THE USE OF ANTIDOTES IN ANAESTHESIA

Consultant Anaesthetist, The Middlesex Hospital, W.1

The number of effective antidotes in the pharmacopoeia of the modern anaesthetist can be counted on the fingers of one hand. It is the purpose of this paper to discuss the value of these few drugs and describe their method of administration and mode of action. For this purpose they have been grouped into four.

1. Antidotes to the Muscle Relaxant Drugs

The introduction of the muscle relaxant drugs has been the greatest advance in clinical anaesthesia of this century. It has enabled profound muscular relaxation to be obtained by the use of virtually non-toxic drugs in the presence of the lightest levels of anaesthesia. The respiratory depression or paralysis associated with this degree of relaxation is overcome by the related techniques of assisted or controlled ventilation. Poisoning by excessive anaesthetic dosage to secure relaxation is now avoided and vasomotor tone is maintained with a consequent lowering in the incidence of peripheral circulatory failure.

Muscle relaxant drugs exert their action at the neuromuscular junction. The complex chemical transmission of nerve impulses into muscular activity is not completely known. Normally motor nerve impulses cause a liberation of acetylcholine at the nerve endplate in contact with the muscle fibre. The acetylcholine attaches itself to an endplate receptor which leads to a depolarization of the muscle fibre in the region of the endplate. The depolarization spreads along the fibre and a contraction follows. For a fraction of a second the muscle fibre is refractory to further stimulation but the acetylcholine is almost instantaneously destroyed by the enzyme cholinesterase. Repolarization of the fibre then occurs and is once again receptive of further stimulation.

Muscle relaxants can be broadly divided into two groups. The curare group which includes the purified extract d-tubocurarine chloride, gallamine triethiodide (‘Flaxedil’), and laudolissen causes neuromuscular block by competing for the endplate receptor for acetylcholine. Acetylcholine continues to be formed as a result of motor nerve impulses but it can no longer cause depolarization. Electrically the curarized muscle remains charged and can still be made to contract by direct stimulation.

The other group of the relaxants, the depolarizing group, resemble acetylcholine in their action and cause muscle relaxation by attaching themselves to the endplate receptor and depolarizing the muscle fibre. This explains the muscular fasciculations that are seen as paralysis occurs with these drugs. Being less easily destroyed than acetylcholine they persist for varying periods and the fibre remains depolarized. During this depolarization the muscle fibre is not susceptible to direct stimulation. The most important drugs in this group are decamethonium iodide and bromide and suxemethonium (‘Scoline’).

(a) Antagonists to the Curare Group

It has long been known that adrenaline and ephedrine have a decurarizing effect on skeletal muscle, but their mode of action is unknown and the action is insufficient for clinical purposes. K+ also reverses curare; it is thought that acetylcholine itself produces depolarization through the medium of liberated potassium (Samson Wright, 1952).

Physostigmine (‘Eserine’). A naturally occurring compound extracted from the calabar bean was the first anticurare drug to be used. It is an anticholine-esterase and by preventing the destruction of naturally formed acetylcholine at the endplate, curare is displaced from the receptor. If nervous activity is depressed acetylcholine is formed slowly and the onset of action of physostigmine is delayed.

The instability of this drug in solution and its marked action on the smooth muscle of the gut precludes its clinical use. The carbamate group in the molecule (see diagram) is the effective portion. Tensilon. This is a synthetic anticurare drug that has an ammonium grouping similar to that of acetylcholine. Its action is a direct one on the endplate which it resensitizes to acetylcholine. Its action is rapid in onset but does not persist and
repeated doses may be needed. This is a disadvantage in clinical anaesthesia as the patient may relapse into respiratory depression on return to the ward. The advantage of tensilon is its freedom from undesirable side effects, particularly those on the cardiovascular system.

Acetylcholine.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br.} \\
\text{CH}_3 & \quad \text{N} \quad \text{C}_2 \text{H}_4 \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

Neostigmine. (Prostigmine)

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br.} \\
\text{CH}_3 & \quad \text{N} \quad \text{C}_6 \text{H}_4 \quad \text{O} \quad \text{C} \quad \text{CH}_3 \\
\text{CH}_2 & \quad \text{O} \\
\end{align*}
\]

Tensilon.

\[
\begin{align*}
\text{CH}_3 & \quad \text{Br.} \\
\text{C}_2\text{H}_2 & \quad \text{N} \quad \text{C}_6 \text{H}_4 \quad \text{O} \quad \text{H} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

Physostigmine.

\[
\begin{align*}
\text{CH}_2 & \quad \text{CH}_3 \\
\text{N} & \quad \text{C}_6 \text{H}_3 \quad \text{O} \quad \text{N} \quad \text{H} \\
\text{CH}_3 & \quad \text{O} \\
\end{align*}
\]

Neostigmine ('Prostigmine'). This is the antichuare drug of choice and, in the writer’s opinion, should be used as a routine and integral part of curare administration. As will be seen from its formula, it possesses both a carbamate and ammonium grouping. Its action is thought to be twofold: It stimulates endplate activity directly and by means of its anticholinesterase action it prevents the rapid destruction of acetylcholine. Neostigmine has an action that is rapid in onset and persistent; in fact once curare has been displaced from the endplate receptor by neostigmine it cannot re-exert a neuromuscular block without further dosage.

Side effects of neostigmine. If given in large doses to an uncurarized animal it causes muscle fasciculations and paralysis. In normal clinical dosage its side effects are those of parasympathetic overactivity, i.e. bradycardia, increased intestinal tone and mucus secretion. In susceptible patients the cardiac effects may progress to heart block or even cardiac standstill.

These side effects can be eliminated if a suitable dose of atropine precedes the neostigmine. Atropine paralyses parasympathetic nerve endings causing an inhibition of intestinal contractions, a decrease in mucus secretion and an increase in heart rate. This mutually antagonistic effect of atropine and prostigmine has recently been utilized in the treatment of accidental atropine poisoning (Popp and Niebauer, 1954). Neostigmine without atropine has been found useful to steady rapid or irregular hearts during thoracic surgery and is protective against excess adrenaline (Sellick, 1955).

Method of administration of neostigmine. Preliminary atropine. Atropine causes a transient slowing of the heart before its vagal depressant effect becomes established. For this reason it should never be given mixed with neostigmine lest a combination of vagal effects leads to a fatal cardiac inhibition. For the same reason rapid intravenous injection of atropine alone should be avoided.

For a normal adult who has had the usual pre-operative atropine or scopolamine a further dose of atropine, 1/100 to 1/50 gr., should be given intravenously a few minutes before it is intended to give the neostigmine. A rise in pulse rate will demonstrate the activity of the atropine.

If complete respiratory paralysis still remains from the curare controlled ventilation should be continued and the neostigmine withheld until some attempts at spontaneous respiration returns.

From the anaesthetist’s point of view the muscle relaxant is only one of many causes of respiratory paralysis. Others include carbon dioxide excess, carbon dioxide depletion, excessive dosage of narcotic or anaesthetic drugs or respiratory inhibition from stimulation of, for example, the inflated cuff of an endotracheal tube. It is good practice to eliminate all these causes of respiratory arrest before administering neostigmine. The optimum time to give the drug is on the return of some attempts to breathe spontaneously—typically heralded by diaphragmatic breathing and tracheal tug.

The practice of using one of the short acting depolarizing agents (see below) at the end of an operation to facilitate closure of the wound calls for especial care in the administration of neostigmine which must not be given until signs of elimination of the depolarizer are present. The presence of respiratory movement indicates that acetylcholine is being formed and that central depression is not complete; as a result the action of neostigmine will be greater. The duration of
relaxation following a dose of curare is largely dependent on the degree of central depression of efferent nerve impulses by deep anaesthesia and consequent inhibition of acetylcholine formation.

**Dosage of neostigmine.** Following atropine the usual adult dose of neostigmine is from 1.0 to 2.5 mg. Doses of 5.0 or even 7.5 mg. may be necessary, but if 2.5 mg. has to be exceeded further atropine will probably be necessary first.

(b) Antagonists to the Depolarizing Group

The depolarizing group of drugs simulate acetylcholine in their action and they are usually short acting. Idiosyncrasy does occur and very prolonged paralysis can occur after repeated doses or in association with deep anaesthesia. There is no satisfactory antidote.

**Decamethonium** can be displaced from the end-plate receptor by lower members of its homologous series. Hexamethonium (C₄) has been used for this purpose, but the profound fall in blood pressure that this drug causes is a strong contra-indication to its use in these circumstances.

**Suxemethonium (‘Scoline’)** is the ultra short-acting relaxant from which have come the most reports of idiosyncrasy. Normally the paralysis from this drug is of two or three minutes' duration, but a ‘scoline apnoea’ of six or eight hours is not unknown. It has been suggested (Evans et al., 1953) that a low plasma cholinesterase is the explanation and that the administration of this substance either as an extract or in fresh blood would overcome the apnoea. Argent et al. (1955) suggest that the low plasma cholinesterase would only account for a slight prolongation and they postulate a central depression as the cause.

Experimentally, as one might expect from its ammonium grouping, neostigmine enhances and prolongs the action of scoline. Argent et al. (1955) found neostigmine of use in the later stages of treatment of some of their cases. This suggests that scoline had already been eliminated from the endplate region and that the neostigmine was reinforcing the depleted acetylcholine formation consequent upon central depression and reduced motor nerve activity. Further proof of their hypothesis comes from the successful response in some of these cases to analeptic drugs. The administration of nikethamide or methylamphetamine is frequently followed by return of spontaneous respiration.

From what has been said it is concluded that it is unwise to use neostigmine in the first 20 minutes of a scoline apnoea but after this time it may have a place in the treatment of this condition.

2. Antidotes to the Barbiturates

Barbiturate overdosage causes an immediate respiratory and cardiovascular depression. Delayed hepatic or renal damage may occur. In dealing with barbiturate emergencies the first consideration is the establishment of a clear airway and maintenance of adequate tidal exchange by means of assisted or controlled ventilation. If cardiovascular depression is present as well, this must be treated before consideration is given to antagonising the barbiturate itself. The hypertensive state resulting from the barbiturates is discussed later.

It is only after these more immediate problems have been overcome that the question of antidotes arises. In the past the standard method of dealing with oral barbiturate overdosage has been gastric lavage, oxygen and the repeated doses of analeptic drugs. This method of cerebral stimulation poising the patient on the brink of a convulsion greatly increases the metabolic demands of the patient and this in association with the reduced respiratory function probably contributed to the fatal outcome of many cases (Nilsson, 1951). Nilsson advanced the theory that the use of assisted or controlled ventilation and maintenance of fluid balance pending the spontaneous elimination of the barbiturate is a more rational method. The use of cortisone has been suggested in the treatment of these cases (when has it not?) but the writer has no experience of its use for this purpose.

Within the last few months an antidote to the barbiturates has been given a clinical trial and there have been a few reports of its use in anaesthetic practice (Harris, 1955). The drug is β méthyl ethyl glutarimide, megimide, or NP1 3.

From the brief reports so far available NP 13 appears to be an innocuous drug which in doses of 50 mg. has no side effects. In large doses in unanaesthetized animals it causes muscular fasciculation and convulsions. It has been used in combination with 2-4-diamino-5-phenylthiazole—a morphine antagonist which has a slight antagonism to the barbiturates—in cases of suicidal barbiturate overdosage.

Patients anaesthetized by thiopentone, 0.5 g., after atropine premedication for short manipulative procedures regained consciousness almost immediately after injection of 50 mg. of NP 13. In those who had longer operative procedures after omnopon and scopolamine premedication con-
sciousness was regained within three to seven minutes after injection of the drug.

Much work will have to be done before this drug becomes accepted by anaesthetists, but if its early promise is maintained it will have many possibilities. Whether it crosses the placenta or not will determine much of its usefulness in obstetrics. Until these researches have been carried out the method of treating barbiturate overdosage must remain that of Nilsson—maintenance of ventilation, circulation and fluid balance pending spontaneous elimination of the drug.

The safety of analeptics such as nikethamide and picrotoxin in the treatment of barbiturate overdosage is questionable.

3. Antidotes to Morphine and Analagous Drugs

Opiate overdosage is characterized by profound respiratory and cardiovascular depression similar to that produced by the barbiturates and requiring a similar method of immediate treatment. Until the last few years analeptics and supportive therapy together with doses of atropine was the basis of treatment.

It has long been known that N-allyl-nor-codeine antagonized the respiratory depression of morphine (Pohl, 1915) but not until N-allyl-nor-morphine was synthesized (Weijlar and Erickson, 1942) was a means of reversing morphine in clinical medicine contemplated (Hart, 1943). Since 1951 this drug has been given extensive clinical trials and it has been found to exert an antagonism to the respiratory and circulatory depression of many drugs analagous to morphine including pethidine ('De-merol'). It has no action on the barbiturate group.

Chemistry. N-allyl-nor-morphine is obtained by substituting an N-allyl group for the N-methyl group in morphine. It is also known as 'Nalorphine' and 'Lethidrone' and has the following structural formula.

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\begin{align*}
N &- CH_2 \ CH = CH_2 \\
\end{align*}
\]

Pharmacology. N-allyl-nor-morphine when given alone in doses of 5 to 15 mg. has an action substantially that of an equal amount of morphine. It produces, perhaps, a lesser degree of analgesia but has the unpleasant property of causing hallucinations in some patients. When given to a patient who has had a small or even normal dose of morphine the drug may increase the morphine effect and produce some degree of respiratory and circulatory depression. Its main effect is noticed when a large or an overdose of a morphine type drug has been given. The respiratory and circulatory depression is then reversed by doses of 10 to 30 mg. of N-allyl-nor-morphine. The level of analgesia is somewhat lessened and although sedation does not seem to be materially altered, the stuporous patient is more readily roused. Another interesting action of this drug is on drug addicts who develop severe withdrawal symptoms after its administration. It has been used in this way as a diagnostic test for addiction (Wickler and Cartier, 1952).

Mode of action. N-allyl-nor-morphine is thought to compete with morphine for the cell membrane receptors.

Clinical uses. From the anaesthetists' point of view N-allyl-nor-morphine is useful in two types of case. The first is where simple overdosage by morphine or its analogues has occurred and respiratory and cardiovascular depression has resulted. This may occur in a number of ways: Inadvertant overdosage of premedication in susceptible patients, for example in the shocked, debilitated and aged, and as a result of repeated small doses of pethidine given during some methods of anaesthesia.

If respiratory rate and depth are inadequate 10 mg. of N-allyl-nor-morphine can be given to an adult in the first instance. This may be repeated once or twice more if some response is obtained, but it must always be remembered that it is a doubled edged weapon and an increased depression may result from too liberal use.

Obstetric analgesia. N-allyl-nor-morphine, like other morphine derivatives, crosses the placenta into the blood stream of the foetus. The use of morphine or pethidine for the relief of pain during labour has frequently led to respiratory depression in the newborn. Timing of doses of analgesic for the mother is notoriously difficult and it has frequently meant that the child has been delivered within a short time of a large dose of analgesic. In these cases newborn depression of respiration can frequently be minimized by the use of N-allyl-nor-morphine, 10 to 20 mg. given to the mother intravenously several minutes before delivery. The drug rapidly crosses the placental barrier and antagonizes the narcotic already in the foetus.

Giving the drug to the mother before delivery is a more satisfactory method than giving it to the child afterwards. But if the newborn child is slow in establishing a satisfactory rate and depth of
respiration the drug can be given into the umbilical vessels in very small doses, 0.2 mg. diluted in 2.0 cc. water (Eckenhoff et al., 1953).

The factors influencing the initiation of adequate respiration in the newborn are many and their differential diagnosis frequently difficult, particularly after instrumental delivery, so that the indiscriminate use of N-allyl-nor-morphine for respiratory inadequacy is to be deprecated. If the respiratory depression in the child is due to one of many other causes, e.g. trauma or excessive maternal anaesthesia, N-allyl-nor-morphine will increase rather than lessen it.

4. Antidotes to Hypotensive States

Hypotension occurring during anaesthesia may be accidental or deliberately induced. Accidental hypotension following loss of circulating blood volume after haemorrhage or trauma must be treated by transfusion either of whole blood, plasma or its substitutes. No drug is a safe antidote to loss of circulating blood volume. This condition is characterized by vasoconstriction and vasopressors merely increase the constriction possibly at the expense of the blood supply to some vital organ such as the kidney. Reflex hypotension may follow surgical stimulation in the under-anaesthetized; the treatment is to request the surgeon to stop operating until anaesthesia has been deepened. Hypotension may follow accidental overdosage by the barbiturates or opiates and is the consequence of central depression and peripheral vasodilatation.

Deliberately induced hypotension by means of ganglion blocking agents is gaining favour for some operations in which haemorrhage would otherwise make the surgery difficult if not impossible. The drugs used for this purpose are mainly hexamethonium bromide or iodide and ‘arfonad’ [(+)-3,4 (1',3'-dibenzyl-2’-keto-imidazolido) 1,2-tri-methylene thiophanum d-camphorsulphonate]. The peripheral vasodilatation produced by these drugs can be antagonized by the vasopressor drugs.

Adrenaline, noradrenaline, ephedrine and many others have been used as antidotes to vasodilated and central depressant hypotension (Dripps et al., 1946). In the writer’s opinion n-methyl-amphetamine (‘Methedrine’) is the drug of choice. This drug has a rapid and very sustained action (Prestcott et al., 1944). Its mode of action is both central and peripheral. Centrally it is a cerebral stimulant, it lightens anaesthesia and increases vasomotor tone. Peripherally it is a vasoconstrictor acting directly on the blood vessels. Providing adequate blood volume is present its vasoconstriction is not detrimental to vital organs. There is an increase in renal blood flow and renal excretion; a fact made use of by the writer to secure ureteric catheter specimens of urine under thiopentone anaesthesia.

Intravenously 5 to 10 mg. seldom needs to be exceeded at one time. Intramuscularly up to 30 mg. may be given. Methedrine in excess causes hypertension, tachycardia and cardiac arrhythmia and must be administered with care to patients with cardiovascular disease.

Discussion

It is argued that to need an antidote at all in anaesthesia is to confess lack of skill, and it is true that the more experienced the anaesthetist the fewer occasions he finds it necessary to use an antidote unexpectedly. It is perhaps fortunate that during the formative years of modern intravenous anaesthesia so few antidotes have been available; there is nothing more conducive to skill and care in the administration of a potent drug than the knowledge that it has no antidote.

The knowledge of anaesthetists is being applied more and more to other branches of clinical medicine. The work of Nilsson in the treatment of barbiturate poisoning is one example, and the need for an effective antidote for this type of case cannot be denied. Apart from the advantages in shortening barbiturate anaesthesia for minor outpatient surgery the use of NP 13 seems limited. It is to be hoped that it will not be used to awaken on the operating table those patients who have been subjected to major surgery and who benefit from the more gradual return to reality that accompanies the spontaneous elimination of the barbiturates.

No drugs are perfect and the use of an antidote to antagonize certain undesirable features so that fuller use can be made of the drug is an essential purpose of antidotes in surgical anaesthesia. The use of atropine and neostigmine to reverse the effects of the curare compounds is probably the most important use to which an antidote is put in practice. The saving in poisonous doses of other drugs and the protection from surgical shock that accompanies the muscle relaxation of this drug more than justifies the necessity for controlled respiration and the need for an antidote to cut short its action.

As yet not so well proven is the value of N-allylnor-morphine to reverse the depressant effects of morphine and pethidine so that greater safety can be obtained in obstetric analgesia.

Summary

The antidotes to the muscle relaxants, barbiturates, opiates and hypotensive states are described. Their dosage, mode of action and side effects are described. Their value in anaesthesia is discussed.

Bibliography continued on page 488.
January 1955

POSTGRADUATE MEDICAL JOURNAL

stetrics, lecture demonstrations, Mondays, Tuesdays and Fridays, 9.15 a.m., Maternity Lecture Theatre, Radcliffe Infirmary. Gynaecology, ward rounds, Wednesdays, 10.30 a.m. and 5 p.m., Radcliffe Infirmary. Obstetrics and Gynaecology, concilia, monthly, alternate Thursdays and Fridays, 3 p.m., Maternity Lecture Theatre, Radcliffe Infirmary. Ante-natal clinics, out-patients, Mondays, 2 p.m., Maternity Home Radcliffe Infirmary and Churchill Hospital, Thursdays, 2 p.m., Radcliffe Infirmary Maternity Home, Fridays, 9.15 a.m., Maternity Lecture Theatre. Post-natal clinics, out-patients, Tuesdays, 10 a.m., Wednesdays, 2 p.m., Radcliffe Infirmary Maternity Lecture Theatre.

General practitioners wishing to avail themselves of the facilities set out in this schedule should apply to the Secretary, Postgraduate Medical Committee, 11 Keble Road, Oxford.

CONFERENCES, PRIZES, Etc.

Butterworth Gold Medal is to be presented annually to the College of General Practitioners (by Messrs. Butterworth & Co., Medical Publishers) for an essay not exceeding 10,000 words, written by a member or associate of the College, on a subject connected with general practice. The title for 1955 is 'The influence of home conditions during the first five years of life on the physical and mental health of children.

Essays must be submitted to the Chairman of the Awards Committee, the College of General Practitioners, 14 Black Friars Lane, London, E.C.4, by September 30th, 1955. They should be typewritten and headed with a motto—the name and address of the sender being enclosed in a sealed envelope with the motto written outside.

Queen Square Prize in Neurology. A prize of £100 will be awarded annually to the postgraduate student, or ex-student, of the Institute of Neurology who presents the best written paper describing clinical work carried out or initiated at the National Hospitals for Nervous Diseases. Entries must be submitted not later than September 30 each year.

Full particulars from the Dean, Institute of Neurology, (Queen Square), The National Hospital, Queen Square, London W.C.1.

Buckston Browne Prize Essay. The prize, consisting of a medal, together with the sum of £100, will be awarded for the best essay on 'Hypertension,' submitted by August 31, 1956. The prize is open to any member of the medical profession registered in the British Isles or Dominions, and is limited to candidates under 45 years of age.

Further particulars may be obtained from the Honorary Secretaries, Harveian Society of London, 11 Chandos Street, Cavendish Square, London, W.1.

Sir David Wilkie Research Fellowship in Surgery and/or Medicine is offered by the Faculty of Medicine of the University of Edinburgh. The Fellowship, of the value of £800 to £1,000 (Sterling) per annum, with a possible allowance for approved expenses of research, and tenable for two years (with possible extension to three years at the discretion of the Senatus Academicus), will be open for award in October, 1956. The Fellowship is open to graduates of any University. The holder will be required to carry out approved research work in surgery and/or medicine in the University, and he must attend the honours class in physiology, unless he is already a graduate in physiology or in science. While undertaking the research work he will be expected to maintain contact with clinical work, but the time to be devoted to this will be restricted to two half-days per week. During his tenure the Fellow will not be permitted to study for or to present himself for any examination leading to a higher diploma in medicine or surgery. Applications must be submitted on a prescribed form, a copy of which may be obtained from the Dean of the Faculty of Medicine, or from the mentioned persons.

Applications from graduates in the following countries must be received by October 31, 1955: Australia. The Chairman, National Health and Medical Research Council, Dept. of Health, Canberra, A.C.T., Australia. Canada. The Awards Officer, National Research Council, Ottawa, Ont., Canada. New Zealand. The Secretary, Medical Research Council, Dept. of Health, P.O.B. 5013, Wellington, New Zealand. South Africa. The Director, South African Institute for Medical Research, Hospital Street, Johannesburg, South Africa. Applications from graduates in the United Kingdom or countries other than those listed above must be received by March 1, 1956, addressed to Dean, Faculty of Medicine, University New Buildings, Edinburgh, 8, Scotland.

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