Various unexpected symptoms and signs were noted in the two groups of patients (including patients who were withdrawn). One patient in the cimetidine group developed pulmonary embolism, one oedema of fingers, one presbyopia, two diarrhoea, and one arterial hypertension. Three patients in the placebo group complained of impotence, headache, and fatigue respectively. Reduced libido was reported by one patient from each group. Laboratory screening tests showed no significantly abnormal findings. Mean blood-pressure values and results of laboratory investigations at the beginning and end of treatment (after completing one year's treatment or at the time of relapse or withdrawal) are shown in table III. During the study one of the departments was moved to another hospital, where different standards were used. This might partly explain the differences in pretrial and post-trial values. The differences between cimetidine and placebo groups, however, were not significant (Mann-Whitney U tests, P ·0·05).

Discussion

The possibility that symptomless relapse occurred in some patients and that symptomatic relapse in others was unaccompanied by renewed ulceration cannot be excluded since no patient underwent duodenoscopy. Such possible discrepancies are, however, of limited practical consequence, and we decided that it was more important to choose a design that imitated so far as possible the conditions under which cimetidine may be used in daily clinical practice. Our findings agreed with those of a similar trial conducted by Bodemar and Walan[6] in showing that maintenance treatment with cimetidine for one year is highly effective, but we also found that the treatment had no lasting effect. Soon after treatment was completed relapses occurred at about the same rate as in patients whose ulcers had healed spontaneously or during a short course of cimetidine. Wallace *et al*[7] reported severe relapses after cimetidine treatment, but we observed no such incidents in the patients who had received cimetidine for one year or in the patients in the placebo group who had received a short course of cimetidine before entering the maintenance trial. No side effects directly attributable to cimetidine were observed during the trial.

Our results suggest that maintenance treatment with cimetidine is a realistic alternative to elective surgery in patients subject to frequent relapses, but several points still need clarification. Firstly, the optimal duration of treatment is not known. Fry[8] and Greibe *et al*[9] have shown that duodenal ulcer disease often resolves after a few years, especially in patients diagnosed in general practice, but the average ulcer history of 13·5 years in our patients also shows that prolonged treatment is needed in some cases. It remains to be proved that such treatment is safe and that patients do not acquire tolerance to cimetidine with time, though limited experience in cases of the Zollinger-Ellison syndrome suggests that this is unlikely.[10]

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Requests for reprints should be addressed to Dr H R Wulff.

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Prolongation and enhancement of serum methotrexate concentrations by probenecid

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Summary and conclusions

The disappearance of methotrexate (MTX) from the serum after an intravenous bolus injection and intravenous infusion was studied over 24 hours in eight and four patients respectively. Probenecid given at the same time as the bolus injection delayed the disappearance of MTX from the serum and resulted in enhanced concentrations throughout the 24 hours studied. At 24 hours the mean concentration was four times higher than in patients not given probenecid. Overall serum concentrations were even greater than those in patients who had received MTX by intravenous infusion.

We suggest that smaller doses of MTX may be given and treatment costs thereby reduced if probenecid is given in addition.

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Introduction

Methotrexate (MTX) has been successfully used in various neoplastic diseases, and knowledge of its pharmacokinetics and metabolism has allowed it to be used at high doses when followed by folinic acid rescue.[1] MTX disappears rapidly from the blood, so that high concentrations are maintained for only short periods, even after high doses.[2] Since its rapid excretion

indicates some renal transport[3] the addition of a drug that inhibits tubular transport, such as probenecid, might inhibit the excretion of MTX and thus delay its disappearance and prolong high concentrations. In monkeys, for example, plasma concentrations of MTX were found to be up to two times higher after premedication with various doses of probenecid,[4] although concentrations were monitored for only four hours.

Using a sensitive radioimmunoassay technique for detecting MTX in serum,[5] we investigated patients receiving MTX to assess the effect of probenecid on the disappearance of MTX over 24 hours. Serum concentrations were compared with those found in patients who received MTX by constant intravenous infusion.

Patients and methods

Twelve patients with inoperable tumours were studied (see table). All were scheduled to receive MTX 200 mg/m² as part of their regular treatment and had given informed consent to the study. Four received MTX alone by intravenous bolus injection, four received MTX by intravenous bolus injection plus various doses of probenecid (see table), and the other four received MTX 200 mg/m² by constant intravenous infusion over 20-24 hours.

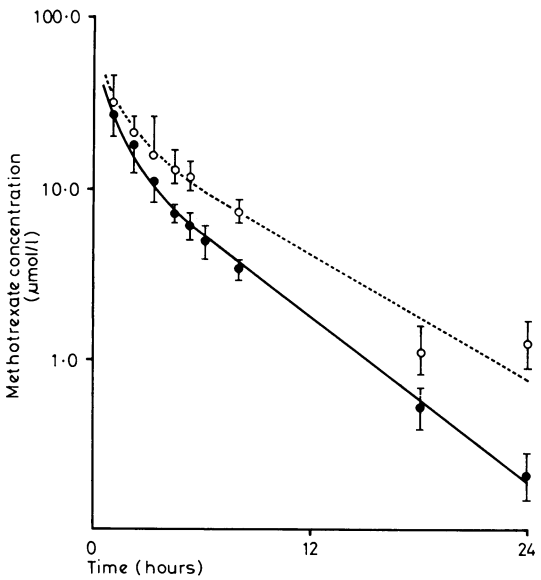
Serum creatinine concentrations were measured as an index of renal function and were within the normal range in every case. No significant myelosuppression was observed during the study. Apart from dextropropoxyphene and nitrazepam, which were given in some cases, no other drugs were administered.

A baseline blood sample was collected through an indwelling venous catheter before the study began, and further samples were taken at frequent intervals during the 24 hours after the administration of MTX. In patients receiving an infusion samples were taken during the infusion period and at intervals for 12 hours afterwards. Blood was allowed to clot at room temperature and the serum stored frozen until assayed. Urine was collected over the same period in aliquots and stored frozen. MTX concentrations were measured by a radioimmunoassay technique.[5]

Results

In the four patients who received a constant infusion of MTX the mean serum steady-state concentration was 4·45 μmol/l (202 μg/100 ml), which was maintained for most of the infusion time. When the infusion was discontinued the drug rapidly disappeared from the blood, the mean (±SE of mean) initial half life being 1·74±0·44 hours. The figure shows the mean serum concentration of MTX in the four patients receiving the drug alone by rapid intravenous injection. The subsequent disappearance of the drug from the blood in these patients was rapid, and the concentration declined biexponentially over 24 hours. The mean initial half life, corresponding to the distribution phase, was 0·29±0·06 hour, and the mean elimination half life 3·75±0·28 hours. In these four patients a mean of 83% of the drug was excreted in the urine during the first 12 hours and 94% over 24 hours. The mean plasma and renal clearances were 107·6±15·5 and 103·5±17·1 ml/min respectively.

MTX disappeared less rapidly from the serum in the four patients given probenecid (see fig). The mean elimination half life was increased to 5·5±0·75 hours ($P < 0·15$), but the initial half life (0·22±0·04 hour) was similar to that of the control patients. At 24 hours the mean serum concentration was 0·88 μmol/l (40 μg/100 ml), which was significantly greater ($P < 0·01$) than the 0·20 μmol/l (9 μg/100 ml) found in patients who had not received probenecid. The mean plasma and renal clearances were decreased to 68·7±14·2 and 45·7±7·5 ml/min respectively ($P < 0·001$), so that only 58% of the drug was excreted in the first 12 hours.



Serum concentrations of methotrexate after intravenous bolus injection in patients receiving methotrexate 200 mg/m² alone (●) and with probenecid (○). Each point represents mean result from four patients. Bars represent 1 SE of mean.

Conversion: SI to traditional units—methotrexate: 1 μmol/l ≈ 45 μg/100 ml.

Discussion

MTX disappears from the blood according to first-order kinetics,[2 6 7] and in our patients the concentrations fell biexponentially over 24 hours. Initial distribution was rapid, with a half life of 17 min, and was complete within two hours. It was followed by an elimination phase with a half life of 3·75 hours. Since 80-100% of the dose was excreted within 24 hours and the urinary clearance was for much of the time greater than that of creatinine some active tubular secretion of MTX must have occurred. Probenecid 500-1000 mg delayed the elimination of MTX to such an extent that only 58% was excreted in 12 hours compared with 83% in patients not given probenecid. This was reflected in the higher serum concentrations over the 24 hours studied, and at 24 hours the mean concentration was four times greater than in patients not given probenecid. Bourke *et al*[4] showed that after various doses of probenecid given to monkeys plasma concentrations of MTX throughout their four-hour

Details of patients receiving methotrexate 200 mg/m² by intravenous infusion and bolus with and without probenecid

Case No	Sex	Age in years	Site of carcinoma	Probenecid dose before and after methotrexate	Methotrexate dose and method of administration
1	M	42	Bronchus		375 mg, bolus
2	F	51	Cervix		350 „ „
3	F	60	Breast		325 „ „
4	M	76	Postnasal sinus		350 „ „
5	M	61	Bronchus	500 mg by mouth 60 min before and five hours after	300 „ „
6	M	55	Bronchus	500 mg by mouth 60 min before and five hours after	400 „ „
7	M	73	Bronchus	500 mg intravenously 15 min before	350 „ „
8*	M	66	Mouth	1000 mg intravenously 60 min before	400 „ „
9	M	57	Bronchus		400 mg, 20-h infusion
10	M	42	Bronchus		375 „ „ „
11*	M	66	Mouth		400 mg, 24-h infusion
12	M	42	Ependymoma		375 „ „ „

*Same patient.

study were double those in control animals given similar doses of MTX alone. We found that this difference was maintained in man for at least 24 hours.

Because the inhibitory effect of probenecid on tubular excretion of MTX varies from patient to patient[9] its effect on prolonging high serum concentrations of the drug will also vary and consequently increase the risk of MTX toxicity. It is therefore important to measure the time taken for MTX to be eliminated. Probenecid also induces changes in the clearance of other acidic drugs, such as ampicillin,[10] indomethacin,[9] and frusemide,[11] which share a common excretory route, so these and other acidic drugs can probably influence MTX excretion. Indeed, in one patient (not in this trial) examined by us and prescribed aspirin and papaveretum tablets during treatment with MTX the elimination half life of MTX was 9·6 hours. Thus to avert toxicity it is important to monitor serum concentrations whenever probenecid or any other drug capable of delaying the excretion of MTX is given concomitantly with MTX. With more recent radioimmunoassay techniques, such as those that use ^{75}Se-labelled MTX,[12] results may be obtained within two to three hours of collecting the blood.

It has been suggested that the minimum effective therapeutic serum concentration of MTX is 1 μmol/l (45 μg/100 ml).[8] This was exceeded for as long a period after a single intravenous bolus injection of MTX and some form of probenecid as during and after a constant intravenous infusion. As the administration of probenecid and MTX by injection is much more convenient we suggest that it may be used to reduce the time spent in hospital by a patient receiving MTX treatment. In addition, patients with a normal glomerular filtration rate may be prescribed MTX with probenecid in order to attain higher serum MTX concentrations than would be attained with similar doses of MTX alone. Alternatively, a smaller dose of MTX may be administered with probenecid to achieve the same serum concentrations as when MTX is given alone. It should therefore be possible to reduce the cost of treatment with MTX without decreasing its efficacy.

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Early results of closed partial meniscectomy

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Summary and conclusions

Thirty patients underwent partial meniscectomy through two puncture incisions by a closed technique under arthroscopic control. "Bucket-handle" fragments were removed from 17 knees, and flaps or tags from the remainder. The mean stay in hospital after operation was 1·3 days and the mean time for return to working fitness was 10·5 days. There were no serious complications. Further study of the long-term results of this technique is needed.

Introduction

Displaced segments of damaged meniscus commonly cause internal derangement of the knee, and, together with the operation of meniscectomy for their relief, give rise to much disability. Morbidity after meniscectomy largely results from surgical damage to the skin, joint capsule, subcutaneous tissue, and synovium, for the meniscus itself is insensitive and avascular and in theory could be cut or trimmed without irritating the joint. Damage to the soft tissues may be reduced by use of a closed technique, whereby meniscal fragments are removed through two puncture incisions, each about 6 mm long. The early results of this technique in 30 patients are presented.

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Patients and methods

Technique—All joints were examined arthroscopically, particular attention being paid to the meniscus. Probing needles passed beneath the meniscus along the joint line were used to lift the meniscus so that its inferior surface could be examined and the integrity of the meniscosynovial junction assessed. When the anatomy of the meniscal lesion had been determined, operating instruments were inserted via the anteromedial route, the mobile meniscal fragments being removed and the meniscus trimmed until an intact, even rim remained. No attempt was made to remove the intact and undamaged parts of the meniscus. The two wounds were closed with one stitch each and a light dressing of plaster wool and crêpe bandage was applied. All patients received physiotherapy before discharge, and a nonsteroidal anti-inflammatory drug (ketoprofen 50 mg thrice daily) was prescribed for 10-14 days after operation.

Patients—Twenty-seven men and three women (mean age 33·7 years; range 18-57) underwent operation. Fifteen patients worked in sedentary occupations (executive, student, draughtsman) and 15 in strenuous occupations (labourer, farmer, waiter). All had symptoms