These results seem to indicate that if either drug is given for short periods to most patients with anxiety and tension about equal benefit will accrue. Some few patients do benefit, however, from meprobamate only and others from sodium amylobarbitone only.

Only longer trials can show whether meprobamate is superior to barbiturates in effectiveness and in freedom from toxicity when given over longer periods. There is little doubt that short-acting barbiturates can become drugs of dependence and addiction; some patients need to go on increasing the dose, and a barbiturate-induced tension state finally results. Barbiturates are also often used in attempts at suicide. If, on longer trial, meprobamate proves to be free from such defects, it could be a useful alternative to other tranquillizing drugs. It is unlikely, however, that any drug which relieves anxiety will ever be entirely free from the disadvantages of producing dependence or causing symptoms on withdrawal.

Summary

Meprobamate is a new tranquillizing drug which in a clinical trial on 151 psychiatric out-patients produced some relief of symptoms in 58% of patients with chronic anxiety and tension states. The drug was not as effective, however, when anxiety or agitation were severe.

A double blind trial was also carried out on 26 patients with states of anxiety and tension, so as to compare the effects of meprobamate with an inert tablet. There was statistically significant therapeutic superiority of meprobamate over the inert tablet.

In a separate double blind trial, meprobamate was also compared with sodium amylobarbitone in a further 51 patients mostly suffering from anxiety and tension states. No marked differences were found in effectiveness between these two drugs. However, clinically, meprobamate often seemed more useful than a barbiturate where irritability was a marked feature.

No serious side-effects were observed, but transient skin rashes occurred in five of the patients treated (2.5%).

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This year the Royal Women's Hospital, Melbourne, celebrated its centenary, the main feature of the celebrations being a week-long scientific and clinical meeting in August on topics of obstetrical and gynaecological interest. Among the distinguished contributors was Professor A. M. CLAYE, of Leeds, who has been working in the hospital during its centenary year. On the last day of the meeting there was a full discussion on obstetric infections. The importance of spore-bearing anaerobes was stressed, and Professor Claye made the point that in Australia the fall in obstetric mortality due to infection did not occur until the introduction of penicillin, whereas in England the sulphonamides achieved this result some years earlier. In Australia the care of the newborn, it appears, is usually left to the obstetrician, and at the meeting much enthusiasm was shown for keeping the babies with their mothers as a means of preventing neonatal sepsis.

THE HYPOTENSIVE ACTION OF MECAMYLAMINE

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Hypotensive therapy with ganglion-blocking compounds, alone and in combination with the rauwolfia alkaloids, has greatly improved the prognosis in malignant hypertension (McMichael and Murphy, 1955; McQueen and Smirk, 1956) and in many patients with severe non-malignant hypertension (Doyle and Smirk, 1955). Most agree that pentolinium is the most generally effective single substance at present available; it has largely replaced hexamethonium as the ganglion-blocking drug of choice in most cases of hypertension, for it has a longer action than hexamethonium; furthermore, it can be successfully used by mouth in 60-70% of patients with hypertension (Doyle and Smirk, 1955), whereas oral hexamethonium controls the blood pressure adequately in only 20-25% of patients (Kilpatrick and Smirk, 1952). Even with pentolinium, however, control of blood pressure can be more easily obtained by parenteral administration than by mouth, for, like hexamethonium, it is poorly absorbed, the oral dose being up to 20 times as great as the parenteral dose (Smirk, 1953; Freis *et al.*, 1954). Moreover, some patients, more especially those requiring large doses, may develop severe constipation with diminished response; this is often followed by diarrhoea with episodes of hypotension, due presumably to increased intestinal absorption.

The reports of Freis (1955) and Ford *et al.* (1956) that a new ganglion-blocking compound, mecamlamine, was fully absorbed from the gastro-intestinal tract, and that it had been successfully used in the treatment of hypertension, were of considerable interest.

Mecamlamine ("inversine") is 3-methylaminoisocamphane, a secondary amine which has been reported to be rather less active than pentolinium in dilating the pupils, but to be more active than pentolinium in abolishing nicotine convulsions in mice (Stone *et al.*, 1956).

We report here the preliminary results of a clinical trial of this substance in 45 hypertensive patients for periods of up to 10 months. Twenty-five have been treated for 6 to 10 months, and 15 for from three to six months. The remaining five discontinued treatment within one month of beginning it.

Methods

We have studied the hypotensive action and the side-effects of oral mecamlamine and have compared them with the effects of subcutaneous and, in some instances, oral pentolinium. Some of the patients selected to

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undergo clinical trials of mecamlamine were those in whom alimentary side-effects had prevented an adequate control of the blood pressure being obtained by oral administration of pentolinium. In assessing the hypotensive response to mecamlamine, we have made hourly estimations of the blood pressure in the standing position for periods of 8 to 12 hours.

Results

Hypotensive Action

The fall in blood pressure produced by oral mecamlamine is more prolonged than that produced by an equally effective dose of oral or parenteral pentolinium. As with pentolinium, the duration of the hypotensive action depends on the size of the dose, but when doses of mecamlamine large enough to reduce the systolic blood pressure to 140–120 mm. Hg are given there is often a substantial reduction of blood pressure even 12 hours after the dose. The prolonged hypotensive action of mecamlamine is a great advantage, for it leads to less variation in blood-pressure levels, and reduces the high peaks of blood pressure which sometimes occur with parenteral or oral pentolinium (see Chart). Furthermore, the abrupt falls to hypotensive levels

Example of the fall of blood pressure after 15 mg. of oral mecamlamine in patient with malignant hypertension. Blood pressure before treatment 270/140 mm. Hg. Note prolonged action, with substantial reduction of blood pressure even after 12 hours. Systolic blood pressure $\times$ — $\times$. Diastolic blood pressure O—O.

which occur so frequently with other ganglion-blocking agents are rare with mecamlamine. Patients taking mecamlamine have noticed the smoother hypotensive effects, and claim that this leads to less disturbance in their normal lives.

Little if any tolerance to the effects of mecamlamine seems to occur. Minor increases or decreases of dose are occasionally necessary—related, for example, to changes in the weather or to the occurrence of infections. We have, however, seen no important or consistent example of the development of tolerance in observations of up to 10 months. Indeed, as is discussed below, reductions in dose are more commonly necessary than increases, once the initially effective dose has been determined.

As with other ganglion-blocking agents, the fall of blood pressure is greatest in the erect posture, and for this reason, as with other similar agents, the postural hypotension must be utilized to obtain adequate results (Smirk, 1953).

The onset of the hypotensive action of mecamlamine does not usually occur for one hour after its administration, and the maximum effect not until up to three to five hours (see Chart). Even after intravenous administration, the onset of the hypotensive action may not occur for 30 to 60 minutes.

The effective oral dose of mecamlamine is usually one to two times the subcutaneous dose of pentolinium; the relationship remains approximately constant for individual patients. The magnitude of response to repeated oral doses of mecamlamine remains remarkably constant in individual cases, as does the duration of the hypotensive action.

The degree of blood-pressure control obtained with oral mecamlamine compared with subcutaneous pentolinium is shown in the Table. In the great majority of cases a better control of the blood pressure was obtained with oral

Comparison of Results with Oral Mecamlamine and Subcutaneous Pentolinium

	O.M. Better than S.P.	Same	O.M. Worse than S.P.
Blood-pressure control	29	8	1
Side-effects:			
Other than gastro-intestinal ..	7	10	11
Gastro-intestinal	6	5	17

O.M. = Oral mecamlamine. S.P. = Subcutaneous pentolinium.

mecamlamine than with parenteral pentolinium. The advantages lay mainly in the duration of hypotensive effects, and in the avoidance of high peaks of blood pressure. An improvement in the casual clinic blood pressures with mecamlamine was also apparent.

Side-effects

As with pentolinium and hexamethonium, the side-effects of mecamlamine seem to be due mainly to the associated parasympathetic blockade. The dominant side-effects of mecamlamine are gastro-intestinal; others, such as blurring of vision, dryness of the mouth, and urinary retention, are sometimes less severe but more protracted with mecamlamine than with pentolinium. Constipation seems generally to be more severe with mecamlamine than with pentolinium, but does not lead to any important diminution of the hypotensive effect. For this reason we have had the impression that the risk of frank paralytic ileus is likely to be less with mecamlamine than with oral pentolinium. Furthermore, the occurrence of diarrhoea and abdominal distension in two patients has not been associated with any increase in the hypotensive action of mecamlamine, and was not followed by ileus. Persistent nausea has occurred in six patients and persistent vomiting in four of these. This is a larger number than we would have expected using parenteral or oral pentolinium. In two patients the persistent vomiting obliged us to discontinue the use of mecamlamine, and two others preferred to return to parenteral pentolinium because of the smaller constipating action.

A comparison of the side-effects of oral mecamlamine with those of parenteral pentolinium in patients in whom a comparison was possible is set out in the Table. It is clear that the majority of patients had no greater discomfort from dry mouth, blurred vision, or bladder symptoms with mecamlamine than with pentolinium, and several claimed relief from these disturbances. By contrast the majority complained of more gastro-intestinal disturbances, mainly constipation.

General Assessment of Effects

In making a general assessment of mecamlamine the improved degree of blood-pressure control, the ease of oral administration, and the predictability of response have been assessed against the increased incidence of side-effects.

The general assessment in the 45 patients shows that in 24 patients the blood-pressure control was good and the side-effects were mild or well tolerated. In 12 patients good control of blood pressure could not be obtained without severe side-effects. In the remaining 9 the side-effects were severe enough to lead to difficulty in establishing a good blood-pressure control. Treatment had to be abandoned in five. In four of these a better result was obtained with parenteral pentolinium. The remaining patient developed a rise in the blood urea both with mecamlamine and other ganglion-blocking agents. This did not occur with hydralazine.

In general, relief of hypertensive manifestations was as striking with mecamlamine as with pentolinium. Most patients, in spite of the frequent increase in severity of

gastro-intestinal side-effects, preferred mecamlamine. This is probably partly attributable to freedom from injections, but also to the freedom from occasionally incapacitating episodes of hypotension.

Suggested Scheme of Treatment

Our results indicate that mecamlamine is an effective hypotensive substance. Although we have been unable to compare the effects of parenteral with oral administration, it is clear that mecamlamine is usually effective by mouth in smaller doses than other ganglion-blocking agents. However, it must be emphasized that, because of the long action, it is desirable to use caution in selecting patients for treatment with this substance. Where there is doubt about the safety of reducing the blood pressure, as in those with coronary ischaemia, cerebral vascular disease, or impaired renal function, cautious dosage with parenteral hexamethonium should be used until it has been established that the blood-pressure reduction is safe. In patients with impaired renal function, the action of mecamlamine may be extremely prolonged, so that a single daily dose, or occasionally a dose every two days, may be used. Other factors may also prolong the action: M. D. Milne (personal communication) has found that the excretion of mecamlamine in man is enhanced by the administration of ammonium chloride and diminished by the administration of alkalis or acetazolamide.

In general, however, the ideal dosage scheme seems to be the administration of two equal doses at 12-hour intervals. The initial dose should not exceed 2.5 mg. twice daily; increments of 2.5 mg. should be added until an effective hypotensive result has been obtained. We prefer not to increase the dose more frequently than at three-day intervals, for we have the impression that the full hypotensive effects of an increased dose may not become apparent for two to three days. In addition, severe gastro-intestinal effects seem less frequent when this dosage scheme is adopted. The dose range in our patients was from 2.5 to 50 mg. twice daily. In most cases the dose was between 10 and 25 mg. twice daily.

The treatment of hypertensive patients with mecamlamine can be readily instituted in out-patients, provided that facilities for measurement of the blood pressure over several hours in the standing position are available. When in-patients are treated it may be found that after discharge from hospital readjustment of the dose is necessary. In our experience out-patients usually required smaller doses than when they were in hospital.

The incidence of constipation is so high that we have found that prophylactic routine administration of laxatives is an advantage. We now give a nightly dose of pil. aloes, and a morning dose of a saline laxative, instructing the patient to adjust the dose until a daily bowel motion is obtained. The administration of parasympathomimetic drugs is sometimes helpful.

Combination with other drugs may help to reduce the incidence of side-effects. We have insufficient evidence to comment on this possibility.

Summary

The hypotensive action of a ganglion-blocking secondary amine, mecamlamine, has been studied in 45 hypertensive patients.

Oral administration leads to falls of blood pressure lasting for 12 hours or more. The hypotensive action seems predictable and acute hypotensive episodes are unusual.

Little if any tolerance occurs.

The side-effects, particularly alimentary, are also prolonged, and four patients preferred parenteral pentolinium.

Our experience suggests that in spite of the frequency of side-effects the advantages of oral administration, prolonged hypotensive action, and predictability of response make this substance the most convenient and reliable hypotensive agent so far available.

We are indebted to Messrs. Merck, Sharp and Dohme for generous supplies of mecamlamine, and to the physicians of Hammersmith Hospital for permission to study their cases.

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PERITONEOSCOPY

AN EVALUATION, WITH REPORT OF 136 CASES

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In some cases of abdominal disease the diagnosis remains in doubt even after the most detailed investigations, and the problem is solved only at laparotomy. Little is lost by operation in such cases if they prove to have a lesion amenable to surgery, but in medical or inoperable conditions unnecessary laparotomy carries a mortality and morbidity of its own. In certain lesions, particularly of the liver and peritoneum, peritoneoscopy offers the opportunity to look inside the abdomen without the risk of operation. It is the purpose of this paper to consider the place of peritoneoscopy in diagnosis and to analyse a short experience of 136 cases.

Peritoneoscopy consists in the inspection of parts of the peritoneal cavity with an instrument similar to a cystoscope, which is introduced through a cannula. In order to give the telescope "elbow room," air is introduced into the peritoneal cavity to form a "bubble," a litre or more in volume. It is only the structures which lie at the surface of this air bubble or project into it which can be seen. The position of the air bubble can be shifted by tilting the patient to bring into view different parts of the abdominal wall and different fixed organs (see Fig. 1). It is generally true to say that only the anterior surface of the liver, the parietal peritoneum of the anterior abdominal wall, and the omentum can nearly always be viewed. The gall-bladder and anterior surface of the stomach are often seen. An enlarged spleen is sometimes visible. By tilting the patient into a steep Trendelenburg position, the uterus and Fallopian tubes, and sometimes the ovaries, can be inspected. For other organs peritoneoscopy is not a useful examination, and the intestinal tract cannot be systematically searched for lesions, even though several coils of bowel may be in view.

Technique

Fig. 2 illustrates the appearance of the peritoneoscope and shows its resemblance to a cystoscope. The examination is