Discussion

Medazepam, a benzodiazepine, is being used in Europe increasingly for the symptomatic relief of neurotic anxiety, but there have been relatively few carefully controlled trials comparing it with established anti-anxiety drugs. The results of our initial investigation on inpatients confirm that it is effective in relieving anxiety. The optimum dose was 10 mg three times a day, and since there were no abnormalities in liver function or blood tests in this group the drug was considered to be safe for outpatient use.

The results of a double-blind crossover comparison show that medazepam 10 mg three times a day is superior to amylobarbitone 60 mg three times a day for the relief of anxiety in outpatients ($P < 0.01$). This was shown by the patients' responses to one or other of the drugs used in an attempt to relieve their presenting symptoms. This comparison might be criticized on the ground that the dose of amylobarbitone was too low. Higher doses are certainly more effective in relieving anxiety, but at the expense of increased drowsiness. Our own previous experience with amylobarbitone suggests that a 60 mg dose three times a day is probably the best dose for most outpatients. In addition to its overall superiority, medazepam was particularly useful for the relief of rumination ($P < 0.05$) and phobias ($P < 0.01$). Drowsiness and ataxia were not major problems with medazepam, but we should add that this series contained no elderly patients, who seem to be most vulnerable to those side effects.

A comparison of the results of this trial with a trial of chlordiazepoxide 20 mg three times a day and amylobarbitone 60 mg three times a day (Jenner, Kerry, and Parkin, 1961) suggests that medazepam 10 mg three times a day is at least as therapeutically effective as chlordiazepoxide 20 mg three times a day. In the present study 24 out of 29 patients (83%) preferred medazepam, whereas the previous trial showed chlordiazepoxide to be preferred by 59 out of 77 patients (77%). A previous comparison of diazepam 5 mg three times a day

and amylobarbitone 50 mg three times a day (Jenner and Kerry, 1967) showed that 15 out of 19 patients (79%) preferred diazepam for the relief of their anxiety. This suggests that 10 mg of medazepam three times a day also has about the same activity as 5 mg of diazepam three times a day.

To evaluate a new tranquillizer is always difficult, and one would now like to see the results obtained by comparing medazepam with other established tranquillizers. The use of these drugs is often accompanied by initial enthusiasm, to be followed later by disappointment. Psychiatrists are often forced to use the available tranquillizers for the relief of anxiety when perhaps psychotherapy would be more appropriate. This was an outpatient trial and no attempt could be made to keep environmental factors uniform; indeed, it would not have been desirable to do so, since the purpose was to assess the drugs as used in daily practice. It seems that medazepam 10 mg three times a day might offer symptomatic relief of anxiety to a considerable proportion of patients without drowsiness and ataxia being a major problem.

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PRELIMINARY COMMUNICATIONS

New Synthetic Agent for the Induction of Ovulation: Preliminary Trials in Women

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Summary

A new compound in the triphenylethylene series has been tested for its effect in causing ovulation in secondary amenorrhoea. Twenty patients were given a total of 40 courses of treatment and ovulation resulted in 16 instances. Three patients became pregnant. Probably this compound can induce ovulation in suitable subjects.

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Introduction

Clomiphene, a triphenylethylene compound, has been used with modest success for some years to induce ovulation. As marketed, the compound consists of a mixture of *cis* and *trans* isomers. The isomer designated by the manufacturers as the *cis* compound was found to be more potent in stimulating ovulation (Charles *et al.*, 1969). A related compound, *p*- β -dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, has recently been synthesized and the *cis* and *trans* isomers separated. In contrast to clomiphene it was found that in this case the compound identified as being the *trans* isomer (Kilbourn *et al.*, 1968) had ovulation-inducing properties. This difference may be more apparent than real, arising from confusion in designation between British and American chemists. The *trans* isomer, ICI 46,474, had antioestrogenic properties, while the *cis* isomer behaved like a conventional oestrogen in animal experiments (Harper and Walpole, 1967a). It was of interest to determine whether the *trans* isomer could also induce ovulation in women, and after extensive toxicological studies permission for a therapeutic trial was obtained from the Committee on the Safety of Drugs.

Patients

A group of volunteers was sought among patients attending an infertility clinic, selecting those in whom failure of ovula-

tion was the only known cause of infertility. Mostly they were women having episodes of amenorrhoea lasting at least three months, but three subjects in the group with cystic glandular hyperplasia of the endometrium had anovulatory metrorrhagia without notable amenorrhoea. The patients chosen for the therapeutic trial included several different clinical entities. As different causes of anovulation respond differently to treatment, the patients were classified and the results in each category examined separately.

Six of the women, designated as the cystic glandular hyperplasia group, had previously been subjected to curettage at least once and noted to have cystic glandular hyperplasia of the endometrium. Before treatment the endometrial finding was confirmed by repeat biopsy. The condition is generally supposed to result from the action of high concentrations of oestrogen, unaffected by progesterone. Hormone assays and endometrial biopsy confirmed the anovulatory state of our patients, but none of the patients in this group had a high oestrogen excretion. The urinary oestrone output before treatment varied between 2 and 7 μ g; a value well below that found during the preovulatory oestrogen peak in the normal cycle.

Three patients presented features of the Stein-Leventhal syndrome in that they were hirsute, fat, infertile, had amenorrhoea, and in two instances polycystic ovarian enlargement. This group was designated as disordered ovarian steroidogenesis.

The third group is a category which has been called "hypothalamic amenorrhoea" by Shearman (1966). It is not a homogeneous group, and our series included one patient with anorexia nervosa and three who were overweight. The pre-treatment oestrone excretion varied from 3 to 10 μ g/24 hours—that is, from low levels to amounts indicating a modest degree of ovarian activity. The common features of the group were that all the women had normal secondary sex characteristics, no hirsutes or masculinization, no endometrial hyperplasia, and had secondary amenorrhoea. No patients with symptoms suggestive of menopause praecox, such as flushing, were included in the group.

Design of Trial

In patients who were still having occasional periods treatment was deferred until day three to five after the beginning of bleeding. In those patients who were treated during a phase of prolonged amenorrhoea preliminary endometrial biopsy and urinary pregnanediol assay confirmed that they were not in the luteal phase when the trial began.

The first five treatments consisted of 5 mg ICI 46,474 twice daily by mouth for four days. This dosage was considered to be inadequate and thereafter all patients were given 10 mg twice daily for four days. At first blood samples were taken weekly for the determination of serum aspartate and alanine aminotransferase, isocitric dehydrogenase, protein bound iodine, and leucocyte count. No significant change was noted in any of these, and the investigations were reduced to two samples per patient—one before and the second a week after treatment. Vaginal examinations were done before, during, and after treatment. Three patients showed a mild transient ovarian enlargement which did not require admission or treatment. No symptoms such as headaches, dizziness, flushes, or nausea were elicited. In one year's clinical trial no untoward side effects have been detected.

Continuous 24-hour urine collections were started two days before treatment and kept up for at least 28 days. Though basal temperature recordings were also done the criteria concerning ovulation were the daily output of oestrone and pregnanediol. Oestrone estimations were done by a modification of the method of Brown (1955) and the pregnanediol estimations by the method of Kloppe *et al.* (1955), substitut-

ing a gas chromatographic endpoint for the spectrophotometric measurement of pregnanediol diacetate.

Results

Forty courses of treatment were given to 20 patients. Ovulation, as judged by a peak of oestrone excretion followed within two days by a rise of pregnanediol sustained for 10 to 14 days and reaching a maximum of 2.5 mg/24 hours, occurred 16 times within 20 days of the start of treatment with ICI 46,474. Normal menstruation occurred after each presumed ovulation except on three occasions when pregnancy resulted. There were no instances of overstimulation, the highest oestrone excretion being 28 μ g/day and ovulation generally occurring following an oestrone peak of 15–20 μ g/day. There was evidence of some ovarian activity on four occasions in the 24 when ovulation was not induced. Three times oestrone levels rose from a baseline of 2–5 μ g to 10–15 μ g, but no subsequent rise of pregnanediol occurred, and possibly there had been some follicular growth without ovulation. In the fourth instance an oestrone rise was followed by a definite increase in pregnanediol (proliferative phase pregnanediol levels range from 0.1 to 0.5 mg by this method) to values ranging between 1 and 1.7 mg/24 hours. Possibly in this case some luteinization of an unruptured follicle occurred.

The time at which ovulation occurred ranged from 6 to 20 days (median 10 days) following the start of treatment, and was not related to the category of patient. Six patients had previously been treated with clomiphene, three of them had responded by ovulation on at least one occasion. All three also ovulated after ICI 46,474, and two of the three patients with negative responses to clomiphene ovulated when treated with ICI 46,474.

The success rate of treatment varied according to the category of the patients. Four courses of treatment were given to three patients with disordered ovarian steroidogenesis. Ovulation was induced three times and one patient became pregnant. She is now at 20 weeks' gestation in a singleton pregnancy confirmed by a sonar scan. Probably this group is the most likely to respond to treatment—a conclusion which has also been reached about treatment with clomiphene (MacGillivray and Kloppe, 1968). In the group with hypothalamic amenorrhoea, 23 treatments were given and ovulation occurred 10 times. Two of the three presumed anovular cycles occurred in this group. Two pregnancies resulted; one patient has now delivered a normal live child at term, and the other is 10 weeks pregnant. In the group with cystic glandular hyperplasia 13 courses of treatment were given, resulting in three ovulations, one presumed anovular cycle, and one presumed follicular luteinization.

Conclusions

In a mixed group such as the patients we have studied some spontaneous ovulations are likely to occur. Possibly some of the ovulations we observed were not the consequence of the treatment, but it is unlikely that spontaneous ovulation occurred 16 times. This therapeutic trial supports the findings of the manufacturers that the compound is free from toxic effects. On a weight-for-weight basis it may be more potent than clomiphene. There appears to be good grounds for more extended clinical trials of the capacity of ICI 46,474 to provoke ovulation.

Two other aspects of the antioestrogenic activity of this compound are worthy of investigation. One is its possible therapeutic effect in menometrorrhagia associated with anovular cycles. We were disappointed with its apparent lack of effect in patients with cystic glandular hyperplasia, but all our patients had low oestrone excretion before treatment. The

second possibility arises from its paradoxical effect in preventing implantation in rats, either by accelerated tubal transport of eggs or by counteracting the oestrogen surge at ovulation (Harper and Walpole, 1967b). Probably small doses of ICI 46,474 given continuously to normally ovulating women might prevent implantation without otherwise interfering with the normal menstrual cycle.

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MEDICAL MEMORANDA

Cullen's Sign in Perforated Duodenal Ulcer

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Cullen's sign of staining at the umbilicus is widely held to be pathognomonic of acute pancreatitis (Zachary Cope, 1963; Hamilton Bailey, 1967). A search of the literature has failed to find any previous mention of this sign in association with perforation of a duodenal ulcer. A case of this obscure occurrence is reported.

Case Report

A 40-year-old housewife was transferred from a mental hospital with increasing central abdominal pain and shock of 24 hours' duration. There was a known 15-year history of intermittent epigastric pain, which had been ascribed to her psychiatric syndrome of anxiety and depression. This pain had been pronounced for two days; she vomited once.

On admission she was pale and sweating, with rapid shallow respiration and peripheral cyanosis, the pulse was barely palpable at 150 beats per minute, and the blood pressure was unrecordable. There were generalized tenderness and rigidity of the abdomen, and an area of bruising and pronounced tenderness around the umbilicus was noted. Her condition improved greatly after the infusion of four units of dried plasma. On clinical grounds the differential diagnosis was considered to be between a perforated duodenal ulcer, favoured by the long history, and acute pancreatitis, thought to be favoured by the bruising around the umbilicus.

Investigations showed: haemoglobin 13.8 g/100 ml; packed cell volume 47%; white blood count 6,500/mm³; serum sodium 128 mEq/l.; serum potassium 6 mEq/l.; serum calcium 10 mg/100 ml; serum amylase 266 Somogyi units; blood urea 76 mg/100 ml.

At laparotomy gross peritoneal contamination by non-sanguineous fluid containing strands of fibrin was found, 2,500 ml of fluid being aspirated. There was a large perforation of a chronic anterior duodenal ulcer. Fat necrosis was not present, the pancreas appeared and felt normal, and there was no obvious haematoma in the falciform ligament or retroperitoneal area. In view of the

patient's poor condition the ulcer was oversewn and no attempt made at ulcer-curative surgery. Convalescence was complicated by a pelvic abscess, which settled. Five months later she was well and the decision was made not to proceed to further surgery.

Comment

The first report in the literature of staining at the umbilicus was by Ransohoff (1905), who recorded a case of bile-staining at that site following spontaneous rupture of the common bile duct. Cullen's name was attached to the sign of periumbilical bruising after he described it in a patient with a ruptured ectopic pregnancy (Cullen, 1918). Grey Turner (1919) observed bruising of the flanks in acute pancreatitis, and Cox (1945) reported a case of umbilical bruising in pancreatitis. Since then it has been accepted as a late indication of acute pancreatitis (Zachary Cope, 1963; Hamilton Bailey, 1967).

The pitfalls in the differential diagnosis of acute pancreatitis have been dwelt on by Trapnell and Anderson (1967). They described a case (No. 2) of strangulation obstruction due to adhesions, associated with bluish discoloration of the flanks, found at necropsy to have a normal pancreas. The mechanism of umbilical and flank bruising occurring in perforation and strangulation is obscure, since the digestive action of released retroperitoneal trypsin cannot be invoked, as it has been, to explain their occurrence in acute pancreatitis. Fallis, quoted by Cox (1945), suggested abnormal apertures in the peritoneum underlying the umbilical region as a route, but considered the falciform ligament to be a more likely possibility, in view of the absence of intraperitoneal blood-stained fluid in two of his cases showing this sign. Whatever the mechanism, bruising around the umbilicus and in the flank cannot be taken in isolation as strong evidence of acute pancreatitis, justifying conservative management when laparotomy is otherwise indicated.

I would like to thank Mr. J. H. H. Webster for his permission to report this case and for his helpful advice in preparing this paper.

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