SEVERE TOXIC EFFECTS OF SODIUM DIPHENYL HYDANTOINATE IN MENTALLY DEFECTIVE EPILEPTICS.

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Selection and Dosage.

The anti-convulsant value of sodium diphenyl hydantoinate (S.D.H.), marketed in America as Dilantin and in England as Epanutin, as found by Putnam and Merritt and introduced by them in the treatment of epilepsy has been amply confirmed by all subsequent reports, as it is by this one. Its clinical application, however, will, it is thought, be modified by reason of its toxic nature becoming more generally known.

Recently a trial series of 20 among 200 male mentally defective epileptics in this hospital was submitted to this form of therapy. Those selected were among the more severe cases of epilepsy, being approximately equal groups of idiot, imbecile and feebleminded patients respectively.

The new drug in replacing previous medication was prescribed with all the precautions recommended by those familiar with its use. It is perhaps due to this care that so few of the cases showed any of the early toxic manifestations hitherto described. These will not be discussed in detail, but it will be recalled that in most of the reports on S.D.H. the drug was discontinued at various intervals from the beginning of treatment and for various reasons. It is presumed, for it is not explicit, that the majority of interruptions in treatment occurred early. Toxic symptoms of a grave nature occurring six weeks or more after the drug was first given, if hitherto reported, have not been uncompromisingly attributed to its action.

The considerable diminution in the total number of fits must be defined as due to the efficacy of S.D.H. over and above the anti-convulsant value of the drugs which, over a period of years, had been found most effectual in each patient. Dosage became a matter for individual assay. It will be seen that, whereas the average dose was 0·3 gm. per day, in no case was the maximum of 0·6 gm. ever reached. This bears upon the question of cumulative effect which had previously been found unlikely. No evidence of pre-existing renal disease was present in any of the toxic or fatal cases in the present series. The

likelihood of specific idiosyncrasy, on the one hand, or high eliminative threshold on the other remains open. However, the statistics here given imply a marked intolerance to S.D.H. among those in whom organic changes in the central nervous system is found. In a few cases recourse was had to luminal in addition to the S.D.H. Its synergistic action in this connection has been well reported, and when used it was found helpful both in the control of seizures and of the unduly excited behaviour that sometimes occurred.

Comparable Reports.

The literature contains three comparable reports: (1) Weaver, Harrell and Arnold treated 14 cases at the Virginia State Colony for Epileptics and Feebleminded Patients. In general the drug was found to be suitable, though sufficient is not said of the six cases, or 43 per cent., whose treatment was interrupted. (2) A. J. M. Butler treated 43 institutional patients. His opinion is that the mentally higher grade patients respond best to the new drug. From the table of statistics given below this fact is very clear, its determination being one of the objects of study. (3) R. Coope, reporting upon 19 non-defective epileptics at the Maghull Colony, Liverpool, is also favourable to S.D.H. therapy, though he concludes his article with an account of two deaths. From his treatment of these fatal cases one gathers that he does not attribute these unfortunate results unreservedly to S.D.H. This is easily understandable when one sees how gradual is the process of mounting toxicity. However, his accurate description of symptoms in the terminal picture closely corresponds to the cases of S.D.H. poisoning here described.

Typical Late Toxicity.

Six weeks or more after S.D.H. is first introduced and quite irrespective of its ability to control the fits, the toxic symptoms make an insidious appearance. The patient is put to bed because of increasing mental dullness. Confusion gradually replaces the dull apathy and small groups of fits spoil the recently good epileptic record. Lapses from consciousness are preceded by absolute insomnia. Constipation is intractable and retention or oliguria is the rule. An intermittent temperature of 100°–102° F. appears late. In one case it rose to 106° F. 48 hours before death, while in the other cases the terminal temperature was subnormal. Widespread furunculosis occurred in one case, oedema of the face in two cases, an urticarial wheal along the mucocutaneous margin of the lips in one case and gingival hyperplasia with bleeding in one. Death was due to bronchopneumonia in one case and to *status epilepticus* in three. Blood-pressure during seizures in one case was 120/90 mm. of mercury in the intervals between fits and a swinging pulse

Clinical Table.

Name.	Case No.	Age.	Dosage in gms.	Months on S.D.H.	Fits per month in the year before S.D.H. therapy.	After S.D.H. therapy.	General type of epilepsy.	Late toxic effects.	Behaviour changes.	Deaths.
							Feebleminded.			
C. H—	1	36	0·3	4	2·5	1	Essential	None	None	..
G. H—	2	32	0·3	4½	2	2	,,	,,	,,	..
F. M—	3	33	0·3	4½	Many *petit mals*	Much improved	,, *petit mal*	,,	Much general improvement	..
O. D—	4	17	0·2	3	22	7	Jacksonian	Tending to *status*; drug withdrawn	Much more difficult	..
R. H—	5	33	0·3	4½	7·5	4	Essential	Early headache, constant yawning	Generally more alert	..
E. E—	6	36	0·3	4½	17	8	,,	None	,, ,,	..
S. R—	7	41	0·3	3	4	6	,,	Gross late toxaemia drug withdrawn	None	Ten days after withdrawal.
							Imbecile.			
E. P—	8	21	0·3	3½	9	3	Idiopathic	Ditto	Much more difficult	..
A. B—	9	32	0·3	1½	7	8	,,	None	Uncontrollable; drug withdrawn	..
C. S—	10	41	0·3	½	3·3	14	Jacksonian	Stuporose and *status epilepticus*; drug withdrawn	Dull generally	..
C. L—	11	27	0·3	4½	22	15	Idiopathic	None	Generally more alert	..
G. W—	12	43	0·2	4½	2·8	..	,,	,,	Much more difficult	..
M. R—	13	23	0·3	3½	9	..	Jacksonian	Gross late toxaemia; drug withdrawn	None	Sixteen days after withdrawal.
F. J—	14	22	0·2	½	8·5	17·4	Idiopathic	*Status epilepticus*; drug withdrawn	,,	..
							Idiot.			
J. E—	15	34	0·3	4	17	0·0	Idiopathic	Confusion, urinary retention; drug withdrawn	Uncontrollable; drug withdrawn	..
H. L—	16	27	0·3	2½	15	1·5	Jacksonian	*Status epilepticus*; with recovery	Generally more alert	..
F. F—	17	27	0·3	2	6·8	4·5	,,	None	None	..
J. C—	18	25	0·2	1½	6·8	14	Idiopathic	Gross early ataxia; drug withdrawn	Generally more difficult	..
G. S—	19	29	0·4	1½	5·5	5·5	Jacksonian	Gross late toxaemia; drug withdrawn	Dull generally	Six weeks after withdrawal.
E. A—	20	33	0·3	2	17	10	,,	Ditto	None	Nine weeks after withdrawal.

pressure with 180/120 approximately as the reading during a fit. The pupils were dilated, equal and reacted sluggishly. The deep reflexes were sluggish and the plantars flexor.

Biochemistry.

After the second death the significance of the biochemistry in what was assuming the proportions of a definite toxic entity became more apparent.

Case 20.—The third fatality showed acetone in the urine, which was in other respects normal.

Case 13.—The fourth fatality was more thoroughly investigated.

Urine was scanty, concentrated and reddish orange in colour; it contained albumin, hyaline casts, haematoporphyrin verified spectroscopically.

Blood count: R.B.C., 5,080,000; polymorphonuclears cells, 80 per cent.; W.B.C., 18,600; lymphocytes, 7 per cent.; haemoglobin, 112 per cent.; basophiles, 1 per cent.; colour index, 1·1; urea, 50 mgm. per cent.

C.S.F.: Urea, 35 mgm. per cent.; no cells present; pressure, 90 mm. of fluid between fits.

Case 8.—Now beginning to recover after weeks of illness, during which his death seemed likely.

Urine: Specific gravity 1020, slightly acid, amorphous urate deposit. Normal in other routine examinations. Haematoporphyrin verified spectroscopically. Urea, 3·47 mgm. per cent.

Blood count: R.B.C., 5,610,000; polymorphonuclear cells, 48 per cent.; W.B.C., 8,000; lymphocytes, 44 per cent.; haemoglobin, 110 per cent.; eosinophiles, 0·5 per cent.; colour index, 1·0; mononuclear cells, 7·0 per cent.; basophiles, 0·5 per cent. Van den Bergh negative. Urea, 5 mgm. per cent. Total serum nitrogen, 1·036 gm. per cent., and total protein, 6·475 gm. CO_2 combining power, 49 vols. per cent. Titratable alkalinity, 0·022 molar.

C.S.F.: Pressure normal; no cells present. Chlorides, 740 mgm. per cent. Sugar, 70 mgm. per cent.

The haematoporphyrinuria apparently does not make its appearance until toxic features have been clinically manifest for some time. As a guide to mounting toxicity its significance will perhaps be evaluated by future experience. The most unusual feature, however, is the blood urea. The figures were given credence only after they had been confirmed by the results obtained on the same blood in another laboratory. Controls were run on all determinations. The readings which indicate the process of recovery are given in sequence from the most toxic day onwards. First day, 5 mgm. per cent.—repeated, 5 mgm. per cent.; second day, 5 mgm. per cent.; ninth day, 7·8 mgm. per cent.; twelfth day, 12 mgm. per cent.; fourteenth day, 12·5 mgm. per cent.; fifteenth day, 15 mgm. per cent.; twenty-first day, 18 mgm. per cent.; twenty-second day, 19 mgm. per cent.

Post-mortem Findings.

Inadequacy of investigation in the earlier deaths due to a reluctance in blaming S.D.H. for the unfortunate outcome make the statistics disappointingly meagre.

The brain was oedematous. There were no haemorrhages in cortex or base.

The liver and kidneys showed cloudy swelling and, in addition, there was acute congestion of the lungs and liver in one case with dilation and congestion of the right heart.

Case 20 was a congenital hemiplegic, with typical right-sided Jacksonian convulsions. He was found to have a uniform atrophy of the left cerebral and right cerebellar hemispheres respectively.

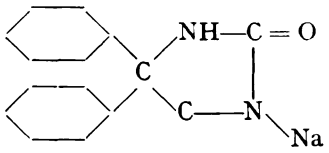
Micro-sections of the brain in three cases are in course of preparation.

Treatment.

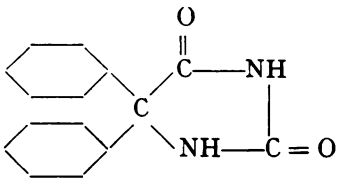
Once the coma becomes established, attempts at resuscitation except as seen in Case 8 were hopeless. Oxygen had the effect of increasing the fits, whereas CO_2 did seem to give some relief. Stomach wash-outs were of value, but the usual practice of leaving a bicarbonate solution in the stomach had no good effect. Intramuscular sodium amytal in one case and paraldehyde, luminal and potassium bromide given in others to control the status appeared to have far less effect than when similarly used in cases of *status epilepticus* not on S.D.H. The beneficial effect of withdrawing the drug seen in the case of the early toxic symptoms made no difference to late toxicity. Moreover, while attempting to interrupt the treatment in the remaining cases after the third death one of the patients developed the usual toxic picture and died in 16 days with bronchopneumonia. Most benefit appeared to result from adrenaline ɱiv *b.d.* of a 1 : 1,000 solution, given because of some of the anaphylactic features, and from daily bowel wash-outs.

S.D.H. and Nirvanol.

In his criticism of the pessimistic attitude of Schlesinger to the advent of sodium diphenyl hydantoinate therapy, Lennox rightly differentiates it chemically as an entirely separate product. It is well known that in spite of the structural similarity of two drugs even a methyl radical will greatly alter the toxicity.



S.D.H.



Nirvanol.

However, here the chemical similarity of derivation and formulae is supported by comparable therapeutic and toxic effects. According to Schlesinger, nirvanol, though used in Europe in the control of epilepsy and latterly of chorea, had a well-known toxic syndrome. Indeed, these toxic changes had to be well established before any therapeutic value could be expected. He mentioned a case of nirvanol poisoning reported by Keller, the description of which accurately fits that of the cases here presented. It is too early to say how much Case 8, who made a tardy recovery, is likely to benefit from his experience in regard to the future control of his epilepsy.

Conclusions.

(1) In the present series the mortality of four cases represents a rate of twenty per cent. This result served as an inducement to publication earlier than was convenient for the completion of biochemical and histological investigations, in the hope that untoward events might be avoided by careful selection before the application of S.D.H. therapy, also that due regard be given to the seriousness of late toxic symptoms.

(2) Amongst oligophrenics, idiot patients are most prone to toxic manifestations and feebleminded patients less susceptible, while imbecile patients occupy a middle position. In spite of relief from fits, it is doubtful if S.D.H. is safe therapy for those with Jacksonian epilepsy.

(3) Wherever it is considered advisable to withdraw S.D.H., a period of weeks should elapse in this process before the final 0·1 gm. per day is withheld. Luminal or potassium bromide in correspondingly increasing doses are good initial substitutes.

(4) The toxic state is chiefly of interest biochemically by the appearance of haematoporphyrin in some cases and in one case by a remarkable fall in blood urea. Neither mechanism has been adequately explored yet.

Summary.

Sodium diphenylhydantoinate exhibited in the treatment of 20 male epileptic oligophrenics resulted in many toxic manifestations clinically identifiable with a state closely resembling nirvanol poisoning. There were four deaths, or a mortality rate of 20 per cent.

Idiot and imbecile patients particularly showed intolerance to the new drug though the feebleminded patients were not immune. These symptoms were delayed six weeks or more after the onset of treatment. There was thought to be a relation between intolerance and pathological changes in the central nervous system.

Post-mortem findings have been inadequately studied, but clinical interest attaches chiefly to one case with a persistently low blood urea and to two cases

of haematoporphyrinuria. There had been no exposure to ultra-violet light. There was no clinical jaundice.

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