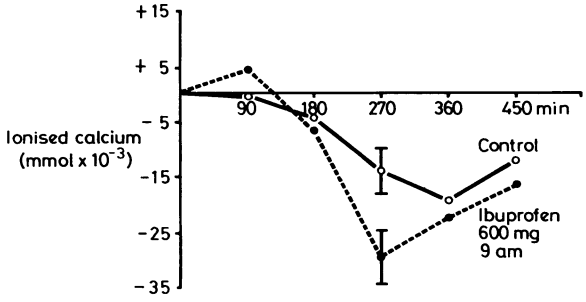
50 patients with rheumatoid arthritis and 50 controls matched for age and sex. Samples for measuring ionised calcium were collected in evacuated containers, allowed to clot at room temperature for 30 minutes, and centrifuged. Serum ionised calcium was estimated on an Orion SS-20 ionised calcium analyser, which incorporates a microcomputer-controlled ion-selective flow-through electrode. All samples were measured in duplicate. Reproducibility was good, between-batch variation being 1·7%. Patients had taken their usual drugs on the morning of the test, between two and five hours before estimation. The results prompted a study of 26 healthy volunteers (17 men, nine women; mean age 27 years); serum ionised calcium concentration was estimated every 90 minutes on control days (no drug treatment) and after ibuprofen 600 mg at 9 am. All subjects remained mobile and were instructed to follow similar degrees of activity for both days.

Seven patients with rheumatoid arthritis had ionised calcium values outside normal (1·15-1·30 mmol/l; 4·62-5·2 mg/100 ml). Two patients were hypercalcaemic and five were severely hypocalcaemic. The "uncorrected" total calcium concentration was often the best predictor of a low ionised value. All patients with hypocalcaemia were postmenopausal women taking non-steroidal anti-inflammatory agents in addition to other drugs.

Of the matched controls, only one had a marginally low ionised calcium concentration (1·14 mmol/l; 4·6 mg/100 ml). In the non-matched group of volunteers ionised calcium fell from a mean 9 am value (±1 SD) of 1·22±0·05 mmol/l (4·9±0·2 mg/100 ml) to 1·20±0·04 mmol/l (4·8±0·17 mg/100 ml) at 3 pm on control days (figure). This pattern was consistent and significant



Mean changes (±SEM) in ionised calcium concentration compared with 9 am value.

($t=3·455$, $p<0·01$, paired t test). On days after ibuprofen 600 mg the mean ionised calcium concentration fell from 1·22±0·04 mmol/l (4·9±0·15 mg/100 ml) at 9 am to 1·19±0·04 mmol/l (4·8±0·18 mg/100 ml) at 1.30 pm ($t=6·373$, $p<0·001$). To assess the significance of this variation the mean differences between the fall in ionised calcium on each day were calculated for each time period. The results confirm that a significant fall occurs four and a half hours after ingestion of ibuprofen ($t=3·227$, $p<0·01$).

Comment

Our results differ from those of Kennedy *et al*[1] as hypocalcaemia, assessed by the ionised calcium fraction, was present in five of our 50 patients whereas only two were hypercalcaemic. Nevertheless, these studies varied in the time that elapsed between taking the drug and measuring calcium. Although in both studies blood was taken in the morning, in the series of Kennedy *et al*[1] drugs were not taken after 6 pm the evening before, whereas all our patients took their usual medication between two and five hours before calcium estimation. The effect observed in our second study is probably inherent in treatment with any non-steroidal anti-inflammatory drugs.

The effect of these drugs on calcium metabolism has been studied in animals, and indomethacin in particular exhibits hypocalcaemic, hyperphosphataemic, and parathyroid hormone inhibitory action in rats.[5] In young healthy adults the drugs can apparently significantly reduce ionised calcium, and five of our subjects became hypocalcaemic. Further studies may show whether this effect is beneficial or detrimental.

In conclusion, hypocalcaemia, as assessed by a low serum ionised calcium concentration, was present in five out of 50 patients with rheumatoid arthritis. Other studies on healthy subjects suggest that these results may be an unreported effect of non-steroidal anti-inflammatory drugs.

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Gonorrhoea presenting as "sterile" pyuria

In men the diagnosis of gonorrhoea depends on the detection of Gram-negative intracellular diplococci in smears and on the culture of *Neisseria gonorrhoeae* from urethral discharge. After inoculation of the specimen the plates are incubated as soon as possible to grow this delicate organism. We describe two recent cases where gonococci were isolated from ordinary mid-stream specimens of urine sent for culture of pathogens causing urinary tract infection more than 24 hours after receipt of the samples. After inoculation of the plates with centrifuged deposit they were left in a carbon dioxide incubator for three days before any recognisable growth was noticed.

Case reports

Two men, aged 17 and 20 years respectively, presented to their family practitioners with a two-to-four day history of dysuria; one had frequency of micturition, but neither had a history of any discharge. The patients were instructed to collect and deliver specimens of mid-stream urine to the laboratory for ordinary culture and sensitivity testing. Microscopy showed over 100×10^6 pus cells/l (100 pus cells/mm^3), but no other abnormalities. Specimens were inoculated on to cysteine, lactose, and electrolyte-deficient medium and placed in a carbon dioxide incubator, together with a primary sensitivity plate of direct sensitivity test agar (DST-Oxoid) medium with 5% lysed blood, in a hot room at 37°C. The next day there was no visible growth on the plates. Instead of reincubating the plates, as is the usual practice, Gram stains were done on the centrifuged deposit of urine, which showed typical Gram-negative intracellular diplococci and no other organisms. The family practitioner was then informed and was asked to obtain a swab of urethral discharge, if any, and a smear if the patient had not already received treatment. At the same time an attempt was made to grow the organism by inoculating the centrifuged deposit of urine on to chocolate agar and GC selective medium (Difco) in the presence of carbon dioxide. After 72 hours' incubation, growth was recognisable. The organism in each case was identified as *N gonorrhoeae* by Gram staining, the oxidase test, and sugar fermentation reactions.

Comment

The use of urine sediment culture for diagnosing gonococcal infection in male patients was first described in 1973,[1] when it was stated that the organisms remained viable at room temperature for as long as two hours. Later, successful culture of gonococci was reported from uncentrifuged, first-voided urine in male patients; in our cases, however, gonococci grew only from the centrifuged deposit. The success rate of isolation from specimens of urine more than one day old, however, must be very low. If we had tried to grow anaerobic or fastidious CO_2 dependent organisms, which have been highlighted recently, on media unsuitable for gonococci or from uncentrifuged urine—instead of looking for gonococci—the diagnosis would have been missed. In the absence of discharge (unless gonorrhoea is

suspected by the practitioner or confessed by the patient), investigations to exclude gonorrhoea are rarely requested for men patients presenting with dysuria, frequency of micturition, or both. Moreover, in our cases gonococci in the urine were not overgrown by other organisms because we have two bench-cool trays (at 4°C), one at the reception and the other within the laboratory, where samples of urine are processed so that all urine samples from the time of receipt to the time of disposal are kept chilled. Nor were the patients treated with any antibiotics before submission of specimens. It therefore seems logical to believe that gonorrhoea may also lead to "sterile" pyuria in women. In conclusion, we wonder whether gonorrhoea should be added to the list of conditions producing "sterile" pyuria in sexually active patients.

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Controlled trial of cromoglycate and slow-release aminophylline in perennial childhood asthma

Cromoglycate and theophylline provide effective prophylactic treatment in childhood asthma.[1 2] Slow-release theophylline preparations simplify treatment, and their use may improve patient compliance and control of symptoms. To assess this we have compared cromoglycate and slow-release aminophylline in a double-blind randomised cross-over trial.

Patients, methods, and results

Seventeen boys and 13 girls aged 5-15 years with perennial asthma were studied. During three randomly assigned four-week periods each took cromoglycate, aminophylline, and placebo. They took cromoglycate or placebo four times daily and slow-release aminophylline or placebo twice daily. Throughout the trial all children used additional salbutamol as required. Persistent severe asthma was treated with a four-day course of prednisolone at home, or admission to hospital if necessary. Before the trial started the dose of slow-release aminophylline was adjusted to give peak plasma concentrations in the therapeutic range 56-112 μmol/l (10-20 μg/ml) 2·5-4 hours after the dose.[3] The mean (±SE) pretrial concentration was 89±6 μmol/l.

Asthma was assessed by using diary cards,[4] on which daily symptom scores, morning and evening peak expiratory flow rates (PEFR), all treatments taken, and possible side effects were recorded. Compliance with treatment was assessed from the diary cards, by counting tablets and capsules returned, and by measuring peak plasma theophylline concentrations at the end of each period of treatment. After completing the trial each child was asked which preparation he or she would prefer to take provided they were equally effective.

The table summarises the symptom scores, PEFR, and use of salbutamol. Mean daily symptom score and use of salbutamol was greater during the placebo period than during both active treatments. Mean PEFR was consistently lower during the placebo period. Mean daily symptom score was significantly lower during treatment with cromoglycate than during treatment with slow-release aminophylline. Although the mean number of symptom-free days was greater and the mean number of days with PEFR under half the predicted value was less during cromoglycate treatment than during slow-release aminophylline treatment, the differences were not significant. Possible side effects such as nausea, vomiting, abdominal pain, and headache were recorded on 5% of trial days. They occurred with similar frequencies throughout all three periods. For severe attacks of asthma, eight children were admitted to hospital and four received prednisolone at home. Eight attacks occurred during placebo periods and two during each period of active treatment ($p<0.05$).

All prescribed aminophylline was taken on 94±SE 3% of trial days while all cromoglycate was taken on only 81±SE 5% of trial days ($p<0.05$). Twice as many doses of cromoglycate, however, were prescribed. Thus equal proportions (93%) of the total prescription of both drugs were taken. Mean plasma theophylline concentration during the trial was 71±SE 6 μmol/l. Some 80% of children preferred slow-release aminophylline tablets compared with 17% who preferred cromoglycate ($p<0.05$); one child had no preference.

Comment

The results confirm that cromoglycate and theophylline are effective drugs in the prophylaxis of perennial asthma in children. Cromoglycate may have been more effective as this treatment was associated with the lowest symptom scores, but this was not confirmed by the other findings.

The willingness of patients to take prescribed treatment may determine the success or failure of prophylaxis in asthma. In this trial compliance with prescribed treatment was probably better for slow-release aminophylline than for cromoglycate, because all doses were taken on significantly more days ($p<0.05$). Some 80% of the children said that they would prefer slow-release aminophylline if it was as effective as cromoglycate. Thus it might be taken more regularly for long periods. Slow-release aminophylline is also cheaper than cromoglycate, costing £1·45 a week compared with £2·90 (*MIMS*).

We are grateful to Napp for providing financial support for this trial. The statistical analyses and conclusions are our own independent assessments. Fisons kindly provided the cromoglycate and placebo. Mrs Sandra Newton and the hospital pharmacy staff allocated treatment.

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Mean (±SE) daily symptom scores, PEFR, doses of salbutamol, and number of symptom-free days during each treatment

Treatment	Symptom score (maximum = 13)	PEFR (%)† am	PEFR (%)† pm	Salbutamol (No of doses daily)	Symptom-free days (%)	Days when PEFR <50% predicted (%)
Cromoglycate	1·69±0·08 ** ***	88±1 ***	91±1 ***	0·95±0·05 ***	47±7	47±9
Slow-release aminophylline	1·98±0·08 *	88±1 ***	91±1 ***	0·92±0·04 ***	40±6	57±9
Placebo	2·27±0·08	84±1	86±1	1·24±0·06	32±5	60±9

Difference between means significant: *$p<0.05$; **$p<0.01$; ***$p<0.001$.
†PEFR as percentage of predicted normal from Godfrey *et al.*[5]