THE CAUSES AND TREATMENT OF PROLONGED APNOEA

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DURING the past few years our knowledge of the underlying mechanism of neuromuscular transmission has made great strides. The clinician can now visualise the passage of acetylcholine ions across the gap between nerve and muscle, their contact with the protein molecules of the motor end-plate and the electrical change (depolarisation) that follows, with the consequent explosion of the muscle-fibre into activity. Nevertheless, it is only recently that this hypothetical picture has gained a touch of reality since Robertson,[1] with the aid of the electron microscope, has been able to demonstrate so clearly an area of specialised structure in the muscle-fibre directly opposite the nerve-ending.

Much of this progress has been due to a combination of physiological and pharmacological techniques in which the muscle-relaxants have played an important part. In view of the minute size of the structures involved it is often necessary to assume something which cannot be proved by scientific investigation. The large volume of available data based upon animal experiment is counterbalanced by the extreme paucity of investigation upon man. Yet it has already been established that some of the reactions to these drugs observed in animals cannot be reproduced in man. In clinical practice a situation has thus arisen in which occasionally the anaesthetist is confronted with certain patients in whom these drugs do not follow the predicted pattern. The result is that the whole subject of a prolonged reaction to a muscle-relaxant has become bedevilled with complex theories that are often far removed from fact, with almost complete absence of supporting evidence.

In considering the possible reasons why a patient does not breathe adequately at the appointed moment the causes are legion and often completely unrelated to the use of a muscle-relaxant. It is necessary, therefore, to establish first whether the cause of the apnoea arises in the brain (central) or from some defect in neuromuscular transmission (peripheral). This crude differential diagnosis can usually be made with ease by applying an electrical stimulus to a peripheral nerve and observing the presence or absence of a contraction in a skeletal muscle supplied by it.[2] Such nerve stimulators are available in most electro-diagnostic departments. Often the practiced eye can determine even minor degrees of neuromuscular block.

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CENTRAL CAUSES

Overventilation; Underventilation; Respiratory Depression. It is not the purpose of this paper to discuss the physiological mechanism of every cause of "prolonged apnoea" but rather to pick out only the most important. It has never been adequately defined when a period of apnoea can justifiably earn the title of "prolonged," but much will depend upon the manner in which respiration has been controlled. Respiration may be controlled in one of three ways. First, by depressing the activity of the respiratory centre with suitable doses of hypnotic or narcotic drugs; secondly, by overventilating the patient so that the carbon dioxide tension of the blood is lowered and the stimulus to the respiratory centre removed; and finally, respiration may be abolished by complete paralysis of all the respiratory muscles. In practice, a combination of all these methods is used, since over a long period each by itself must be considered dangerous.

A careful study of a series of cases reported as "prolonged apnoea" has revealed that the activity or sensitivity of the respiratory centre is of paramount importance. If one imagines this zone of sensitivity like a broad band appearing in the centre of a spectrum (fig. 1 A) it is easy to visualise how—with the aid of overventilation—spontaneous respiration ceases as the concentration of carbon dioxide in the blood falls and the centre is no longer stimulated. Conversely, a move in the opposite direction by allowing

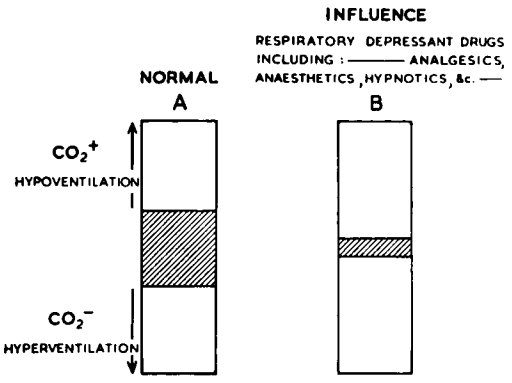

FIG. 1. Zone of sensitivity of the respiratory centre under normal and depressed condition.

the concentrations of carbon dioxide in the blood to rise may—after a short period of increased stimulation—poison and depress the respiratory centre. The exact level of carbon dioxide at which this depression first becomes apparent is unknown, but it appears to be related not only to the concentration of carbon dioxide but also to the duration of exposure of the respiratory centre. Such a hypothesis may help to explain some of the extremely long periods of apnoea or inadequate ventilation (6–12 hours) that are occasionally attributed to the use of muscle relaxants.

Theoretically, a heavy premedication followed by the liberal use of intravenous analgesics during operation reduces the size of this "band of sensitivity" of the respiratory centre so that a much narrower zone of activity now exists (fig. 1 B). In such circumstances, it is easy to pass without response through the narrow band of sensitivity by skipping from too little to too much carbon dioxide, in which case respiratory activity may be delayed for many hours. The objective in the administration of an anaesthetic, therefore, is to provide adequate relaxation for the surgeon by a combination of partial neuromuscular blockade with mild overventilation, while maintaining the sensitivity of the respiratory centre relatively unimpaired. Respiratory depressant drugs must be used with extreme caution and upon this basis it is preferable to use very small doses of a volatile anaesthetic agent (which can be rapidly eliminated) to supplement the nitrous oxide/oxygen anaesthesia rather than to rely on the longer-acting and more powerful respiratory depressants, *e.g.*, the intravenous analgesics.

Central Action of a Relaxant. Attention to the above principles has produced a remarkable drop in the incidence of so-called "prolonged apnoea." Nevertheless, it would also be fair to say that in England there appears to have been a steady decline in the popularity of the long-acting relaxant drugs for the poor risk patient in favour of a combination of short-acting relaxant with volatile anaesthetic agents. This shift in opinion is probably due to the attention that has been called to the dangers of the use of *d*-tubocurarine in severely debilitated patients.[3] The speculation that *d*-tubocurarine may pass directly into the brain cells and depress their activity is based on very fragile evidence in animals.[4] There is evidence in man that large relaxing doses may be given without producing any change in the level of consciousness.[5] Nevertheless, the suggestion has been made that in the poor risk case the serum potassium may be lowered and this results in a change in the properties of the blood-brain barrier which permits *d*-tubocurarine to bring about a direct depression of the respiratory centre.[4] No other relaxant has, as yet, been incriminated. Paton [6] has drawn attention to two pieces of evidence that fail to support this hypothesis. First, the central effects of *d*-tubocurarine in animals are primarily epileptogenic, and when it is applied centrally *d*-tubocurarine acts as a good antagonist to barbiturate anaesthesia. Secondly, the total amount that would reach the brain, after allowing for dispersal throughout the body, is small and unlikely on quantitative grounds to produce a substantial effect.

PERIPHERAL CAUSES

The commonest cause of a prolonged action of a drug is simple overdosage. Yet it is unlikely that successive doses of a relaxant would be used unless the clinical conditions demanded it. Nevertheless, occasionally a partial respiratory obstruction may be wrongly interpreted by the person inflating the lungs as a sign of returning power in the respiratory muscles and a further dose of relaxant used. Fortunately such mistakes are rare. Once the relaxant drug has reached the area of the motor end-plate the

duration of its stay will depend upon a number of factors. Prominent among these is the blood supply to a particular muscle, because this will control both the concentration and the eventual removal of the drug. The strength of the bond between the relaxant and its receptor is unknown; much more experimentation is needed before it will be possible to determine whether some relaxant drugs are held more firmly than others.

Blood Flow. In any laboratory study of the relaxant drugs the importance of muscle blood-flow soon becomes apparent. Measures designed to increase the flow—such as exercise, warmth, or sympathetic block—all lead to a rapid onset and a quick recovery from the effects of the muscle relaxant. On the other hand, cold and a poor peripheral circulation bring about a slow onset of paresis, which, once established, may persist for an hour or more.[7] These changes can be reproduced with both depolarising and nondepolarising drugs. In clinical practice, therefore, it is safe to conclude that the duration of activity of a muscle relaxant is intimately related to the blood flow in the particular muscle. A study of the factors affecting muscle blood flow has shown that the induction of anaesthesia is accompanied by a great increase in both skin and muscle blood-flow, with a return to the previous level in about one hour.[8] This would be consistent with a rapid action of the relaxant followed by a more gradual recovery. Haemorrhage and deep anaesthesia may cut short the phase of vasodilatation. In the poor risk case, therefore, a low blood volume may be present and this can be accompanied by a poor cardiac output and hypotension; the result is a sluggish peripheral muscle blood-flow, which must surely involve the diaphragm—particularly if it has been "resting" under the benefits of controlled respiration. It is known that inactive skeletal muscle remains paralysed for long periods in the presence of intense vasoconstriction. Why, therefore, is it necessary to postulate some complex electrolytic change to explain a prolonged paresis of the respiratory muscles when a simple explanation is available? In other words, many of the cases of "prolonged apnoea" in the poor risk patient may merely be due to defective blood-flow through the respiratory muscles. Further evidence on this point is required.

Alterations in Body Temperature. Bigland and her co-workers [9] have successfully demonstrated in animals that a reduction in body temperature influences neuromuscular block. Briefly, their results were as follows: first, that a lowering of the muscle temperature increased both the duration and magnitude of action of a depolarising drug at the motor end-plate, and this effect was reversed by rewarming. The effect of cooling applied equally to decamethonium and succinylcholine; yet, since succinylcholine is inactivated by plasma cholinesterase,[10] whereas decamethonium is not,[11] it was inferred that this effect was not related to enzyme activity. Secondly, the magnitude of block produced by a nondepolarising drug (*d*-tubocurarine) was reduced by cooling (*i.e.*, the drug had less effect) but the duration remained unaffected. Finally, the hypothermia was shown to have no action upon the normal characteristics of the blood. These authors did not believe that alterations in blood supply to the muscle played a significant part in their results.

Zaimis, Cannard and Price [12] have found a similar response in anaesthetised man. Clinically, this finding emphasises the possible dangers of the use of a depolarising relaxant drug in the presence of hypothermia. Furthermore it has been suggested that the increase in duration and magnitude of the block with depolarising drugs might explain some of the causes of prolonged apnoea with succinylcholine. However, it is not known whether the diaphragm in man undergoes severe cooling during a prolonged abdominal or thoracic operation. Although such an event seems probable, this explanation cannot be used to explain a prolonged reaction to *d*-tubocurarine as the duration of the block should be shortened by a lowered body temperature.

Whether muscle blood flow or temperature is the principal factor at work is largely a matter of academic interest, since clinically the two causes are inseparable. Nevertheless, measures designed to combat these complications might reduce the duration of the apnoea in certain cases.

Neostigmine-resistant Curarisation. This term originally coined by Hunter,[13] has a very palatable flavour and has already come to be accepted as a definite entity, particularly in

association with a low intracellular potassium and a poor risk patient. Nevertheless, there is no evidence at present to show that neostigmine has actually failed to reverse a neuromuscular block. As has already been intimated, there are many causes of the prolonged cessation of respiration, and before the term "neostigmine-resistant curarisation" can be accepted it is first necessary to prove that a neuromuscular block was in fact present, and secondly that the neostigmine reached the affected muscle but failed to reverse the blockade. This evidence is not available. Although it might be difficult to obtain for the respiratory muscles, it would nevertheless be easy to show a similar circumstance in the skeletal muscle of the limb. As yet there is no reason to suspect that the diaphragm behaves very differently from other skeletal musculature so that at present it would be unwise to accept this term on its face value.

The Breakdown Products of Succinylcholine. The whole process of the rapid breakdown of succinylcholine by plasma cholinesterase to succinylmonocholine, followed by the slower hydrolysis of the monocholine element to succinic acid and choline, has already been admirably told.[14] Most anesthesiologists at some time or another have encountered a patient in whom an apparently normal dose of succinylcholine led to a prolonged reaction of twenty to forty minutes. Subsequently the plasma cholinesterase level may be found to be low. It is generally believed, however, that even if the destructive enzyme is absent, the succinylcholine will be broken down by the alternative method of alkaline hydrolysis so long as a respiratory acidosis is prevented. In any event one would not expect this apnoea to last longer than 60 minutes. This conception is not intended to suggest that a low plasma cholinesterase level is the only cause of a prolonged response to succinylcholine as all the usual factors still apply, but in a series of patients under investigation it has been found to be the most common.

The monocholine derivative of succinylcholine, however, is also capable of producing neuromuscular block of the depolarising type in its own right. It has only about one-eightieth of the activity of its dicholine parent, but the hydrolysis rate is some six to eight times slower. Theoretically, therefore, it is possible during a large infusion of succinylcholine (1.0–2.0 Gm.) for the monocholine derivative to accumulate and lead to a prolonged neuromuscular block.

Dual Neuromuscular Blockade. For some years clinicians have been content to divide the muscle relaxants into two groups—those that acted by depolarisation, like acetylcholine, and those that acted by nondepolarisation, like *d*-tubocurarine. The discovery by Zaimis [15] in animals and Churchill-Davidson and Richardson [16] in myasthenic patients, that the administration of a depolarising relaxant (decamethonium) first produced a depolarisation followed rapidly by a nondepolarisation block, led to the supposition that a similar type of "dual block" might appear during clinical anaesthesia if repeated doses of the relaxant were given. Since then it has been found that neostigmine apparently reverses the paralysis produced by decamethonium or succinylcholine.[17-21] Clinically, this cause is most likely to be present if large doses of a depolarising relaxant (*e.g.*, 1.0 Gm. or more of succinylcholine) have been used.

Miscellaneous Causes. In this group are included neurological diseases such as myasthenia gravis, failure of afferent stimulation of respiration and possible involvement of the small motor fibre system. The incidence of undiagnosed myasthenia gravis is not sufficient to account for the numerous reports of a prolonged response to a muscle relaxant. Nevertheless, there is an increasing weight of evidence of the association of neoplasms—particularly of the lung—with some abnormality of neuromuscular transmission.[22] For this reason all relaxant drugs should be used with caution in such cases, and a history of muscle weakness treated with great respect.

The stimulation to respiration afforded by cutting the skin, stretching the anal sphincter or blowing up the cuff of an endotracheal tube is familiar to all. Frequently the release of the cuff at the end of an operation is the signal for the immediate resumption of respiratory activity. Movement of the endotracheal tube *in situ* often produces similar results. In some cases this reflex pathway may be depressed or even blocked by local analgesic drugs, and

therefore such stimulus is unavailable for the initiation of respiration.

The synergistic effect of the combination of ether and *d*-tubocurarine is well known. The relative newcomer to inhalational therapy—halothane—appears to act in a similar manner but the potentiation of the hypotensive activity of *d*-tubocurarine often figures more prominantly than its effect on skeletal musculature. But the reduced cardiac output, hypotension and poor peripheral blood flow (following the use of halothane) may be found to increase the duration of all types of relaxant. As the hypotensive action is not so marked in the presence of gallamine triethiodide, this relaxant has been found more suitable for combination in clinical practice.

Nitrous oxide thiopental (dose 0.5–1.0 Gm.), meperidine (10–100 mg.) and small concentrations of cyclopropane (5 per cent) have not been found to produce significant effects at the neuromuscular junction.

The part played by a low intracellular potassium in enhancing neuromuscular block is still obscure. The subject might be fairly described as a theorist's dream or a clinician's nightmare! The suggestion has been made that the neuromuscular block of *d*-tubocurare is increased and prolonged in the presence of a low intracellular potassium. Clinically this does not always appear to be true but the difficulties of deterring a true intracellular (as apposed to extracellular) potassium level are great. Further evidence must be awaited with interest.

The Diagnosis and Treatment of Prolonged Apnoea

A prolonged apnoea often occurs unexpectedly, and with so many possible causes to choose from it is essential that some attempt be made to pin-point the principal factor. When suddenly confronted with this problem a brief review of the anaesthetic technique employed will often reveal essential evidence. Following this a nerve stimulator should be applied to a peripheral motor nerve—the ulnar nerve being particularly convenient. A vigorous response of the skeletal muscle suggests (but does not prove) that the diaphragm is not being influenced by peripheral causes but rather that the fault lies in respiratory inactivity of some central origin.

Central Respiratory Inactivity. Assuming that central inactivity is implicated, the level of carbon dioxide in the blood is most important. Laboratory data will reveal the effectiveness of the previous ventilation. However, laboratory facilities are not always available and then the clinician must rely on cruder methods. For example, if a high level of carbon dioxide is suspected, vigorous overventilation for five minutes may be practiced with fresh soda lime in the circuit; rapid warming of the absorber suggests the presence of a high alveolar carbon dioxide level. Alternatively, if a low level of carbon dioxide is believed to be the cause, the patient's lungs can be ventilated for five minutes with a mixture containing 5 per cent carbon dioxide. Such methods, however, are haphazard and cannot be recommended for the ordinary case.

The aim of all treatment of central respiratory inactivity can be summarised as follows: (1) the establishment of a normal carbon dioxide level in the blood, (2) increasing the sensitivity of the respiratory centre, and (3) provision of adequate afferent stimulation.

The first criteria can only be achieved by the continued maintenance of adequate ventilation. On the other hand, the sensitivity of the respiratory centre will depend upon the amount of depressant drugs—particularly analgesics like morphine and meperidine—that have been used both as premedication and during anaesthesia. Whereas the effect of such drugs on respiratory activity can easily be assessed when the patient is breathing spontaneously, this is not the case in the paralysed patient. The use of respiratory depressant drugs, therefore, in the presence of controlled respiration is not recommended, since—particularly in unskilled hands—it considerably increases the incidence of "prolonged apnoea" at the end of the operation. Volatile anaesthetics, which can be more easily eliminated at the appropriate moment, or drugs which leave the respiratory centre virtually unaffected, are preferable. The actual sensitivity of the centre can be increased by the use of analeptic drugs. For this reason, both nikethamide and picrotoxin have been used with success in the treatment of cases of prolonged apnoea. Also, if intravenous anal-

gesics have been used their depressant action can be reversed by the appropriate antidote—nalorphine and allied compounds.

At this stage the sensitivity of the respiratory centre has been restored and the normal level of carbon dioxide in the blood ensures continued activity once the act of respiration has been re-established. It remains, therefore, only for a suitable afferent stimulus to set the ball rolling. Stimulation of the mucous membrane of the trachea is particularly effective; this may take the form of either gently moving the tube in the trachea or alternately inflating and deflating the balloon of a cuffed Magill tube.

Peripheral Neuromuscular Block. Assuming that peripheral nerve stimulation has revealed the presence of a severe degree of neuromuscular block, the commonest cause is an "*overdose*" of a particular muscle relaxant. Sometimes a single dose of succinylcholine is followed by many minutes of apnoea. A low plasma cholinesterase level is almost always responsible. Although fresh blood transfusion and the injection of the enzyme extract "cholase" have been recommended, it is rarely necessary to do more than patiently ventilate the lungs until spontaneous respiration returns.

On the other hand, if a long-acting relaxant or an infusion of succinylcholine has been used the relative concentration of the drug in the motor end-plate region may be high. At the end of a long and severe operation the peripheral blood flow may also be low. Any measures, therefore, designed to increase this muscle-flow will aid in the "washing-out" process and reduce the activity of the drug. Similarly, renal vasoconstriction will reduce the excretion rate of both types of relaxant drug. Blood transfusion, by increasing the blood volume, may stimulate the cardiac output and raise the systemic pressure so that the whole peripheral flow is improved.

The muscle temperature—particularly that of the diaphragm—must also be considered. If the abdominal or thoracic cavities have lain exposed for some hours, the muscle of the diaphragm may have suffered severe cooling. This will tend to increase both the duration and magnitude of a depolarising block (succinylcholine) whereas it should tend to shorten the activity of one due to nondepolarisation (*d*-tubocurarine). Changes in room temperature—for example, from a cold operating room to a warm recovery ward and *vice versa*—offer an intriguing theoretical exercise in the possible alterations in the magnitude of the neuromuscular block. The best single method of rapidly rewarming the diaphragm and the other respiratory muscles is probably by the use of short-wave therapy. Nevertheless, the simple expedient of skin warming soon results in a general rise in body temperature.

The use of large doses of a nondepolarising relaxant (*i.e.*, *d*-tubocurarine) is an indication for the reversal of its neuromuscular-blocking activity by the antidote—neostigmine methylsulphate. Sometimes, the breathing at the end of an operation is so vigorous and adequate that anti-cholinesterase therapy is considered unnecessary and even undesirable. However, most cases benefit from its use. If apnoea is present it would seem logical to try to reverse any neuromuscular block that is a contributing factor. This can usually be achieved by 2.5 mg. neostigmine, given in divided doses intravenously, and preceded two to three minutes earlier by 1 mg. atropine sulphate. It is seldom necessary to exceed 2.5 mg. and the necessity for such a measure should be verified by first giving an evanescent anti-cholinesterase—edrophonium (10 mg.). An improvement in muscle-power which lasts only a few minutes is a clear indication that more neostigmine is required. Nevertheless, it must be borne in mind that neostigmine—even in the presence of atropine—is an extremely unpleasant drug to receive in the conscious state. In the absence of a nondepolarising block doses of neostigmine in excess of 2.5 mg. are capable of producing neuromuscular block in their own right and, therefore, this limit should not be exceeded except in the circumstances outlined above.

Following the use of large doses of the depolarising drugs the characteristics of the neuromuscular block may change so that it now resembles a nondepolarisation type of block, *i.e.*, dual block. The presence or absence of such a block should again first be tested by the use of edrophonium. As mentioned above, if there is a notable improvement in the volume of ventilation then neostigmine therapy should be used.

Finally, the foregoing analysis of the possible causes of prolonged apnoea has tended to put

an undue emphasis upon its incidence. It is almost always true to say that the cause is maladministration rather than a peculiarity of patient or drug; the condition should be regarded merely as an inconvenience and—provided adequate ventilation is maintained—a successful outcome is assured.

Summary

The possible causes of a "prolonged apnoea" have been considered under two main headings. First, central causes affecting the activity of the respiratory centre: overventilation, underventilation and the use of respiratory depressant drugs (particularly morphine and meperidine), figure prominently in this group. Secondly, peripheral causes include simple overdose, sluggish muscle blood-flow, low muscle-temperature, poor renal excretion and reduced plasma cholinesterase activity. The possible alterations in the characteristics of a depolarisation block are discussed. Various suggestions on treatment are given.

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