therapy (see Drug Interactions).

Valproic acid is partially eliminated in the urine as a ketone-containing metabolite which may lead to a false interpretation of the urine ketone test.

Driving and Hazardous Occupations

Valproic acid may produce CNS depression, especially when combined with another CNS depressant, such as alcohol. Therefore, patients should be advised not to engage in hazardous occupations, such as driving a car or operating dangerous machinery, until it is known that they do not become drowsy from the drug.

Drug Interactions

Depakene (valproic acid) may potentiate the CNS depressant action of alcohol.

There is evidence that valproic acid may cause an increase in serum phenobarbital levels, although the mechanism is unknown. Patients receiving concomitant barbiturate therapy should be closely monitored for neurological toxicity. Serum barbiturate drug levels should be obtained, if possible, and the barbiturate dosage decreased, if indicated.

There is conflicting evidence regarding the interaction of valproic acid with phenytoin. It is not known if there is a change in unbound (free) phenytoin serum levels. The dose of phenytoin should be adjusted as required by the clinical situation.

The concomitant use of valproic acid and clonazepam may produce absence status.

Caution is recommended when valproic acid is administered with drugs affecting coagulation, e.g. acetylsalicylic acid and warfarin (see Adverse Reactions).

ADVERSE REACTIONS

The most commonly reported adverse reactions are nausea, vomiting and indigestion. Since Depakene (valproic acid) has usually been used with other anticonvulsants, it is not possible in most cases to determine whether the adverse reactions mentioned in this section are due to valproic acid alone or to the combination of drugs.

Gastrointestinal

Nausea, vomiting and indigestion are the most commonly reported side effects at the initiation of therapy. These effects are usually transient and rarely require discontinuation of therapy. Diarrhea, abdominal cramps and constipation have also been reported. Anorexia with some weight loss and increased appetite with some weight gain have also been seen.

CNS Effects

Sedative effects have been noted in patients receiving valproic acid alone but are found most often in patients on combination therapy. Sedation usually disappears upon reduction of other anticonvulsant medication. Ataxia, headache, nystagmus, diplopia, asterixis, "spots before the eyes," tremor, dysarthria, dizziness, and incoordination have rarely been noted. Rare cases of coma have been reported in patients who were also on phenobarbital.

Dermatologic

Transient increases in hair loss have been observed. Skin rash and petechiae have rarely been noted.

Psychiatric

Emotional upset, depression, psychosis, aggression, hyperactivity and behavioural deterioration have been reported.

Musculoskeletal

Weakness has been reported.

Hematopoietic

Valproic acid inhibits the secondary phase of platelet aggregation. This may be reflected in altered bleeding time. Relative lymphocytosis and mild thrombocytopenia have also been noted in isolated cases. Leukopenia has been reported.

Hepatic

Increases in serum alkaline phosphatase and serum glutamic oxaloacetic transaminase have been noted. Isolated cases of severe hepatotoxicity have been reported (see Warnings).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In a reported case of overdosage with Depakene (valproic acid) after ingesting 36 g in combination with phenobarbital and phenytoin, the patient presented in deep coma. An EEG recorded diffuse slowing, compatible with the state of consciousness. The patient made an uneventful recovery.

As valproic acid is absorbed very rapidly, gastric lavage may be of limited value. General supportive measures should be applied with particular attention to the prevention of hypovolemia and the maintenance of adequate urinary output.

DOSAGE AND ADMINISTRATION

Depakene (valproic acid) is administered orally. The recommended initial dose is 15 mg/kg/day, increasing at one week intervals by 5 to 10 mg/kg/day until seizures are controlled or side effects preclude further increases. The maximum recommended dose is 30 mg/kg/day. When the total daily dose exceeds 250 mg, it is given in a divided regimen.

Table of Initial Doses by Weight (based on 15 mg/kg/day)					
Weight		**Total Daily Dose (mg)**	**Number of Capsules or Teaspoonsful of Syrup**		
kg	**lb**		**Dose 1**	**Dose 2**	**Dose 3**
10-24.9	22-54.9	250	0	0	
25-39.9	55-87.9	500	1	0	1
40-59.9	88-131.9	750	1	1	1
60-74.9	132-164.9	1,000	1	1	2
75-89.9	165-197.9	1,250	2	1	2

As the dosage of valproic acid is raised, blood levels of phenobarbital and/or phenytoin may be affected (see Precautions).

Patients who experience G.I. irritation may benefit from administration of the drug with food or by a progressive increase of the dose from an initial low level. The capsules should be swallowed without chewing to avoid local irritation of the mouth and throat.

AVAILABILITY

Depakene (valproic acid) is available as orange-coloured, soft-gelatin capsules of 250 mg in bottles of 100 and as a red syrup containing the equivalent of 250 mg valproic acid, as the sodium salt, per 5 mL in bottles of 450 mL. Depakene is a prescription drug (Schedule F).

1. Roberts, E.: Formation and utilization of gamma-aminobutyric acid in brain. In: S.R. Korey & J.I. Nurnberger (Eds.), Progress in Neurobiology. I. Neurochemistry. Hoeber-Harper, New York 1956, pp. 11-25.
2. Simon, D., Penry, K.J.: Sodium Di-N-Propylacetate (DPA) in the Treatment of Epilepsy, Epilepsia 16, 549-573, 1975.
3. Pinder, R.M. et al.: Sodium valproate: A Review of its Pharmacological Properties and Therapeutic Efficacy in Epilepsy. Drugs 13, 81-123, 1977.