Drug Treatment of Disease

ADMINISTRATION OF DRUGS BEFORE ANAESTHESIA

BY

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The administration of drugs of some sort before an anaesthetic is an almost universal practice. Yet the reasons for it do not always appear to be clear. In many cases the drugs given are unnecessary because they confer no benefit on the patient and needlessly complicate the subsequent anaesthetic. In others the wrong drug is chosen, and the desired effect is not achieved.

Aims of Premedication

(1) To prevent undesirable side-effects of the anaesthetic on various organs. These include those on the salivary glands, on the heart, and on the alimentary canal.

(2) To make the induction and maintenance of anaesthesia more easy. The induction of anaesthesia in an unpremedicated, lively, robust patient, even without the added complication of emotional upset, may be a very different affair from that in a similar patient who has had a suitable combination of sedative and anti-sialogogue drugs.

(3) To prevent undesirable autonomic reflex responses to stimuli arising mostly from the operation area.

(4) To lessen pre-operative anxiety, fear, and emotional tension in general. This has been put last, not because it is less important than the others, but because a real need for this effect is not nearly so commonly apparent to-day as it was in years gone by. The anaesthetist cannot help, to a certain extent, identifying himself with his patient and imagining that he must be fearful and hence require sedatives or hypnotics. A very careful objective assessment of each patient should be made and depressant drugs ordered only when either emotional stress is obvious or when the patient spontaneously asks to go to sleep in his bed or at least to be made sleepy, or to have no memory of the induction of anaesthesia.

The last three objectives are usually achieved by the same drug. In general, anaesthetists are coming to the view that sedative drugs should be given only when there is a clear need for them and not as a routine. Certainly every patient must be regarded as an individual. The increasing skill of anaesthetists, the gradual disappearance among the public of the fear of anaesthesia, and the wider range of anaesthetic drugs, all combine to make heavy sedation of the patient less necessary. The growing custom of gaining the confidence of the patient by personal contact cannot be too highly praised. A pre-operative visit is often as effective as an injection of morphine.

Factors Affecting the Dose of Pre-anaesthetic Drugs

Age and Weight.—The effect of drugs in general and of sedatives in particular is closely related to the metabolic activity and general excitability of the

patient. The dose per unit weight is therefore scaled down with increasing age. The metabolism of old people is low; in the young it is high. At birth, the dose per unit weight for a particular effect is greater than that for the adult. The dose/weight ratio rises until between the ages of 6–10 it is about 25% more than the adult ratio. It then gradually drops until at the age of 20 the individual is considered an adult, and needs the "average" or "usual" dose. In practical terms, therefore, the dose per pound of body weight for an adult must be increased by approximately 25% for a healthy child of, say, 6 years in order to achieve the same effect.

Body weight is clearly a most important factor affecting dosage. Most of the classical cautions regarding the use of sedative drugs in children probably stem from too large a total dose being given in the past. Thus, in the case of morphine, 15 mg. (gr. $\frac{1}{4}$) for an adult of 10 stones (63 kg.), is a dose: weight ratio of gr. 1/40 per stone (0.2 mg. per kg.). If an infant is given morphine on this scale, the effect produced will be a little less than that seen in the adult because of the difference in metabolism already pointed out.

Temperature.—Febrile patients need slightly increased doses to show the same effect, because of the rise in metabolism. This need must be balanced against any suspected lowered resistance to drugs due to the toxæmia of the disease.

Pain.—Pain is an indication for analgesics like morphine rather than hypnotics like the barbiturates. The administration of a barbiturate to a patient in pain may lead to uninhibited reflex reaction to the pain in the form of restlessness. Post-operatively, even though the patient is not awake, restlessness may be so marked as to be a problem to the nurses, and it may even introduce the risk of injury and, in certain circumstances, of haemorrhage. The child after tonsillectomy exemplifies this state of affairs.

Emotion.—The relation between the dose of sedative drugs and emotional stress needs no emphasis.

Physical States.—Patients vary a great deal in their general state of health. The anaemic, listless girl of 18 presents quite a different problem to her robust, games-playing sister. The former may need no sedative drugs at all or at most a relatively small dose. If a "normal" dose is given to such a patient severe depression may follow and the patient perhaps need resuscitation.

Anaesthetic to be Administered.—The pre-anaesthetic drugs form part of the anaesthetic procedure, and in ordering them the anaesthetist must bear in mind their possible interaction with the anaesthetic. For example, powerful respiratory depressants are best avoided before anaesthetics like ether, with which good spontaneous respiration is essential if deep anaesthesia is to be achieved.

SEDATIVES AND ANALGESICS

Morphine

A preparation of opium is still the commonest form of sedative before an anaesthetic. Its powerful effects in relieving pain, removing fear, producing euphoria, and relaxing tension account for its popularity. The reduction in reflex excitability facilitates the induction of anaesthesia. However, respiration is depressed, and, partly as a result, this is accompanied by circulatory depression. Respiration becomes slower and shallower. The dose is all-important. In a healthy adult of 10 stones (140 lb., 63 kg.) 10 mg. (gr. 1/6) of morphine usually produces adequate analgesia and euphoria without serious respiratory depression. For the best and safest effects it is important that morphine or an opiate, if given hypodermically, should be injected about 1½ hours before the proposed time of operation, so that the peak depressant effect is present or has just passed when anaesthesia is induced.

Morphine has certain other undesirable side-effects. Nausea and vomiting are more common than is generally believed. Morphine has a direct effect on the medullary vomiting centre. This action is exhibited to an even more striking degree by morphine's close relative, apomorphine. The incidence post-operatively of nausea and vomiting due to morphine is probably at least as high as 20%. When administered apart from operation and anaesthesia, nausea and vomiting is uncommon in patients in bed, but it occurs frequently if they are ambulant. An incidence as high as 40% for nausea and 16% for vomiting is reported. There is no doubt that morphine given as premedication increases the tendency of patients to vomit post-operatively. If this factor in post-operative vomiting is to be avoided, morphine must be replaced by some other sedative which does not have this effect.

Other undesirable side-effects of morphine are its spastic action on the gastro-intestinal tract leading to constipation and its spastic effect on the bronchial musculature. Substitutes should therefore be considered for patients with, for example, biliary colic or bronchial asthma.

Two preparations of opium need special mention. Papaveretum (or "omnupon") contains all the opium alkaloids and is standardized to contain half its weight as morphine. The adult dose of 20 mg. (gr. ½) therefore contains 10 mg. (gr. 1/6) of morphine. It is believed by many to be less liable to produce nausea and vomiting because the papaverine which it contains counteracts some of the gastro-intestinal spastic action of morphine. Since the other opium alkaloids are also sedatives, 20 mg. (gr. ½) of papaveretum has about the same sedative effect as 15 mg. (gr. ⅓) of morphine.

"Nepenthe" is a proprietary liquid preparation of opium containing morphine. This preparation was originally intended as a somewhat elegant alternative to tinct. opii, to be taken by mouth. It has, however, become much favoured for administration to children by hypodermic injection, perhaps because the widely used dosage scale of "one minim per year" is easy to remember. Nepenthe by injection as a pre-operative sedative for young infants cannot be recommended. It is difficult to measure one or two minims let alone a fraction of a minim with accuracy, and errors in measurement of perhaps over 100% are inevitable. In addition, children of the same age vary widely in weight

and physical state. The difficulty of estimating and measuring the dose of this preparation for an infant of under 1 year is therefore obvious. The author has seen a variation in effect in infants, ranging from apparently none to obvious overdose, leading to a comatose infant with pin-point pupils. When morphine is to be administered to infants it is better to use the alkaloid itself and to calculate the dose from the body weight, by using the formula gr. 1/40 per stone (0.1 mg. per lb., 0.2 mg. per kg.).

Pethidine

This is a synthetic compound which differs from morphine in that it has some atropine-like effects. Clinically the effects on the intestinal tract are less spastic, and on the bronchi even relaxant. Its analgesic effects are particularly marked when the pain arises in certain hollow viscera such as the uterus. Given in equipotent doses to morphine, however, it appears to depress respiration less. Pethidine is often combined with some other sedative drug to provide an analgesic component to the mixture.

Barbiturates

These drugs are sedative or hypnotic, the result depending on the dose, but have no analgesic power. Those with a medium duration of action—for example, quinalbarbitone ("seconal," pink capsules), or pentobarbitone ("nembutal," yellow capsules), are commonly given by mouth for this purpose. At least two or three hours should be allowed for absorption from the alimentary canal and for the onset of the peak effect. This time can be shortened if the capsule is pierced. These drugs are valuable for children. They fall asleep and usually have no memory of going to the operating-theatre or of the induction of anaesthesia. For an adult, an oral dose of at least 3 gr. (200 mg.) of either of these is needed if sleep is desired, and this may be combined with a small dose of morphine if pain is present. For children under 6 or 7 stones (80–100 lb., 38–44 kg.) in weight, a dose of gr. ½ per stone (2 mg. per lb., 5 mg. per kg.) will usually induce sleep if the child is left quiet. A disadvantage of the oral route is that fear may delay the desired effect by inhibiting intestinal activity, including emptying of the stomach.

Increasingly, barbiturates are being administered to children by the rectum. This method is particularly valuable in children and infants because of the ease of administration and certainty of action. The dosage scale is 20 mg. of thiopentone per pound body weight (45 mg. per kg.) (or 1 g. for 50 lb.). 1 g. is dissolved in 50 ml. of tap water and 1 ml. is administered for each pound body weight (2.2 ml. per kg.) by means of a syringe and small catheter. Sleep comes on rapidly within a quarter of an hour and passes off during the following hour. The manufacturers of "pentothal" now offer a ready-mixed emulsion of thiopentone in multi-dose disposable syringes. Detachable rectal applicators enable the same syringe to be used for more than one patient.

Phenothiazine Derivatives

Some of these drugs are very effective as sedatives before anaesthesia. They have a powerful potentiating effect on the general anaesthetics, and it can be expected that reduced doses of the latter will suffice. Two examples, though there are others, are promethazine ("phenergan") and chlorpromazine ("largactil"). In

proper doses these drugs relax the patient and make him calm and comfortable without depressing respiration. If left alone, patients tend to go to sleep but are easily aroused and then are mentally clear. Induction and maintenance of anaesthesia are considerably facilitated. They also have important anti-emetic effects and are valuable in patients who fear or have a predisposition to post-operative vomiting. Nevertheless, there are disadvantages. Their effects are prolonged and may last many hours. Circulatory depression with a varying amount of hypotension is not uncommon, especially with chlorpromazine. Pallor is often striking.

A satisfactory combination for an adult is promethazine 50 mg., pethidine 50 mg., and atropine 0.6 mg. intramuscularly 1½ hours before anaesthesia. Chlorpromazine may be substituted for the promethazine in doses of 12–25 mg. intramuscularly.

Other Sedatives

Many other sedative drugs, some old and some new, can be used successfully before anaesthesia. These include such old friends as chloral hydrate, paraldehyde, and even aspirin. Of the newer drugs, mention can be made of two codeine derivatives—dihydrohydroxycodone (oxycodone) pectinate ("proladone") and dihydrocodeine bitartrate ("D.F.118"). These are potent long-acting analgesics. Another drug which has received many enthusiastic reports is methylpentynol ("oblivon"). This is a sedative advocated for children, in whom it induces calmness and mild euphoria before such operations as tonsillectomy. It has a wide margin of safety—for example, a child of 5 to 8 years receives 2–3 teaspoons of the elixir, of which each teaspoon contains 250 mg. of methylpentynol.

Control of Secretion

All anaesthetics, with perhaps the exception of nitrous oxide and halothane, cause an increase in salivary secretion during induction and light anaesthesia. In any case normal secretion is not abolished. If not checked, the foaming of saliva may cause serious respiratory obstruction, and not only interfere with the smooth course of the anaesthetic but may put the patient's life in hazard. It is now almost universally regarded as essential that every patient, except those having the briefest of anaesthetics, should receive a drug which reduces the secretion of saliva.

Atropine is the one most commonly given for this purpose. A dose of 0.6 mg. (gr. 1/100) in an adult depresses salivary secretion by about 50% and in practice this effect is sufficient. Hyoscine ("scopolamine") is an alternative to atropine, and, being slightly more potent, the dose is reduced to 0.4 mg. (gr. 1/150). Both atropine and hyoscine depress the central nervous system and causes a varying amount of drowsiness. Hyoscine is more active in this respect and noticeably potentiates the effect of other sedative drugs.

The depression of salivary secretion is even more important in children than in adults; the larynx and trachea are so small that a small quantity of secretion may seriously impair respiration. The increased metabolism of the child indicates a higher dose-to-weight ratio than an adult. A combination of these two factors explains why in the past such apparently excessive doses of atropine or hyoscine for a child were given; it is not because infants, as some imagine,

have a peculiar tolerance for atropine. Nevertheless, overdosage of infants with atropine must be avoided, since it depresses sweating and disturbs the heat-regulating mechanism; this may lead to dangerous overheating in these young subjects. The following guide to atropine dosage may be found useful:

Age in Years						Dose
Newborn	..	..	..	..	..	gr. 1/400 (0.16 mg.)
Up to 1	..	..	..	..	..	.. 1/300 (0.22 ")
1–	..	..	..	..	..	.. 1/200 (0.32 ")
2–	..	..	..	..	..	.. 1/150 (0.43 ")
Over 4	..	..	..	..	..	.. 1/100 (0.65 ")

An important effect of atropine and hyoscine is to depress vagal nerve endings in the heart and produce tachycardia. This is believed to give some protection against the vagal stimulating effect of anaesthetics like chloroform, trichloroethylene, cyclopropane, and halothane. Atropine also causes bronchodilatation and helps to prevent bronchospastic reflexes during anaesthesia. Some protection against visceral reflex responses during abdominal operations is also given.

SPECIAL PROBLEMS

The Chronic Alcoholic and the Drug Addict

These patients are generally tolerant of sedative drugs, and considerably larger doses than usual may be required to produce a satisfactory effect. Generally the best way to produce tranquillity in such patients is to give them a suitable dose of what they are accustomed to.

Pregnancy

Unless the patient is at or near term she may be treated like any other woman. However, if premedication is connected with operative obstetrics, sedatives are best avoided. If they have to be used, the effect on the baby must be considered. All the drugs already described cross the placenta rapidly, and within minutes circulate in the foetal blood in the same concentration as in the mother's. The baby at the time of birth will therefore be nearly as sedated as the mother at that moment. To avoid the danger of serious respiratory depression of the baby, the dosage of the sedative must be smaller than usual, and it must be given either more than 3–4 hours before the expected delivery or, in the case of morphine and similar drugs, with an antidote. Nalorphine (N-allylnormorphine) or levallorphan ("lorfan") may be combined with morphine or pethidine. A ready-mixed combination with pethidine is available and is known as "pethilorfan," in which the proportion of the antidote, levallorphan, is such (1:80) that, while serious respiratory depression is prevented, much of the analgesic and sedative properties of pethidine is retained.

Pulmonary Disease and Respiratory Obstruction

Care should be taken in administering sedatives to patients with these diseases. Their very life may depend on their ability to make a maximal breathing effort. Any reduction in this by sedatives may have disastrous consequences.

Sensitivity from Other Drugs

Patients receiving certain drugs as treatment for a co-existing disease may be specially sensitive to sedatives. Examples are antihistamines, tranquillizers, hypotensive drugs, and disulfiram.