REVIEW ARTICLE

Drug toxicity

H A Bird

Cost-benefit equation

No drug is without side effects, so the decision to prescribe one implies a calculated gamble on the part of the doctor or the patient, or both, that the benefits of treatment will outweigh the disadvantages. This review does not attempt to assess the benefit but concentrates on the risk side of the equation.

The concept of therapeutic risk is well recognised but is harder to define.^{1 2} The circumstances and expectations of each patient vary. Attempts have been made to explain relative risks by comparison with better understood concepts, such as the risk of lightning strike or road accident.³ The risk of death may be the easiest of all to comprehend but fails to take into account most side effects which are trivial, though can still add to the misery of disease. The associated financial and social costs, perhaps of regular monitoring by blood tests, also require consideration. In 1974 Girdwood suggested that gold salts were significantly more toxic than any other treatment available in the United Kingdom.⁴ When Rainsford catalogued the reports per year of deaths per million prescriptions⁵ antirheumatic drugs in the top 26 offenders included oxyphenbutazone, acetylsalicylic acid, phenylbutazone, and indomethacin. These figures date from before the widespread introduction of other non-steroidal anti-inflammatory drugs (NSAIDs) such as propionic acids.

Methods of assessing toxicity

Information on adverse drug reactions derives from several sources. For a new drug initial information on side effects comes from clinical trials.^{6 7} Patients participating are understandably anxious, side effects occurring commonly both in treatment and placebo groups. As confidence is gained reports become less common. Serious adverse events may not be detected at this stage and some form of post-marketing surveillance^{8 9} is required to detect less common adverse effects and rare idiosyncratic events. The Committee on Safety of Medicines (CSM) encourages manufacturers to undertake this but cannot enforce it. No single method of postmarketing surveillance is perfect and adequate control groups are essential.

The yellow card system organised by the CSM in the United Kingdom^{10 11} may offer most potential but is handicapped by a particularly low reporting rate, despite the inclusion of report-

ing forms in both FP10 prescription pads and in the *British National Formulary*. The system, which can only be controlled by comparison with other drugs, depends upon the doctor's critical and accurate attribution of an adverse event to the drug. This judgment may be influenced by advertisement or media attention.

Prescription event monitoring is organised by Professor Inman's Drug Safety Research Unit at Southampton.^{12 13} Prescriptions for drugs under scrutiny are collected from the prescription pricing authority and a green form is sent to the prescribing doctor at a fixed interval after the prescription's issue. It is hoped the doctor will recall all medical events attributable to the drug and the prescriber is not asked to make judgment on causation, which might introduce bias. Doctors' records may be incomplete, however, and prescriptions issued from hospitals are excluded. Response rates, sometimes as low as 45%, are still much higher than those for the yellow card system.

Prospective cohort studies may be best and computer drug surveillance is already commonplace in some rheumatology units.¹⁴ The expense of this has led industry to sponsor long term side effect surveillance studies for recently marketed drugs,¹⁵ but these easily overlap with concealed marketing. The monitoring of safety of 'over the counter' drugs, such as ibuprofen and paracetamol, raises additional problems,¹⁶ though most drugs in this category are either harmless or have already been subject to extensive earlier surveillance.¹⁷

Analgesics

A placebo effect may occur in up to 30% of patients receiving analgesics,^{18 19} but this may be more relevant to soft tissue rheumatism than to arthritis. Single ingredient preparations remain safer than compound analgesic preparations, even though these are popular here and in the United States.²⁰ The principal anxiety about compound preparations concerns the inequality of half life of the two component parts. Co-proxamol (paracetamol plus dextropropoxyphene in the ratio 10:1) is a particular offender,²¹ even though it is widely prescribed for the relief of arthritic pain. The occurrence of analgesic nephropathy^{22 23} may correlate more closely with the availability of phenacetin than with accumulative analgesic dose in hot climates. Opioid derivatives are unlikely to be used for the treatment of arthritis.

Non-steroidal anti-inflammatory drugs

The gastrointestinal tract, the kidney, and the skin are organs placed at particular risk with the prescription of NSAIDs. Unfortunately, it is not always easy to prove a link between drug and tissue damage.

The prevalence and mortality of peptic ulcer increases dramatically in patients over the age of 65, a group for which NSAIDs are often prescribed. Dyspepsia causes patients to discontinue their NSAIDs, but this does not always correlate with the presence of gastric mucosal damage.²⁴ Conversely, peptic ulceration may be pain free in the elderly receiving NSAIDs.²⁵ Endoscopic studies on rheumatic patients confirm that findings do not correlate with symptoms in this group²⁶ or with the presence of faecal blood loss measured by standard tests for occult blood.²⁷ Spontaneous ulcer formation and healing is seen by endoscopy in patients receiving placebo drugs,²⁶ causing difficulty in assessing the therapeutic response to drugs that are marketed for ulcer healing.

Set against this background, studies from gastroenterologists seem to show a clear association between NSAIDs and bleeding peptic ulcer,²⁸⁻²⁹ though not necessarily with perforation.³⁰ Damage may be partly disease related. Gastric ulceration occurs more commonly in patients with rheumatoid arthritis than in other arthritic patients taking NSAIDs.³¹ The controversy is fully reviewed elsewhere.³²⁻³⁴ Enteropathy mimicking Crohn's disease has recently been described as an additional complication arising from NSAIDs.³⁵

Opinions also diverge on the drugs most likely to cause damage. Gastric ulceration is conventionally associated with indomethacin treatment³⁶ and aspirin.³⁷ Piroxicam has been more recently incriminated,³⁸ but such allegations require careful analysis. CSM data from the yellow card reporting scheme do not always confirm an association with a particular drug and draw attention to errors that may easily creep into study design. Thus, if analysis is against prescriptions issued, the average script for an NSAID of long half life lasts twice as long as a script for an NSAID of shorter half life. Prescribing patterns also vary with age—use of ibuprofen being particularly common in the young whereas piroxicam is more commonly prescribed for the elderly, a group who may be at particular risk. Drugs of long half life are more often prescribed for rheumatoid arthritis. Recent CSM data overall rank azapropazone, diflunisal, flurbiprofen, and piroxicam as equal offenders ahead of sulindac and then diclofenac. For diclofenac, flurbiprofen, and piroxicam gastrointestinal adverse drug reaction reports are more common than skin reports. For azapropazone, benoxaprofen, fenclofenac, and feprazone (the last three now withdrawn in the United Kingdom) the reverse is true. Reformulation of drugs into a form that allows gradual release in the small intestine does not always spare patients endoscopic evidence of ulceration.³⁹

Interpretation of renal impairment that might be produced by NSAIDs presents similar difficulties.⁴⁰ Renal tubular disorders are found in

unselected patients with rheumatic diseases and do not obviously correlate with drug treatment.⁴¹⁻⁴² Microscopic haematuria, unrelated to drug treatment, occurs in rheumatoid arthritis,⁴³ and reversible deterioration in creatinine clearance may be associated with the introduction of an NSAID, probably because of the inhibition of prostaglandin synthetase in the kidney.⁴⁴⁻⁴⁵ The optimum method for determining renal impairment when NSAIDs are used is still unresolved. Dipsticks provide only coarse information and there are even errors inherent in the use of creatinine clearance.⁴⁶ Set against this, background drugs such as sulindac and pro-drugs such as nabumetone have been claimed to show less reversible renal change than other NSAIDs, though it has also been argued that the doses at which these drugs are prescribed may not be equivalent, implying that more renal change might be seen if the dose were increased.

Skin reactions are more commonly seen with propionic acids,⁵ and with some propionic acids these may be photosensitive, though patients with rheumatoid arthritis are susceptible to vasculitic induced skin rash and some rheumatoid patients may overlap with systemic lupus erythematosus. Photosensitivity was initially thought to be linked with the use of phenylalkanoic acid derivatives,⁴⁷ but epidemiological evidence from the CSM is less supportive of adverse events that affect particular organs being restricted to particular chemical classes of NSAIDs.

Hepatic events are occasionally caused by NSAIDs, though haematological problems are much less commonly seen since the withdrawal of phenylbutazone and its close relatives. Such rare side effects are unlikely to emerge from early clinical trials and drug companies increasingly present large data bases to the licensing authorities before product licences for their drugs are granted. For tenoxicam, an NSAID recently introduced in the United Kingdom, the worldwide data base at the time of introduction comprised 9990 patients treated with tenoxicam, 4125 of whom had participated in trials in the United Kingdom. These data were compared with 3423 patients receiving comparator drugs. A subgroup of 657 patients receiving tenoxicam was compared with 663 patients receiving piroxicam in double blind fashion. Many more trivial side effects were reported in the double blind subgroup, though these were evenly distributed between both treatments, emphasising the inherent anxiety on the part of both patient and doctor in clinical trials. Insistence on the reporting of all events occurring during treatment (rather than those thought by the doctor to be attributable to the drug) is preferable but requires the availability of adequate control groups.

Alternative formulations

Non-steroidal anti-inflammatory drugs may be reformulated as suppository or slow release (sometimes enteric coated) preparations. Delivery systems are available that release the drug in the small bowel rather than in the stomach,

though these do not always confer additional benefit³⁹ and may have additional disadvantages as in the case of 'osmosin' (now withdrawn). Opinions differ on the extent to which suppository formulation spares the gastric mucosa, a proportion of the gastric side effects being thought to be due more to circulating metabolites than to local irritative effect of the disintegrating tablet. It is possible that prepyloric ulcers, such as those which can result from indomethacin treatment, may be caused by metabolites, whereas the erosions from aspirin reflect a more local effect.

Injectable NSAIDs are popular in Europe and there has been a recent influx of topically applied NSAIDs which can be rubbed over the painful joint. Absorption through the skin is usually effective, though slow, and the speed of absorption may account for the reports of lower side effects. Adequate pharmacokinetic studies are often lacking. When performed,⁴⁸ they tend to show high absorption of the drug into the synovial fluid of joints distant to the site at which the application has been made. 'Prodrugs' have also been claimed to reduce the rate of side effects. Opinions divide on whether this represents a genuine advance or whether circulating metabolites guarantee the expected side effects when the oral dose of the pro-drug is increased to concentrations that give adequate therapeutic benefit.

Groups at particular risk

The elderly are at particular risk. Absorption, drug distribution, and elimination of drug are all altered in the elderly as an accompaniment of the normal physiological changes with aging.⁴⁹ Pharmacodynamics may be altered in subtle fashion and compliance may be reduced. Drug interaction and adverse drug reactions are all more common.⁵⁰ As musculoskeletal diseases are more common in the elderly this group of patients are at risk from excessive prescribing of NSAIDs. Where possible, a safer analgesic should be substituted, particularly in women. If this is not possible the dose of the NSAID should be reduced (often by as much as 50%) and repeat prescriptions should be reviewed regularly. Regimens should be simplified as far as possible. Special labels may be necessary for the partially sighted. Many elderly patients have impaired renal function and particular precautions are required.⁵¹ Non-steroidal anti-inflammatory drugs, particularly aspirin, may cause sodium and water retention. In patients with renal impairment there is increased risk of gastrointestinal bleeding.

Detailed review articles are available on the prescription of drugs during pregnancy^{52 53} and during lactation.⁵⁴

Disease modifying antirheumatic drugs

Comprehensive review articles already exist detailing the side effects for sodium aurothiomalate (injectable gold),⁵⁵ D-penicillamine,⁵⁶ antimalarial agents,⁵⁷ sulphasalazine,⁵⁸ methotrexate,⁵⁹ azathioprine,⁶⁰ auranofin,⁶¹ and cyclophosphamide.⁶² Less conventionally used

drugs for which disease modifying action has also been claimed include cyclosporin,⁶³ dapsone,⁶⁴ levamisole,⁶⁵ chlorambucil,⁶⁶ thymic hormones,⁶⁷ and mechanical methods of immunosuppression such as thoracic duct drainage and plasmapheresis.⁶⁸

Some of these drugs have been selected by chance, others have been the result of semi-systematic exploration. Sodium aurothiomalate is one of several gold compounds originally considered for the treatment of tuberculosis, and D-penicillamine was one of several compounds evaluated by Jaffe. Both have less toxicity than their close relations. What has been less consistent is a pharmacokinetic evaluation to ensure that these compounds are now used at optimum doses. For penicillamine and methotrexate, doses have been gradually reduced as a result of successive clinical trials. The safest dose of injectable gold is still in dispute. As these drugs have such potent side effects their use always represents a calculated risk and it is important to prescribe at the lowest possible dose compatible with clinical remission. Unfortunately, plasma drug concentrations, where they can be easily measured as in the case of sulphasalazine,^{69 70} do not always correlate with clinical efficacy or with side effects. Some drugs of potential promise, such as clobazart,⁷¹ have been withdrawn on the basis of side effects that might have been acceptable to patients who derived benefit from the drug.^{72 73} Inevitably, drug companies are cautious with the current high costs of litigation. The obvious solution is to extend the legal patent life, allowing drug companies who have developed compounds more time to accrue profits and avoiding the need for an explosive introduction. Rational drug development comprises the assessment of appropriate pharmacokinetics in animal models of arthritis that respond, followed by the extrapolation of these results to humans with the disease so that the optimum dose for the longer first therapeutic trial may be selected.

Steroid treatment

Systemic steroids are occasionally invoked as 'third line' agents for the treatment of rheumatoid arthritis, with all their attendant side effects.^{74 75} Rheumatologists are more likely to resort to intra-articular injection, though this also depresses the hypothalamic-pituitary-adrenal axis⁷⁶ and may cause local tissue necrosis if triamcinolone is inexpertly injected into joints or tendon sheaths. Steroid injections are not given often enough to mimic long term oral steroid administration, though, recently, pulsed intravenous steroids, particularly methylprednisolone, have been popular.⁷⁷ Pharmacokinetic studies^{78 79} leave little doubt that this route is similar in effect to pulsed oral steroid therapy. By implication the side effects are likely to be similar.

Prediction of those at risk

There are many reasons why patients vary in their propensity to develop drug toxicity; these have been fully reviewed for NSAIDs.⁸⁰ Demo-

graphic factors include age, sex, body weight, fat to muscle ratio, HLA status, and race. The Japanese, for example, are particularly prone to eye problems with antimalarial drugs. Pharmacokinetic variation may occur in the rates of absorption, metabolism, and excretion. Metabolic factors contributing include sulfoxidation status, acetylator status, and plasma protein availability, which determines the ratio of bound to unbound drug. There may be a diurnal variation in drug handling as well as in symptoms of disease.

Accepted predictive factors of gold toxicity include a total cumulative dose of sodium aurothiomalate greater than 150 mg a week,⁸¹ possibly the presence of HLA-B8 and DRw3 producing proteinuria^{82 83} and HLA-DRw3 producing an increased risk of skin rash and proteinuria.⁸⁴ Interestingly, certain tissue antigens appear more predictive of specific organ damage than of widespread side effects. Pre-treatment with D-penicillamine may protect against toxicity. The sulfoxidation ability of patients may be measured easily and is determined genetically. Patients developing gold toxicity are more likely to be poor sulfoxidizers,⁸⁵ renal and skin side effects being more closely related than haematological side effects.⁸⁶ A diurnal variation in gold excretion has been claimed⁸⁷ and concentrations of free gold may correlate better than total gold in the prediction of side effects.⁸⁸

For D-penicillamine no correlation has been found between side effects or plasma concentrations of the drug, though there is a marked variation in pharmacokinetic indices among patients.^{89 90} Allergic reactions to previous penicillin treatment do not predict toxicity,⁹¹ though HLA-B8 and HLA-DRw3 may be associated with proteinuria⁹² and poor sulfoxidation status may also contribute.⁹³ Penicillamine toxicity may be enhanced after previous gold toxicity, particularly for proteinuria and marrow depression, though there appears to be no cross sensitivity for the skin rash.⁹⁴

Patients withdrawing from sulphasalazine treatment because of nausea are likely to have a higher peak concentration of drug and greater area under the curve after a single dose.⁷⁰ Slow acetylation is associated with high concentrations of sulphapyridine, correlating significantly with nausea but not with other side effects.⁹⁵

For methotrexate no particular clinical or genetic variable that might predict drug toxicity has emerged,⁹⁶ though HLA-DR1 and HLA-DR7 were significantly associated with raised liver enzymes in an Israeli population.⁹⁷ For cyclosporin concomitant administration of NSAIDs has been incriminated in renal toxicity.⁹⁸ Drug interactions clearly deserve more attention.

Drug interactions

Buckingham's two 1978 articles in the *Bulletin on the Rheumatic Diseases*, on interactions involving antirheumatic agents, published by the American Arthritis Foundation have dated little so still provide a comprehensive review.^{99 100} The *British National Formulary* provides more

condensed information and is widely available.¹⁰¹ A recent review article from Tomkin and Wing¹⁰² provides a most comprehensive theoretical update, particularly for NSAIDs. Conventional areas of concern include the interaction of NSAIDs with anticoagulants and oral antidiabetic agents, their enhancement by concomitant administration of probenecid,¹⁰³ and their interaction with diuretics and antihypertensive agents. This review concentrates on selected aspects only.

Interactions may be pharmacodynamic (when two drugs compete at the same receptor for effect) or pharmacokinetic. Pharmacokinetic interactions are more common in rheumatological practice and may occur at the site of absorption, at the level of protein binding, during metabolism, or at excretion. Analgesics may be prescribed with analgesics, often in compound fixed dose preparations. The dangers are described above, but no pharmacokinetic interactions occur. In general, no interactions occur if an analgesic is prescribed 'for pain' with an NSAID 'for stiffness'.¹⁰⁴ The evidence for interactions between NSAIDs prescribed simultaneously is more confusing. In animal models synergism or antagonism may occur according to whether the drugs are given together, before or after the induction of arthritis.¹⁰⁵ Pharmacokinetic studies in which NSAIDs are added to each other in human volunteers have shown a large number of interactions. Highly acidic drugs such as acetylsalicylic acid (aspirin) are likely to reduce circulating drug concentrations of less acidic NSAIDs. Whether this has clinical relevance is doubtful.¹⁰⁶ In arthritic patients, although a reduction in ibuprofen concentrations when aspirin is added has been confirmed, the two drugs still appear to have weakly additive clinical effect provided the dose exceeds 1600 mg a day for ibuprofen and 3600 mg a day for aspirin. There are, however, variations among patients and many factors may come into play.⁸⁰ Interaction or not, on clinical grounds it seems inappropriate to prescribe two NSAIDs simultaneously, particularly now that so many are available in suppository formulation, the commonest previous reason for prescription of one NSAID, usually indomethacin, with another.

The theoretical risk of altered absorption or altered excretion when strongly acidic or alkaline drugs are given simultaneously with NSAIDs seems to produce little practical clinical effect and the anxiety about protein displacement with oral antidiabetic drugs may be exaggerated, though it is prudent to be more cautious when prescribing NSAIDs and simultaneous anticoagulants.

The interaction between diuretics and NSAIDs is felt to affect prostaglandin synthesis in the kidney.^{107 108} The interaction with β blockers may also necessitate care in the control of hypertension when an NSAID is introduced.¹⁰⁹ Non-steroidal anti-inflammatory drugs given with potassium sparing diuretics present particular problems,¹¹⁰ and there is evidence that sulindac may have less adverse effect on renal haemodynamics than other NSAIDs.^{111 112} If the kidneys are unstressed there seems to be little evidence for a deleterious

effect of an NSAID on baseline renal function, particularly in low dose.¹¹³

Among disease modifying antirheumatic drugs, the absorption of D-penicillamine may be reduced by 30% with concomitant administration of iron tablets or vegetables rich in iron. In practice, the theoretical interaction between salicylates and methotrexate has proved unimportant, probably because methotrexate is given in such small doses to patients with rheumatic diseases.¹¹⁴ There is an increasing trend towards giving disease modifying antirheumatic drugs in parallel or in combination in the hope of obtaining greater clinical benefit. Controlled studies have been on small numbers of patients and at this stage it is too early to determine whether such drug combinations produce pharmacodynamic interactions, though this may be likely for disease modifying antirheumatic drugs of related chemical structure.

- 1 Hawkins C, Nuki G. Gout and rheumatoid arthritis. In: Burley D, Inman W H W, eds. *Therapeutic risk: perception, measurement management*. New York: Wiley, 1988: 67-72.
- 2 Price T. Costs versus benefit: a treatment audit. In: Goddard G, Butler R, eds. *Rheumatoid arthritis: the treatment controversy*. London and Basingstoke: Macmillan, 1984: 131-49.
- 3 Pullar T, Feely M, Wright V. Patients and doctors perception of 'acceptable' risk with anti-rheumatic treatment [Abstract]. *Br J Rheumatol* 1988; 27 (suppl 2): 112.
- 4 Girdwood R H. Death after taking medications. *Br Med J* 1974; i: 501-4.
- 5 Rainsford K D. Side-effects of anti-inflammatory/analgesic and anti-rheumatic drugs. In: Williamson W R N, ed. *Anti-inflammatory compounds*. New York and Basle: Marcel Dekker, 1987: 359-407.
- 6 Hampton J R, Jullian D G. Role of the pharmaceutical industry in major clinical trials. *Lancet* 1987; ii: 1258-9.
- 7 Smith R N. Role of the pharmaceutical industry in major clinical trials. *Lancet* 1987; ii: 1464.
- 8 Griffin J P. Post marketing surveillance of licence, medicinal and other products. *Health Trends* 1981; 13: 85-8.
- 9 Rawlins M D. Post marketing surveillance of adverse reactions to drugs. *Br Med J* 1984; 288: 879-80.
- 10 CSM update. Annual review of yellow cards—1985. *Br Med J* 1986; 293: 688.
- 11 Bem J L, Breckenridge A M, Mann R D, Rawlins M D. Review of yellow card (1986): report to the Committee on Safety of Medicines. *Br J Clin Pharmacol* 1988; 26: 679-89.
- 12 Inman W H W, Rawson N S B, Wilton L V. Prescription event monitoring. In: Inman W H W, ed. *Monitoring for drug safety*. 2nd ed. Lancaster: MTP Press, 1986: 213-35.
- 13 Inman W H W, Rawson N S B, Wilton L V, Pearce G L, Speirs C J. Post marketing surveillance of enalapril 1: Results of subscription event monitoring. *Br Med J* 1988; 297: 826-9.
- 14 Davis M J, Dawes P T, Shadforth M F. Three years experience of a computer based drug surveillance system [Abstract]. *Br J Rheumatol* 1988; 27 (suppl 2): 193.
- 15 Anonymous. Post marketing surveillance—How should doctors get involved? [Editorial]. *Drug Ther Bull* 1988; 26: 89-91.
- 16 Volans G N. Monitoring the safety of over the counter drugs. *Br Med J* 1987; 295: 797-8.
- 17 Rawlins M D. Spontaneous reporting of adverse drug reactions 1: the data. *Br J Clin Pharmacol* 1988; 26: 1-5.
- 18 Beecher H K. The powerful placebo. *JAMA* 1955; 159: 1602-6.
- 19 Levine J D, Gordon N C, Fields H L. The mechanism of placebo analgesia. *Lancet* 1978; ii: 654-7.
- 20 Beaver W T. Combination analgesics. *Am J Med* 1984; 77: 38-53.
- 21 Anonymous. Distalgesic: Safe and effective? [Editorial]. *Lancet* 1984; ii: 616.
- 22 Cove-Smith J R, Knapp M S. Analgesic nephropathy: an important cause of chronic renal failure. *Q J Med* 1978; 47: 49-69.
- 23 Kincaid-Smith P. Analgesic nephropathy. *Br Med J* 1981; 282: 1790.
- 24 Semble E L, Wu W C. Anti-inflammatory drugs and gastric mucosal damage. *Semin Arthritis Rheum* 1987; 16: 271-86.
- 25 Scander N P, Ryan F P. Non-steroidal anti-inflammatory drugs and pain free peptic ulceration in the elderly. *Br Med J* 1988; 297: 833-4.
- 26 Collins A J, Davis J, Dixon A St J. Contrasting presentation and findings between patients with rheumatic complaints taking non-steroidal anti-inflammatory drugs in the general population referred for endoscopy. *Br J Rheumatol* 1986; 25: 50-3.
- 27 Collins A J, Du Toit J A. Upper gastrointestinal findings and faecal occult blood in patients with rheumatic diseases taking non-steroidal anti-inflammatory drugs. *Br J Rheumatol* 1987; 26: 295-8.
- 28 Summerville K, Falconer G, Langman M. Non-steroidal anti-inflammatory drugs and bleeding peptic ulcers. *Lancet* 1986; ii: 462-4.
- 29 Clinch D, Banerjee A K, Levy D W, Ostick G, Faragher E B. Non-steroidal anti-inflammatory drugs and peptic ulceration. *J R Coll Physicians Lond* 1987; 21: 183-7.
- 30 Collier D St J, Pain J A. Non-steroidal anti-inflammatory drugs and peptic ulcer perforation. *Gut* 1985; 26: 359-63.
- 31 Jick S S, Perera D R, Walker A M, Jick H. Non-steroidal anti-inflammatory drugs and hospital admission for perforated peptic ulcer. *Lancet* 1987; ii: 380-2.
- 32 Farah D, Sturrock R D, Russell R I. Peptic ulcer and rheumatoid arthritis. *Ann Rheum Dis* 1988; 47: 478-80.
- 33 Summerville K W, Hawkie C J. Non-steroidal anti-inflammatory agents and the gastrointestinal tract. *Postgrad Med J* 1986; 62: 23-8.
- 34 Docherty M, Hunt R H, Langman M J S, et al. Management of NSAID induced gastrointestinal disturbance. *Ann Rheum Dis* 1987; 46: 640-3.
- 35 Banerjee A K. Enteropathy induced by non-steroidal anti-inflammatory drugs. *Br Med J* 1989; 298: 1539-40.
- 36 Taylor R T, Huskisson E C, Whitehouse G H, Dudley-Hart F, Trapnol D H. Gastric ulceration occurring during indomethacin therapy. *Br Med J* 1968; ii: 734-7.
- 37 Loebl D H, Craig R M, Culic D, Ridolfoas-Falk J, Schmid F R. Gastrointestinal blood loss. Effect of aspirin, fenoprofen and acetaminophen in rheumatoid arthritis as determined by sequential gastroscopy and radioactive fecal markers. *JAMA* 1977; 237: 976-81.
- 38 Bortenichak E A, Gordon A J, Stevens E A. Ulcerogenicity of piroxicam: an analysis of spontaneously reported data. *Br Med J* 1987; 294: 1289.
- 39 Collins A J, Davis J, Dixon A St J. A prospective endoscopic study of the effect of orudis and oruval on the upper gastrointestinal tract in patients with osteoarthritis. *Br J Rheumatol* 1988; 27: 106-9.
- 40 Bird H A. The kidney in rheumatic diseases. *Ann Rheum Dis* 1989; 48: 1029-30.
- 41 Bird H A, Yu H, Cooper E H. Renal proximal tubular dysfunction in patients with rheumatic diseases. *Br Med J* 1984; 288: 1044-5.
- 42 Hordon L D, Bird H A, Cooper E H. Renal tubular dysfunction in rheumatic diseases [Abstract]. *Br J Rheumatol* 1989; 28 (suppl 1): 14.
- 43 Kelly C A, Mooney P, Hordon L D, Griffiths I D. Haematuria in rheumatoid arthritis—a follow up study [Abstract]. *Br J Rheumatol* 1988; 27 (suppl 1): 40.
- 44 Unsworth J, Sturman S, Lunec J, Blake D R. Renal impairment associated with non-steroidal anti-inflammatory drugs. *Ann Rheum Dis* 1987; 46: 233-6.
- 45 Dixon J S, Bojar R, Bird H A. Renal impairment in relation to non-steroidal anti-inflammatory drugs. *Ann Rheum Dis* 1988; 47: 260-4.
- 46 Gabriel R. Time to scap creatinine clearance? *Br Med J* 1986; 293: 1119-20.
- 47 Bird H A, Wright V. Analgesics and non-steroidal anti-inflammatory drugs. In: Bird H A, Wright V, eds. *Applied drug therapy of the rheumatic diseases*. Vol 4. Bristol, London, Boston: Wright, 1982: 62-88.
- 48 Dawson M, McGee C M, Vine J H, Nash P, Watson T R, Brooks P M. The disposition of biphenylacetic acid following topical application. *Eur J Clin Pharmacol* 1988; 33: 639-42.
- 49 Swift C G, Triggs E J. Clinical pharmacokinetics in the elderly. In: Swift C G, ed. *Clinical pharmacology in the elderly*. New York and Basle: Marcel Dekker, 1987: 31-82.
- 50 Divoll M K, Greenblatt D J. Drug interactions and adverse drug reactions in the elderly. In: Swift C G, ed. *Clinical pharmacology in the elderly*. Vol 5. New York and Basle: Marcel Dekker, 1987: 119-48.
- 51 *British National Formulary*. No 17. London: British Medical Association and the Pharmaceutical Society of Great Britain, 1989: 14-26.
- 52 Needs C J, Brooks P M. Anti-rheumatic medication in pregnancy. *Br J Rheumatol* 1985; 24: 282-90.
- 53 Brooks P M. Related drug treatment problems during pregnancy and the puerperium. In: Scott J S, Bird H A, eds. *Pregnancy, auto-immunity and connective tissue disorders*. Oxford: Oxford University Press, (in press).
- 54 Needs C J, Brooks P M. Anti-rheumatic medication during lactation. *Br J Rheumatol* 1985; 24: 291-7.
- 55 Adachi J D, Bensen W G, Kassam Y, et al. Gold induced thrombocytopenia: 12 cases and a review of the literature. *Semin Arthritis Rheum* 1987; 16: 287-93.
- 56 Lyle W H. Penicillamine. In: Huskisson E C, ed. *Anti-rheumatic drugs*. Eastbourne and New York: Praeger, 1983: 521-54.
- 57 Easterbrook M. Occular effects and safety of anti-malarial agents. *Am J Med* 1988; 85 (suppl 4A): 23-9.
- 58 Watkinson G. Sulphasalazine, a review of 40 years experience. In: *Drugs*. Vol 32, suppl 1. Auckland: Addis Press, 1986: 1-11.
- 59 Furst D E, Kramer J M. Methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1988; 31: 305-14.
- 60 Huskisson E C. Azathioprine. In: Huskisson E C, ed. *Anti-rheumatic drugs*. Eastbourne and New York: Praeger, 1983: 597-604.
- 61 Blodgett R C, Heuer M A, Piedrusko R G. Auranofin: a unique oral chrysotherapeutic agent. *Semin Arthritis Rheum* 1984; 13: 255-73.

- 62 Clements C J. Cytotoxic immunosuppressive drugs. In: Paulus H E, Furst E D, Dromgool S A, eds. *Drugs for rheumatic diseases*. New York: Churchill Livingstone, 1987: 135-56.
- 63 Dougados M, Duchesne L, Awada H, Amor B. Assessment of efficacy and acceptability of low dose cyclosporin in patients with rheumatoid arthritis. *Ann Rheum Dis* 1989; 48: 550-6.
- 64 Grindulis K A, McConkey B. Outcome of attempts to treat rheumatoid arthritis with gold, penicillamine, sulphasalazine or dapsone. *Ann Rheum Dis* 1984; 43: 398-401.
- 65 Symoens J, Schuermans Y. Levamisol. In: Huskisson E C, ed. *Anti-rheumatic drugs*. Vol 28. Eastbourne and New York: Praeger, 1983: 569-96.
- 66 Amor B, Mery C. Chlorambucil in rheumatoid arthritis. In: Huskisson E C, ed. *Anti-rheumatic drugs*. Eastbourne and New York: Praeger, 1983: 605-22.
- 67 Hirschberg J, Paulus H E. Immunomodulators and other disease modifying anti-rheumatic drugs. In: Paulus H E, Furst E D, Dromgool S A, eds. *Drugs for rheumatic diseases*. New York: Churchill Livingstone, 1987: 177-202.
- 68 Garrett R, Paulus H E. Non-cytotoxic modification of immune mechanism. In: Paulus H E, Furst E D, Dromgool S A, eds. *Drugs for rheumatic diseases*. New York: Churchill Livingstone, 1987: 157-76.
- 69 Taggart A J, McDermott B, Delargy M, et al. The pharmacokinetics of sulphasalazine in young and elderly patients with rheumatoid arthritis. *Scand J Rheumatol [Suppl]* 1987; 64: 29-36.
- 70 Pullar T, Capell H A. Variables affecting efficacy and toxicity of sulphasalazine in rheumatoid arthritis: a review. In: *Drugs*. Vol 32, suppl 1. Auckland: Addis Press, 1986: 54-7.
- 71 Bird H A, Dixon J S, Finney P L, Leatham P A, et al. A clinical and biochemical evaluation of Clozic, a novel disease modifying drug in rheumatoid arthritis. *Clin Exp Rheumatol* 1983; 1: 93-9.
- 72 Bird H A. Rheumatology in the pharmaceutical industry. *J Rheumatol* 1983; 10: 663-9.
- 73 Mills J A. Rheumatology in the pharmaceutical industry. *J Rheumatol* 1983; 10: 531-2.
- 74 Miles A B, Daley J R. *Cortico-steroid and ACTH treatment: principles and problems*. London: Arnold, 1974.
- 75 Azarnoff D. *Steroid therapy*. Philadelphia and London: Saunders, 1975: 1-340.
- 76 Bird H A, Ring E F J, Bacon P A. Thermographic and clinical comparison of long-acting intra-articular steroid preparations in rheumatoid arthritis. *Ann Rheum Dis* 1979; 38: 36-9.
- 77 Shipley M E, Bacon P A, Bury H, et al. Pulse methylprednisolone in active early rheumatoid disease: a dose ranging study. *Br J Rheumatol* 1988; 27: 211-4.
- 78 Smith M D, Ahern M J, Roberts-Thomson P J. Pulse steroid therapy in rheumatoid arthritis: Can equivalent doses of oral prednisolone give similar clinical results to intravenous methylprednisolone? *Ann Rheum Dis* 1988; 47: 28-33.
- 79 Al-habet S M, Rogers H J. Methylprednisolone pharmacokinetics after intravenous and oral administration. *Br J Clin Pharmacol* 1989; 27: 285-90.
- 80 Day R O, Brooks P M. Variations in response to non-steroidal anti-inflammatory drugs. *Br J Clin Pharmacol* 1987; 23: 655-8.
- 81 Furst D, Levine S, Srinivasan R, et al. A double blind trial of high versus conventional dosage of gold salts for rheumatoid arthritis. *Arthritis Rheum* 1977; 20: 1473-6.
- 82 Wooley P H, Griffin J, Panayi G S, et al. HLA-DR antigens and toxic reaction to sodium aurothiomate and D-penicillamine in patients with rheumatoid arthritis. *N Engl J Med* 1980; 303: 300-2.
- 83 Stastny P. Rheumatoid arthritis: relationship with HLA-D. *Am J Med* 1983; 75: 9-15.
- 84 Perrier P, Raffoux C, Thomas Ph, et al. HLA antigens and toxic reactions to sodium aurothiopropanol sulphate and D-penicillamine in patients with rheumatoid arthritis. *Ann Rheum Dis* 1985; 44: 621-4.
- 85 Madhock R, Capell H A, Waring R. Does sulphoxidation state predict gold toxicity in rheumatoid arthritis. *Br Med J* 1987; 294: 483.
- 86 Ayeshe R, Mitchell S C, Waring R H, et al. Sodium aurothiomate toxicity and sulphoxidation capacity in rheumatoid arthritis patients. *Br J Rheumatol* 1987; 26: 197-201.
- 87 Heath M J, Swannell A J, Williams C R, Palmer T. Patterns of urinary excretion of gold in patients with rheumatoid arthritis undergoing chrysotherapy. *Ann Rheum Dis* 1987; 46: 823-36.
- 88 Heath M J. Measurement of 'free' gold in patients receiving disodium aurothiomate and the association of high free to total gold levels with toxicity. *Ann Rheum Dis* 1988; 47: 18-21.
- 89 Brooks P M, Miners J O, Smith K, et al. Dose, plasma concentration and response relationships of D-penicillamine in patients with rheumatoid arthritis. *J Rheumatol* 1984; 11: 772.
- 90 Muijsers A O, Stadt R J van de, Henrichs A M A, et al. D-penicillamine in patients with rheumatoid arthritis: serum levels, pharmacokinetic aspects and correlation with clinical course and side-effects. *Arthritis Rheum* 1984; 27: 1362-9.
- 91 Bell C L, Graziano F M. The safety of administration of penicillamine to penicillin-sensitive individuals. *Arthritis Rheum* 1983; 26: 801-3.
- 92 Panayi G S, Griffen A J, Wooley P H, Gibson G J, Batchelor J R. Benefit and predisposition to gold and D-penicillamine toxicity. *Arthritis Rheum* 1979; 22: 645.
- 93 Panayi G S, Huston G, Shah R R, et al. Deficient sulphoxidation status and D-penicillamine toxicity. *Lancet* 1983; i: 414.
- 94 Smith P J, Swinburn W R, Swinson D R, Stewart I M. Influence of previous gold toxicity on subsequent development of penicillamine toxicity. *Br Med J* 1982; 285: 595-6.
- 95 Pullar T, Hunter J A, Capell H A. Effect of acetylator phenotype on efficacy and toxicity of sulphasalazine in rheumatoid arthritis. *Ann Rheum Dis* 1985; 44: 831-7.
- 96 Gispén J G, Alarcon G S, Johnson J J, Acton R T, Barger B O, Koopman W J. Toxicity to methotrexate in rheumatoid arthritis. *J Rheumatol* 1987; 14: 74-9.
- 97 Tishler M, Caspi D, Roxenbach T O, et al. Methotrexate in rheumatoid arthritis: a prospective study in Israeli patients with immunogenic correlations. *Ann Rheum Dis* 1988; 47: 654-9.
- 98 Van Rijthoven A W A M, Dijkman B A C, Goei The H S, et al. Cyclosporin treatment for rheumatoid arthritis: a placebo controlled, double blind, multicentre study. *Ann Rheum Dis* 1986; 45: 726-31.
- 99 Buckingham R B. Interactions involving anti-rheumatic agents. Part I. Atlanta, Georgia, Arthritis Foundation. *Bull Rheum Dis* 1977/78; 28: 960-5.
- 100 Buckingham R B. Interactions involving anti-rheumatic agents. Part II. Atlanta, Georgia, Arthritis Foundation. *Bull Rheum Dis* 1977/78; 28: 966-71.
- 101 Drug interactions. In: *British National Formulary*. No 17. London: British Medical Association and the Pharmaceutical Society of Great Britain, 1989: 440-52.
- 102 Tomkin A L, Wing L M H. Interactions of non-steroidal anti-inflammatory drugs. In: Brooks P M, ed. *Ballière's Clinical Rheumatology*. Vol 2, *Anti-rheumatic drugs*. London: Ballière Tindall, 1988: 455-83.
- 103 Skeith M D, Simkin P A, Healey L A. The renal excretion of indomethacin and its inhibition by probenecid. *Clin Pharmacol Ther* 1968; 9: 89-93.
- 104 Hemming J D, Bird H A, Pickup M E, Saunders A, Lowe J R, Dixon J S. Bioavailability of aspirin in the presence of dextropropoxyphene/paracetamol combination. *Pharmatherapeutica* 1981; 2: 543-6.
- 105 Kaiser D G. Interaction of ibuprofen with aspirin. *Research Communications in Chemical Pathology and Pharmacology* 1974; 9: 583.
- 106 Grennan D M, Ferry D G, Ashworth M E, Kenny R E, Mackinnon M. The aspirin-ibuprofen interaction in rheumatoid arthritis. *Br J Clin Pharmacol* 1979; 8: 497-503.
- 107 Favrel Glasson P, Riondel A, Vallotton M B. Interaction of diuretics and non-steroidal anti-inflammatory drugs in man. *Clin Sci* 1983; 64: 407-15.
- 108 Koopmans P P, Thien T, Gribnau F W J. Influence of non-steroidal anti-inflammatory drugs on diuretic treatment of mild to moderate essential hypertension. *Br Med J* 1984; 289: 1492-4.
- 109 Wong D G, Spence J D, Lamki L, Freeman D, MacDonald J W D. Effect of non-steroidal anti-inflammatory drugs on control of hypertension by beta blockers and diuretics. *Lancet* 1986; i: 997-1001.
- 110 Bailey R R. Adverse renal reactions to non-steroidal anti-inflammatory drugs and potassium sparing diuretics. *Adverse Drug Reaction Bulletin* 1988; 131: 492-5.
- 111 Swainson C P, Griffiths P. Acute and chronic effects of sulindac on renal function in chronic renal disease. *Clin Pharmacol Ther* 1985; 37: 298-300.
- 112 Swainson C P, Griffiths P, Watson M L. Chronic effects of oral sulindac on renal haemodynamics and hormones in subjects with chronic renal disease. *Clin Sci* 1986; 70: 243-7.
- 113 Passmore A P, Copeland S, Johnstone G D. A comparison of the effects of ibuprofen and indomethacin upon renal haemodynamics and electrolyte excretion in the presence and absence of frusemide. *Br J Clin Pharmacol* 1989; 27: 483-90.
- 114 Gispén J G, Alarcon G S, Johnson J J, et al. Toxicity to methotrexate in rheumatoid arthritis. *J Rheumatol* 1987; 14: 74-9.