A STUDY OF THE CARDIOVASCULAR EFFECTS OF CHLORMETHIAZOLE

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SUMMARY

A study of the cardiovascular effects of intravenous chlormethiazole (Heminevrin) was carried out on five volunteers. It showed that induction of light anaesthesia was easy, maintenance easy, and the recovery period short and uneventful. During induction, maintenance and recovery the only cardiovascular disturbance noted was an increase in heart rate; cardiac output was maintained at the pre-induction level. In view of the results obtained in this series and the clinical experience of its use in an assisted ventilation unit, it is suggested that chlormethiazole would be a suitable agent to provide sedation during many of the procedures required in an intensive care unit.

Chlormethiazole (Heminevrin) is a powerful hypnotic and anticonvulsant derived from the "thiazole" portion of thiamine hydrochloride (vit B₁) (Charonnat, Lechat and Chareton, 1957). It is widely used in the treatment of delirium tremens and status epilepticus and its anaesthetic properties were first investigated by Laborit and associates (1957). Dundee (1958) found that, although it produced sleep, the lack of analgesic properties made it generally inferior to thiopentone. Gabrielson, Halldin and Palmer (1961), on the other hand, reported favourably on its use, especially during surgery on the aged. More recently its use in the management of pre-eclamptic toxemia has been described by Duffus, Tunstall and MacGillivary (1968).

Although clinical observations have suggested its freedom from circulatory and respiratory depression, it was felt that a detailed investigation into its haemodynamic effects should be undertaken. The need for this was suggested by the possible use of chlormethiazole both in anaesthesia and in sedation during intensive care. In both circumstances the absence of cardiovascular effects would be beneficial, especially in the presence of myocardial depression.

METHOD

Five healthy adult male volunteers were studied; their ages ranged from 27 to 35 years and their weights from 68 to 85 kg. Cardiac output was measured by the indo-cyanine green dye dilution method, using a Waters XE302 earpiece and densitometer. Dye was injected via a central venous catheter, inserted percutaneously into a cubital fossa vein and advanced into the thorax. Central venous pressure was recorded through the same catheter using a Sanborn pressure transducer No. 267 A.C. The electrocardiograph was run continuously and the heart rate deduced therefrom using a Sanborn cardiotachometer 350-3400A. All recordings were made simultaneously on a Sanborn 7700 multichannel recorder. Arterial blood pressures were measured by standard sphygmomanometry, mean arterial pressures being taken as the diastolic pressure plus one-third of the pulse pressure.

With the subject lying supine and comfortable, four cardiac output estimations were made at 2-minute intervals to obtain control readings. A Sanborn 130 cardiac output computer was of considerable help in assessing circulatory stability or any changes that might be occurring.

A 0.8 per cent solution of chlormethiazole in dextrose was then infused, using a standard drip set and an intravenous polyethylene cannula in a vein on the dorsum of the hand, at a fast rate (12-20 ml/min). Unconsciousness was maintained for a variable time during which frequent estimates of cardiac output were made and these were continued during the recovery period.
RESULTS

Induction, maintenance and recovery. The time to produce unconsciousness varied from case to case, being 8 min on average (range 5–11). This required approximately 1–2 g of chlormethiazole. The drip rate was then slowed and unconsciousness maintained for a mean duration of 16 min (range 12–22). The drip was then stopped. The average dose of chlormethiazole was approximately 2.4 g. Recovery time from cessation of infusion to ability to reply coherently to questions varied from 6 to 13 min (mean 9 min). All the subjects were able to rise and walk 15–50 min after the chlormethiazole was stopped.

Cardiac output. It is appreciated that estimation of cardiac output using an earpiece is open to criticism especially in regard to calibration and the presentation of results in absolute figures. However, changes in cardiac output in a single subject can usually be followed without difficulty if posture is kept stable and there is good circulation through the ear. Following administration of the chlormethiazole there was little change in the cardiac output (fig. 1). In two cases there was an increase, one during infusion and one shortly after, but this was probably due to a degree of restlessness seen in these subjects, with a resulting increase in muscular activity.
Mean arterial pressure. The changes in this parameter were slight and not significant (fig. 1).

Central venous pressure. This also remained stable through the procedure (fig. 1).

Heart rate. This increased markedly in all cases (fig. 2); this increase was significant (average of 48.7 per cent over the resting rate). Thus stroke volume is decreased in the absence of a commensurate increase in cardiac output.

Respiration. In four subjects there was no change in respiratory pattern as judged clinically. In the fifth case, a short period of apnoea developed just after the loss of consciousness.

Subjective effects. All the subjects found the onset of unconsciousness smooth and pleasant. During recovery all complained of some degree of nasal congestion, similar to an attack of coryza; this lasted for 2–3 hours. Otherwise recovery was reported as being similar to that from any other form of light general anaesthesia. Three of the subjects had transient pruritus, in one localized to the scalp, in the other two of a more general nature, and this appeared to be the cause of the restlessness seen in these two cases (v.s.).

Late effects. Three of the subjects developed a superficial phlebitis at the site of injection of the chlormethiazole; this extended no further than about 1 inch from the point of puncture of the vein.

DISCUSSION
The only circulatory change of note which occurred in the subjects investigated was an increase in heart rate. The mechanism of this is at present obscure, but in quality it appears similar to that produced by atropine, i.e. an increase in heart rate without an increase in cardiac output. Although the drug is said to be relatively free from effect on the autonomic nervous system (Huguenard, 1960), it has been found to produce inhibition of the vagus nucleus in chloralosed dogs (Lechat, 1966). Whether this tachycardia is clinically important would depend on whether it augmented a pre-existing tachycardia. From the clinical reports of its use in delirium tremens, in which tachycardia is common, this does not appear to be the case. Rotter (1966) found that tachycardia and arrhythmia in fact disappeared after intravenous administration.

The extrapolation of results found in healthy volunteers to those likely to be obtained in ill patients must be cautious. However, the rate of administration of chlormethiazole in this series far exceeded that recommended by the manufacturers who suggest a maximum of 8 ml/min.

The rate used in this study was 2–3 times greater than this. As with other intravenous anaesthetics, the cardiovascular effects are likely to be maximal immediately following induction. The fact that a very fast rate of infusion failed to affect cardiac output adversely, encourages the belief that dangerous haemodynamic effects are unlikely to occur.

A drug which can give deep sedation, short of surgical anaesthesia, with little or no cardiovascular or respiratory depression can have many uses in clinical practice. We have used chlormethiazole on many occasions to sedate patients undergoing artificial ventilation for respiratory failure. Following admission to an intensive care unit, such patients often have to suffer numerous unpleasant procedures such as endotracheal intubation, tracheal toilet, insertion of chest drains, physiotherapy, etc. Deep sedation for up to 24–48 hours has become possible with very few side effects apart from localized venous thrombosis. The quietness of these patients, their unresponsiveness to uncomfortable manoeuvres and the absence of fighting against the ventilator all greatly assist in their management.

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REFERENCES
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BOOK REVIEW


This is an enlarged and rewritten edition of the book first published ten years ago, and most of the 93 papers are concerned with descriptions of the mode of operation of almost all the machines available for pulmonary ventilation. It need hardly be said, therefore, that it is most unlikely to be read through by any one person, but it is a major work of reference necessary for all anaesthetic libraries. The general style of the book matches its encyclopaedic weight and content, and there are appendices which contain a list of manufacturers, a short glossary, and a guide to the functional characteristics of ventilators (a folder enclosed with the book lists these in symbol form for each machine, and in many instances the text contains volume/pressure graphs for various control settings). No attempt has been made to group ventilators according to their operating characteristics, chapter following chapter in alphabetical order, and no reader could overestimate the extreme industry and persistence required to compile the catalogue which Chapters 9 to 90 comprise. The preface says: "It is not more ventilators that are needed but more understanding of the effects of the ones available and of their clinical use", a welcome comment which may meet reaction in some quarters, but which emphasizes that far too many ventilators have found their way on to the market; indeed, there may eventually be sound practical and financial indications for some restriction of choice. At the same time, there is unquestioned acceptance of the need for more ventilators' rooms.

As for the rest of the book, there are two chapters (93 pages, including basic principles and application) relating to the physics of automatic ventilators; another on the "butterfly diagram" (offered as a basis for determining the mode of action of ventilator controls); 8 pages on pulmonary ventilation in infants, a few more on the laboratory testing technique used by the authors, and 25 interesting pages on the historical background of "artificial respirators". The first two chapters deal with physiological and clinical aspects of controlled ventilation; perhaps because they are directed partly at practitioners outside anaesthesia, they sometimes seem to state the obvious (although rather well), as shown on the very first page. Elsewhere, there is some unevenness with just a few dubious comments, for example: "The danger of hypoxia needs no emphasis and its recognition is generally easy" (the text later reflects a change from this over-optimistic view). This neglects one of the major lessons of the last decade of "automatic ventilation", namely that the clinician is frequently surprised to find, by blood-gas measurement, unsuspected lowering of arterial Po2 (when PaCO2 is normal or reduced) especially in patients in accident or intensive care units. Again, the rate of rise of PaCO2 in apnoea is rather more than the 3 mm Hg stated here; and more convincing evidence is needed that "the introduction of negative pressure clearly reduces the brain volume"; a ten-year-old reference that gastrostomy may be indicated if paralysis is likely to be of some duration is, at best, quaint. Of course, there may be other areas where the reader's and the authors' views do coincide, and it is stated, modestly, at the end of these early chapters that they are not intended as a substitute for more detailed reading.

The remaining two chapters deal with manually-operated ventilators and a large number of "valves for use in controlled ventilation". This book is unique, and good value at its high price. Not only for the ventilators' sake, it is hoped that few new ventilators will be on the scene before the next revision is required. As for the irrational fear that any kind of machine will "replace" the anaesthetist, all experience shows that a ventilator displaces an anaesthetist only if it is supervised by one.

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