NOW AND THEN

Drugs and the elderly

H A Bird

Rheumatologists unhesitatingly prescribe drugs for their patients, who are often elderly, living as we do in an era blessed with increasing longevity. Prudent prescribers will follow the cautionary guidelines on reduced dosing in the elderly offered in a variety of national formularies and textbooks. Fewer doctors will understand pharmacokinetics and pharmacodynamics, terms that may seem as indigestible as the topics themselves.

'Pharmacokinetics' is a mathematical analysis of the time course of a drug's concentration in the body, including the contributing factors of absorption, distribution, metabolism, and excretion. 'Pharmacodynamics' refers to the effect of a given concentration of a drug at its site of action. Both change with aging, the latter clearly being of more functional interest. Unfortunately, the plethora of pharmacokinetic studies in the elderly compared with the paucity of pharmacodynamic studies reflects the practical difficulties in executing them.¹

Most drugs are absorbed by passive diffusion across the gut wall. In general, absorption is unaffected in the elderly.² Drug distribution in the elderly may be reduced by changes in protein binding,³ red cell binding,⁴ body composition,⁵ and tissue permeability.⁶ As old people shrink their proportion of fat to muscle and water increases, reducing the distribution of volume for polar drugs such as digoxin,⁷ but increasing it for fat soluble drugs such as diazepam.⁸ If the volume of distribution for a drug is reduced, peak plasma concentrations will increase. Plasma albumin concentration also falls with age, permitting the unbound fraction of some drugs to increase, further enhancing their volume of distribution.

Most drugs are eliminated by a first order process, so that the concentration of drug falls exponentially. The plasma half life (the time taken for the concentration to halve) is directly proportional to the amount of drug in the body available for elimination (volume of distribution) and inversely related to the clearance of the drug, by all routes. Even if clearance remains normal the change in distribution can thus alter the rate of removal, a factor that mainly accounts for the prolonged half life of diazepam in the elderly.⁹

The accepted fall in glomerular filtration rate to 50% by the ninth decade implies only a twofold increase in drug plasma concentrations, so increased renal clearance is only clinically significant for drugs with a narrow therapeutic index that are mainly excreted by the kidney—for example, digoxin. Additional renal impairment, either due to disease or to previous drug treatment, may additionally have occurred in patients with rheumatic diseases.¹⁰

In the 1982 calamity of benoxaprofen (half life 25-35 hours), the drug, first introduced in 1980, was withdrawn from the market after reports of

hepatic and renal dysfunction together with deaths in elderly patients following its use.¹¹⁻¹³ This has led to more precise guidelines from the registration authorities on the need for new drugs to be evaluated in the elderly populations for which they will be prescribed rather than merely in young student volunteers. All non-steroidal anti-inflammatory drugs (NSAIDs), particularly those with prolonged half lives, should be used with caution in the elderly. That point made, it should also be stressed that many of the patients developing serious side effects with benoxaprofen probably had pre-existing liver or kidney disease before taking the drug.

For piroxicam, a commonly prescribed NSAID with an even longer half life, the evidence, though conflicting, is not exactly alarming. The half life and systemic metabolic clearance of the drug in patients older than 65 years is similar to that in younger patients even though the apparent volume of distribution increases with age.¹⁴ The drug has not been found to accumulate in the aged and as renal function plays only a small part in piroxicam elimination the effect of age related reduced creatinine clearance is small.^{15 16} Contrasting with these studies, Richardson *et al* studying single dose piroxicam kinetics in the young and elderly found the piroxicam body clearance in elderly women to be about 33% lower than in young women, the difference reflected by the significantly different half lives of 61.7 and 44.9 hours respectively.¹⁷ Interindividual variation was high, supporting the hypothesis that the elderly are a heterogeneous group, some aging prematurely in physiological terms whereas others seem to 'retain their youth'.

The interpretation of possible drug related side effects in the elderly is also made more difficult by the variation that can occur in the normal ranges of laboratory variables, particularly of leucocyte count, albumin, globulin, urea, creatinine, alkaline phosphate, and calcium. Moreover, fluctuation, sometimes diurnal, can occur in these when they are measured in patients with active rheumatoid arthritis. Both hepatic produced alkaline phosphatase and γ -glutamyltransferase as well as platelets and haemoglobin all act as indices of disease activity, sometimes tempting unwary investigators to attribute disease related changes to the drugs being evaluated.

An exciting but hitherto almost completely unexplored area is the extent, if any, to which the disease itself might influence drug metabolism. Genetic influences are already well established,¹⁸ though probably affect drug metabolism less than acquired factors such as smoking.¹⁹ The number of human pharmacogenetic differences that have been described in the last 30 years is substantial and expanding. Most phase I metabolic oxidations are performed by the cytochrome P-450 system in

the liver. There is no great evidence to suggest a genetic linkage to susceptibility for rheumatic diseases such as ankylosing spondylitis or rheumatoid arthritis, but increasing evidence is accumulating that such oxidative systems can be influenced by interleukins, the concentrations of which may certainly fluctuate in chronic inflammatory polyarthritis.^{20 21} Whether the rate of drug metabolism is thereby altered with disease activity, whether the magnitude of this effect if present has clinical relevance, and whether this is accentuated or reduced in the elderly are all fundamental questions now requiring resolution.

Set against this extremely complex background, the 11th Harrogate annual day conference in the series 'Growing points in the treatment of rheumatic diseases' was devoted to the theme of 'Antirheumatic drugs in the elderly'. Although it has only proved possible to touch the tip of the iceberg, the ensuing conference report follows.

- 1 Crooks J. Aging and drug distribution: pharmacodynamics. *J Chronic Dis* 1983; 36: 85-90.
- 2 Stevenson I H, Salem S A M, Shepherd A M M. Studies on drug absorption and metabolism in the elderly. In: Crooks J, Stevenson I H, eds. *Drugs and the elderly*. Vol 6. London: Macmillan, 1979: 51-63.
- 3 Tozer T N. Concepts basic to pharmacokinetics. *Pharmacol Ther* 1981; 12: 109-31.
- 4 Nation R L, Vine J, Triggs E J, Learoyd B. Plasma levels of chlormethiazole and two metabolites after oral administration to young and aged human beings. *Eur J Clin Pharmacol* 1977; 12: 137-46.
- 5 Vestal R E. Drug use in the elderly: a review of problems and special considerations. *Drugs* 1978; 16: 358-82.
- 6 Bender A D. Age and its influence on drug action in adults. *Drug Information Bulletin* 1969; 3: 153-8.
- 7 Ewy G A, Kapadia G G, Yao L, Luillin M, Marcus F I. Digoxin metabolism in the elderly. *Circulation* 1969; 39: 449-53.
- 8 Macklon A F, Barton M, James O, Rawlins M D. The effect of age on the pharmacokinetics of diazepam. *Clin Sci* 1980; 59: 479-83.
- 9 Klotz U, Avant G R, Hoyumpa A, Schenker S, Wilkinson G R. The effects of age and liver disease on the disposition and elimination of diazepam in adult man. *J Clin Invest* 1975; 55: 347-59.
- 10 Bird H A. The kidney in rheumatic diseases. *Ann Rheum Dis* 1989; 48: 1029-30.
- 11 Prescott L F, Leslie P J, Padfield P. Side effects of benoxaprofen. *Br Med J* 1982; 284: 1783.
- 12 Shedden W I H. Side effects of benoxaprofen. *Br Med J* 1982; 284: 1630.
- 13 Taggart H M, Alderdice J M. Fatal cholestatic jaundice in elderly patients taking benoxaprofen. *Br Med J* 1982; 284: 1372.
- 14 Woolf A D, Rogers H J, Bradook I D, Corless D. Pharmacokinetic observations on piroxicam in young adults, middle aged and elderly patients. *Br J Clin Pharmacol* 1983; 16: 433-7.
- 15 Bollet A J. Piroxicam serum levels in patients treated for rheumatic diseases. *Semin Arthritis Rheum* 1985; 14 (suppl 1): 25-8.
- 16 Darrugh A, Gordon A J, Byrne H O, Hobbs D, Casey E. Single-dose and steady-state pharmacokinetics of piroxicam in elderly versus young adults. *Eur J Clin Pharmacol* 1985; 28: 305-9.
- 17 Richardson C J, Blocka K L N, Ross S G, et al. Effects of age and sex on piroxicam disposition. *Clin Pharmacol Ther* 1985; 37: 13-18.
- 18 Nebert D W. Clinical pharmacology: possible clinical importance of genetic differences in drug metabolism. *Br Med J* 1981; 283: 537-42.
- 19 Sjögqvist F, Alvan G. Aging and drug disposition metabolism. *J Chronic Dis* 1983; 36: 31-7.
- 20 Dinarello C A. Interleukin-1 and the pathogenesis of the acute-phase response. *N Engl J Med* 1984; 311: 1413-8.
- 21 Dinarello C A. Interleukin-1. *Ann NY Acad Sci* 1988; 546: 122-32.

CONFERENCE REPORT*

Antirheumatic drugs in the elderly

H A Bird

An audience of 70, drawn from rheumatologists, geriatricians, pharmacists, paramedicals, and industry, discussed a variety of aspects of drug treatment in elderly patients with arthritis during the course of the annual day conference on 'Antirheumatic drugs in the elderly' held at Harrogate on 3 May 1990.

Papers in the morning session, chaired by Dr H A Bird, discussed general aspects of drug treatment in the elderly. Dr E Burns, department of medicine for the elderly, St James's University Hospital, Leeds, reviewed age related changes in drug handling in her keynote address. The number of 'very elderly' (over 85 years) is increasing, and 15% of the population are now aged over 65. Thirty per cent of all drugs are prescribed for the elderly and, with concomitant disease, polypharmacy is often necessary with its risk of reduced compliance. The pharmacokinetic changes present in the elderly might be summarised under the headings of absorption, distribution, metabolism, and elimination.

Although the gastric pH rises and splanchnic blood flow falls with age, changes in absorption are probably not important except for drugs such as sulphasalazine, which undergo activation in the gut. During distribution, changes in serum albumin may affect steady state plasma concentrations of acidic agents, and disease modifying antirheumatic drugs might have greater toxicity. Liver blood flow is reduced, resulting in a decreased ability to metabolise drugs, though interindividual variation in drug metabolism caused by environmental pollutants such as tobacco usually outweighs the effects of aging. At excretion, the elimination of hydrophilic drugs is reduced in predictable fashion as glomerular filtration rate falls steadily with increasing age. The effect of age on hepatic excretion is less easy to predict, but in general there is a reduced clearance of drugs that have a high hepatic extraction ratio. In discussion it was noted that certain subjects seemed to age faster than others physiologically. It behaved

The University of Leeds,
Royal Bath Hospital,
Cornwall Road,
Harrogate,
North Yorkshire
HG1 2PS
H A Bird

*The eleventh in a series of annual day conferences devoted to the theme 'Growing points in the treatment of rheumatic diseases' held at the Yorkshire Regional Health Authority, Park Parade, Harrogate, North Yorkshire, on 3 May 1990.