Physiological Responses to Intermittent Methohexitone for Conservative Dentistry

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Summary: Intermittent methohexitone for conservative dentistry has been shown to cause clinically undetectable respiratory obstruction, depression of the laryngeal reflex, and arterial hypoxaemia. Because of the pronounced decrease in total peripheral resistance, the blood pressure was maintained only by large increases in cardiac output. Furthermore, the output of the heart could not increase when challenged by hypoxia.

Introduction

Methohexitone was introduced in this country in 1960 and its intermittent injection was recommended for use in conservative dentistry by Drummond-Jackson in 1962. Several advantages have been claimed for this technique: (*a*) it is not an anaesthetic, producing chemical hypnosis only; (*b*) the laryngeal reflexes remain competent; (*c*) there is no respiratory depression; (*d*) there is maintenance of cardiovascular integrity; (*e*) there is a rapid and complete recovery; and (*f*) operating conditions are ideal.

Since the introduction of the technique disquiet about its safety has been expressed (Report of a Joint Subcommittee on Dental Anaesthesia, 1967). As no scientific investigation has so far been undertaken to establish these claims, it was decided to investigate the physiological responses to intermittent injection of this drug in a number of fit, healthy volunteers undergoing conservative dentistry.

Methods

The patients were selected, either at their own request or on account of a previous failure of local anaesthesia. Those with an adverse medical history were specifically excluded from the study. All patients included in the study were interviewed at least one week in advance, and the nature and extent of the study carefully explained by two members of the team.

The so-called minimal-incremental technique of administering methohexitone as described by Drummond-Jackson (1962) was used. This technique is one in which 50 mg. or less of the drug is given, followed by 5- to 10-mg. increments as indicated by the patient's response to stimulus.

The following criteria were measured: electrocardiogram (E.C.G.), electroencephalogram (E.E.G.), and blood pressure by oscillotonometry. The central venous pressure was recorded by means of an electromanometer and the respiratory pattern by a bellows stethograph and electromanometer. The finger plethysmograph was obtained from a photocell and bridge circuit. All electrical signals were amplified with Devices amplifiers and recorded on a 12-channel U/V recorder. The acid-base state and oxygen tension of arterialized venous blood and central venous blood was estimated by means of Radiometer electrodes. The ratio of lactate to pyruvate in the central venous blood was estimated by an enzymatic method (Gloster and Harris, 1962).

The results from this part of the study indicated that tissue hypoxia may have been occurring in the presence of peripheral vasodilatation (and also suggested that the laryngeal reflex was not competent). It was decided, therefore, to extend the investigation. Arterial cannulation was performed to allow measurement of actual arterial blood gas tensions and continuous monitoring of arterial blood pressure with an electromanometer. Cardiac output was obtained by using a dye dilution technique with Cardio green (indocyanine green), the dye curve being sensed with a Gilford densitometer and its area computed by an analogue computer. The larynx was challenged (Tomlin, Howarth, and Robinson, 1968) by placing radio-opaque material on the back of the tongue.

Results

There were 30 patients in the trial, 12 men and 18 women. The mean age was 24 years, range 17 to 48. The type of dental work undertaken was mainly conservation, averaging seven fillings, with a range of 4 to 15. Five patients also had extractions, two had root fillings and apicectomies performed, and two had extensive crown work. The operating conditions were very good on 13 occasions, adequate on six, prejudicial to good dentistry on eight, and poor on three. The mean duration of anaesthesia was 74 minutes, and ranged from 37 to 120 minutes. The mean dose of methohexitone was 460 mg., ranging from 200 to 825 mg. and averaging 5·7 mg./minute, with a range of 2·4 to 8·1 mg./minute, and no other adjuvants were given. The anaesthetist and dental operator had had considerable previous experience with the technique before embarking on the study. Owing to the mass of data obtained in this study—that is, in excess of 1,000 individual values—what follows is an abstract of the significant data.

E.E.G.—The recordings of the right or left fronto-occipital E.E.G. showed that at some time during the procedure the E.E.G. was equivalent to advanced surgical anaesthesia (Wyke, 1965) with some low-voltage discharge of 6 c./sec. but predominantly delta activity. These E.E.G. changes always occurred after supplementary doses of methohexitone, and towards the end of the procedure could occasionally be induced by doses as small as 5 mg.

Respiratory Responses

Two-thirds of the patients at some time showed some degree of respiratory obstruction, as judged by simultaneous decreases in the respiratory excursion recorded from the stethograph and wide swings of central venous pressure occurring with inspiratory effort (Fig. 1). The episodes of obstruction lasted from 30 to 120 seconds, despite adherence to the recommended technique in which a nurse was supporting the chin. Unless the

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obstruction was severe it was clinically undetectable by two experienced anaesthetists. On three occasions the respiratory obstruction produced such an intense cyanosis as to require treating the patient with oxygen. Periods of apnoea of 20 seconds were commonly observed.

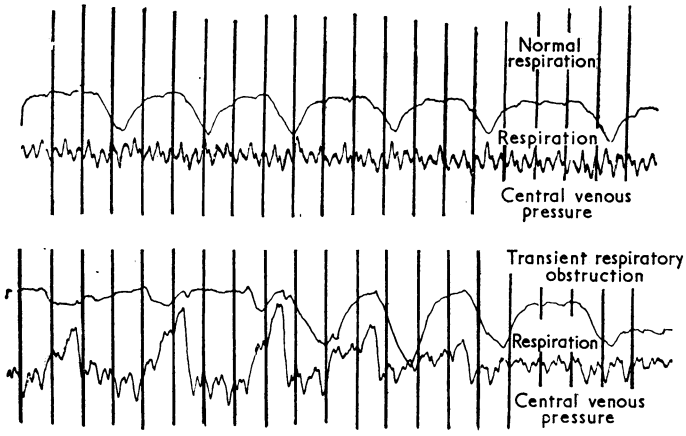

FIG. 1.—Respiratory obstruction during intermittent methohexitone anaesthesia. The upper trace shows normal central venous pressure and respiratory movement. The lower trace shows marked respiratory obstruction with reduced amplitude of respiratory excursions and marked accentuations of central venous pressure. As the respiratory obstruction is relieved, so the venous pressure and respiratory movement return to normal.

The mean control respiratory rate was raised, as was to be expected in these slightly apprehensive patients, and it increased further to a frequency of 22 to 25/minute during anaesthesia. There were relatively insignificant changes in arterial carbon dioxide tension; the mean $Paco_2$ rose from a control of 35·5 to 38·5 mm. Hg, the greatest rise being that from 40·4 to 44·5 mm. Hg.

The first seven patients all showed an oxygen tension in their central venous blood that was greater than expected, suggesting that there was some peripheral arteriovenous shunting. This was confirmed in 12 of the 14 patients who had simultaneous determination of arterial and central venous oxygen tensions; these 12 patients showed narrowing of the a-vPo_2 differences from the control values. Five patients showed severe arterial hypoxaemia in that at some time their Pao_2 was below 70 mm. Hg, the lowest recorded being a Pao_2 of 35 mm. Hg. This does not represent all patients at all times, since on occasion the hypoxia was clinically so severe that oxygen administration was started before an arterial sample could be obtained.

The laryngeal reflexes were challenged in the manner described above when the patient could respond to verbal commands either during dentistry or immediately afterwards. In 45% of cases tested the contrast media placed on the tongue and swallowed entered the bronchial tree and could be seen later on a chest radiograph.

The ratio of lactate to pyruvate can under certain circumstances be taken as an index of tissue hypoxia (Huckabee, 1958), and a total of 120 determinations was made of lactate/pyruvate ratio measured before, during, and on recovery from anaesthesia in 16 patients. The results are given graphically in Fig. 2, with the standard deviations of the means as these varied with time. It can be seen that there is an initial rise from the control values, probably due to catecholamine release because of preoperative apprehension, the lactic acid being gradually released and entering the circulation after the first 20 minutes. The lactate/pyruvate ratio then shows another increase during the rest period at about 50 to 60 minutes. (These rest periods have been described by Drummond-Jackson (1967) as necessary for both patient and operator.) During the postoperative period there was again an appreciable rise in lactate/pyruvate ratio as more lactic acid was washed out from the tissues. In two patients standard bicarbonate fell to 17 mEq/l., and even more significant was the rapid rate of the fall occurring within four to five minutes of a hypoxic episode, suggesting a decrease in tissue oxygen reserve.

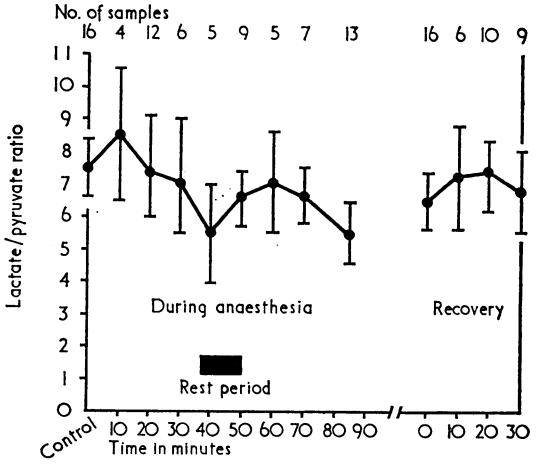

FIG. 2.—Lactate/pyruvate ratio changes with time during intermittent methohexitone anaesthesia. The vertical bars are standard deviation of the mean.

Cardiovascular Responses

The most striking observation was the large increase in finger blood flow, indicated by the transillumination plethysmograph. This occurred on administration of the induction dose of methohexitone and then gradually receded (Fig. 3). It recurred with each dose of methohexitone until finally the vasodilatation became permanently established.

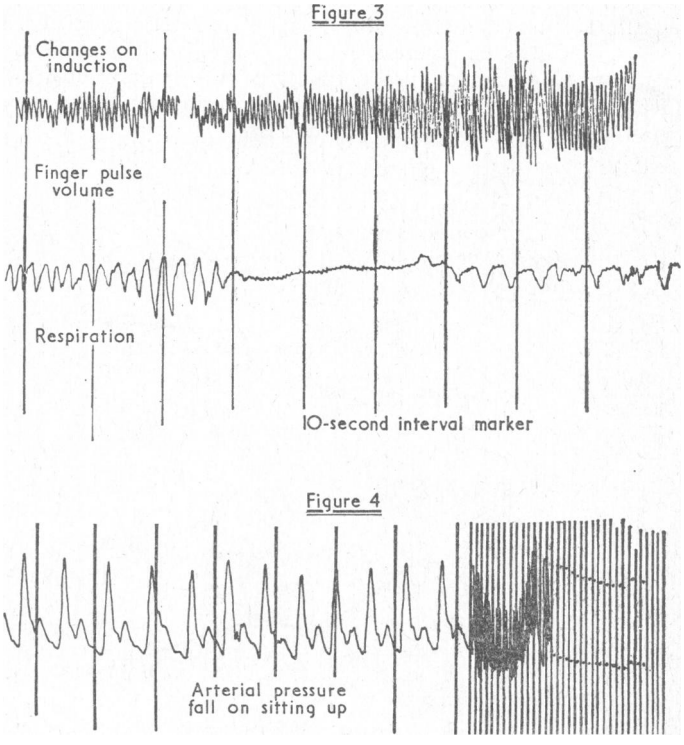

FIG. 3.—Finger plethysmograph during induction of anaesthesia with methohexitone. FIG. 4.—Orthostatic hypotension after sitting up. Note time scale change. (Vertical bars 1 second intervals.)

Of the 30 patients in this study five required atropine because excessive salivation became prejudicial to the dentistry. The 25 patients who had not received atropine all showed a tachycardia with a mean increase in heart rate of 30 beats/minute. The tachycardia was variable, often rising from control values

of 75–80 beats/minute to 150–180 beats/minute. No other E.C.G. changes were found. Apart from the pronounced swings seen during obstructive episodes, there were no significant changes in central venous pressure.

A blood pressure rise of 20 mm. Hg or more was noted in 60% of patients. One patient's blood pressure rose transiently from a control of 140/75 up to 220/120 mm. Hg. Falls below control levels of 20 mm. Hg or more occurred at some time in 25% of patients, and in one patient a 40 mm. Hg fall to 80 mm. Hg systolic was noted. Postoperative hypotension, defined as a fall in systolic blood pressure of more than 20 mm. Hg, occurred in two-thirds of the patients when they stood up, though at this time the patients were fully conscious and able to co-operate (Fig. 4). The orthostatic hypotension was somewhat slow in onset and did not become manifest until up to three minutes after the patient had stood up.

In six patients repeated cardiac output determinations were performed with a dye dilution technique. In four conscious patients control cardiac output determinations were obtained, though it is realized that such determinations have a limited value under the conditions of the investigation (a crowded dental surgery containing a mass of bizarre apparatus). Nevertheless, on three occasions they provided reasonably normal resting levels of cardiac output from which subsequent changes could be interpreted.

All patients during methohexitone anaesthesia showed a pronounced increase in cardiac output, and cardiac indices of twice the basal level were obtained on a number of occasions. Furthermore, the cardiac output changes indicated a progressive increase as the total drug dosage was increased (Fig. 5), except in the case of one subject who had a very high resting cardiac output but who, during anaesthesia, showed a return to expected basal values. This patient was extremely fit, being a professional footballer. It should be noted that in the latter period of each anaesthetic a small (up to 50 mg.) increase in the total quantity of the drug given occasionally produced a very large change, whereas a similar increment in the early part of the anaesthetic produced comparatively small changes. It is significant that when measured during an obstructive episode the cardiac output did not rise.

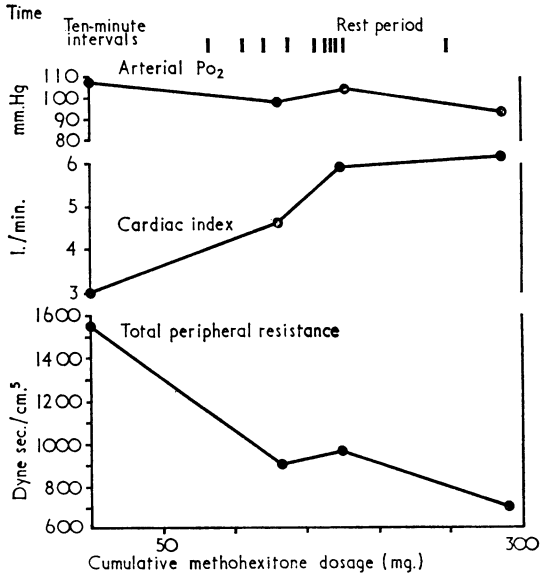

FIG. 5.—Circulatory response to methohexitone in a typical case.

The total peripheral resistance per second was derived from the formula:

$$\text{T.P.R.} = \frac{60\ (\text{mean B.P.} - \text{mean C.V.P.})\ \text{mm. Hg} \times 1332}{\text{cardiac output ml./min.}}\ \text{dyne sec./cm.}^5$$

Except in the case of the footballer, there was a pronounced and progressive fall in resistance during the anaesthetic.

Discussion

The purpose of the investigation was to determine the physiological responses to repeated doses of methohexitone in order to establish whether the claims for the safety (Drummond-Jackson, 1967) of the technique were upheld or whether the theoretical risks outlined in the Report of a Joint Subcommittee on Dental Anaesthesia (1967) were indeed real.

The statement that the patients are subjected not to anaesthesia (Clarke, 1967) but to chemical hypnosis is difficult to define scientifically and is at variance with the observed E.E.G. data. These patients were repeatedly having surgical anaesthesia induced, recovering, and then being reinduced. The decreasing dosage of the drug required to produce these effects was typical of a drug which behaves in a cumulative manner.

The respiratory effects are of concern for several reasons. The first is that minor degrees of respiratory obstruction could not be detected clinically and, furthermore, arterial hypoxaemia could occur in the absence of respiratory obstruction while cyanosis was masked owing to the pronounced peripheral vasodilatation. The statement (Bourne, 1967) that the laryngeal reflexes are at all times fully active is shown to be in error ; the finding of contrast media in the lungs in 45% of cases cannot be safely ignored.

From the results presented it would appear that one or two doses of methohexitone probably cause no great physiological upset, but, because the administration is cumulative, more than 200 mg. leads to widespread vasodilatation with a noticeable reduction in peripheral resistance. A relatively normal blood pressure is maintained only by virtue of the large increase in cardiac output. Moreover, it was noted that if peripheral resistance was suddenly increased in response to pain the raised cardiac output into the rising resistance system caused quite severe hypertension.

The progressive decrease in peripheral resistance in response to incremental doses of methohexitone is typical of a drug which has a cumulative effect, and this, together with the observed post-anaesthetic orthostatic hypotension, suggests that return to consciousness alone cannot be taken as the index of cardiovascular integrity. It is obvious that the heart is under severe stress to maintain the blood pressure in the presence of vasodilatation, and it is disquieting to find that the 20% increase of cardiac output expected (Fishman *et al.*, 1960) with the levels of hypoxia observed in the study were not obtained. The normal circulatory reflex response to hypoxaemia appeared to be obtunded.

Despite the fact that vasodilatation occurs, tissue perfusion appears to be reduced, as indicated by the increased lactate/pyruvate ratio. This vasodilatation with increase in cardiac output has not been reported but is not unexpected, since MacCannell (1969) found similar effects with other barbiturates in dogs. That the drug is less likely to produce hypotension than thiopentone (Dundee and Moore, 1961) now appears to be due to the increase in cardiac output which occurs, and this is supported by the common finding of a tachycardia during the use of the drug (Rowlands *et al.*, 1967).

It would seem that the fears of the Joint Subcommittee on Dental Anaesthesia have been substantiated, for the technique produces fluctuating levels of anaesthesia with loss of integrity of the respiratory and cardiovascular systems. Concern was also felt because on a number of occasions the anaesthetic conditions produced were prejudicial to good dentistry.

Several deaths associated with this technique have been reported in the press, but it is difficult to gauge the overall number of patients who may be at risk with the drug. Buxton (1967) suggested that several million administrations had been given, and Kurland (1967) suggested 7,000,000 without mortality. These figures are difficult to believe, because they imply that from 1962 to 1967 the number of anaesthetics given for conservation per year was the same as the number administered for dental extraction, which is unlikely. Further-

more, confidential inquiries among the distributors to the dental profession strongly suggest that these figures represent a far greater dosage of the drug than was handled by these distributors in the United Kingdom. The number of patients at risk would not appear to be as great as has been suggested. Nevertheless, on the evidence presented, the technique of intermittent methohexitone must be regarded as having serious detrimental physiological effects, which may well have been the cause of the reported deaths.

We extend our sincere gratitude to the patients who volunteered to take part in our study and indeed made it possible. Our thanks are due also to Professor J. Osborne and Professor D. S. Shovelton for making their extensive facilities available to us, and to the members of the nursing staff who assisted us so willingly. This work was supported by the Endowment Fund of the United Birmingham Hospitals.

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Malabsorption of Folate Polyglutamates in Tropical Sprue

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Summary : Malabsorption of folate polyglutamates prepared from yeast has been shown in eight patients with untreated tropical sprue and in three out of six patients receiving therapy for sprue. The absorptive defect for folate polyglutamates among these 14 patients occurred more frequently and in all but one patient more severely than for folic acid.

Folate polyglutamates, the principal dietary form of folate, probably require deconjugation by the jejunal enzyme, folate conjugase, before absorption. The mean concentration of jejunal folate conjugase of 21 patients with untreated sprue and of 13 patients with sprue receiving therapy were both significantly less than the mean concentration in a control group. Nevertheless, all but five of the 34 patients had jejunal folate concentrations within the control range. There was no correlation in the individual patients between the jejunal folate conjugase concentration measured in vitro and the ability to absorb folate polyglutamates—nine patients having normal jejunal folate conjugase levels despite showing malabsorption of folate polyglutamates.

Introduction

Tropical sprue affects the structure and function of the jejunal mucosa, the principal site of folate absorption. The most likely explanation for the severe folate deficiency found in this disease is malabsorption of dietary folate. In some patients with sprue and severe folate deficiency, however, normal absorption of folic acid has been reported (Paterson *et al.*, 1965 ; Klipstein, 1966, 1968), and such patients may show a haematological response to folic acid in physiological doses by mouth despite failing to respond to much greater amounts of ingested dietary folate (Sheehy *et al.*, 1961). These observations suggest that patients with tropical sprue may have a much greater and more consistent defect of absorption of food folate than of folic acid itself. Food folate consists mainly of folate polyglutamates in which there are six, seven, or more glutamate moieties linked to the pteroyl portion of the molecule. Streiff and Rosenberg (1967) suggested that when these compounds are ingested in relatively pure form they are split to folate monoglutamate before entry into the blood stream by the enzyme folate conjugase present in the jejunal mucosa.

The present study was undertaken to compare directly the absorption of folate polyglutamates and of folic acid in tropical sprue and to measure the concentration of the enzyme folate conjugase in the jejunal mucosa of patients with this disease. The results show that folate polyglutamate is less well absorbed than folate monoglutamate in patients with tropical sprue but that only in a minority of the patients is this absorptive defect associated with a subnormal jejunal mucosal folate conjugase level.

Subjects Studied

Patients with Tropical Sprue.—A total of 36 patients with tropical sprue were studied, 34 from Puerto Rico and two from Haiti. The diagnosis in each was made on the basis of a clinical history of anorexia, diarrhoea, and loss of weight ; biochemical evidence of intestinal malabsorption, including an abnormal xylose excretion test, steatorrhoea, or malabsorption

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