THIOPENTONE IN DYSTROPHIA MYOTONICA

BY

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INTRODUCTION

Dystrophia myotonica (myotonia atrophica) is an hereditary familial disease with features intermediate between the myotonias and myopathies. It is transmitted as a simple dominant, and the onset of the disease in the children is at an earlier age than in the parent, until, after a generation in which the onset occurs before sexual maturity, it ceases to appear in that family. Males are affected more often than females, and the disease is generally latent until early adult life. The first symptom is usually a difficulty in relaxing the grip, and myotonic phenomena often develop in other muscles, so that, for example, a smile may be slow to disappear. The lower limbs are rarely affected. Exposure to cold aggravates the myotonia, as does acetylcholine, neostigmine and potassium. There is concurrent progressive muscular weakness and wasting, but the most conspicuous myotonia often occurs in muscles free from wasting, and conversely wasted muscle may not be myotonic.

Associated with the disease are various signs of premature senility, such as testicular or ovarian atrophy, frontal baldness, and mild euphoric dementia; and at least half the cases develop senile cataracts. Degeneration of various endocrine glands has occasionally been found, particularly the anterior pituitary, the thyroid, and the adrenal cortex, and thyroid adenomas and diabetes mellitus may also occur. Such metabolic changes as have been found are similar to those in other muscular dystrophies; the most notable is a disorder of creatine metabolism.

Creatine (Wright, 1952), which is synthesized in the liver, and is taken up from the blood by the muscles as needed, is stored in normal resting muscle mainly as creatine phosphate, the phosphate group being linked to creatine by a high-energy phosphate bond; it is formed by the reaction of creatine with adenosine triphosphate, and this reaction is reversible. Creatine phosphate can normally be stored in muscle, and its high-energy bonds are available for the rapid resynthesis of adenosine triphosphate, which is required for muscular work, from adenosine diphosphate. Creatine is not normally found in the urine except in children, but, in addition to certain other conditions, it may appear in the presence of pathological states of muscle, notably the myopathies, because of the poor ability of the diseased muscle to store creatine.

CASE REPORT

The patient, a male, aged 50, weight 10 st. 3 lb., was admitted under the care of Mr. J. Gibson Moore for the removal of a cataract from the left eye. He had been in Chase Farm Hospital fifteen years before with staphylococcal septicæmia, and in 1946 a cataract was removed from his right eye under local anaesthesia at another hospital; he was employed in the making of television tubes, and, unaware of his disease, and not conscious of any disability, he lived a normal active life. Routine pre-anaesthetic examination revealed no obvious abnormality. He received papa-veretum 1/8 grain (20 mg), hyoscine 1/150 grain (0.45 mg) one hour before operation; and anaesthesia was induced with thiopentone 500 mg followed by suxamethonium 50 mg. The larynx was sprayed with 4 per cent lignocaine solution, and a cuffed endotracheal tube was passed. The lungs were inflated with nitrous oxide-oxygen mixture and pethidine 20 mg was given. He did not start to breathe, and at the end of the operation, about 45 minutes later, there was no response to carbon dioxide, nor to an intravenous injection of 2 ml nikethamide. He was returned to the ward, and artificial respiration was continued with nitrous oxide-oxygen mixture and pethidine 20 mg was given. Shortly afterwards a transfusion of one pint (592 ml) of fresh blood was set up, and it was then noticed that the muscles of the upper arms were...
slightly wasted; this raised thoughts of muscular dystrophy, and it was decided to obtain a neurological opinion at a later date. A little later it was remarked that the type of respiration was now much more consistent with depression of the respiratory centre, and particularly resembled pethidine respiration. An intravenous injection of naltorphine 5 mg was given, with dramatic effect, and within five minutes and 3½ hours after induction of anaesthesia the patient was able to breathe adequately on his own. During this time the pulse and blood pressure had been within normal limits; serum potassium was 17 mg per cent (4.4 m. equiv/l) and serum pseudocholinesterase was 24.6 units (the normal range by the method of estimation being 13 to 31 units). He gradually regained consciousness, but by midnight, six hours later, he had developed pulmonary oedema. The chest was full of moist sounds, and the pulse was irregular and weak, rate about 90; the systolic blood pressure was 100 mm Hg. He was put on nasal oxygen, and was given 1 ml of 40 per cent alcohol by Collison's inhaler, repeated hourly. His breathing was much improved by morning, and he made an uninterrupted recovery over the next few days. It was noticed that his speech was at times a little difficult to understand and that some of his reactions were excessively emotional; this caused anxiety about his mental state, but it was ascertained from relatives that he had been so for some years. This helped to confirm the suspicion that he was suffering from myotonic dystrophy, and he was then referred to Dr. E. C. O. Jewesbury, who reported: "This is an interesting case of dystrophia myotonica. He is prematurely bald, has cataracts, loss of sternomastoids, weakness of limbs, slight wasting, myopathic speech, expression and gait, gonadal atrophy, and absent tendon reflexes, but no obvious myotonia. His father, also, was prematurely bald." X-ray screening showed normal diaphragmatic action. He has been followed up during the past twelve months, and has returned to work, and continues to lead a normal life; the ophthalmic result was excellent. When last seen he was engaged in painting the outside of his house, and his disability did not deter him from climbing ladders.

**INVESTIGATION**

The patient was recently persuaded to receive test injections of thiopentone and pethidine while spirometry tracings were being taken, and these, together with a normal response (T.D.B.), are shown in figure 2.

The normal response to 50 mg of thiopentone shows an increase in the depth of respiration lasting about one minute; there was drowsiness for a short time but no loss of consciousness. There was no significant response to 10 mg of pethidine.

The patient responded to the same dose of thiopentone by two or three deep breaths followed by profound respiratory depression, amounting to apnoea lasting for about one minute. Spontaneous breathing started at the moment that bemegride (Megimide) was injected, and this drug appears to have had no effect; again there was drowsiness only. After 10 mg of pethidine respiration slowed from 15 to 10 breaths per minute, returning to the previous rate after 8 minutes. It was not considered reasonable in a conscious patient to try the effect of suxamethonium; however, no abnormal reaction was noticed at the time of the operation, although it is interesting to note the reported aggravation of the myotonia by acetylcholine and neostigmine.

**DISCUSSION**

Only three cases of abnormal response to thiopentone in dystrophia myotonica have previously been reported (Dundee, 1952). In these cases the duration of narcosis appeared to be normal, and carbon dioxide failed to stimulate respiration; there was a very transient stimulation by nikethamide, which "suggests that the overaction of thiopentone is peripheral rather than central in origin and is probably an action..."
on abnormally sensitive muscles” (Dundee, 1956).

In the patient described above it is clear that at the time of operation there was, in addition to the thiopentone effect, central respiratory depression from papaveretum and pethidine; hence it was not possible at that time to relate the duration of narcosis, and the apnoea, directly to the dose of thiopentone. However, the subsequent investigation clearly demonstrated the abnormal effect of thiopentone, and the spirometry tracing could reasonably be interpreted as an initial central stimulation of respiration abruptly obscured by muscular paralysis as the drug reached the periphery. There was also, compared with the control, an increased response to pethidine, which in view of events at the time of operation appears to be of significance. It is doubtful whether this can be attributed solely to the relatively small difference in weight between the patient and the control. It is interesting to note this pethidine effect, which would seem to be central, in contradistinction to that of thiopentone.

It is attractive to attempt to relate the muscular effect of thiopentone to the abnormal creatine metabolism that occurs in dystrophia myotonica. Dundee (1956) discusses the tissue enzymes concerned in the metabolism of thiopentone, and refers to a cell-free homogenate of rat liver which is able to detoxicate the drug. “For maximum activity of this preparation cytochrome c, adenosine triphosphate, nicotinamide and a substrate are necessary.” However, there is still considerable doubt about the mechanisms involved, for he later states “whether or not the energy for metabolic transformation of thiopentone is derived from Krebs cycle oxidations or from high-energy phosphate bond compounds result-
ing from these oxidations is not established. A complete inhibition of phosphocreatine synthesis, by 2.4 dinetophenol, depresses thiopentone metabolism by only 30 per cent, suggesting that a source of energy other than phosphocreatine stores is available for the breakdown of the drug.” Thus there remains ample scope for speculation and, perhaps more profitable, for research.

CLINICAL IMPLICATIONS

Although this is a rare disease, it is stated that at least 50 per cent of patients develop cataracts, and it seems likely that anaesthetists may be faced more often with the problem of the patient suffering from dystrophia myotonica if the present trend towards general anaesthesia for ophthalmic surgery continues; and the disability may not be obvious. Thus in the younger patient with cataracts both diabetes mellitus and dystrophia myotonica must be born in mind, and it should also be remembered that these conditions can co-exist. Local anaesthesia is the method of choice, but if for any reason it is desired to use thiopentone it should be given very dilute, and a 1 per cent solution is suggested for controllability, although it has to be considered whether apnoea might occur without loss of consciousness; Dundee (1956) recommends that the dose should not exceed 100 mg. If a large dose is given by mistake the patient may regain consciousness before breathing becomes adequate, and because of this, and for physiological reasons, artificial respiration must be maintained with nitrous oxide and oxygen, not with oxygen alone. It would also appear that these patients need smaller doses than normal of pethidine and other respiratory depressants. Another condition in which the presence of this disease may be considered is adenoma of the thyroid, although the association must be extremely rare. It is not known whether the same susceptibility exists to thiopentone when the disease is latent, and there is probably no means of knowing until after the event; the patient described above has no children, so it was not possible to investigate this aspect of the problem.

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REFERENCES