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THIOPENTONE SENSITIVITY AND DYSTROPHIA MYOTONICA

BY

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Since its introduction to clinical practice in 1934, thiopentone has come to be used universally on a very large scale for the induction of general anaesthesia and also as the sole anaesthetic agent for certain short operative procedures. After initial setbacks the common dangers attendant upon the use of the drug are now well appreciated. These dangers are many, and anaesthetists have written at length concerning the use and abuse of thiopentone. In addition to the common dangers there are a number of rare conditions which put the patient at risk when thiopentone is used. Amongst these may be mentioned porphyria, myasthenia gravis, Addison's disease, and dystrophia myotonica.

Dystrophia myotonica is a rare disease, but many practitioners must know of cases amongst their patients, and, in spite of its rarity, it is felt that the extraordinary sensitivity towards thiopentone shown by subjects with this disease should be brought again to the attention of all who are in the habit of using the drug.

The literature contains reference to only four instances of the use of thiopentone in dystrophia myotonica. A further case is recorded, and I have knowledge of two other persons who suffer from the disease.

Dystrophia Myotonica

Dystrophia myotonica is a hereditary familial disease affecting both males and females and usually appearing between the ages of 15 and 35 years. It does not of itself materially shorten life, but death usually occurs during the fifth decade from intercurrent infections. The features of the disease can be grouped under three heads.

1. *Myotonia*.—An involuntary persistence of muscular contraction following its voluntary initiation. It may be present in any group of muscles and is intensified by acetylcholine and by neostigmine and potassium.

2. *Muscular Atrophy*.—This quite characteristically involves the sternomastoids and facial muscles. Also involved may be the muscles of the shoulder-girdle, forearms, and hands, the quadriceps femoris, and the leg muscles below the knees. The atrophy is usually symmetrical on the two sides of the body; the affected muscles are weak but show no fibrillation. Tendon reflexes are diminished or absent. The rate of development is variable, usually proceeding over a period of some years, but it may

be much more rapid. The wasting bears no constant relationship in either time or site to the myotonic symptoms.

3. *Others*.—Cataract appears in about 50% of cases, and may be seen in otherwise healthy siblings of those who show the muscular changes. It tends to appear at an earlier age in successive generations. Premature frontal baldness is a common feature, as also are ovarian and testicular atrophy. Less frequently seen are adenomata of the thyroid, diabetes mellitus, and abnormalities of the pituitary and adrenals. Mental changes are often present.

Histologically the disease has been shown to be confined entirely to the muscles; neither the central nor the peripheral nervous system shows any abnormality. There is no uniform atrophy of muscle fibres; healthy and degenerating fibres are seen side by side. Some fibres appear larger than normal, and in the early stages of degeneration show loss of transverse striation with proliferation of sarcolemmal nuclei; eventually the fibre is completely replaced by fat and connective tissue.

Diagnosis of the developed case is simple. When myotonia precedes muscle-wasting, the age of onset will distinguish it from Thomsen's disease (myotonia congenita). In the absence or late development of myotonia, the sternomastoid wasting is characteristic.

No treatment will arrest the progress of the disease. Quinine, 10–30 gr. (0.65–2 g.) daily is said to improve the myotonia, and the use of procaine amide has been reported (Geschwind and Simpson, 1955).

Case History

A woman aged 30, who had suffered from dystrophia myotonica for 14 years, had the classical features of myotonia and facial and sternomastoid wasting, and was of above average intelligence. She was to undergo an abdominal operation. Premedication, given one hour pre-operatively, with pethidine, 100 mg., and scopolamine, 1/150 gr. (0.43 mg.), did not appear to have unduly depressed her in any way. General anaesthesia was induced with 2.5% thiopentone, and a dose of 100 mg. was given. This dose produced loss of consciousness and apnoea, the latter lasting for 20 minutes, and thereafter respirations remained depressed for a further 20 minutes. The apnoea was accompanied by a state of complete muscular flaccidity comparable to complete curarization—direct laryngoscopy being easily possible. The quality and rate of the pulse remained unaltered during inflation with nitrous oxide and oxygen, and there was nothing to suggest waking. Subsequently the response to D-tubocurarine was normal.

Discussion

This case, which was referred to by Langton Hewer (1957), corroborates the experiences of the three authors who have previously reported the idiosyncrasy. Dundee (1952) reports three cases, and Bourke and Zuck (1957) the fourth.

It has been found that in dystrophia myotonica normal doses of thiopentone cause profound depression of respiration amounting to apnoea. Doses of 500 mg. produced apnoea lasting 10 minutes in one of Dundee's cases, and lasting two hours in Bourke and Zuck's case; in both there followed a prolonged period of depressed respirations insufficient to maintain adequate oxygenation. These three authors were also able to show that so small a dose as 50 mg. of thiopentone produced a very marked depression of respiration almost amounting to apnoea, without producing loss of consciousness. The normal transient initial stimulation of respiration is not seen.

It is not intended to suggest that the use of thiopentone should be abandoned for this type of patient, though it is possible that some of the unexplained deaths occurring during thiopentone induction and anaesthesia could be attributed to this hypersensitivity. It is intended rather to point out the hazards, to emphasize certain basic principles, and to suggest that this rare disease may not in fact be exceedingly rare. To suspect every case of premature baldness or thyroid adenoma may be overcautious, but the

routine taking of family histories should not be omitted. Bourke and Zuck point out the significance of the high incidence of cataract in these patients and the modern trend towards general anaesthesia for ophthalmic surgery. Particular care should be taken, when thiopentone is used for dental extractions in the chair, to be on the look-out for respiratory depression after unusually small doses. A means of ventilating the patient should always be at hand. The possibility of meeting a case of dystrophia myotonica in these circumstances, among other reasons, should discourage any but the most experienced from administering thiopentone in the dental chair.

In the United States thiopentone is more widely used as a 2.5% solution than in this country. There is much to recommend this practice and little, if anything, to condemn it. In known or suspect cases of dystrophia myotonica a dilute solution, not stronger than 2.5%, should be used and a dose of 100 mg. has been recommended: respiratory depression seems to be inevitable, and with doses smaller than 100 mg. there is the chance that loss of consciousness may not result. Apparatus for the artificial inflation of the lungs must be at hand, and Dundee recommends inflation with nitrous oxide and oxygen rather than oxygen alone, because of the possibility of a return to consciousness whilst apnoea persists. If it is desired to intubate the trachea, this will usually be found possible without the use of a relaxant.

I am indebted to Dr. C. Langton Hewer for his advice, and to Mr. John Beattie under whose care the case described was treated.

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EFFECTS OF NYDRANE ON EPILEPSY IN MENTAL DEFECTIVES

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Notwithstanding the claims made concerning the efficiency of many of the recently introduced anticonvulsant drugs, epilepsy still remains a considerable medical and nursing problem. This is confirmed by Tredgold (1952), who states that fits occur in 11% of the feeble-minded, in 42% of imbeciles, and in 56% of idiots.

We decided to investigate the effects of a recently introduced anticonvulsant known as "nydrane." This drug is a benzylamide, N-benzyl- β -chloropropionamide, known in England as nydrane, in the U.S.A. as "hibicon," and on the Continent as "posedrine." It differs considerably from both the barbiturates and the hydantoin, having the structural formula:

It is a white crystalline solid with a molecular weight of 197.6 and a melting point of 94° C. The preparation is marketed in tablet form, the tablets being 0.5 g. in weight.

Previous clinical trials in Great Britain have been carried out by Hoenig *et al.* (1956) and by Robinson (1957), while Hawkes (1952) and Merlis and Martin (1956) have reported on its use in the U.S.A. There are also numerous references to its use in France and Italy.

Clinical Trial

We must emphasize that our primary aim was to discover whether this drug was objectively useful in the management of the chronic epileptic patient. We have divorced ourselves from the intricacies of the E.E.G. and concentrated on the reported day-to-day clinical state of the patient. We may stand condemned for issuing a report on an anticonvulsant without accompanying E.E.G. evidence. Surely the fact remains that with a chronic epileptic, especially in these days of staff shortages, what we wish to know is not his E.E.G. pattern but whether we have stopped or controlled his convulsions.

We may summarize our aims as follows: (1) to discover whether grand-mal epilepsy reacts favourably or otherwise with this drug; (2) to observe any change in behaviour and general conduct of the patient; and (3) to observe if any toxic effects are produced during the course of the trial.

Method and Material.—The clinical material used was 25 certified mentally defective patients of Botleys Park Hospital. They were all males aged from 17 to 50 years. Their I.Q.s ranged from 30 to 80. Eighteen of the cases were labelled as idiopathic epilepsy, six were of the traumatic type, and one of epiloia. All the cases demonstrated chronic grand-mal seizures and had previously been treated with barbiturates, phenytoin, and primidone, either singly or in combination. The method of control was similar to that carried out by one of us in a previous trial, using primidone (Sharpe, 1954)—namely, the patient acted as his own control in that an accurate assessment of his previous fit record and conduct was obtained from scrutiny of the patient's own epileptic record chart.

Dosage.—The scheme of dosage followed closely on that of other workers—namely, it is additive in the first instance, and finally any other anticonvulsants are replaced with nydrane. Irrespective of what previous drugs were being used, 0.5 g. of nydrane a day was added to the patient's treatment for the first seven days. Following this, the previous anticonvulsants were gradually withdrawn and substituted by 0.5 g. of nydrane weekly until the maximum dose was reached. In this series the maximum maintenance dose was found to vary from 3 to 4 g. a day, and usually this was divided into three equal parts. In practice we started withdrawing the hydantoins first and then gradually withdrew the barbiturates. We did attempt to control the epilepsy with nydrane alone. Unfortunately, this was found to be impossible, as in all except three cases a maintenance dose of barbiturates had to be given. The full course of treatment lasted for six months.

Toxic Effects

As nydrane is a relatively new and little-used drug in this country we decided to investigate thoroughly its possible toxic effects after prolonged usage, bearing in mind that we were subjecting our patients to large doses over many months. The scheme of investigation was as follows.

Pre-treatment.—Full blood count, Hb, R.B.C., W.B.C. and differential. Urine examination for albumin by the salicyl-sulphonic acid test, Benedict's qualitative test for reducing substances, and an examination of the centrifuged deposit.

During Treatment.—Weekly: routine examination of the urine as above. When reducing substances were found these were subjected to further examination to identify them. "Tes-tape" was used to detect glucose. The non-glucose reducing substances were subjected to paper chromatography and compared with known marker substances. Monthly: routine blood counts, Hb, W.B.C. and differential. After three and six months: serum proteins were estimated