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Treatment of Childhood Epilepsy with Dipropylacetic Acid (DPA)

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Summary. Dipropylacetate (DPA) was used in the treatment of different types of epilepsy in 112 children aged 1—20 years, with a mean age of 9.2 years, for a period of 19.8 months, ranging from 1 to 49 months. Of this group, 64 children were therapy-resistant to other antiepileptic medications prior to the introduction of DPA; 31 were treated for the first time with an antiepileptic drug, which was DPA; 44 were treated with DPA alone; and 68 had one or more additional antiepileptic medication.

The following results were found while DPA was administered in a relatively high dosage with a mean of 48 mg/kg body weight/day an ranging from 7 to 125 mg/kg/day.

1. Statistically, the results are significantly better in primary generalized epilepsy than in partial or in secondary generalized epilepsy.

2. Ninety-two percent of 51 patients who had absences were treated successfully. The same applies to 87% of 30 patients with primary generalized grand mal with spike wave, to all four patients who had impulsive petit mal, and to 47% of the 15 patients who had centrencephalic myoclonic-astatic petit mal.

3. Positive effect of DPA in partial epilepsy and secondary generalized epilepsy was seen only if the EEG pattern was 'centrencephalic' besides focal changes. During therapy with DPA, five patients with pure focal EEG showed an increase in seizure frequency, which demonstrated complete therapeutic failure.

4. Centrencephalic seizure activity (irregular spike wave, 3/s spike wave, and more than 3.5/s spike wave) were treated successfully ($P < 0.001$). Focal changes or focal sharp wave with tendency to spread or generalization were treated unsuccessfully.

Key words: Antiepileptic therapy – Dipropylacetic acid.

Zusammenfassung. 112 Kinder mit unterschiedlichen Epilepsien wurden im Alter von durchschnittlich 9,2 Jahren (1—20 Jahre) 19,8 Monate (1—49 Monate) mit Dipropylacetat (DPA) behandelt. 64 Kinder waren vorbehandelt,

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hatten jedoch auf die vorausgegangene Medikation nicht angesprochen, 31 erhielten DPA als erstes Medikament. Insgesamt wurden 44 Kinder allein mit DPA, 68 in Kombination mit anderen Medikamenten behandelt. Die Dosierung betrug durchschnittlich 48 mg/kg/die (7—125 mg/kg/die). Folgende Ergebnisse wurden erzielt:

1. Generalisierte primäre Epilepsien wurden statistisch signifikant günstiger beeinflußt als generalisierte sekundäre oder fokale Epilepsien.

2. Bei den generalisierten primären Epilepsien fand sich eine Wirksamkeit von 47—100%: centrencephale myoklonisch-astatische Anfälle 47%, Spike-wave-Absencen 92%, Grand-mal-Anfälle mit Spike-wave-Gruppen 87%, Impulsiv-Petit-mal-Anfälle 100%.

3. Positive Effekte bei den generalisierten sekundären (Lennox-Syndrom) und fokalen Epilepsien traten nur dann auf, wenn im EEG „centrencephale" EEG-Muster nachweisbar waren. Bei 5 Patienten mit alleinigen herdförmigen EEG-Veränderungen wurden erhebliche Verschlechterungen beobachtet.

4. „Centrencephale" EEG-Muster (irreguläre Spike-wave-Gruppen, 3/s und $>3{,}5$/s Spike wave) wurden signifikant beeinflußt ($P<0{,}001$), herdförmige Veränderungen und Sharp-wave-Foci mit Ausbreitung oder Generalisation zeigten keine Veränderung.

Schlüsselwörter: Antiepileptische Therapie – Dipropylacetat.

Introduction

In 1964, Carraz and co-workers [4] were the first to report on dipropylacetic acid (DPA), generic name for valproic acid, 2-propylvaleric acid or 2-propyl-pentanoic acid, and its anticonvulsant effects in man. Since that report, various clinical investigations [2, 3, 7, 8, 12, 14—17, 20, 21, 23—26, 29] and a survey [27] have been published. Animal experiments have suggested [11] that this substance, novel in antiepileptic therapy, acts via an increase in gamma-aminobutyric acid (GABA), the naturally occurring inhibitory substance of postsynaptic discharges. This effect is supposed to be due to competitive inhibition of gamma-aminobutyric acid transaminase, which catalyzes the transamination from GABA to succinic acid.

The aim of this investigation is to evaluate treatment with DPA in childhood epilepsy.

Methods

1. Patients

We report the results from 112 patients aged 1—20 years with a mean age of 9 years (Fig. 1); 55 were boys, 57 girls; 96 had primary generalized, 4 secondary generalized (Lennox syndrome), and 12 partial epilepsies. At the time of treatment, 64 patients were still suffering from convulsions, despite various medications in maximal dosage prior to treatment with DPA. Thirty-one patients were treated initially with DPA and 17 were treated with DPA for other reasons (Fig. 2).

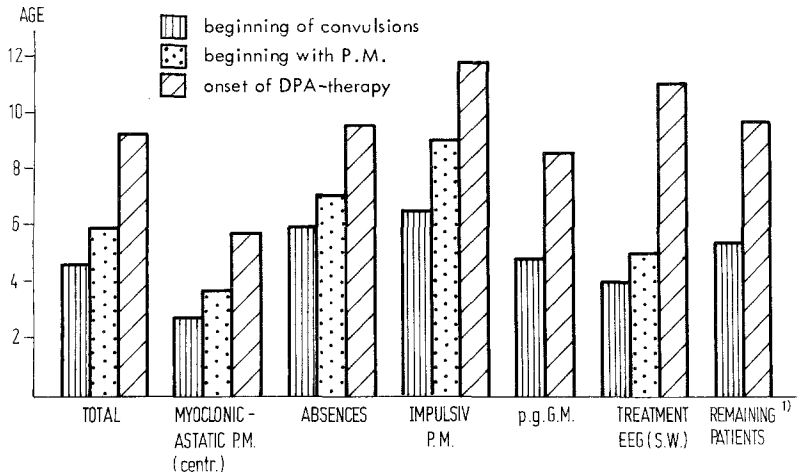

Fig. 1. Onset of seizures, onset of P.M., and onset of therapy with DPA
[1] Remaining patients = Lennox syndrome ($n = 4$) and partial epilepsy ($n = 12$)

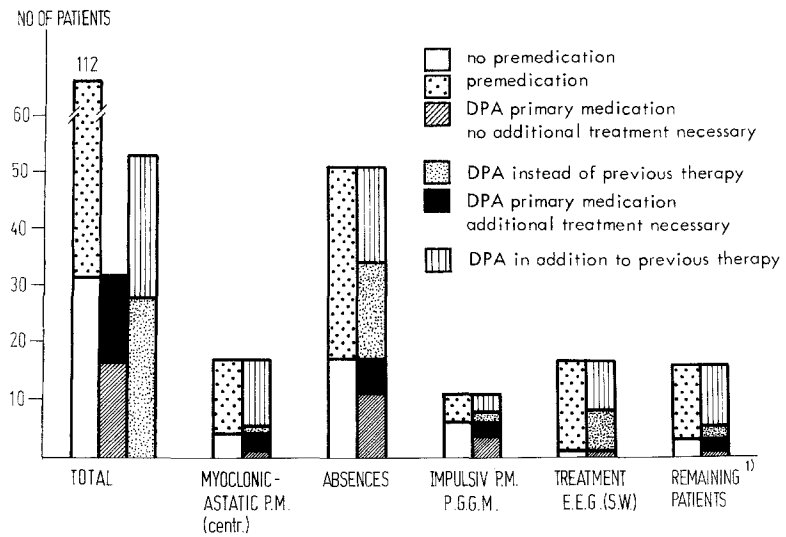

Fig. 2. Single or combined therapy with DPA
[1] Remaining patients = Lennox syndrome ($n = 4$) and partial epilepsy ($n = 12$)

The family history for epileptic seizures was positive for 24 children, 18 with primary generalized and 6 with partial epilepsy. Cerebral organic dysfunction was confirmed in 19 children, 10 with primary generalized and 9 with partial epilepsy.

Seizures during the neonatal period and convulsions in early infancy (massive myoclonic jerks) were found twice each in patients with partial epilepsy. We found a history of a grand mal condition with seizures lasting over 30 min in four patients out of every group. Of the group with primary generalized epilepsy, 13 patients had had a petit mal condition.

2. Grouping of Patients

The grouping of all patients was done according to the proposal of Gastaut [10, 19], with a slight modification by introducing special seizure subgroups [5, 6]:

I. Primary Generalized Epilepsies ($n = 96$, Fig. 1)

(a) Centrencephalic Myoclonic-Astatic Petit Mal [5]. 17 patients. Children with primary generalized myoclonic-astatic seizures and with facultative additional absences ($n = 11$) and centrencephalic EEG changes (irregular spike wave and/or generalized 3—5/s spike wave and/or abnormal rhythms).

(b) Absences. 51 patients. Mostly pyknoleptic absences with 3/s spike wave or more than 3.5/s spike wave in the EEG and facultative additional irregular spike wave.

In 9 children the absences began before the age of four: absences of early childhood [21].

(c) Impulsive Petit Mal (Massive Bilateral Myoclonus or Petit Mal Myoclonus). 4 patients. Myoclonic seizures at the beginning of puberty and polyspike and wave in the EEG.

(d) Primary Generalized Grand Mal. 7 patients. Primary generalized grand mal with centrencephalic EEG pattern (irregular spike wave, often additional abnormal rhythms).

(e) Treatment of EEG Changes. 17 patients. Various primary generalized seizures, at the moment without convulsions, but with constant generalized paroxysms (generalized irregular spike wave, 3—5/s spike wave) of high frequency (more than 1 paroxysm/20 s). DPA was added to the therapeutic regimen in low or medium dosage (Fig. 2). Included is one patient without seizures but with increasing generalized irregular spike wave during puberty.

II. Secondary Generalized Epilepsy ($n = 4$)

(a) Lennox Syndrome [9]. 4 patients. Seizures like those under (a), basically petit mal seizures but with spike-wave variant pattern in the EEG and often different kinds of focal signs during the interval.

III. Partial Epilepsies ($n = 12$, Fig. 1)

(a) Secondary Generalized or Focalized Grand Mal (Focal Grand Mal). 5 patients. Primary generalized or focalized grand mal seizures with focal pattern in the EEG.

(b) Focal Seizures (Partial Epilepsy with Elementary Symptomatology). 3 patients. Two patients with Jacksonian seizures and one with adversive seizures.

(c) Secondary Generalized Grand Mal in Combination with Focal Seizures. 4 patients.

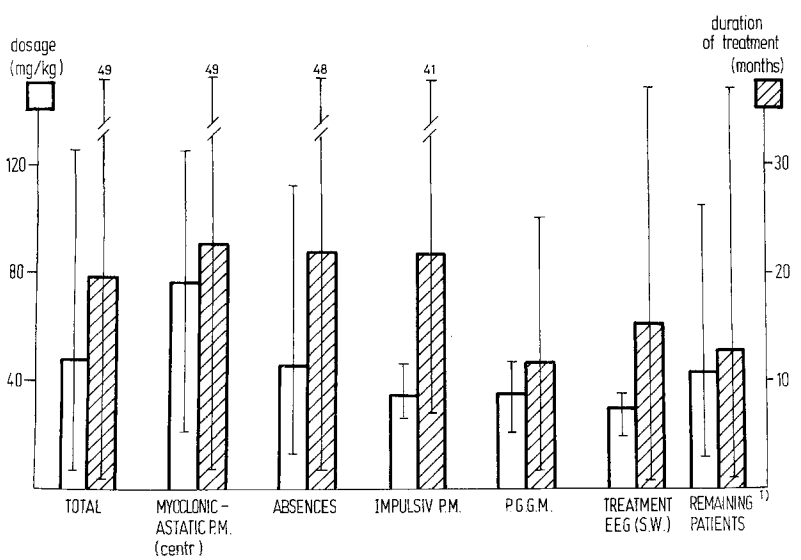

Fig. 3. DPA dosage and duration of treatment
[1] Remaining patients = Lennox syndrome ($n = 4$) and partial epilepsy ($n = 12$)

3. Therapeutic Procedures

In previously treated patients who still had occasional convulsions, DPA was administered in increasing doses up to a maximum of 1200—1800 mg/day in small children, and up to 2400 mg/day in school children (Fig. 3). The previous medication was reduced simultaneously and, in some cases, withdrawn completely (Fig. 2). Medium dosage for all patients was 48 mg/kg body weight/day, ranging from 7 to 125 mg/kg/day (Fig. 3).

Children not previously treated were started on DPA in the same manner. If this therapy was inadequate or unsuccessful, a second medication was initiated (Fig. 2). DPA therapy was rarely started while the patients were hospitalized. Most of them were outpatients seen every 2—4 weeks until convulsions were no longer recorded; from then on they were seen bimonthly.

4. Time of Controlled Study

Seventy-nine patients were controlled on an outpatient basis in our special epilepsy ambulance. The course of the disease was satisfactorily documented. The time of control after the treatment with DPA was complete and sufficient: 19.8 months with a range from 1 to 49 months.

5. Criteria of Therapeutic Success

Frequency of convulsions was noted by the parents of our children by aid of a special daily 'convulsion diary'; very rarely was it necessary to recheck these diaries by hospitalization. In those types of convulsions that were seen very infrequently, such as grand mal and focal seizures, the criteria was the frequency of convulsions seen before therapy with DPA. Double the time of previous intervals was judged to be a sufficient standard for therapeutic success. To control regular medication by the parents, we did not determine serum levels of DPA.

6. Documentation and Statistics

EEG findings in 874 EEGs, which amounts to 8 EEGs per patient, and the clinical course were noted on specially prepared data sheets and statistically evaluated using a Telefunken computer, System TR 440.

Statistical methods applied in this study [22] included descriptive statistics and the following methods:

(a) Point and Interval Estimation of Parameters. Assuming that we dealt with a random sample, the probability of therapeutic success, π, was estimated as $\frac{x}{n}$ (relative frequency). Upper and lower limits of the two-sided confidence interval defined by $P(\pi_l \leq \pi \leq \pi_u) = 0.95$ were estimated by using the F distribution.

(b) Fisher's Exact Probability Tests. To compare independent samples, we applied Fisher's exact probability test because it allows for small expected numbers in the contingency tables. The hypotheses tested were: either $H_0 : \pi_1 \leqq \pi_2$ against $H_1 : \pi_1 \geqq \pi_2$ or $H_0 : \pi_1 \geqq \pi_2$ against $H_1 : \pi_1 < \pi_2$ (one-sided tests). The level of significance was chosen as 0.05.

(c) McNemar's Test. McNemar's test was used to evaluate the change of proportion of two dependent variables (comparison of condition before and after treatment). The notation used was as follows: b = observed number of patients with positive sign before treatment and with negative sign after treatment, c = observed number of patients with negative sign before treatment and positive sign after treatment, β = relative frequency of patients in the population corresponding to group b of the sample, γ = relative frequency of patients in the population corresponding to group c of the sample.

The hypotheses tested were: $H_0 : \beta : \gamma \leq 1$, i.e., any difference between b and c in favor of b is due to chance, $H_1 : \beta : \gamma > 1$ (one-sided tests). In case $b + c < 30$, the computation of the test statistics included a correction for continuity. The level of significance was fixed as above.

7. Abbreviations Used

EEG = electroencephalogram, P.M. = petit mal, G.M. = grand mal, p.g. = primary generalized, s.g. = secondary generalized, centr. = centrencephalic, SW = spike and wave, DPA = sodium-di-N-propylacetate.

Results

1. Primary Generalized Epilepsy

The therapeutic results for primary generalized epilepsy (centrencephalic myoclonic-astatic petit mal, absences, impulsive petit mal, and primary generalized grand mal with spike wave) are summarized in Table 1. One patient each, with centrencephalic myoclonic-astatic petit mal and with absences, suffered a relapse for a short time even after maximal doses of DPA; these patients are listed under "no effect."

The results in centrencephalic myoclonic-astatic petit mal are distinctly worse than in all other primary generalized forms of convulsions; this statement refers to petit mal as well as grand mal seizures. One child out of the four treated with DPA as the initial drug had no further seizures; another had rare small seizures. Of 13 previously therapy-resistant patients who were treated with DPA in addition to previous medication, five showed complete success and one had rare

Table 1. Effect of DPA on primary generalized epilepsy and centrencephalic EEG pattern (3/s S.W., more than 3.5/s S.W., irregular S.W., and polyspike and wave).

	No. of patients	No. of seizure types	Effect of DPA				100% + 90% responders in % of total
			100%	90%	50%	no effect	
1. Myoclonic-astatic P.M.	17	15	6	1	3	5	47
additional G.M.		6	4	0	1	1	67
additional absences		11	5	1	1	4	55
2. Absences	51	51	43	4	3	1	92
additional G.M.		15	13	1	0	1	93
3. Impulsiv P.M.	4	4	4				100
additional G.M.		2	2				100
additional absences		3	3				100
4. P.g. G.M.	7	7	7				100
5. Treatment EEG (S.W.)[a]	17	17	5	6	3	3	65
Total (without 5.)	79	114	87	7	8	12	83

[a] We applied low to medium dosage in treatment of these patients

small seizures. Previous medication was reduced in seven patients and omitted in one child. Patients who were not successfully treated with DPA did not respond to any other drug but did respond to hormonal treatment. Two of the six patients with concomitant grand mal seizures suffered from short tonic seizures during the morning, not influenced by DPA.

Children with therapy-resistant absences prior to the initiation of DPA therapy ($n=34$) could be treated as successfully as those who received DPA as their first medication ($n=17$): Of these 34 patients, 32 responded completely after DPA, one suffered from rare absences, and one did not respond at all. Of the 17 patients, 11 were completely free of seizures after therapy with DPA, three suffered from rare absences, and in three the frequency of the absences was reduced to 50%. All eight patients not responding to DPA were brought into remission by further increase of the dosage or by additional administration of succinimides. The two patients with absences who had been treated with DPA without success and were still suffering from grand mal seizures were brought into remission by a small additional dose of primidone.

Impulsive petit mal and grand mal seizures were successfully treated in all patients (Table 1).

2. Confidence Intervals Concerning Therapeutic Success

Upper and lower limits of confidence intervals as defined above were calculated for three subgroups of the patients. With a chance of error $a=0.05$, these intervals include the true parameters π indicating the proportion of greater or complete success in the populations as being estimated from the data of our sample.

For the centrencephalic myoclonic-astatic patients, seven of whom showed at least a 90% improvement under treatment, the point estimation $\hat{p}=\frac{x}{n}$ is 0.47, and lower and upper limits of the confidence interval are 0.21 and 0.73, i.e., the proportion of complete or high therapeutic success should be found between 21% and 73%. For the 51 patients of the absence group with 47 highly successful treatments, the corresponding values are $\hat{p}=0.92$; lower limit of the interval 0.81, upper limit 0.98.

For the 28 patients of the grand mal group with 25 highly successful treatments, $\hat{p}$ is 0.89; the limits of the interval are 0.72 and 0.98. As these results demonstrate, an estimation based on a small sample results in a relatively wide interval whereas larger samples lead to estimations with narrower limits.

3. Treatment of EEG Changes (Table 1)

Of 17 patients who did not have seizures after different other medications, but who still had generalized centrencephalic paroxysms and in part substantial side effects from the other drugs, $n=12$, 16 were treated with a medium dosage DPA regimen: the previous medication was omitted in seven patients, and was reduced in six. Those 12 children with side effects were more alert after DPA therapy and increased their school ratings. One child without seizures but with increasing

Table 2. Effect of DPA on secondary generalized (Lennox syndrome) and partial epilepsy.

	No. of patients	No. of seizure types	Effect of DPA				Wors-ening	100% + 90% responders in % of total
			100%	90%	50%	no effect		
1. Lennox-Syndrom	4	4	1			2	1	25
additional G.M.		1				1		0
additional partial/ seizures		1				1		0
2. s.g. G.M.	5	5	1		1	2	1	20
3. partial seizures	3	3		1		1	1	33
4. s.g. G.M. and partial seizures	4							
s.g. G.M.		4	1			1	2	25
partial seizures		4	1			1	2	25
Total	16	22	4	1	1	9	7	23

s.g. = secondarily generalized

generalized spike wave was put on DPA as well. Irregular spike wave were seen 17 times before DPA therapy and 6 times after DPA therapy; 3/s spike wave were reduced to one-third, more than 3.5/s spike wave were reduced to two-fifths, and stroboscope sensibility was reduced to about three-fifths. A decrease of generalized-paroxysm frequency was seen in all patients.

4. Statistical Evaluation

Absences with or without grand mal could be treated equally well, and the same applies to absences without grand mal starting before age four ($P < 0.05$). There were no significant differences between generalized grand mal with spike wave and those with concomitant absences or myoclonic-astatic seizures. The differences with respect to secondary generalized grand mal was highly significant ($P < 0.001$).

Therapeutic success did not depend on the sex of the child. Positive cerebral organic disturbances in grand mal seizures could be treated less successfully ($P < 0.05$), but if they were connected to absences or centrencephalic myoclonic-astatic petit mal they could be treated equally well. There were no differences related to the duration of the disease, over or under two years in absences or centrencephalic myoclonic-astatic petit mal, while grand mal seizures of less than two years duration were treated significantly better than those of a longer duration ($P < 0.05$).

5. Treatment of Secondary Generalized and Partial Epilepsies (Table 2)

Of the 16 patients subgrouped here, four had centrencephalic EEG changes in addition to the focal pattern, all with abnormal theta ryhthms, twice generalized,

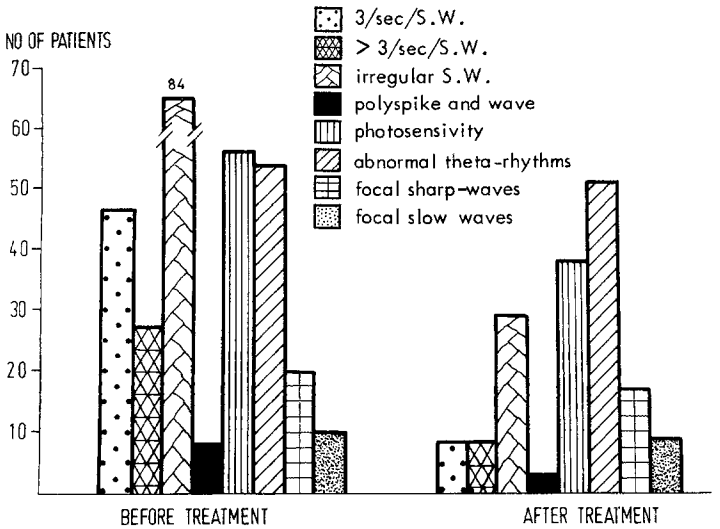

Fig. 4. EEG pattern before onset of therapy with DPA and during maximal effect of therapy (EEG characteristics were rated independently of each other)

irregular spike wave. Three of these patients were free of seizures after additional treatment with DPA in addition to their basic medication, one patient each with Lennox syndrome, secondary generalized grand mal and focal motor seizures; one patient was still suffering from rare partial seizures. There are bad results in the last 12 patients with only focal EEG patterns without additional centrencephalic changes. Seizures were reduced to 50% in one patient with secondary generalized grand mal, and six patients did not respond. In five patients an increase, at times substantial, in the seizure frequency was recorded, prompting immediate withdrawal of DPA.

6. EEG Changes under DPA Treatment (Fig. 4)

The development of centrencephalic seizure activity under DPA therapy is listed in Figure 4. There was a statistically significant effect on irregular spike wave, 3/s spike wave, and more than 3.5/s spike wave ($P < 0.001$). The same could be demonstrated for photosensitivity, and polyspike and wave ($P < 0.05$).

Abnormal theta rhythms and changes of background activity were not influenced significantly by DPA medication.

Focal changes in the EEG and the expansion or generalization of focal sharp wave was not influenced.

6. Side Effects

During the initial period, 14 patients complained of indigestion or, very rarely seen, of vomiting. The complaints were successfully treated in all cases with additional short-term medication of an antacidic and/or antiemetic drug. In five patients an increased loss of hair was seen over a period of 3—7 weeks, 1—4

months after DPA was started. There was spontaneous remission without change in the DPA medication. Patients treated solely with DPA never complained of drowsiness, slowing down, cerebellar disturbances, or disturbances of the general drive. These symptoms were seen only when DPA was administered in combination with barbital, benzodiazepines, primidone, or even carbamazepines ($n=15$). These side effects were decreased by reducting the additional, not the DPA, medication.

We observed a temporary increase of appetite in five patients; this increase was persistent in two children and resulted in a substantial weight gain.

Disturbances of the kidney function, liver function or heart, allergic phenomena, and endocrinologic disturbances were not recorded.

7. Laboratory Results

The following tests were performed repeatedly, with a minimum of three times and a maximum of 14 times during the study: complete blood smear including platelets, liver transaminases including gamma-GT, bilirubin, alkaline phosphatase, lactic dehydrogenase, and creatine phosphokinase. Serum electrolytes were studied including calcium, phosphorus, magnesium, copper, and iron. BUN, total serum protein, and albumin were also estimated. Anti-DNA factors were investigated in 72 patients.

There were no abnormalities in these laboratory tests that could be connected to therapy with DPA. Increases in gamma-GT and in alkaline phosphatase were seen only in combination with other antiepileptic drugs such as barbital, primidone, DPH, and carbamazepine.

8. DPA Combined with Other Drugs

Table 3 shows the effect of DPA in combination *with other antiepileptic drugs* on primary generalized grand mal seizures with spike-wave pattern. Of the 30

Table 3. Effect of DPA in grand-mal seizures

	No. of patients	Effect of DPA				Worsening
		100%	90%	50%	No effect	
p.g. Grand Mal (with spike-wave P.)	30	26	1	1	2	
p.g. G.M. without P.M.	7	7				
only DPA	3	3				
DPA plus others[a]	4	4				
p.g. G.M. and P.M.	23	19	1	1	2	
only DPA	12	9	1	0	2	
DPA plus others[a]	11	10	0	1	0	
s.g. G.M. (with focal changes or SW-variant DPA plus others[b]	10	2	0	1	4	3

[a] All patients under DPA plus primidone

[b] All patients under DPA plus primidone ($n=1$), primidone plus carbamazepine ($n=5$), primidone, phenytoin plus carbamazepine ($n=4$)

patients, 26 (87%) were free of seizures; 15 were on DPA alone and the others were treated with a combination of DPA plus primidone. Our treatment had no effect in only two patients.

Discussion

DPA had a very good effect on primary generalized epilepsies, but failed largely in the therapy of secondary generalized and partial epilepsy. Especially spike-wave absences do respond very well to treatment with DPA. This has also been reported by other groups [2, 7, 8, 12, 17, 18, 21, 26, 28, 29]. However, the results in the reports cited do differ markedly. They have a range from 20% [18] to 85% [28] success. The rate of success is higher in the studies with a higher basic dosage of DPA than in those with a lower dose regimen, [21] and [25] versus [7] and [29]. It may be concluded that the therapeutic success in this most frequently treated group of primary generalized epilepsy not only depends on the group composition but also on the dosage applied.

We completely suppressed seizures in 92% of the patients, most probably directly dependent on the dosage used. In the small number of patients with absences who did not respond to DPA, the seizures always vanished after additional therapy with low-dose succinimides. This has also been reported previously by other in vestigators [24, 29].

Therapeutic results in generalized tonic-clonic seizures differ even more in the reports known to date. No success [17] as well as moderate success [1, 14, 18] and good success have been reported [2], approaching almost complete success [8, 29]. In these reports, a discrimination can very rarely be made between generalized seizures with spike wave in the EEG in the group of grand mal seizures.

In our group, patients with primary generalized grand mal ($n = 30$) with ($n = 23$) or without ($n = 7$) additional petit mal and generalized irregular spike wave in the EEG were free of seizures in 87% or they had only very infrequent seizures. Fifteen patients each were treated with DPA alone or in combination with primidone. We suppose that due to the high incidence of seizure-free patients (87%), a sometimes lack of effect of DPA is overcome by the combination with primidone. This is supported by the observation that none of the 28 patients with absences treated exclusively with DPA developed grand mal seizures during the course of the disease. To differentiate between grand mal seizures is an urgent necessity. This is demonstrated by a comparison between the ill effect in the ten patients suffering from secondary generalized grand mal (Table 3), who were treated almost without an effect. The differentiation would be according to their course—primary or secondary grand mal.

In patients with secondary generalized grand mal DPA, always in combination with two or more antiepileptic drugs, led to a marked ill effect in 30%; it was without effect in another 40%.

We conclude that DPA has nearly the same good effect in primary generalized grand mal with spike wave as in absences. These results are in accordance with those of other authors [8, 29].

The variations in the results of treatment in atonic-akinetic seizures are mostly due to differing subgrouping of distinctly different diseases into this syndrome [8, 13, 17, 23], e.g., (a) primary generalized type with akinetic seizures and centrencephalic EEG (irregular spike wave, 3—5/s spike wave), so-called centrencephalic myoclonic-astatic petit mal [5] and (b) secondary generalized type with the same seizures but focal changes, generalized sharp waves or S. W. variant pattern (so-called Lennox syndrome [9, 10]).

Our results in primary generalized type, centrencephalic myoclonic-astatic petit mal compare well with those of Völzke and Doose [29], in our patients we reached good to very good results in 47% compared with 60% [29].

If the results of DPA treatment in partial and in secondary generalized epilepsy are compared with those in primary generalized epilepsy, the distinct difference, 90 or 92% vs. 25%, is evident. An exception can be seen in those forms of the first group that have a centrencephalic pattern in the EEG besides focal changes. The patients responding to DPA treatment all had this EEG pattern, whereas there was almost no therapeutic success or even worsening in patients with pure focal EEG pattern. This has also been seen by Völzke and Doose [29]. Without discrimination of the EEG according to focal or centrencephalic pattern, some authors had good results [8, 14, 25] while others reported no influence of DPA on partial or secondary generalized epilepsies [17, 21].

Centrencephalic seizure activity, irregular spike wave, 3/s spike wave, and more than 3.5/s spike wave were positively influenced by treatment with DPA ($P < 0.001$). However, there was no reaction in focal changes (focal sharp wave, focal slow wave), and in spreading forms of focal sharp wave (generalized sharp wave and S. W. variant). These differences in the therapeutic effect of DPA were related clinically to the different effect on centrencephalic and focal epilepsy.

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