Once an adrenal origin has been excluded the treatments available for PCO are temporary or symptomatic. Clomiphene can only be used short term under well-controlled conditions in women who want to have children—in one case the ovaries were equal in size and in another the contralateral ovary turned out to be the larger one. The policy was to remove the larger ovary.

Postoperatively blood testosterone levels fell in all patients and became normal in eight. A regular ovulatory cycle developed immediately after surgery in all patients.

In five patients the indication for treatment was infertility and in another two testosterone levels have risen slightly in two patients. They were operated on in 1980, conceived within 6 months and have been delivered of healthy full-term babies. The remaining two patients were operated on very recently.

Echography has revealed that the remaining ovary has become normal in size and that the microcysts have disappeared. The hypertrichosis, present in all ten patients, has not got worse. There has been no new or greater hair growth and neither hair removal techniques have usually been applied less frequently. At the request of one patient she was given anti-androgens. One patient who has had severe premenstrual tension and heavy periods after PCO and all ten women still have regular ovulatory cycles. Blood removal techniques have usually been applied less frequently. At another patients PCO and the microcysts have disappeared. The policy was to remove the larger ovary.

A major disadvantage of bilateral wedge excision is the unequal size of the remaining ovaries. However, the unequal size was not reduced by unilateral oophorectomy (a shorter procedure) and we have found this to be temporary by some workers and long-lasting by others. A regular ovulatory cycle developed in five of these patients, who were operated on in 1980, conceived within 6 months and have been delivered of healthy full-term babies. The remaining two patients were operated on very recently.

This pilot study suggests that simple unilateral oophorectomy can probably replace bilateral wedge excisions from ovaries in patients with PCO.

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Johan Hamerlynck

INTRACAVERNOUS INJECTION OF PAPAVERINE FOR ERECTILE FAILURE

Sir,—The mechanism for the filling of the cavernous bodies at the onset of erection is still in dispute. 1 Accidental intracavernous injection of papaverine during a surgical shaving procedure2 produced a prolonged fully rigid erection of two hours' duration. This fact, combined with observation of improvement of erectile function reported by impotent patients after they had been treated by intracavernous injection of papaverine (80 mg) and has been used in laboratory studies of vasoactive drugs, as a control substance. 6 Two levels of action seem possible: inhibition of cyclic AMP phosphodiesterase7 or an anticonstrictor effect. 8 Artificial erections achieved with normal saline are associated with volume changes and the development of pressure inside the cavernous bodies. The mean value of the ICP increase was much higher when the trial was done during general anaesthesia (mean ICP increase 70 mm Hg) compared with 40 mm Hg without anaesthesia. This effect was related to increased arterial flow, as shown by Doppler studies, plethysmography, and arteriography. The peak effect, depending on the state of the arteries, was obtained after 2–15 min, and an effect lasted for from 10 to 120 min. There were no general or local complications.

Seven of the fifteen patients with an organic aetiology reported significantly improved erections in the days after the procedure, but none of the non-organic cases reported any changes in their erectile capability. All seven had arteriolar lesions in the distal part of the internal pudendal artery and/or in the cavernous arteries. In the light of these results thirty impotent patients (including twelve with diabetes mellitus) who had Doppler and arteriographic evidence of arterial insufficiency were selected for conservative therapy. Intracavernous injection of papaverine (80 mg) was followed, after 15 min observation of the drug's effect, by infusion of 1% heparin in normal saline via an infusion pump, to obtain and maintain a rigid erection for a 15 min period. No anaesthesia was used.

The procedure was repeated 2 months later and then every third month or according to the clinical status. Of the fourteen patients (seven with diabetes) who had two or more artificial erections, four reported a return to a normal sexual life; nine described a significant improvement in penile rigidity; in one there was no effect and an arterial revascularisation procedure was done. Few clinical studies have been done on the effects of drugs on penile erection. 2 No vasoactive drug has proved effective in controlled studies. Papaverine is a powerful smooth-muscle relaxant and has been used in laboratory studies of vasoactive drugs, as a control substance. 6 Two levels of action seem possible: inhibition of cyclic AMP phosphodiesterase 7 or an anticonstrictor effect. 8 Artificial erections achieved with normal saline are associated with vasodilatation of branches of the pudendal arteries, and we agree that there must be mechanical action at the level of the cavernous tissue.

I thank Dr Gorm Wagner, Panum Institute, University of Copenhagen, for comments.

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R. Virag

RELEASE OF HISTAMINE BY H2-RECEPTOR ANTAGONISTS

Sir,—There has been a good deal of debate in The Lancet lately about cardiac effects of H2-receptor antagonists. Earlier reports of cardiac dysfunction have largely concerned intravenous cinetidine. 1 We report here findings with both cimetidine and ranitidine given intravenously (i.v.).

The study followed a chance observation. We were investigating the release of histamine by plasma substitutes and seeking to prevent adverse effects. Before infusion of the plasma substitute monitoring of intracavernous pressure (ICP). To study the condition of the arterial vessels, ultrasonic continuous measurement (Doppler method) and pulse plethysmography were used. Later, selective bilateral internal iliac arteriography was done. Our preliminary findings relate to fifteen organic cases and ten non-organic cases of impotence.

The immediate reaction was an increase in ICP, indicating volume changes and the development of pressure inside the cavernous bodies. The mean value of the ICP increase was much higher when the trial was done during general anaesthesia (mean ICP increase 70 mm Hg) compared with 40 mm Hg without anaesthesia. This effect was related to increased arterial flow, as shown by Doppler studies, plethysmography, and arteriography. The peak effect, depending on the state of the arteries, was obtained after 2–15 min, and an effect lasted for from 10 to 120 min. There were no general or local complications.

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REFERENCES


some subjects were given i.v. saline, some i.v. cimetidine, and some both cimetidine and chlorpheniramine. Blood was taken for plasma histamine assay by a fluorimetric method which, because it does not depend on histamine methyltransferase, is valid in the presence of cimetidine and ranitidine. After cimetidine 10 mg/kg two subjects showed a rise in plasma histamine of more than 1 ng/ml (table I), giving levels which can produce cardiac arrhythmias in susceptible subjects. When both cimetidine and chlorpheniramine were used four of the seven subjects showed a rise of at least 1 ng/ml. These results were worrying, but the cimetidine dosage was much greater than the conventional clinical dose and had been chosen on the basis of animal studies. We decided to investigate this further, using normal clinical doses of both ranitidine and cimetidine.

Ten subjects were given cimetidine 200 mg or ranitidine 80 mg i.v. over 30 s on consecutive days in a single-blind study. The order of the drugs was randomised. The study was confined to doctors who were fully informed of the nature and hazards of the investigation.

Satisfactory samples were obtained from nine doctors but in the tenth blood sampling was difficult and subsequent haemolysis made the proper preparation of plasma samples impossible. None of the nine subjects showed a plasma histamine rise of 1 ng/ml, nor was there any subjective evidence of histamine release.

We conclude that there is a risk of a dangerous rise in plasma histamine if a high dose of cimetidine (and, possibly, other H2-receptor blocking agents) is given by rapid i.v. injection. However, standard doses of cimetidine or ranitidine given by slow i.v. injection do not have this effect. The data sheets produced by Smith, Kline and French and Glaxo, respectively, emphasise the slow i.v. injection do not have this effect. The data sheets produced by Smith, Kline and French and Glaxo, respectively, emphasise the importance of this is not widely appreciated. Our studies suggest that injection over 30 s into a peripheral vein is safe. We have no information about the effects of H2-receptor antagonists given into central venous lines, but it seems reasonable to suppose that this route may be particularly hazardous.

We have not identified the source of the histamine which can be released under these circumstances. However, human myocardial tissue contains approximately 1000 ng of histamine per g wet weight.5 The release of only a small proportion of this histamine could give rise to severe cardiac arrhythmias and the exact form of such cardiac effects seems likely to be unpredictable, especially if histamine receptors are already partly antagonised.

We thank Glaxo Group Research Ltd for the gift of ranitidine and for financial support for this study.

TABLE I—INCREASE IN PLASMA HISTAMINE LEVELS (ng/ml): FIRST STUDY

<table>
<thead>
<tr>
<th>Subject</th>
<th>After saline</th>
<th>After cimetidine 10 mg/kg</th>
<th>After cimetidine 5 mg/kg + chlorpheniramine 0.3 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
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<td>0-35</td>
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<tr>
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<td>0-25</td>
<td>1-35</td>
<td>1-1</td>
</tr>
<tr>
<td>7</td>
<td>0-25</td>
<td>1-85</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Total showing rise: 3/7
Rise > 1-0 ng/ml: 0/7

TABLE II—INCREASE IN PLASMA HISTAMINE LEVELS (ng/ml): SECOND STUDY

<table>
<thead>
<tr>
<th>Subject</th>
<th>After cimetidine 200 mg</th>
<th>After ranitidine 80 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0-2</td>
<td>0-1</td>
</tr>
<tr>
<td>2</td>
<td>0-9</td>
<td>0-1</td>
</tr>
<tr>
<td>3</td>
<td>0-9</td>
<td>0.7</td>
</tr>
<tr>
<td>4</td>
<td>0-2</td>
<td>0-1</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>6</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.1</td>
</tr>
<tr>
<td>8</td>
<td>0-2</td>
<td>0.2</td>
</tr>
<tr>
<td>9</td>
<td>0-9</td>
<td>0.1</td>
</tr>
</tbody>
</table>

Total showing rise: 6/9
Rise > 1-0 ng/ml: 0/9

LACK OF RESPONSE TO INTRAVENOUS CALCIUM IN SEVERE VERAPAMIL POISONING

Sir,—Verapamil is a slow calcium channel blocker which depresses sinus and atrioventricular node activity as well as producing a negative inotropic effect on the myocardium. Although this drug has been available for 20 years, only thirteen reports (seven in English6–12) of poisoning have been published, three of which include supporting analytical data.5,7,12 We report here the most severe case of verapamil poisoning so far described.

A 39-year-old woman was admitted unconscious (grade 3 coma) after a presumed overdose. On admission she had an unrecordable blood pressure and bradycardia (48/min), but there were no focal neurological signs; ventilation was adequate after endotracheal intubation. An ECG showed alternating junctional and sinus rhythm with abnormal intraventricular conduction, first-degree heart block (PR 0.44 s) and negative P waves. There was circumstantial evidence of acute beta-adrenergic blocking drug overdose so glucagon 10 mg, prenalterol 10 mg, and atropine 1 mg were given intravenously, but without improvement. Because of marked hypotension and anuria, infusions of dopamine (2–5 µg/kg/min), frusemide (2 mg/min), and dobutamine (increasing doses to 40 µg/kg/min) were started. 90 min after admission it was learned that the patient had ingested at least 1200 mg verapamil up to 18 h before admission, and this was confirmed analytically.13 We found a total of 240 ml over 44 h, as an adjunct to other supportive measures. Despite the dobutamine infusion the blood pressure remained unrecordable and bradycardia persisted. An infusion of isoprenaline (5 mg over 30 min) was therefore started and continued at a rate of 2 µg/min. Within 15 min the pulse was 80/min and the blood pressure 90/60 mm Hg. Subsequently, on withdrawal of dobutamine, it was necessary to increase the dose of