Therapeutics

A survey of current prescribing practices of anti-inflammatory and urate-lowering drugs in gouty arthritis in New South Wales and Queensland

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ABSTRACT **We recently have conducted a cross-sectional survey to determine the prescribing practices of rheumatologists and a random sample of general practitioners in New South Wales and Queensland. While in general there was agreement as to the preferred management of gout, several important differences were noted between the two groups of doctors. In particular, general practitioners were more liberal than were rheumatologists in their use of allopurinol. However, they were less likely to cover the introduction of allopurinol with anti-inflammatory agents, to titrate the dose against the serum uric acid level or to adjust the dose according to the serum creatinine level. A small number of doctors continued to use urate-lowering drugs as a routine in the treatment of entirely asymptomatic hyperuricaemia. The data indicate a continuing need to disseminate information regarding the preferred management of hyperuricaemic states.**
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In recent years, there has been a number of important developments in the pharmacological management of hyperuricaemic states. In particular, phenylbutazone has been withdrawn from common usage by several regulatory agencies because of the availability of less toxic alternatives.[1,2] It has been well-demonstrated that not all patients who experience a first attack of gout require immediate life-long therapy with urate-lowering agents.[3] Moreover, allopurinol is not the most appropriate agent for every patient.

Observations on the pharmacokinetics and pharmacodynamics of allopurinol have led to it being administered by a once-a-day schedule, and in the presence of renal impairment, the dose usually is reduced.[4,5] Given a tendency for an acute reduction in the serum urate level to precipitate an acute attack of gout, urate-lowering agents usually are introduced at a low dose, under cover of an anti-inflammatory agent, and the dose is titrated upward against the serum urate level. Finally after several years of controversy, it now is accepted that the vast majority of patients with entirely asymptomatic hyperuricaemia do not require treatment with urate-lowering agents.[6,7] In view of such important developments, we elected to survey the prescribing practices of general practitioners and rheumatologists in New South Wales and Queensland.

Subjects and methods

A 26-item questionnaire was developed, pretested, revised, formatted, and then distributed by post to every rheumatologist in New South Wales and in Queensland ($n = 85$) and a random sample of 430 general practitioners in active practice in New South Wales and Queensland. The subjects were identified from a number of sources, including a pharmaceutical company's up-to-date listing, the most recent (1980) *Medical Directory of Australia* and a current Australian Rheumatism Association listing. Second and third mailings to non-respondents were sent out at intervals of approximately one month. The questionnaire contained two demographic questions and 24 items that examined the selection and prescription of antirheumatic drugs in patients with acute gout, chronic tophaceous gout and asymptomatic hyperuricaemia.

In addition to the computing of descriptive statistics, continuous data were compared by means of Student's *t*-test and categorical data by means of the χ^2 statistic. Where necessary, non-parametric techniques were employed (that is, the Mann-Whitney *U* test). For those questions where responses were categorized as "always", "usually", "occasionally", "rarely", and "never", $2 \times k$ contingency tables (where $k = 5$) were constructed, analysed and interpreted with due regard for the response patterns that had been observed in the contingency tables. Although all analyses were planned *a priori*, in view of the multiple statistical comparisons that were made, we have corrected the type-1 error by accepting a *P* value of equal to or less than 0.001 as being significant.[8]

Results

Response data

Responses were obtained from 72 rheumatologists and 254 general practitioners. Therefore, the response rates were 85% and 59%, respectively. The mean year of graduation from medical school of respondents was: rheumatologists, 1969 (range, 1930–1980); and general practitioners, 1968 (range, 1930–1985). The mean year of graduation from medical school of non-respondents was 1967 for rheumatologists (range, 1954–1976; $P = 0.69$), and 1968 for general practitioners (range, 1939–1986; $P = 0.78$).

The majority of general practitioners and rheumatologists had supervised actively the care of patients with acute gouty arthritis (general practitioners, 99%; rheumatologists, 94%) or asymptomatic hyperuricaemia (general practitioners, 88%; rheumatologists, 64%) in the six months that immediately preceded the survey, while more rheumatologists (general practitioners, 50%; rheumatologists, 87%) had supervised patients with chronic tophaceous gout. Over all, in the preceding six months, more general practitioners than rheumatologists had managed patients with acute gouty arthritis (75% of general practitioners compared with 46% of rheumatologists had supervised one to nine patients). Asymptomatic hyperuricaemia also was seen more frequently by general practitioners than by rheumatologists (64% of general practioners compared with 34% of rheumatologists had seen between one and nine cases in the preceding six months).

On the other hand, chronic tophaceous gout more commonly was managed by rheumatologists than by general practitioners; in fact, 50% of general practitioners had not supervised a case of chronic tophaceous gout in the preceding six months. As no significant differences were noted in the prescribing styles of the doctors in New South Wales and those in Queensland, all data have been reported as comparisons between general practitioners and rheumatologists.

Management of acute gouty arthritis

Non-steroidal anti-inflammatory drugs. Indomethacin was the most frequently prescribed anti-inflammatory drug by both general practitioners and rheumatologists (Table 1), utilization rates being significantly greater among the latter group ($P = 0.001$). The most

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TABLE 1: Management of acute gouty arthritis

Management	General practitioners	Rheumatologists	Significance of difference
Frequency of prescribing anti-inflammatory drugs.			
Indomethacin	67%	89%	$P=0.001$
Colchicine	17%	6%	$P=0.023$
Naproxen	9%	4%	$P=0.277$
Phenylbutazone	3%	1%	$P=0.700$
Diclofenac	2%	0	$P=0.516$
Ibuprofen	1%	0	$P=0.825$
Frequency of colchicine usage			
Prevent recurrent attack	15%	67%	$P<0.001$
Abort impending attack	33%	34%	$P=1.00$
Intravenously administered colchicine	6%	38%	$P<0.001$
In addition to a non-steroidal anti-inflammatory drug	31%	27%	$P=0.600$
Prescribing of urate-lowering drug therapy at the time of the acute attack in patients already receiving urate-lowering therapy			
Continue at same dose	55%	75%	$P=0.005$
Continue at increased dose	11%	6%	$P=0.295$
Stop, and recommence when attack over	26%	17%	$P=0.167$
Other (unspecified)	8%	3%	$P=0.155$

frequently prescribed dosage regimen for indomethacin in the first 24 hours of an acute attack was 50 mg by mouth three times a day. Infrequently, doctors reported a preference for the following non-steroidal anti-inflammatory drugs: naproxen, phenylbutazone, diclofenac and ibuprofen.

Colchicine. Colchicine was the second most frequently chosen anti-inflammatory drug by both general practitioners and rheumatologists for acute attacks of gout. Rheumatologists were much more likely to use colchicine as a prophylactic agent to prevent recurrent attacks than were general practitioners ($P<0.001$), although approximately 33% of both groups used colchicine to abort an impending attack. Rheumatologists showed a greater ($P<0.001$) propensity to administer colchicine by the intravenous route when indicated than did general practitioners. Fewer than one-third of doctors used non-steroidal anti-inflammatory drugs and colchicine in combination to treat acute attacks of gout.

Urate-lowering drugs. In patients who already were receiving urate-lowering drugs at the time of an acute attack, and who were fully compliant with their medication, a few doctors indicated that they normally ceased the urate-lowing agent until the acute attack was over and then restarted it. However, the majority of respondents in both groups recommended the continuation of urate-lowering therapy either at the same dose, or at an increased dose.

Long-term management

Timing the introduction of urate-lowering therapy. Most doctors only commenced urate-lowering therapy after a patient had experienced recurrent attacks of acute gouty arthritis; general practitioners generally started treatment after the second attack and rheumatologists started treatment after the third attack (Figure 1). However, 42% of general practitioners and 7% of rheumatologists ($P<0.001$) commenced such treatment after the very first attack of gout (Table 2). Those doctors who initiated treatment after the first attack also were more likely to recommend treatment at more modest elevations of serum urate levels ($P<0.001$) than were those who as a routine waited for clinical signs of recurrence.

For patients who already were not receiving a urate-lowering drug at the time of an acute attack, the vast majority of doctors postponed the introduction of such therapy until some time after the acute attack had resolved (Figure 2). Of those doctors who elected to postpone therapy, rheumatologists tended to wait longer after the resolution of an attack (mean, 2.7 weeks) than did general practitioners (mean, 1.9 weeks), although this difference was not statistically significant. All doctors who elected to commence urate-lowering therapy in patients selected allopurinol rather than probenecid or sulphinpyrazone.

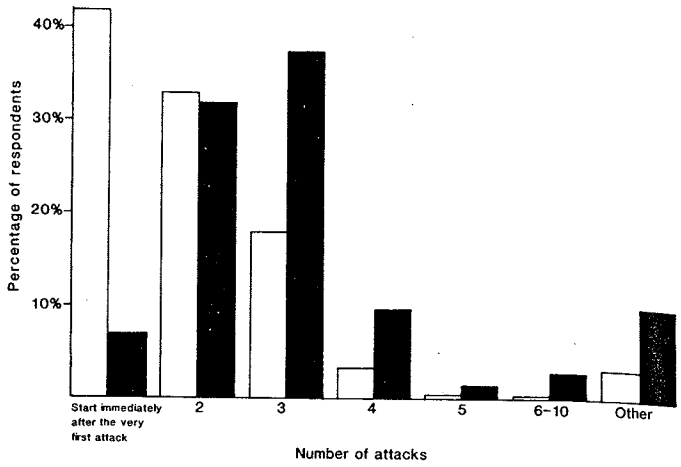

FIGURE 1: Number of attacks of acute gouty arthritis that were tolerated by general practitioners (□) and rheumatologists (■) in a one-year period before urate-lowering therapy was introduced.

TABLE 2: Long-term management

Management	General practitioners	Rheumatologists	Significance of difference
Timing the introduction of urate-lowering therapy			
Start immediately after first attack	42%	7%	$P<0.001$
Postpone until acute attack resolved	87%	97%	$P=0.020$
Introduce at time of acute attack	13%	3%	$P=0.024$
Identification of patients requiring treatment			
24-hour urinary urate excretion, normal diet	69%	43%	$P=0.002$
24-hour urinary urate excretion, low-purine diet	29%	52%	$P=0.006$
Therapy obligatory if serum urate level			
Less than 450 μmol/L	18%	0	$P=0.001$
450–600 μmol/L	55%	26%	$P<0.001$
Greater than 600 μmol/L	27%	74%	$P<0.001$
Selection and utilization of urate-lowering drugs			
Prescribe allopurinol (initially)			
At 300 mg/day	65%	22%	$P<0.001$
At 100 mg/day	27%	67%	$P<0.001$
Titrate dose against serum urate level until normal	43%	67%	$P=0.001$
Prescribe fixed dose irrespective of reduction in serum urate level	49%	24%	$P<0.001$
300-mg/day doses prescribed once a day	93%	96%	$P=0.644$
Divide 300 mg into 100 mg three times a day	4%	3%	$P=0.873$
Divide dose of greater than 300 mg/day	27%	32%	$P=0.522$
Adjust dose according to serum creatinine level	40%	73%	$P<0.001$
Control of potential aggravating factors			
"Covering" agents			
Colchicine alone	22%	45%	$P<0.001$
Non-steroidal anti-inflammatory drug alone	67%	20%	$P<0.001$
Both colchicine and non-steroidal anti-inflammatory drug	8%	25%	$P<0.001$
Other (unspecified)	3%	10%	$P=0.031$
Aggravating factors controlled			
Alcohol intake	92%	91%	$P=1.00$
Avoid high-purine foods	89%	82%	$P=0.206$
Thiazide-diuretic therapy	91%	87%	$P=0.508$
Concomitant low-dose salicylate therapy	37%	77%	$P<0.001$
Colchicine prescribed as adjunctive therapy in chronic tophaceous gout	25%	50%	$P<0.001$

Identification of patients requiring treatment. In making treatment decisions, rheumatologists more frequently measured the 24-hour urinary urate excretion than did general practitioners ($P<0.001$;

Prescribing Information

COMPOSITION Cefotaxime sodium

Description. Claforan is a semisynthetic cephalosporin for use by injection only. It is a white to pale yellow crystalline powder, soluble in water (greater than 20%) and produces a pale yellow solution. The pKa value is 3.35. The pH of the formulated material is 4.5 to 6.5. Raising the pH (as by addition of strong base) will result in an intense yellow colour and possible degradation. The sodium content of the formulated material is approximately 2.09 mmol (48 mg) per g of Claforan.

Pharmacology pharmacokinetics. Claforan is very poorly absorbed after oral ingestion and therefore is administered by intramuscular and intravenous injection. Following intramuscular administration of a 1g dose of Claforan to normal volunteers, the mean peak plasma concentration at 30 minutes post administration was approximately 20 mcg/mL.
After intravenous dosage, administered over a 2-5 minute period, a peak plasma level of approximately 102 mcg/mL was obtained. For intravenous infusion administered over a 30 minute period, a mean concentration of approximately 40 mcg/mL was obtained. The respective concentration declined as follows:

(1g)	1 hour	2 hours	3 hours
IV	20 mcg/mL	8	1.8
IV infusion	14	4	1.5
IM	15	10	4.0

Repetitive dosing showed no significant evidence of accumulation. The mean elimination half-life after intramuscular administration was 1.45 hour, 1.06 hour after rapid intravenous injection, and 1.13 hour after 30 minute intravenous infusion. Claforan is desacetylated in the body, with concentrations of the desacetyl metabolite appearing both in the blood and urine. The process is rapid with measurable levels detectable in the plasma within 5 minutes after administration. The desacetyl metabolite is microbiologically active against a similar spectrum of bacteria, but is less active by a factor of 2 to 3. The desacetyl metabolite has also been shown to be degraded to an open lactone form. This metabolite is not microbiologically active and only very low levels can be detected in the plasma after administration of normal therapeutic doses. Studies in human volunteers measuring radioactive recovery in the urine have indicated that 20 – 36% of administered drug is excreted as unchanged drug, 15 – 25% as the desacetyl metabolite and 20 – 25% as the opened lactone derivative of the desacetyl metabolite.
Claforan is 32 – 44% bound to plasma protein, while the desacetyl derivative is only bound by half of this value. The affinity for plasma proteins is low, as evidenced by the high urinary clearance. 85 – 90% of the administered dose is recovered in the urine, while the faeces accounted for 7 – 9.5% of the recovery total. 70 – 80% of the administered dose is recovered in the first 4 hours after administration. The elimination half-life of Claforan is 0.7 – 1.3 hours, while that of the metabolites is approximately 2 hours.
Mean peak urinary concentrations obtained after 1g administration of Claforan intravenously, intramuscularly and by intravenous infusion at 4 hours were 1309 mcg/mL, 903 mcg/mL, and 599 mcg/mL, respectively.
Following IV administration of 1g Claforan mean peak concentrations of 35 mcg/mL were recorded in the bile after 30 minutes and declined to 3.30 mcg/mL after 4 hours. Concentrations of Claforan in the CSF are considerably lower than in the plasma.
Following 1g intramuscular dosage the mean plasma clearance is 318 mL/min/1.73m². Studies have shown that concomitant use of 0.5% lignocaine solution does not affect the pharmacokinetics or bioavailability of Claforan form intramuscular administration.
Interaction studies between parenterally administered Claforan and orally ingested probenecid, showed that probenecid increased the retention of Claforan by 14 – 40%, and decreased the renal clearance by 11 – 32%.

Microbiology. At plasma concentrations achieved with the recommended therapeutic doses Claforan is usually active against the following micro-organisms in vitro:
Gram-positive: staphylococci, including penicillinase producing strains, **Streptococcus pyogenes, Diplococcus pneumoniae, (Streptococcus faecalis are mostly resistant).**
Gram-negative: **Escherichia coli, Klebsiella pneumoniae, Haemophilus influenzae,** Neisseria sp., gonococcus (including penicillin resistant gonococcus), **Proteus mirabilis, Proteus morganii, Proteus vulgaris, Proteus rettgeri, Serratia marcescens.**
Approximately 25% of **Pseudomonas aeruginosa** strains and 43% of bacteroides strains have an in vitro MIC of less than or equal to 16 mcg/mL.
There is in vitro evidence of synergy between Claforan and aminoglycoside antibiotics such as gentamicin against some species of Gram-negative bacteria including some strains of pseudomonas. Claforan is resistant to many B lactamases (penicillinases and cephalosporinases). Claforan's bactericidal effect is due to inhibition of cell wall synthesis.

Susceptibility tests. Quantitative methods that require measurement of zone diameters give the most precise estimates of antibiotic susceptibility. Interpretation involves correlation of the diameters obtained in the disc test with minimum inhibitory concentration (MIC) values for Claforan.
Reports from the laboratory giving results of the standardised single disc susceptibility test using a 30 mcg Claforan disc should be interpreted according to the following criteria:
Susceptible organisms produce zones of inhibition 23 mm or greater indicating sensitivity and that the tested organism is likely to respond to therapy. Organisms of intermediate susceptibility produce zones of inhibition 15 to 22 mm, indicating that the tested organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids (eg. urine) in which high antibiotic levels are attained.
Resistant organisms produce zones of 14 mm or less, indicating that other therapy should be selected.
A bacterial isolate may be considered susceptible if the MIC value for Claforan is less than 16 mcg/mL.
Organisms are considered resistant if the MIC value is greater than 32 mcg/mL.

INDICATIONS Treatment of infections caused by susceptible microorganisms. Efficacy has been demonstrated in the following: infections of the respiratory tract (upper and lower); infections of the urinary tract; septicaemia (cefotaxime has been administered with gentamicin for septicaemia, and such therapy may be instituted prior to isolation of causative organism); intra-abdominal infections; gonorrhoea (including gonorrhoea caused by B lactamase producing strains of N. **gonorrhoeae**); ENT infections; soft tissue infections; bone and joint infections; meningitis (Claforan should be combined with chloramphenicol in the initial treatment of meningitis in adults and children pending the availability of culture and sensitivity results, appropriate therapy should then be instituted, it should not be used either as a single drug in initial therapy or in infants and neonates).
In serious cases Claforan may be used before the results of sensitivity tests become available.
Claforan may be used for the prevention of postoperative infection in obstetrical surgery, vaginal hysterectomy and abdominal hysterectomy (see Dosage and Administration).

CONTRAINDICATIONS Claforan should not be used in patients with known hypersensitivity to cephalosporins. Caution should be exercised in penicillin allergic patients, as the possibility of cross sensitivity exists.
Lignocaine hydrochloride should not be used as a diluent for intramuscular injection in patients who are sensitive to lignocaine.

WARNINGS Claforan is physically incompatible with aminoglycosides. Where an aminoglycoside antibiotic is administered at the same time as Claforan they should be administered separately and not mixed together as a single preparation.
As with other broad spectrum antibiotics, colitis including rare instances of pseudomembranous colitis, has been reported with Claforan.

PRECAUTIONS Claforan should be used with caution in patients with known hypersensitivity to penicillin or other B lactam antibiotics. The possibility of severe or fatal anaphylactic reactions should be borne in mind and appropriate treatment kept available.

Use in pregnancy. The safety of Claforan in pregnancy has not been established. Claforan has not been shown to cause any embryotoxic or teratogenic effects in animals. However, Claforan crosses the placenta and it should be administered during known or suspected pregnancy only if in the judgement of the treating clinician such use is deemed essential to the patient's welfare and the expected benefits outweigh any potential risks.

Use in lactation. Claforan is excreted in the milk. Peak concentrations, measured 2 or 3 hours after IV administration of 1g doses, ranged from 0.25 to 0.52 mcg/mL (mean 0.32 ± 0.09). These concentrations in breast milk could affect the oropharyngeal flora of the suckling infant. Therefore, Claforan is not recommended for nursing mothers unless the expected benefits outweigh any potential risk or if alternative arrangements for feeding the infant can be made.

Liver and renal disease. Transient rises in hepatic enzymes, urea and creatinine have been seen in some patients given Claforan, so careful monitoring of hepatic and renal function is advised where any dysfunction exists. For dosage adjustment in moderate and severe renal impairment see Dosage and Administration.
Repeated use of lignocaine hydrochloride should be avoided in patients with severe liver disease or decreased hepatic blood flow due to the possibility of lignocaine toxicity (resulting from decreased metabolism and accumulation).
Superinfection with nonsusceptible organisms, including fungi, may occur and requires appropriate therapy.
Cephalosporin antibiotics in high doses should be given with caution to patients receiving aminoglycoside antibiotics or potent diuretics such as frusemide.

ADVERSE REACTIONS Hypersensitivity. Skin rashes eg. maculopapular rash or urticaria, pruritus, eosinophilia, fever and rarely other allergic reactions have been reported.

Blood. Leucopenia and granulocytopenia have been reported rarely. Some patients have developed positive direct Coombs tests during treatment with Claforan.

Liver. Increases in serum transaminases and alkaline phosphatase levels have been noted.

Local reactions. Pain, phlebitis and tenderness have been reported in approximately 4.8% of cases.

Gastrointestinal. Nausea, diarrhoea. As with other broad spectrum antibiotics colitis including rare instances of pseudomembranous colitis, has been reported with Claforan.

Kidneys. Elevations in serum creatinine and blood urea have been reported infrequently.

DOSAGE AND ADMINISTRATION Claforan should be administered only by the intramuscular or intravenous routes.
The dosage, route of administration and dosage interval will depend on the site and severity of the infection, sensitivity of the pathogens and condition of the patient.

Dosage in adults. For urinary tract infections the recommended dose is 2g daily in divided doses. For other infections the minimum recommended dosage is 2g daily in divided doses. This dosage may be increased to 3, 4 or 6g daily according to the severity of the infection, sensitivity of causative organisms and condition of patient.

For prevention of postoperative infection. In vaginal or abdominal hysterectomy: 1g should be administered intramuscularly 30 to 60 minutes before incision and repeated thereafter on completion of surgery and at 8 hourly intervals for a total duration of 24 hours.
In obstetrical surgery (Caesarian section): 1g should be administered intravenously after the cord has been clamped and thereafter at 6 and 12 hours.

For the treatment of gonorrhoea. Uncomplicated gonorrhoea due to non B lactamase producing organisms: one single intramuscular dose of 1g.
Uncomplicated gonorrhoea due to B lactamase producing organisms: one single intramuscular dose of 0.5g of Claforan plus probenecid, 1g orally, given 1 hour earlier.

Paediatric dosage. Children: The usual dosage range is 100 to 150 mg/kg/day in 3 to 4 divided doses. However in very severe infections doses of up to 200 mg/kg/day may be required.
Neonates: There is insufficient data to recommend the use of Claforan in neonates.

Mode and duration of administration. Intravenous injection: For intravenous injection the contents of one vial of Claforan 1g are dissolved in at least 4mL Water for Injection and then injected over a period of 3 to 5 minutes either into a vein or into the distal part of a clamped off infusion tube.
Intravenous infusion: For short infusion, 2 vials Claforan 1g are dissolved in 40mL Water for Injection or an infusion solution (eg. Dextrose Solution, Haemaccel, Macrodex, Rheomacrodex) and then infused over 20 to 30 minutes. For continuous intravenous infusion, 2 vials Claforan 1g are dissolved in 100mL of an isotonic saline or dextrose solution and infused over 4 hours. Sodium bicarbonate solutions must not be mixed with Claforan.
Intramuscular administration: For intramuscular injection the contents of one vial of Claforan 1g are dissolved in 4mL Water for Injection and then injected laterally deep into the gluteus muscle. It is not advisable to inject more than 4mL into either buttock. The pain of injection can be avoided by dissolving Claforan 1g in 4mL of 0.5% lignocaine solution, (see Precautions and Contraindications). Intravascular injection of this solution must be strictly avoided.
If the daily dose exceeds 2g, or if Claforan 2g is administered more than twice daily, intravenous injection is to be preferred.
In administering the 500mg dose, half the amount of any one of the solutions mentioned above may be used.
The duration of treatment depends on the patient's response. It should be continued for at least three days after normalisation of the body temperature.

Use in patients with impaired renal function. From the limited data available in this patient population the biological half-life of the desacetyl metabolite of cefotaxime increases significantly and progressively below creatinine clearance of 20mL/minute.
Furthermore, when the creatinine clearance is less than 5mL/minute the half-life of the parent compound is also increased. Because of these changes in the pharmacokinetics of the drug it is recommended that dosage adjustments should be made in patients with creatinine clearances of less than 20mL/minute in order to achieve approximately equal peak serum levels during repeated dosage.
As a guide it is suggested that the dose be reduced by half in patients with creatinine clearances less than 20mL/minute with further reductions in patients with a clearance of less than 5mL/minute.

DRUG INTERACTIONS Claforan exhibits an additive microbiological effect with gentamicin. However, because of physical incompatibility Claforan should not be mixed with an aminoglycoside antibiotic into a single preparation.
Administration of oral probenecid decreases renal clearance slightly and increases total body concentrations. (See Pharmacokinetics).

Compatibility. Claforan is compatible with the following commonly used intravenous infusion fluids which do not contain sodium bicarbonate and in which it retains satisfactory potency for up to 24 hours at 25 degrees C: Sodium Chloride Injection BP, 5% Dextrose Injection BP, Dextrose and Sodium Lactate Injection BP, Compound Sodium Lactate Injection BP (Ringer-Lactate Injection).
Claforan is also compatible with 0.5% lignocaine. Freshly prepared solutions should be used. Caution: These solutions for I.m. injections only.
Provided the recommended storage conditions are observed, there is no change in potency or safety. After the period mentioned above any unused solution should be discarded.

OVERDOSAGE No cases of Claforan overdosage have been reported. Animal evidence suggests that Claforan has a very low toxic potential. The LD50 studies in rats and mice administered Claforan intravenously have shown no mortality nor associated symptoms of intoxication up to doses of 2000 mg/kg and 716 mg/kg respectively.
Serum levels of cefotaxime may be reduced by haemodialysis.

PRESENTATION Injection, vials 500 mg, 1g, 2g: 1s.

Storage. The vial containing the powder should be stored in a cool area (below 25 degrees C) and away from heat and light. The shelf life of the powder, when stored under these conditions, is 2 years.
Reconstituted solution: 1g of Claforan reconstituted with 4mL of Water for Injection is stable for up to 24 hours under refrigeration.

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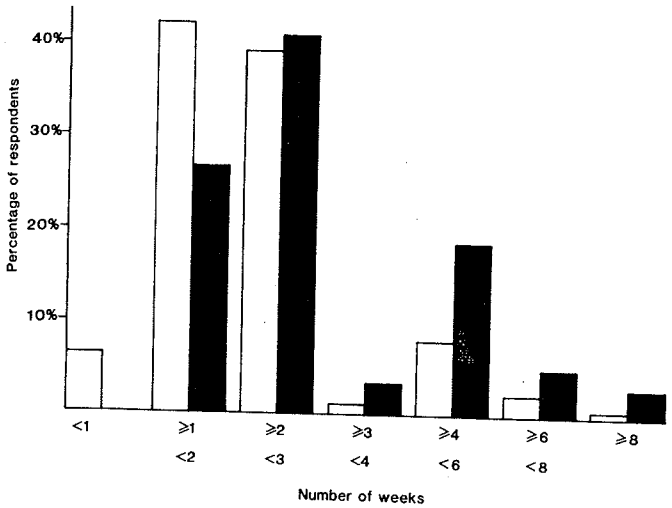

FIGURE 2: Lapsed time after the resolution of an acute attack before general practitioners (□) and rheumatologists (■) introduced urate-lowering therapy.

TABLE 3: Treatment decisions

Frequency with which respondents:	Always	Usually	Occasionally	Rarely	Never	Significance of difference
Measured 24-hour urinary urate excretion						
General practitioners	5%	8%	18%	12%	57%	$P<0.001$
Rheumatologists	6%	24%	24%	28%	19%	
Were influenced by the serum urate concentration in commencing urate-lowering drug therapy						
General practitioners	28%	46%	17%	3%	6%	$P<0.001$
Rheumatologists	6%	44%	22%	18%	10%	
"Covered" the introduction of urate-lowering drug therapy with either colchicine or a non-steroidal anti-inflammatory drug						
General practitioners	35%	24%	16%	8%	18%	$P<0.001$
Rheumatologists	85%	13%	1%	0	1%	
Initiated urate-lowering therapy for entirely asymptomatic hyperuricaemia						
General practitioners	9%	21%	25%	17%	28%	$P<0.001$
Rheumatologists	0	6%	22%	41%	31%	

Table 3). Such collections usually were made while patients were eating a normal diet and less frequently while patients were ingesting a diet that was low in purine content. In spite of the relative infrequency of the prescribing of uricosuric drugs and of the determination of the 24-hour urinary urate excretion, the utilization of uricosuric therapy was significantly greater in patients with demonstrable hypouricosuria (general practitioners, 61%; rheumatologists, 52%) or normouricosuria (general practitioners, 24%; rheumatologists, 10%) than in those with hyperuricosuria (general practitioners, 10%; rheumatologists, 5%) ($P<0.001$). Nevertheless, there was still a small (5%) percentage of doctors who prescribed uricosuric agents in the face of hyperuricosuria, while significant numbers of doctors prescribed allopurinol when hypouricosuria had been demonstrated (general practitioners, 39%; rheumatologists, 48%).

The serum urate concentration frequently influenced whether urate-lowering therapy were initiated (Table 3); general practitioners considered the serum urate level more frequently than did rheumatologists in making their decision about this ($P<0.001$). In addition, in comparison with rheumatologists, general practitioners tended to regard rather modest elevations of serum urate levels as being worthy of treatment ($P<0.001$). Given that clinicians used different biochemistry laboratories, and that variability in treatment decisions may have been a result of this rather than differences in clinical philosophy, we corrected our data accordingly.

The correction was made by dividing the lowest serum urate level concentration that was regarded by each individual respondent as necessitating urate-lowering therapy by the upper limit of the normal (reference) range for serum urate levels that was reported for that clinician's own reference laboratory (that is, a ratio of 1.39 indicated that the respondent regarded treatment as obligatory if the serum urate were at least 1.39-times greater than the upper limit of the normal reference range). When these corrected values (treatment threshold ratios) were compared, general practitioners still recommended treatment at more modestly elevated levels of serum urate (mean, 1.19; median, 1.15; mode, 1.00) than did rheumatologists (mean, 1.43; median, 1.43; mode, 1.43; $P<0.001$).

The selection and utilization of urate-lowering drugs. While the majority of general practitioners who used allopurinol prescribed a dose of 300 mg a day initially, most rheumatologists prescribed a dose of 100 mg a day ($P<0.001$). When prescribing allopurinol, more rheumatologists than general practitioners titrated the dose against the serum urate level until this became normal ($P<0.001$), but more general practitioners than rheumatologists prescribed a fixed dose of allopurinol irrespective of the reduction in the serum urate level that was achieved ($P<0.001$). Doctors in both groups advised patients to take 300-mg-a-day doses of the drug on a once-a-day schedule, while a minority of doctors recommended dividing the dose (that is, 100 mg by mouth, three times a day). However, almost one-third of prescribers divided the dosage if the total daily dose were greater than 300 mg a day. Rheumatologists were much more likely than were general practitioners to adjust the prescribed dose of allopurinol according to the serum creatinine level ($P<0.001$).

Control of potentially aggravating factors. To decrease the risk of a "flare" of gouty arthritis during the introduction of urate-lowering therapy, rheumatologists were much more likely than were general practitioners to attempt to reduce this risk by the coadministration of either colchicine or a non-steroidal anti-inflammatory drug ($P<0.001$). Of these two agents, colchicine was favoured by rheumatologists ($P<0.001$) and non-steroidal anti-inflammatory drugs were favoured by general practitioners ($P<0.001$); a minority (but particularly rheumatologists [$P<0.001$]) used a combination of both drugs. The remainder used other, often unspecified, alternative agents. Doctors regarded control of the alcohol intake and the avoidance of foods that were high in purine content, thiazide diuretic therapy and concomitant low-dose salicylate therapy as important. Rheumatologists were more likely than were general practitioners to avoid concomitant low-dose salicylate therapy ($P<0.001$) and also were more likely than were general practitioners to prescribe colchicine as an adjunctive therapy in the treatment of chronic tophaceous gout ($P<0.001$).

Asymptomatic hyperuricaemia

The final questions concerned treatment decisions regarding the management of asymptomatic hyperuricaemia (Table 3). While the majority of rheumatologists considered the treatment of entirely asymptomatic hyperuricaemia with urate-lowering agents as unnecessary, general practitioners were more likely than were rheumatologists to initiate treatment ($P<0.001$). Even when the data were corrected according to the treatment threshold ratio, the propensity to treat entirely asymptomatic hyperuricaemia appeared to increase as a function of the level of serum urate (Figure 3) (mean: general practitioners, 1.25; rheumatologists, 1.45. Median: general practitioners, 1.22; rheumatologists, 1.43. Mode: general practitioners, 1.00; rheumatologists, 1.43. $P<0.32$). Of those doctors who based their treatment decisions on the 24-hour urinary urate excretion rate (general practitioners, 14%; rheumatologists, 26%), a positive association again was noted between the propensity to treat and the level of uricosuria (Figure 3) (mean: general practitioners, 1.11; rheumatologists, 1.14. Median: general practitioners, 1.00; rheumatologists, 1.17. Mode: rheumatologists, 1.00; general practitioners, 1.00. $P<0.22$).

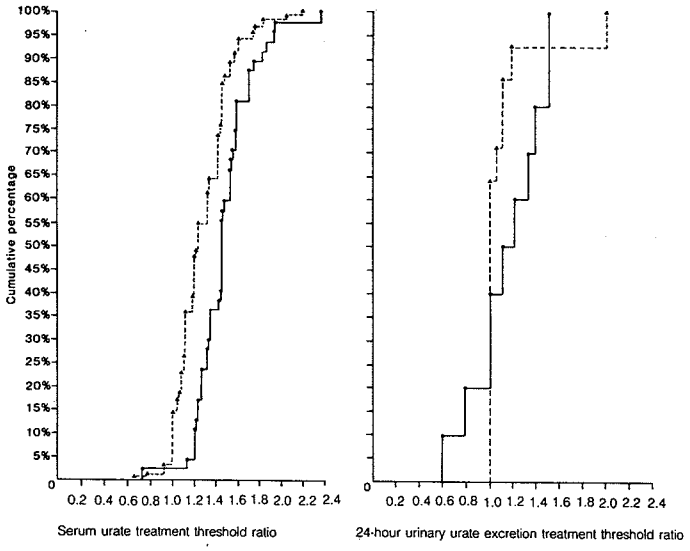

FIGURE 3: The treatment threshold ratios of serum urate levels and the 24-hour urinary urate excretion above which general practitioners (▲— — —▲) and rheumatologists (●————●) recommended treatment with urate-lowering therapy for patients with asymptomatic hyperuricaemia.

Discussion

In interpreting survey data, it should be noted that the techniques that were used examined the opinions of respondents, and made no attempt to audit prescribing practices directly, to assess accuracy in diagnosis or to assess the comparability of patients in different practices. We consider that rheumatologists are likely to see more complex cases and that any inherent bias would be likely to operate in the direction of specialists having to be more, rather than less, aggressive in their prescribing.

Response rates of around 60% generally are regarded as usual in surveys of this type, although response rates of more than 80% are preferable given the possibility of a non-response bias.[9] The 60% figure was far exceeded by rheumatologists but was approximated by general practitioners. However, a non-response bias could be operating and could distort prescribing characteristics, particularly of the general-practitioner sample. The direction and magnitude of such a bias are difficult to predict. However, as clinicians who responded to the survey were likely to be better informed than were those who did not so respond, this bias would tend to diminish the contrasts between the two groups. Thus, even with a non-response bias operating, the general pattern of results is likely to hold true. Furthermore, it is acknowledged that the year of graduation is one of the determinants of prescribing practice,[10] and as there is no statistically significant difference between respondents and non-respondents in this respect, we are confident that the survey results are generalizable.

It is not surprising that indomethacin was regarded as the treatment of choice in patients with acute gouty arthritis as most major reviews cite this as the principal agent.[3] Our observation of the rarity (3% of doctors) of the prescribing of phenylbutazone contrasts with that (33% of doctors) of Faragher and Caelli in a group general practice in Victoria.[11] We believe that there rarely is any need to use phenylbutazone given the availability of safer alternatives. In Australia, the use of phenylbutazone has been restricted to patients with acute gout or with seronegative arthropathies that have not responded to other non-steroidal anti-inflammatory drugs.

The infrequent usage of colchicine in this and Faragher and Caelli's study[11] probably is a result of the high frequency of diarrhoea during its administration.[12,13] This high risk–benefit ratio contrasts with the low risk–benefit ratio of indomethacin.

Very few general practitioners reported they would ever use intravenously administered colchicine. We recommend that all doctors who use this route of administration should be aware of the potential risks. The intravenous administration of colchicine may be associated with significant side-effects, including local tissue necrosis, median-nerve neuritis and bone-marrow suppression.[14] Fortunately, with the widening range of non-steroidal anti-inflammatory drugs and other methods to treat "resistant" acute gout, including the use of intra-articular corticosteroid therapy, there rarely is any need for intravenously administered colchicine.

We agree with respondents that it is important for patients to continue urate-lowering drugs even if acute attacks of gout occur. If these drugs are ceased during an attack of gout, their reintroduction well may precipitate further attacks.[15]

It has been noted that 7% of patients do not experience a recurrent attack of acute gout even after 10-or-more years, and that 31% of patients will not experience a recurrence for at least 12 months after the initial attack.[3] Therefore, it is surprising that 42% of general practitioners and 7% of rheumatologists commenced urate-lowering therapy as a routine after the first attack of gout. It is our opinion that a first attack of uncomplicated gout does not necessitate the introduction of urate-lowering agents.

In Faragher and Caelli's study, 67% of patients who commenced allopurinol therapy apparently received no "coverage" with either colchicine or a non-steroidal anti-inflammatory drug.[11] The investigators assumed that the prescribing doctors may not have recorded such therapy in the progress notes or felt that the incidence of acute gout during the introduction of urate-lowering therapy was a theoretical concern.[11] Our data suggest that the latter is the more plausible explanation since only 35% of general practitioners reported that they always used either form of prophylaxis.

With respect to the prescribing of allopurinol, most rheumatologists, but fewer than half the general practioners, titrated the dose against the serum urate level. The initial dose that was prescribed by general practitioners was high, given that some authorities recommend starting with a low dose in order to avoid the precipitation of an acute attack.[16] The suggestion that a fixed dose of allopurinol should be prescribed, irrespective of the reduction in serum urate level that is achieved, is of concern and clearly merits further evaluation.

Adverse reactions to allopurinol are more likely to occur in patients with renal impairment and, although it remains the preferred uricosuric agent in such patients, the dose of allopurinol should be reduced according to the serum creatinine level.[16,17] In spite of a substantial literature regarding the potential toxicity of allopurinol,[18,19] it still was preferred by the vast majority of respondents irrespective of the level of uricosuria. We believe that the opportunity to select specific agents for different patients was not exploited fully. Thus, the routine determination of the 24-hour urinary urate excretion would allow hypouricosuric and normouricosuric individuals to be considered for uricosuric therapy.

Although doctors in general appreciated the value of controlling the alcohol intake and the intake of dietary purines, and of avoiding thiazide-diuretic therapy in patients with gout, general practitioners regarded concomitant low-dose salicylate therapy as important infrequently. We suspect that the differential effects of high- and low-dose salicylate therapy on urate excretion[3] may not be appreciated generally.

It is evident from our data that a significant proportion of clinicians remains perplexed about the preferred management of asymptomatic hyperuricaemia, as 30% of general practitioners and 6% of rheumatologists always, or usually, initiated treatment with urate-lowering agents in such patients. A number of recent studies attests to the excellent prognosis of asymptomatic hyperuricaemia in the majority of patients,[6,7] and to the unnecessary mortality and morbidity which may occur with the inappropriate use of allopurinol.[18,19] We believe that treating doctors should consider both the serum urate level and the 24-hour urinary urate excretion, should identify any correctable factors of aetiological importance, and should decide what, if any, benefit may accrue (and at what risk) from the use of urate-lowering agents.

In summary, while significant variability occurs in the management of hyperuricaemic states and of gouty arthritis, with few exceptions there is a high level of compliance with traditional teaching standards among general practitioners and rheumatologists. We remain concerned regarding the premature introduction of urate-lowering drugs in patients who have suffered a single attack of acute gouty arthritis only. Finally, it is probable that entirely asymptomatic hyperuricaemic individuals continue to receive unnecessary treatment with urate-lowering compounds — an anomaly that is correctable by the broader dissemination of recent overviews regarding the preferred treatment of this common benign condition.[20]

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