DOSES OF CURARE
A Plea for their Reduction

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The major development in anaesthesia during the last decade has been "to give light general anaesthesia to ensure unconsciousness, and then to abolish reflex response to stimuli by one of the relaxants which in themselves do not cause any metabolic upset" (Macintosh, 1955). While many anaesthetists are trying to reduce the analgesic and hypnotic agents to a minimum, relaxants are being given with little restraint because they are assumed to be innocuous. Often curarization is used to cover up poor anaesthesia (Cullen, 1954). In Britain doses of d-tubocurarine (dtc) are large. With or without a test dose (Gray and Halton, 1948) the initial dose frequently reaches 30 mg or more. For instance, Grigor (1954) used 35 mg for intubation in a case of mitral stenosis. Collier (1956) injects 25-30 mg for intubation for Caesarean section, and Lawson (1956a) gave 120 mg gallamine for intubation to a man of 73 whose abdominal muscles were already relaxed by spinal analgesia.

In view of several reports of death after heavy curarization, and of the assumption that there occur more anaesthetic deaths in curarized than in noncurarized patients (Beecher and Todd, 1954) the time may have come to reconsider the dosage of curarizing agents. This paper is a plea for individualizing the doses of the nondepolarizing relaxants and for moderation in their use.

Lately, fatalities after large doses of dtc have been reported in this journal (Foster, 1956) which were thought to be caused by potassium depletion and not by an overdose of relaxant. One of these cases is quoted in full in order to show how its problems could be seen in a different light:

A man of 78 years was treated for 8 days in a medical ward for chronic intestinal obstruction caused by a carcinoma of the pelvic rectal junction. This was precipitated into an acute obstruction by the use of barium in X-ray studies. He became grossly distended and vomited considerable amounts of fluid which were inadequately replaced with saline and dextrose.

He was presented for emergency surgery dehydrated, and with electrolyte depletion—serum Na 130.5 m.equiv/l., K 3.2 m.equiv/l., Cl 82.4 m.equiv/l. His blood urea had recently risen to 115 mg per cent. Premedication was with atropine 0.6 mg and morphine 10 mg.

The patient was given oxygen to breathe for several minutes and then nitrous oxide and oxygen (6 l./min and 2 l./min respectively). Simultaneously an intravenous test dose of 5 mg dtc was given. This did not evoke an abnormal depression of breathing, so that a further 25 mg was given as consciousness was lost, and the patient intubated. He was so restless—moving his arms and legs, shaking his head, opening his eyes, and breathing—that within 10 minutes a further 10 mg of dtc was given. This had little immediate effect, but after about 10 minutes again he suddenly became quiet, remaining thus throughout the operation. Towards the end a further dose of 10 mg dtc was given during closure of the very distended abdomen. This total dose of 50 mg dtc spread over 1½ hours operating time is not considered unusual for the technique employed.

Faint respiratory movements were present at the end of operation, so atropine 1.2 mg was given intravenously, followed by neostigmine 5 mg for reversal of curarization. The effect was barely perceptible. A further dose of 2.5 mg neostigmine was given after 15 minutes, and this dose was repeated at hourly intervals. In the meantime, other resuscitative measures were tried, including nalorphine, bemepride (Megimide), nikethamide, alterations in inspired carbon dioxide tension, inflation with pure oxygen, intravenous potassium infusion, and intravenous noradrenaline infusion when it was found that his blood pressure had fallen to about 65 mm Hg systolic. (On admission his blood pressure had been 200/100 mm Hg.) None of these measures produced more than a mild transient response, bemepride being the most effective. After the last dose of neostigmine, when 15 mg had been given altogether over 3 hours, res-
pilation virtually ceased. Despite prolonged ventilation with oxygen, his unconsciousness persisted, together with inadequate respiration and hypotension that responded but poorly to noradrenaline infusion. He died about 14 hours after the operation.

From the description of the induction two facts stand out:

(1) d-Tubocurarine did not act in a way one would expect.

(2) The patient was not asleep—as opening of eyes, moving of limbs and shaking of the head are as much signs of being awake as of potassium loss.

The delayed action of dtc—it did act after 20 minutes—may be explained by lack of potassium, or by dehydration, or by metabolic changes or by some toxin (Stewart, 1956) just as the duration of the dtc effect in these cases is prolonged (Morkane and Pryor, 1956). Whatever the reason, it has no bearing on the need for revision of technique. A patient who retains voluntary movements under an appropriate mixture of nitrous oxide and oxygen ought to be anaesthetised, not relaxed. In a case of deranged metabolism this is best done by any of the gaseous agents, as they pass through the body unchanged, be it cyclopropane, be it "minimal" ether. If after light surgical anaesthesia had been established, dtc had not acted, one might have considered trying a different relaxant; e.g. 20 mg gallamine can, in my experience, change an incomplete dtc relaxation into a very satisfactory one; or one might have had to deepen general anaesthesia. But little can ever be gained by pushing a drug which does not seem to act in a given individual in the average way. An initial dose of 30 mg dtc appears to be unduly large for an old, seriously ill patient who could most likely have been intubated with ease on 12–15 mg. To this relative overdose a further 20 mg were added within an hour. On the other hand, for maintenance he received only nitrous oxide which offers poor protection of the central nervous system against stimuli which an operation on an irritated peritoneum elicits.

Since Pick and Unna's (1945) work it has been known that large doses of dtc cause central depression in frogs. In the cited case a central effect manifested itself by depressed respiration and circulation, and by persistent unconsciousness which should have passed quickly once nitrous oxide was discontinued. The depression may have been simply due to overdose—50 mg dtc for an aged, dehydrated, toxic and uraemic patient—or, as Foster suggests, to an alteration in the selectiveness of the blood brain barrier which might have enhanced the effect of this large dose. In any case, one cannot help wondering whether the same course of events would have followed if an aggregate 20–25 mg dtc had been given and fewer painful stimuli had reached the brain.

The anaesthetic technique for closure of the abdomen does not appear quite logical as dtc was tried again though a delayed action ought to have been expected after the initial experience. There seems to have been the choice between two possibilities: either relaxation had worn off, then a different relaxant might have been tried, or—a frequent occurrence in cases of ileus which receive ample doses of relaxant at the beginning—the abdominal muscles were still well relaxed but the distended bowel could not be returned into the abdomen. As relaxants cannot reduce distension of the gut other measures have to be applied by the surgeon: a needle or a rubber tube is inserted into the bowel through the centre of a field surrounded by a purse string suture and the gases or fluid are removed by suction. In addition, the anaesthetist can break the operating table in such a way that head and feet are raised and the bowel sinks back into the abdominal cavity.

Two further aspects of the technique might have had a bearing on the outcome:

(1) Blood transfusion has not been mentioned. We transfuse every case of intestinal obstruction during operation because we feel certain that it is beneficial to a seriously ill patient during a shock-producing operation, as such a laparotomy is bound to be due to handling of the gut during the search for the obstruction, or extrusion of bowel, or bowel resection. Besides most of our patients suffer from secondary anaemia; amongst our new immigrants especially we hardly ever find more than 11–13 g haemoglobin per 100 ml blood. Our slightly anaemic patients recover more quickly if part of their deficiency has been made good during operation. As a corollary, we introduce at least some blood with a normal potas-
sium content, even if an existing hypokalaemia has not been corrected before the start.

(2) An intravenous noradrenaline infusion was given when the patient’s blood pressure had fallen to about 65 mm Hg systolic. In our own practice the circulation of a hypertensive patient of 200/100 mm Hg, as the cited case, receives support already when the pressure drops to about 130, usually by speeding the blood transfusion, and if this does not reverse or at least stop the fall, by the use of a vasopressor. We believe that it is much easier to stay out of trouble than to extricate oneself from serious difficulties once they have arisen. Lawson (1956b) has enumerated four factors which can lead to fatal results in such cases: too much relaxant, too much anaesthesia, too much premedication, and too little resuscitation.

It is the excellent and detailed description of the case which lays it open to criticism because it makes it easy to visualize the course of events. There are sure to be many more cases managed by similar technique. For instance, Hunter (1956) collected six cases where after tubocurarine or suxamethonium respiration did not return, neostigmine did not have any effect and the patients died. He states that in every case the patient was elderly and in poor condition, but that the relaxant dose was “not excessive”. Scott and Clarke (1956) gave to a “small wizened lady of 67, weighing 6½ stone” 80 mg of gallamine, a dose which will produce temporary apnoea in many a muscular man. These examples could probably be multiplied if one analyzed the doses of curare given to those “neostigmine-resistant” patients whose deaths have been reported in the wake of Dr. Hunter’s paper.

To illustrate my plea for individualized doses I report briefly on four cases whose general anaesthesia was maintained by different techniques:

**CASE 1**
A.B., 61 years old, male. Small bowel ileus.
*Operation.* Laparotomy revealed patchy gangrene of large parts of small bowel; extensive resection.
*Anaesthesia time.* 1 hour 50 min.
*General condition.* Good physical habitus, but very ill.
*Premedication.* Morphine 10 mg and atropine 0.5 mg.

**CASE 2**
A.F., 63 years old, male. Carcinoma ventriculi.
*Operation.* Subtotal gastrectomy.
*Anaesthesia time.* 4 hours.
*General condition.* Fair. Blood pressure 195/95 mm Hg. Emphysematous thorax, severe kyphoscoliosis. Hb 8.8 grams per cent after transfusion.
*Premedication.* 30 mg pethidine and 0.5 mg atropine.
*Induction.* 500 mg 2.5 per cent thiopentone in 3 doses. 50 mg suxamethonium, inflammation, spray, intubation.
*Maintenance.* Nitrous oxide-oxygen and “minimal ether” (35 ml in Heidbrink machine). Before opening of the peritoneum 15 mg dtc, requiring controlled respiration for one hour, then aided ventilation. No further dtc required. Once 50 mg thiopentone were needed when an attempt to continue without ether failed. Towards closure of peritoneum 50 mg thiopentone, for closure 20 mg gallamine. Awake on table with satisfactory spontaneous respiration. Received 1,200 ml citrated blood during operation. Uneventful recovery.

**CASE 3**
H.K., 80 (or more) years old, female. Incarcerated para-umbilical hernia.
*Operation.* Herniotomy and hernioplasty of paramesial and umbilical herniae.
*Anaesthesia time.* 1 hour 20 min.
*Premedication.* 0.25 mg scopolamine.
*Induction.* 400 mg 2.5 per cent thiopentone in 2 doses, 20 mg suxamethonium, inflammation, spray, intubation.
*Maintenance.* Nitrous oxide-oxygen and trichloroethylene; controlled ventilation by means of Salt valve. 5 mg dtc after skin incision, a further 6 mg 5 minutes later. Another 4 mg required after 40 minutes. Awake on table with sufficient respiratory excursions. Received 400 ml citrated blood during operation. Uneventful recovery.

**CASE 4**
R.S., 70 years old, female. Severe obstructive jaundice.
*Tumour.*
*Operation.* Exploration, carcinoma of pancreas found, choledocho-jejunostomy.
*Anaesthesia time.* 2 hours 15 minutes.
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General condition. Poor, blood sugar 205 mg per cent, no sugar in urine. Hb 10.8 g per cent.

Premedication. 0.5 mg atropine.

Induction. 200 mg 2.5 per cent thiopentone in 2 doses which sufficed for intubation after spray, though there was a little bucking on the tube.

Maintenance with intermittent cyclopropane and nitrous-oxide; 6 mg dtc after skin incision, 3 mg before opening of the peritoneum. Aided ventilation. Additional 3 mg required after further 40 minutes, 20 mg gallamine for closure of peritoneum. Awake with last skin suture, sufficient respiratory excursions. Received 400 ml citrated blood during operation. Uneventful recovery.

The following principles are followed in this type of anaesthesia. After any suitable induction intubation is performed under suxamethonium unless prolonged apnoea is feared, as in case 4. Light anaesthesia is established and stabilized while the patient is placed and draped. This provides a base line from which to observe the effect of the relaxant which is injected soon after the beginning of the operation in a dose thought by experience to be appropriate for that particular patient. Before the peritoneum is reached, one can judge from the respiratory excursions or from the feel of the rebreathing bag whether this dose will suffice or whether a further injection must be added; e.g., in case 2, 15 mg dtc lasted surprisingly enough for more than 3 hours while in case 3 the initial dose had to be repeated almost immediately. In case 1 dtc did not act satisfactorily and the relaxant was changed. By thus testing the effect on the individual the required relaxation is achieved with a minimum amount of drug. Further doses during the course of the operation usually have a definite relation to the aggregate amount which was needed for the opening of the abdomen. The first repeat dose is about half that amount, later ones are smaller. For closure one can either give the last dtc injection not less than 40 minutes before the end of the operation (Hewer, 1957) or, as such accurate timing is not always possible, inject a small dose of gallamine before suture of the peritoneum. Usually sufficient spontaneous respiration has returned before the skin is closed.

Average doses. For a healthy muscular man we start with 15 mg dtc which in rare cases have to be raised to 18 or 20 mg. In an elderly or ill man 12 mg are tried. A normal female patient receives 12 mg for upper abdominal surgery, 9 mg for gynaecological operations. These doses would also suffice in most cases for intubation if one wanted to avoid suxamethonium. If much distension is expected, or if the patient is either hefty or old, or in poor condition, the amounts are increased or decreased respectively.

This dosage of relaxants is neither original nor new. In fact, it approaches the amounts advocated by Gray and Halton (1946) in their original publication, where they stated that 20 mg dtc were sufficient to relax the average healthy abdomen, that intermittent doses of 2–4 mg were added after induction with a barbiturate and 15 mg dtc, and that in the aged an initial dose of 10 mg was suitable.

There are exceptions to these averages. Firstly, those patients in whom any possible reaction to laryngoscopy and intubation has to be avoided, i.e., cases of raised intracranial pressure or gross circulatory disturbances. Luckily they are not the ones in whom a persistent suxamethonium apnoea may be expected. Therefore the suxamethonium dose can be ample, 70 mg for a female, up to 100 mg for a man. Secondly, the patient whose distended abdomen is closed by through-and-through sutures and where, therefore, complete relaxation has to be procured up to the very end of the operation. Thirdly, the case where exploratory laparotomy reveals an inoperable condition and closure has been completed before the effect of the relaxant has worn off. In the latter two instances one might be justified in using neostigmine.

If the patient is very ill and it is difficult to judge whether closure of the abdomen can be effected without adding more relaxant, we request the surgeon to try whether he can close the peritoneum easily. If not, we ask him to wait for the effect of a further small injection of relaxant. In these cases we deliberately do not anticipate the surgeon's requirements but prefer a slightly impatient surgeon to a depressed or apnoeic patient. Most surgeons will readily agree to a delay of two or three minutes, once they realize that this adds to the patient's safety.

For the main part of the operation our choice is generally dtc because with a rise of pulse rate and blood pressure after gallamine it is sometimes difficult to determine whether it is due to
the drug or to other causes. But once a patient's pulsee rate and blood pressure have remained steady through most of the operation, a rise after gallamine for closure is no reason for concern, as its cause is not in doubt. It is my clinical impression that gallamine given in equipotent doses of dtc gives the more complete relaxation. Apart from this profound flaccidity, gallamine for closure has the advantage that a small dose in combination with any dtc which remains in the body will go far, and that its effect passes off quickly. Gallamine alone is used when bronchospasm is feared or when a short operation is anticipated.

These are personal preferences which will vary with the anaesthetist. But whether one likes to use dtc alone, or gallamine alone, or both combined, a technique can usually be found of dosing and timing which will leave the patient at the end of the operation with sufficient spontaneous respiration to make the use of antidotes superfluous. Neostigmine has a mortality of its own. Since Macintosh (1949) drew our attention to it, many cases have been reported, e.g., 5 cases have been collected lately (Edwards et al., 1956). It ought not to be used routinely but only when specially indicated. Hewer (1957) rightly considers the use of an antagonist a confession of failure. If at the end of an operation respiratory depression has partially passed off it is safer to continue with aided ventilation until satisfactory respiratory excursions are restored. If after some trial sufficient respiratory exchange does not return, neostigmine can be injected 5–10 minutes after 0.5 mg atropine, starting with 1 mg (Doughty and Wylie, 1952) with increments of 0.5 mg until the desired effect is obtained. While hardly a day passes without my injecting dtc and/or gallamine to several patients, the need for neostigmine arises three or four times a year.

During the lively discussion which followed Hunter's (1956) paper on neostigmine-resistant curarization it has been suggested that the combination of suxamethonium followed by one of the competitive relaxants may have led to persistent apnoea which neostigmine could not reverse (Gordon, 1956; Verrill, 1956; Beardsworth, 1956). Using this combination as a standard technique for at least three years we have never experienced such an event. This strengthens our conviction that the doses and not the drugs are the cause of such incidents.

Doses of curare are not the same everywhere. Our American colleagues seem to get satisfactory results with much smaller amounts, just as their thiopentone doses are about half those used in Britain (Dundee, Price and Dripps, 1956). For instance, Patterson (1952) advocates 3–9 mg dtc, thiopentone and an analgesic spray for intubation, and maintains relaxation by repeated injections of fractional doses of one of the relaxants. Sadove et al. (1955) use 6–8 mg dtc for intubation of patients due to undergo mitral commissurotomy. They take special care that bucking does not occur. There seems to be too wide a gap between this dose and the 35 mg of Grigor (1954) for the same kind of case.

Nosworthy stated in 1953 that "by an accurately judged dose of relaxants—or by a series of graded injections—it should not be too difficult to produce just about that degree of peripheral suppression which one has learned is required for any given procedure". His sound advice ought not to be forgotten. The relaxants have enabled us to carry the old, the frail, and the very ill safely through long hours of difficult surgery. It would be a great pity if one of the greatest boons in anaesthesia were discredited through injudicious use and overdose. We all have learned to work satisfactorily with "minimal ether" i.e. with amounts which just suffice to produce a required result. It might reduce anaesthetic fatalities if we trained ourselves, too, to use "minimal curare".

**SUMMARY**

While anaesthetists try to reduce the use of analgesic and hypnotic agents to a minimum, relaxants are given in large doses as they are thought to be innocuous. As several deaths have been reported after heavy curarization, though they are ascribed to other causes, it is suggested that the dosage should be modified.

One fatal case reported in the literature is analyzed in detail. The author's technique of achieving the required relaxation with a minimal amount of nondepolarizing relaxants is illustrated by case reports.

It is suggested that by correct dosing and
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timing of relaxants the use of antagonists should be avoided.
A plea is made for the use of “minimal curare”.

REFERENCES


ASSOCIATION OF ANAESTHETISTS OF GREAT BRITAIN AND IRELAND

JUBILEE MEETING

The Association of Anaesthetists of Great Britain and Ireland is celebrating the twenty-fifth anniversary of its formation this year, and is holding its Annual Meeting on December 4, 5, 6 and 7, 1957, at the Royal College of Surgeons, Lincoln’s Inn Fields, London, W.C.2.

The provisional programme is as follows:

Wednesday, December 4
Evening: The Association will hold a Cocktail Party to welcome those overseas visitors who will attend the meeting.

Thursday, December 5
Morning session: Papers.
Afternoon session: Annual General Meeting, Frederic Hewitt Lecture.
Evening: Annual Dinner.

Friday, December 6
Evening: Cocktail Party given by the Faculty of Anaesthetists. Dance.

Saturday, December 7
Morning session: Symposium.
Throughout the Meeting there will be a Scientific Exhibition and a Trade Exhibition.
The final date for submission of papers for presentation at this meeting is June 1, 1957.
Further particulars will be available later on application to the Secretary, Association of Anaesthetists of Great Britain and Ireland, 45 Lincoln’s Inn Fields, London, W.C.2.