THE MUSCLE RELAXANTS IN OBSTETRICS

BY

M. E. TUNSTALL

Department of Anaesthetics, Aberdeen Royal Infirmary, Aberdeen, Scotland

Curare was first used in obstetric anaesthesia (Whitacre and Fisher, 1945; Gray, 1947) three years after its introduction into anaesthesia (Griffith and Johnson, 1942).

It was found to give satisfactory operative conditions at light levels of anaesthesia. This greatly benefited the newborn baby because less drug depression of the mother resulted in less drug depression of her child at birth. In this indeed lies the prime purpose of the use of the relaxant drugs in obstetrics.

By controlling undesirable reflexes with the relaxants the mother may conveniently undergo obstetric procedures at analgesic and amnesic levels of anaesthesia only. This enables the needs of the mother, the baby and the obstetrician to be met. Further, the relaxants facilitate endotracheal intubation and controlled respiration. Adequate maternal ventilation and oxygenation, which is vital to the foetus, is thus safeguarded. There is likewise no tendency to maternal hypotension. This approach also permits short induction-delivery intervals when this is important and the easy addition of any other drug that may be required.

THE PLACENTAL TRANSMISSION OF THE RELAXANT DRUGS

Practically all publications on the relaxants in obstetrics confirm that in clinical use the newborn baby appears to be unaffected by their administration to the mother before delivery.

The subject of placental transmission has been reviewed in detail and with many references by Moya and Thorndike (1962). They emphasize that any substance found in the maternal or foetal blood will be able to penetrate the placenta to some extent unless it is destroyed or altered during passage. However, a very low degree of permeability may slow the entry to a rate which renders a drug physiologically inactive and pharmacologically undetectable.

All membranes allow the transfer of non-ionized drugs more readily than those which are ionized. The passage of drugs is therefore favoured by changes in pH in the direction which increases the concentration of the undissociated form. Non-ionized drugs with high fat solubilities are transferred rapidly whereas lipid insoluble drugs penetrate poorly even if they do not ionize readily. These facts are in accordance with the widely accepted concept which considers the plasma membrane boundary of cells throughout the body as a fat-like layer interspersed with small pores which more easily pass substances of molecular weight below 100.

Drugs containing a quaternary nitrogen group are highly ionized and possess a low degree of fat solubility. Suxamethonium and d-tubocurarine are examples of such drugs.

Moya and Thorndike name other factors which affect the possible concentration in the foetal blood of drugs given to the mother, such as the concentration gradient, distribution throughout the maternal and foetal extracellular space, protein binding, excretion and metabolism by the mother, infant and placenta. Factors which can affect the permeability of the placenta are disease, circulatory upset and asphyxia. They summarize by stating that the placental barrier to relaxants is relative rather than absolute.

Suxamethonium.

Following a single injection of suxamethonium there is an initial rapid fall of its level in the maternal blood. Kvisselgaard and Moya (1961a) found, in pregnant women at term, that 85 per cent of the drug was destroyed in the first half-minute and after 4 to 5 minutes its level in the serum was only just detectable (1 μg/ml). They suggested that enzymatic hydrolysis by plasma cholinesterase was the most important factor involved.
Low blood levels were found in pregnant women on suxamethonium infusion set at a rate sufficient for controlled respiration. A theoretical appeal of the infusion technique over intermittent injections is, therefore, that the concentration gradient across the placenta would be uniformly low. In practice intermittent doses of the order of 25–100 mg of suxamethonium appear to be satisfactory and not to give rise to trouble.

Moya and Kvisselgaard (1961) found that suxamethonium in usual clinical doses did not cross the placenta in demonstrable quantities and the infants did not appear to be affected. But it was found that single doses of 300 to 500 mg of suxamethonium were necessary before small but definitely detectable quantities were found in the umbilical vein blood of the infants (Kvisselgaard and Moya, 1961b). This, however, produced no visible effect on the infant. Moya and Margolies (1961) found that the destruction of the drug by the placenta did not significantly contribute to the placental “barrier”.

Hodges and Tunstall (1961) have stated their reasons for preferring suxamethonium to other relaxants in obstetric anaesthesia. It provides conditions favourable for immediate endotracheal intubation and ensures complete paralysis in doses which, relative to the antidepolarizing relaxants, do not result in postoperative respiratory impairment. It readily allows controlled intermittent positive pressure respiration and control of reflex responses in the lightest plane of anaesthesia. Suxamethonium is applicable to all obstetric situations requiring operative delivery under general anaesthesia and is particularly useful in those emergencies where speed is important.

Hodges et al. (1959) did observe an abnormal neuromuscular response to suxamethonium in a number of patients who had been receiving prolonged oxytocin infusions. But the management of such cases presented no serious problems. In the cases described the response may have been due to factors other than oxytocin. Keil (1962) after administering oxytocin for short periods to rabbits, sheep and pigs, found no change in their neuromuscular response to suxamethonium.

About 1 in 3,000 of a specified Canadian population have been shown to be liable to prolonged apnoea following single ordinary doses of suxamethonium (Kalow and Staron, 1957) owing to their inability to destroy this drug in a normal manner. It would be reasonable to assume that, if one of these patients were given suxamethonium at operative delivery, there would be a more prolonged and higher concentration gradient across the placenta than under normal circumstances. Furthermore, small quantities of suxamethonium crossing the placental barrier might affect a baby if it possessed the same abnormality as its mother. Prolonged apnoea due solely to neuromuscular blocking drugs, however, does not endanger life if adequate artificial respiration is maintained and treatment is carried out along proper lines (Churchill-Davidson, 1959; Churchill-Davidson and Wise, 1960; Vickers, 1963). Bingham (1957) reported a case of suxamethonium apnoea at Caesarean section but the baby was unaffected. From the details that were given it would appear that the mother may have been in the class with a low dibucaine number (Kalow and Genest, 1957; Bush, 1961).

d-Tubocurarine chloride.

The classic work by Crawford and Gardiner (1956) showed that in clinical use only traces of d-tubocurarine chloride appeared in the serum of the foetus. In spite of the sensitivity of the newborn to antidepolarizing relaxants (Stead, 1955), d-tubocurarine chloride used in obstetric anaesthesia is without significant effect on the newborn.

Curare has been used in small doses, without anaesthesia, to assist women in labour. Laborit and Chaillot (1949) claimed that strong uterine contractions were stimulated, the perineum became supple and the threshold to pain was raised. This is unconfirmed and is mentioned as of historical interest only.

Gallamine triethiodide.

Thomas and Gibson (1953) described the use of 100-mg doses of gallamine in 501 obstetric patients. There was no significant effect on the babies. But Crawford and Gardiner (1956) found that gallamine appeared in foetal serum in readily detectable and possibly significant amounts.

Decamethonium iodide (C.10).

Organe (1949) used 3-mg doses of decamethonium in several women about 10 minutes before delivery and their babies appeared to be unaffected. Young (1949) found the rabbit and guineapig placenta a very effective barrier to the passage of decamethonium in either direction.
THE COMPLICATIONS OF THE USE OF RELAXANTS IN OBSTETRICS

Inhalation of gastric contents.

The use of relaxants in obstetrics cannot be considered without the problems of aspiration of vomit, the major anaesthetic hazard for the woman in labour. A paralyzed patient cannot vomit but she may regurgitate. A semi-paralyzed patient may do both. Any relaxant technique in obstetrics, where the use of an endotracheal tube is not envisaged, must include plans for emptying the stomach and neutralizing its acidity either preoperatively or following the completion of inhalational induction and before any relaxant is given.

An endotracheal tube is now generally considered a necessary part of obstetric anaesthesia in order to prevent access of stomach contents to the lower respiratory passages. If it is intended to facilitate intubation by means of a relaxant, one with a rapid action is preferable. It is used in conjunction with the cricoid pressure technique for the prevention of regurgitation (Sellick, 1961) or with the head down and left lateral position which renders entry into the trachea of any material regurgitated before intubation less likely (Bourne, 1962).

Positive pressure inflation of the lung before intubation is dangerous. A period of preliminary inhalation of oxygen should be substituted. The Sellick manoeuvre may be combined with the head-up position (Elliot, 1963). As the left lateral 20° head-down position has certain advantages in cases of prolapsed cord, anaesthetists should have some experience of this method also.

Clark and Riddoch (1962) have shown experimentally that atropine increases the gastric opening pressure of the cardia in anaesthetized subjects. As it is so common for atropine to be administered intravenously prior to anaesthesia for emergency obstetrics it may be one of a number of factors which help to reduce the incidence of regurgitation. It might also help to counteract the effects of raised intragastric pressure caused by twitchings of the abdominal muscular wall when suxamethonium is first administered (Andersen, 1962; Roe, 1962).

Muscle pains due to suxamethonium.

A recent investigation on muscle pains due to suxamethonium by Bryson and Ormston (1962) showed a 15.7 per cent incidence of severe pains in 130 cases of Caesarean section. This incidence is likely to be higher after procedures which are followed by early ambulation, such as, for example, examination under anaesthesia, external version, etc. The outstanding advantages of suxamethonium in obstetric anaesthesia, however, outweigh the disadvantages of muscular pains which, it is admitted, can be unpleasant. There is a possibility that thiopentone given shortly before suxamethonium might result in a lower incidence or reduced severity of muscle pains compared to suxamethonium given after an inhalational induction (Burtles and Tunstall, 1961).

The disadvantage of intubation under an antidepolarizing relaxant is that full relaxation takes several minutes to develop and conditions for intubation may not be as good as under the paralysis due to suxamethonium. Intubation can be readily performed without relaxants, especially when there is hyperventilation induced by the inhalation of mixtures containing carbon dioxide (Inkster, 1963), but many anaesthetists are likely to prefer the speed and neatness of the preoxygenation, thiopentone, suxamethonium, intubation sequence.

Awareness during surgery.

By paralyzing the mother before delivery the anaesthetist avoids depression of the foetus by taking the mother as near to "awareness" as possible, as, for example, when maintenance is effected solely by nitrous oxide and oxygen, 8 l./min and 4 l./min respectively. Speed, within the limits of average dexterity, in establishing nitrous oxide equilibrium (Eger, 1960) in the patient, before the effect of the sleep dose of thiopentone has disappeared, is important. This is facilitated by hyperventilation and the administration of a high total gas flow (Hodges and Tunstall, 1961).

The author had occasion to anaesthetize for a Caesarean section an intelligent woman who was "aware" in accurate detail, but without pain, during a period of a Caesarean section performed two years previously. The "awareness" was, however, confined to a period of administration of pure oxygen in the interval just before delivery. She was not "aware" during a second section when she received premedication with atropine only, induction with 200 mg of thiopentone and 100 mg of suxamethonium given rapidly after pre-oxygenation, and maintenance by vigorous ventilation with nitrous oxide and oxygen after intubation (8 l./min and 4 l./min respectively).
Considering the various cases of "awareness" that have been reported (Crawford, 1962), it would seem that, where nitrous oxide has been the principal agent, analgesia develops before amnesia, so that, with nitrous oxide and oxygen only, the possibility of a being "aware" of pain while paralyzed during an operation and then not remembering afterwards probably does not arise. The evidence assembled by Parkhouse (1960) appears to support this point of view. There is no need to administer to the mother any inhalational agent other than nitrous oxide (at the very maximum 70 per cent) in oxygen before the delivery of her baby.

While it is not the place of this article to elaborate on the interesting problem of "awareness", there are some relevant points of interest. One of the attributes of consciousness is the ability to assess the relative significance of two or more stimuli. Awareness and memory are related to the degree of significance of stimuli. The absence of relaxation increases the number and intensity of stimuli, and the number is further increased by reflex muscular response to outside stimuli. A derogatory remark about a patient who is undergoing surgery at amnesic and analgesic levels may result, owing to its high degree of significance, in awareness and memory when otherwise there would have been amnesia.

Finally, it cannot be stressed too often that various combinations of
(a) too slow an injection of a sleep dose of thiopentone,
(b) prolonged intubation time,
(c) low fresh gas flows,
(d) inadequate ventilation, and
(e) partial paralysis,
may result in awareness at some stage when using a nitrous oxide, oxygen and relaxant technique.

THE EFFECT OF MUSCLE RELAXANTS ON THE UTERUS

There is no hard evidence to support the view that the relaxant drugs affect the uterus either directly or indirectly.

Scutt (1951) measured the pressure of the liquor amnii in the uterus in two cases during Caesarean section. One received d-tubocurarine chloride and the other decamethonium iodide. There was a fall in pressure in both cases. This disposed of the vague belief of the day in an oxytocic effect of curare.

Alver and his colleagues (1962) claim that suxamethonium produces useful uterine relaxation. They were able to demonstrate a dose-response relationship in a series of 70 women to whom suxamethonium was given deliberately to relax the uterus. The results were classified according to the obstetrician’s report. Critical readers might suggest that the uterine relaxation observed was the effect of relaxing the abdominal wall and so reducing the intra-abdominal pressure. It is significant, however, that 41 of the cases were listed as "trapped" placentas and were given suxamethonium to relax the lower uterine segment.

Wiqvist and Wihlin (1962) observed no changes in uterine motility, following paralyzing doses of suxamethonium, either in cats, or in human subjects at the 3rd or 4th month of pregnancy when contractions were stimulated by oxytocics.

Physiological basis.

Uterine smooth muscle behaves as a functional syncytium. Certain cells act as pacemaker cells owing to their spontaneous activity. Their membrane potentials are unstable and lead off to spike potentials which may be propagated from one cell to the other. Sensitivity and conductivity are influenced by hormonal factors. Burnstock and Holman (1963) in their review of autonomic nerve transmission to smooth muscle summarized by saying that:

(a) transmission of excitation from autonomic nerves to smooth muscle is essentially similar to that found at other neuromuscular junctions;
(b) it is possible that, unlike other known neuro-effector junctions, the axons passing close to muscle fibres release transmitter substances at intervals along their length and do not possess many discrete endings at all;
(c) electro-physiological observations on the action of transmitter substances at the membrane level suggest that the smooth muscle membrane has many properties in common with the endplate regions of skeletal muscle; for example, acetylcholine increases the permeability of the membrane to sodium, potassium and probably other ions.

There is thus some reason to suppose that suxamethonium could have an action on the uterus. Suxamethonium acts similarly to acetylcholine at the neuromuscular junction. Embrey (1958)
has shown that an intravenous infusion of acetylcholine stimulates uterine contractility. The oxytocic effect is not blocked by atropine and is accompanied by general effects which indicate that it is a nicotine-like response and cannot be ascribed to parasympathomimetic action.

Alver et al. (1962) postulate that the uterine action of suxamethonium indicates a possible general property with respect to sympathetically innervated smooth muscle. It is known that adrenaline decreases and noradrenaline increases uterine contractility (Garrett, 1954).

Adams and Hall (1962) have suggested that suxamethonium in man has both a nicotinic and muscarinic action. That suxamethonium acts elsewhere in man other than at the neuromuscular junction of striated muscle is a matter of common observation.

In general, however, the physiology and pharmacology of the uterine muscle has not been fully explored.

REFERENCES


BOOK REVIEW

*Electrical Measurement in Anaesthesiology* (Supplement XI). Edited by Henning Poulsen. Price Dkr. 60.00.

The Scandinavian Society of Anaesthesiologists at their Seventh Congress devoted the first half of their Scientific Programme to methods for electrical measurement in anaesthesia. The lectures and the concluding panel discussion have now been published as a Supplement to *Acta Anaesthesiologica Scandinavica*. No less than 170 anaesthetists participated in the intensive course of instruction and this book is welcomed, for it will allow many more to benefit from this valuable get-together of electronic engineers and anaesthetists.

The principles of measurement in anaesthesia are discussed by the late Professor Woolmer who emphasized that it was important to be able to quantitate changes in certain parameters but warned that the equipment used for these measurements must not be allowed to take control.

The following topics are dealt with in an elementary but detailed way: the fundamentals of electricity; electric circuits; basic methods for measurement of current voltage and impedance; transmission of electrical signals in R.C. networks with the use of amplifiers to allow interpretation of detected signals. The problems associated with the teaching of medical electronics by demonstrations are discussed.

Anaesthetists are usually familiar with the electrocardiograph, electroencephalograph and the cathode ray tube. How they work is simply explained, and Dr. Hill discusses the teaching of medical electronics.

Advances in anaesthesia have necessitated the development of equipment to allow newer techniques to be safely used and this applies to telethermometry, measurement of pressure both in arteries and other areas in the body, and the available apparatus is described with details of the physical principles upon which they are based.

Anaesthesia is very dependent upon respiration and pneumotachography, gas analysis and the measurement of pH, in conjunction with electrodes now available for blood and gas Pco2 and Po2 estimations, open up new spheres and their use can give much valuable information. All these topics are fully discussed and many problems clarified.

The application of these techniques of measurement to the supervision of patients during the postoperative period may mark a new era in medical treatment. Suitable equipment for this purpose is described.

The climax of this book is the panel discussion in which eminent participants ask pertinent questions covering many aspects of measurement relating to clinical accuracy, problems of maintenance of electronic equipment, whether recording apparatus is essential, and the contribution such measurements make to the safety of the patient during and after anaesthesia are answered by the panel.

This book makes available much specialized information and should be read by all anaesthetists thinking of including in their future hospital requests for equipment apparatus dependent upon electricity for measurement.

*J. C. Geddes*