osteoarthritis treated intermittently with aspirin; a 10-year history of adult-onset diabetes mellitus treated with diet; and mild renal insufficiency. Abnormal physical findings were limited to the central nervous system, with left-sided deficits. Laboratory investigation showed that creatinine concentration was 159 $\mu\text{mol/l}$ (1.8 mg/100 ml), blood urea nitrogen 12.8 mmol/l (36 mg/100 ml), and creatinine clearance 64 ml/min. Computerised tomography (CTT) of the skull with dye contrast using 120 ml of sodium iohalamate injection was performed on the day of admission and showed a right parietal-occipital infarction. Physiotherapy, digoxin, frusemide, spironolactone, and a 2-g sodium diet were begun, and the patient's condition improved until seven days after admission, when he complained of arthralgia in his lower back. Lumbar sacral films were consistent with osteoarthritis, and he was given ibuprofen 400 mg four times daily. After six days' ibuprofen treatment (13 days after CTT) his urinary output decreased from an average of 1440 ml/24 h to 300 ml/24 h. At this time his blood urea nitrogen concentration was 27.8 mmol/l (78 mg/100 ml), and creatinine 318 $\mu\text{mol/l}$ (3.6 mg/100 ml). Acute renal failure was suspected, and spironolactone and ibuprofen were discontinued. Renal function improved over the next eight days (serum creatinine concentration 186 $\mu\text{mol/l}$ (2.1 mg/100 ml); blood urea nitrogen 14.3 mmol/l (40 mg/100 ml)). He was discharged, taking frusemide, spironolactone, and digoxin, with minimal neurological residual signs and stable renal function. Six months after discharge his condition remains stable.

Comment

Ibuprofen is a non-steroidal analgesic, antipyretic, and anti-inflammatory agent used in treating rheumatoid arthritis and osteoarthritis. Adverse effects are primarily gastrointestinal; dermatological, central nervous system, otic (tinnitus), and ophthalmological side effects occur less frequently.³

The two possible causes of the sudden onset of renal failure were the intravenous dye contrast material and the ibuprofen. The patient received intravenous dye contrast material 13 days before renal function was clinically decreased. Two cases of acute renal failure after injection of contrast media for CTT have been recently reported.⁴ In both, however, renal failure occurred within 24 hours and these times of onset were consistent with other reported episodes of acute renal failure induced by contrast media (usually occurring within 12 to 24 hours). Possibly this patient had undetected renal insufficiency after CTT, since laboratory data were not collected immediately after this procedure. As oliguria usually occurs con-

currently with dye-induced acute renal failure and is of short duration, we think that this patient's renal insufficiency was not related to the dye. Oliguria developed on the sixth day of ibuprofen treatment with no other changes in treatment, thus strongly implicating this drug. He had not taken ibuprofen before. He had been receiving frusemide, digoxin, and spironolactone in therapeutic doses for at least nine months without clinical evidence of adverse reactions, and did not react adversely when this treatment was reinstituted at discharge.

Ibuprofen is a potent inhibitor of prostaglandin synthesis and may thus be capable of decreasing renal function,⁵ since prostaglandin E_2 affects renal blood flow and is a factor in the regulation of the glomerular filtration rate. We believe that ibuprofen was the precipitating factor in this patient's acute oliguric renal failure and suggest that fluid input and output as well as renal function should be carefully monitored in such cases. The acute renal failure appears to be reversible, as renal function improved when the drug was discontinued.

We thank Dr John Romankiewicz for his help in preparing this report.

¹ Murray, M, *British Medical Journal*, 1972, 1, 479.

² Wiseman, E H, and Reinert, H, *Agents and Actions*, 1975, 5, 322.

³ Cardoe, N, *Rheumatology and Physical Medicine*, 1970, 10, Suppl, p 28.

⁴ Hanaway, J, and Black, J, *Journal of the American Medical Association*, 1977, 238, 2056.

⁵ Kimberly, R P, and Plotz, P H, *New England Journal of Medicine*, 1977, 296, 1169.

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(We suggest to readers that any suspected adverse reaction to a new drug should be reported to the Committee on Safety of Medicines, preferably on a yellow card. Serious or unusual reactions to all drugs should also be reported.)

SHORT REPORTS

Heparin and infusion phlebitis

The problem of infusion phlebitis has produced a variety of explanations and advice on avoidance. The cause is not known—particularly, infection,¹ reaction to the canula² and to infusion fluids,³ or simple trauma are all possible but unproved causes. In some hospitals the policy is to change the site of drips every day.¹ In a busy surgical unit there is not the time available for this and many patients do not have suitable veins. In practice, most drips are left in situ until early phlebitis occurs, they stop spontaneously, or are no longer required. Anecdotaly, heparin is said to prolong the life of drips but the advice on this is conflicting.^{4,5} The present study was designed to test the hypothesis that small doses of heparin, either subcutaneously or added to the infusion, both prolong drip life and reduce infusion-related phlebitis.

Methods and results

A total of 60 consecutive patients entering a general surgical unit under the care of one particular consultant, having intravenous infusions expected to continue for more than two days, were entered for this trial. They included patients admitted for routine and emergency procedures but excluded those actively bleeding from any site. No other groups were excluded. Patients admitted for routine procedures at high risk from pulmonary embolus received as routine practice 5000 units of subcutaneous (sc) heparin three times a day. Patients were alternately allocated to a control group receiving no intravenous (iv) heparin or to a group receiving a total of 2000 units of heparin per day via the infusion. This was divided into four doses

of 500 units given six hourly into the infusion bags and did not affect the partial thromboplastin time.

When a drip was discontinued the length of time it had been running and the reason for its discontinuation were recorded. Three reasons for discontinuing were recognised; (1) local pain, redness, and swelling (phlebitis); (2) spontaneous stoppage, cause unknown (often called tissueing); and (3) elective removal. Within both the control and added iv heparin groups there were some patients who had routinely received sc heparin; initially

Drip life and reasons for discontinuation in control patients and those receiving subcutaneous (sc) or intravenous (iv) heparin

		Controls	sc heparin	iv heparin
Mean ($\pm$ SD) drip life in days (n)		2.1 $\pm$ 1.0 (23)	3.4 $\pm$ 1.6 (15)	5.2 $\pm$ 3.2 (21)
P values		0.005 0.025 0.001		
Reasons for discontinuation	Phlebitis	6	4	5
	Spontaneous stoppage	8	4	1
	Elective removal	9	7	15
P values for spontaneous stoppage versus elective removal		NS 0.025		

they were analysed separately. Although making a difference in the control group, in the iv heparin group giving sc heparin (eight patients) or not (13 patients) made no difference and therefore the results of these two groups were combined in the table. The results on drip life were analysed by the Student's *t* test, and the comparisons between rates of spontaneous stoppage and elective removal by χ^2 with Yates's correction.

Both sc and iv heparin prolonged the life of a drip (see table), there being significant differences between the control group and both the heparin groups, and also between the two heparin groups themselves. In the iv heparin group there was a significant increase in elective removals, with a parallel decrease in spontaneous stoppages as compared with control patients.

Comment

This study showed that small doses of heparin had a significant effect on the life of a drip. This was almost entirely due to reducing spontaneous stoppage and is presumably related to prevention of clotting in or around the canula tip. No significant reduction in thrombophlebitis was found. In patients with poor peripheral veins this simple intravenous heparin regimen usefully prolongs drip life without increasing the incidence of thrombophlebitis.

I thank the staff of the surgical unit at Musgrove Park Hospital, Taunton, for all their help during this study, and Dr M Brodie for advising on presentation.

¹ Collin, J, *et al*, *Lancet*, 1975, **2**, 150.

² Thomas, E T, Evers, W, and Racz, G B, *Anesthesia and Analgesia*, 1970, **49**, 150.

³ Vere, D, Sykes, C, and Armitage, P, *Lancet*, 1960, **2**, 627.

⁴ Hohn, A R, and Lambert, E C, *Journal of the American Medical Association*, 1966, **197**, 658.

⁵ Roy, R B, Wilkinson, R H, and Bayliss, C E, *Canadian Medical Association Journal*, 1967, **96**, 94.

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Bacterial growth in raw and pasteurised human milk

Human milk is generally agreed to be the food of choice for most newborn babies, but there is controversy over the safest form of breast milk for sick or premature neonates when normal breast feeding is impossible. Pooled raw human breast milk, recommended by some,¹ affords greater protection against neonatal necrotising enterocolitis than pasteurised breast milk.² Others, however, emphasise the risks of bacterial contamination in untreated breast milk and suggest that pasteurisation preserves some desirable antimicrobial properties in human milk.³ We have tested one effect of heating breast milk by its ability to support bacterial growth before and after pasteurisation.

Methods and results

Paired samples of fresh breast milk were either pasteurised at 62.5°C for 30 minutes or untreated. Twelve paired samples were then inoculated at room temperature with an enteropathogenic *Escherichia coli* O125 inoculum

Bacterial counts (Miles and Misra) in raw and pasteurised milk after inoculation with test organism and incubation for 18 hours

Test organism	No of paired samples	Filtration	Mean bacterial count		<i>t</i>	P
			Raw	Pasteurised		
<i>E coli</i> ..	12	No	7.5 × 10 ⁴	55 × 10 ⁴	4.455	<0.001
Oxford	6	No	4 × 10 ⁴	1.8 × 10 ⁷	>10	<0.001
Toxigenic <i>Staph aureus</i>	6	Yes	11 × 10 ⁴	23 × 10 ⁷	>10	<0.001

containing 10⁵ organisms/ml. A further six paired samples were inoculated with the Oxford strain of *Staphylococcus aureus*. Bacterial growth was compared in raw and pasteurised milk by Miles and Misra counts after 14 hours' incubation at 37°C.

All pasteurised samples were sterile before inoculation while raw milk samples invariably contained a variety of bacterial contaminants. To eliminate the effect of incidental bacterial contamination on growth of the inoculum raw milk was passed through a Seitz E K filter and shown to be bacteria free. Six paired samples treated in this way were then tested by the described method, an enterotoxigenic strain of *Staph aureus* (NCTC 10657) being used as the inoculated organism. Bacterial counts in raw and pasteurised samples were compared by paired *t* tests (table). Highly significant differences in bacterial growth were found with *E coli* and *Staph aureus*. Similar results were obtained with filtered milk.

Comment

Pasteurisation reduces the concentration of IgA, virtually destroys IgM and lactoferrin,⁴ and inactivates complement in human milk. Our findings show both the reduced antimicrobial properties of pasteurised milk and the inhibition of bacterial growth by untreated milk. Inhibition of coagulase-positive *Staphylococci* is greater than of *E coli*, which may be due to a specific heat-labile antistaphylococcal factor in raw milk.⁵ Variable numbers of benign contaminants, predominantly coagulase-negative *staphylococci*, were found in raw milk samples and these may have competitively inhibited the growth of the experimental inoculum. Tests with bacteria-free filtered raw milk show that any such effect is negligible. Filtered raw milk inhibited bacterial growth to the same degree as unfiltered milk despite the inevitable removal of macrophages and neutrophils. This underlines the importance of non-cellular antibacterial constituents in raw milk. We conclude that unheated, compared with pasteurised, breast milk has bacterial growth inhibitory properties and that these may protect the neonatal gut against harmful bacterial colonisation. The need for careful and hygienic methods of milk collection in conjunction with bacteriological monitoring is clear.

We acknowledge the technical assistance of Mrs S Coton.

¹ Williamson, S, *et al*, *British Medical Journal*, 1978, **1**, 393.

² Barlow, B, *et al*, *Journal of Pediatric Surgery*, 1977, **9**, 587.

³ Lucas, A, and Baum, D, *British Medical Journal*, 1978, **1**, 781.

⁴ Evans, T J, *et al*, *Archives of Disease in Childhood*, 1978, **53**, 239.

⁵ Gyorgy, P, Dhanamitta, S, and Steers, E, *Science*, 1962, **137**, 338.

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Serum 24,25-dihydroxyvitamin D and 25-hydroxyvitamin D concentrations in femoral neck fracture

Low serum 25-hydroxyvitamin D (25-OHD) concentration and impaired conversion of 25-OHD to 1,25-dihydroxyvitamin D (1,25(OH)₂D) have been suggested as important factors in the pathogenesis of osteomalacia and fracture of the proximal femur in elderly people.^{1,2} Recent studies have shown the importance of another metabolite, 24,25-dihydroxyvitamin D (24,25(OH)₂D), in normal bone mineralisation and structure.³ We have therefore investigated whether conversion of 25-OHD to 24,25(OH)₂D is impaired in patients with fracture of the proximal femur.

Patients, methods, and results

Serum concentrations of radioassayable 25-OHD and 24,25(OH)₂D were measured according to Weisman *et al*⁴ in 22 patients (mean (±SD) age 74.7 ± 8.4 years) admitted to Ichilov-Hospital, Tel-Aviv, with fracture of the proximal femur. Control sera were obtained from 18 young (mean age