The Clinical Pharmacology of Ageing, edited by Dr A.A. Mangoni and colleagues, Department of Healthcare for the Elderly, Guy's, King's and St Thomas' School of Medicine, Kings College London, London, UK.

Adverse drug reactions in elderly patients

P. A. Routledge, M. S. O'Mahony[1] & K. W. Woodhouse[1]

Departments of Pharmacology, Therapeutics and Toxicology and [1]Geriatric Medicine, University of Wales College of Medicine, Heath Park, Cardiff, Wales, UK

Correspondence
Professor P. A. Routledge,
Department of Pharmacology,
Therapeutics and Toxicology,
University of Wales College of
Medicine, Heath Park, Cardiff CF14
4XN, Wales, UK.
E-mail:
proutledge@compuserve.com

Many studies from around the world show a correlation between increasing age and adverse drug reaction (ADR) rate, at least for some medical conditions. More than 80% of ADRs causing admission or occurring in hospital are type A (dose-related) in nature, and thus predictable from the known pharmacology of the drug and therefore potentially avoidable. Frail elderly patients appear to be particularly at risk of ADRs and this group is also likely to be receiving several medicines. The toxicity of some drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone. In order to recognize and to prevent ADRs (including drug interactions), good communication is crucial, and prescribers should develop an effective therapeutic partnership with the patient and with fellow health professionals. Undergraduate and postgraduate education in evidence-based therapeutics is also vitally important. The use of computer-based decision support systems (CDSS) and electronic prescribing should be encouraged, and when problems do occur, health professionals need to be aware of their professional responsibility to report suspected adverse drug events (ADEs) and ADRs. 'Rational' or 'obligatory' polypharmacy is becoming a legitimate practice as increasing numbers of individuals live longer and the range of available therapeutic options for many medical conditions increases. The clear risk of ADRs in this situation should be considered in the context that dose-related failure of existing therapy to manage the condition adequately may be one of the most important reasons for admission of the elderly to hospital. Thus, age itself should not be used as a reason for withholding adequate doses of effective therapies.

Extent of the problem

Adverse drug reactions (ADRs), including interactions, in older people are a common cause of admission to hospital [1, 2], are common in elderly patients in hospital [3], and are an important cause of morbidity and death. Even after excluding errors in drug administration, noncompliance, overdose, drug abuse, therapeutic failures, and possible ADRs, Lazarou *et al.* found the overall incidence of serious ADRs in the general hospitalized population of the USA to be 6.7% [4]. The incidence of fatal ADRs was 0.32% amongst patients from 39 prospective studies included in this meta-analysis [4]. Thus, ADRs are likely to be between the fourth and sixth leading cause of death in the USA [4]. The evidence quickly dispels any complacency or suggestion that this

problem is not an international one. An excellent systematic review by Wiffen *et al.* showed that the incidence of ADRs in European studies was around twice that in the USA, in those conducted either before or after an arbitrary cut-off date of 1985. In the more recent (post-1985) studies in the geriatric setting, the ADR rate for the USA and Europe studies was even greater (20%) than in studies carried out in general medicine settings [5]. Few would argue that this rate of ADRs is not a major public health problem. The Audit Commission has calculated that ADRs to medicines and medication errors cost the NHS £0.5 billion each year in longer stays in hospital [6]. Wiffen *et al.* used Department of Health statistics for 2000 to calculate that 38 000 admissions were due to ADRs in England alone, and that

ADRs were likely to have caused over 1.5 million extra bed-days, the equivalent of filling over 13 average-sized (400-bed) hospitals in 1 year [5].

There has been much debate on whether advancing age *per se* is a cause of increased risk of ADRs. Gurwitz and Avorn concluded that 'patient-specific physiological and functional characteristics are probably more important than any chronological measure in predicting both adverse and beneficial outcomes associated with specific drug therapies' [7]. Nursing home (generally frail) patients appear to be particularly vulnerable to ADRs. A prospective study of two nursing homes in Georgia found that >67% of 332 residents experienced probable ADRs [8]. ADRs were associated with polypharmacy, the mean number of drugs per patient in the ADR group being 7.8, compared with 3.3 amongst residents who did not experience them [8]. Other studies have also clearly shown that the risk of ADRs (including interactions) is related to the number of medicines taken [9–11], and that the elderly receive more medicines, sometimes inappropriately [12, 13]. Indeed, it is possible that the risk of ADRs is exponentially rather than linearly related to the number of medicines taken, and the ADR rate was 50% in 9000 mostly elderly Italian patients receiving 10 medicines [11]. Thus, many studies from around the world show a correlation between increasing age and ADR rate, at least for some medical conditions [14–16].

Nature of the problem

It is also clear that more than 80% of ADRs causing admission or occurring in hospital are type A in nature [17]. Type A ADRs are dose related, an 'accentuation' of the known pharmacological effect of the drug, and thus predictable and potentially avoidable [18–22]. Antibiotics, anticoagulants, digoxin, diuretics, hypoglycaemic agents, antineoplastic agents and nonsteroidal anti-inflammatory drugs (NSAIDs) are responsible for 60% of ADRs leading to hospital admission and 70% of ADRs occurring in hospital [5]. Other cardiovascular medicines and analgesics are also important clinically [23]. These are generally drugs with a low therapeutic ratio (ratio between the average therapeutic and toxic dose). In addition, they all figure highly in lists of medicines most likely to be used in the elderly, and likely to be associated with adverse drug interactions. It has been suggested that type A ADRs are more common in the elderly and the unpredictable type B ('bizarre' or idiosyncratic reactions) less common [24]. However, some important and occasionally serious examples of type B toxicity (e.g. hepatotoxicity in association with the antibiotic flucloxacillin or the antibiotic combination,

coamoxiclav) appear to be commoner in elderly than younger individuals [25–27].

Frail elderly patients appear to be particularly at risk of ADRs. In some cases, this is because insufficient account is taken of the effect of age and frailty on the disposition of the drug, especially in relation to hepatic [28] and renal elimination [29], and too large a dose is prescribed. On other occasions, the increased pharmacodynamic sensitivity of the elderly to several commonly used drugs (particularly those affecting the cardiovascular and central nervous systems) is not taken into account when choosing the dose. These issues are all the more important because several diseases of these two systems, such as heart failure or epilepsy [30], are much commoner in the elderly. In addition, cardiovascular agents and anticoagulants are more likely than most other agents to cause ADRs that result in, or prolong hospital stay [10, 15].

The relationship between the number of medications taken and ADR risk has already been highlighted. Although around 10% of the general population take more than one prescribed medicine, the incidence of combination therapy is greatest in the elderly, in females, and in those who have had a recent hospital admission [31, 32]. A review of several studies indicated that patients aged >65 years use on average two to six prescribed medications, and 1–3.4 nonprescribed medications [33]. The potential dangers of what has been termed 'polypharmacy' have been known for some time [34] and indiscriminate polypharmacy has been identified as a major medical problem in some developing countries and a challenge for the World Health Organization's action programme on essential drugs [35]. However, the recognition that several common conditions such as hypertension or epilepsy can only be adequately treated with more than one agent in a significant proportion of patients has led to the use of the terms 'obligatory' [36] or 'rational' polypharmacy. Nowhere is this a greater challenge than in the elderly population.

The toxicity of drug combinations may sometimes be synergistic and be greater than the sum of the risks of toxicity of either agent used alone. NSAIDs can increase the risk of peptic ulcer by around four-fold in patients aged ≥65 years [37]. The relative risk of the development of peptic ulcer disease among current users of oral corticosteroids (but not NSAIDs) was 1.1 (i.e. a 10% increase in risk) [38]. However, patients concurrently receiving corticosteroids and NSAIDs had a risk of peptic ulcer disease that was 15 times greater than that of nonusers of either drug [38]. Similarly, the relative risk of hospitalization for haemorrhagic peptic ulcer disease in patients aged ≥65 years receiving oral anticoagulants

compared with nonusers was 3.3 and for NSAID users, 2. However, compared with nonusers of either drug, the relative risk of haemorrhagic peptic ulcer disease among current users of both anticoagulants and NSAIDs was 12.7. Nevertheless, the prevalence of NSAID use among anticoagulant users was 13.5%, the same as in those who were not using anticoagulants [39], suggesting that this marked synergism of toxicity is still not widely recognized by prescribers.

Recognition and reporting of ADRs

Although many type A ADRs are recognized during the drug development process and before licensing, this is not always the case, especially when they are uncommon or rare. In addition, the drug may be used off-label, sometimes at doses higher than those recommended. Even the initial manufacturers' recommended doses may be too high for some, particularly elderly individuals. The NSAID benoxaprofen was marketed in 1980. A year later, photosensitivity and serious hepatotoxicity (associated with 61 deaths in the UK) were reported in association with the drug and it was withdrawn in 1982. Only in 1982 were data published that indicated that withdrawal of the drug due to toxicity was necessary in 35% of 300 individuals taking the drug and in 69% of the 42 patients aged $\geq$70 years in one study. The authors concluded that the manufacturer's recommended dosage of 600 mg daily was associated with an unacceptable incidence of side-effects in the elderly [40]. Since only around 3000 subjects receive a medicine prior to marketing, it is not surprising that less frequent (particularly type B) ADRs are often recognized only after marketing. Nevertheless, delays in recognizing even these ADRs (e.g. the 20 years from initial marketing of flucloxacillin to the recognition of its hepatotoxic potential, particularly in the elderly) suggest that available postmarketing surveillance systems are not being used optimally. As a result, patients, including the elderly, may suffer unnecessarily.

Avoidance of ADRs

Since most ADRs in the elderly are predictable and therefore potentially avoidable, good communication is pivotal in developing an effective therapeutic partnership with the patient and with fellow health professionals. Three hundred and twelve patients from the practices of five cardiologists and two internists who were returning for their routine follow-up visits in Boston were interviewed and discrepancies between medication bottles and medical records were present in 239 patients (76%). The 545 discrepancies in these patients were the result of patients taking medications that were not recorded (51%); patients not taking a recorded medication (29%); and differences in dosage (20%) [41]. The age of the patient and his/her number of recorded medications were the two most significant predictors of medication discrepancy. This indicates that physicians should check medication lists with patients carefully (even obsessively) if ADRs and interactions are to be avoided, and illustrates that good communication is an essential prerequisite for rationalization of therapy [42]. This regular review process should continue, whether the elderly patient is in a hospital, nursing home or in the community, and a prescribing partnership between the prescriber, patient and other health professionals should be encouraged [43] so that good communication exists.

Whenever possible, the careful prescriber, faced with a choice, should choose the drug with the highest therapeutic ratio, provided efficacy is comparable. He/she should avoid combinations that exhibit additional or synergistic toxic effects (e.g. two substances with anticholinergic activity) [43]. Doses should be titrated up carefully from a low starting dose if pharmacokinetic or pharmacodynamic sensitivity are likely to be problems. In some cases, therapeutic monitoring of plasma drug concentrations (TDM) may be an adjunct to, but not a replacement for careful clinical observation [44]. The number of drugs prescribed should be kept to a minimum, and as few physicians [45] and dispensing pharmacies [46] as possible should be involved in the patient's care, since these measures have been shown to reduce the risk of receiving potential interacting drug combinations.

Physicians often look to their pharmacist colleagues for advice in relation to drug interactions. The ability of pharmacists at various stages of their training to identify potential drug interactions was studied by Weideman *et al.* [47]. Simulated medication profiles were created from a list of 16 drugs. The subjects detected only 66% of the interactions in the two-drug profiles, and 17% of the interactions in the 16-drug profile. None of the pharmacists in the study detected all interactions in the eight- or 16-drug profiles [47]. The only characteristic that correlated highly and positively with pharmacists' recognition of potential drug–drug interactions was the number of years since qualification [47]. Thus, experience (and training) appeared to be valuable. However, physicians with more experience were more likely to choose a longer- rather than shorter-acting benzodiazepine hypnotic for elderly people than those qualified more recently. This suggests that some prescribers select medicines out of habit rather than application of pharmacological principles [48]. In addition, physicians who

graduated from Canadian medical schools after 1989 were more likely to prescribe β-blocking drugs to elderly patients for secondary prevention after myocardial infarction than earlier graduates, so that important prescribing messages may not be getting through to doctors after they qualify [49]. There were also systematic differences between graduates of the different Canadian medical schools in this study. These findings indicate that the provision of good undergraduate education (ideally encompassing a core curriculum in clinical pharmacology) and continued professional development of graduate prescribers in evidence-based therapeutics are essential if old habits are to be replaced by new behaviour.

Even if all present and future prescribers (including nurses, pharmacists and other health professionals) are offered, and take up educational opportunities in therapeutics, it will still be difficult to keep completely abreast of this rapidly changing field, and one of the most important skills for the future will be to know where to find relevant and reliable information. Although 'to err is human', mistakes in prescribing or dispensing can cost lives. No pharmacist (even the most experienced) studied by Weideman and colleagues correctly recognized all the potential drug–drug interactions when presented with scenarios involving eight or more medicines [47]. The Audit Commission report has highlighted that many adverse drug events (ADEs, a broader definition than ADRs) are related to medication (e.g. prescribing or dispensing) errors. The US Agency for Healthcare Research and Quality (AHRQ) has also published a review of computer-based decision support systems (CDSS) to reduce prescribing errors [50] and the impact of CDSS has also been systematically reviewed [51]. Overall, these systems appear to reduce the numbers of ADEs. Wiffen *et al.* have reviewed the strengths and weaknesses of this approach, and outlined some examples of how decision support systems have promoted best practice [5]. The use of CDSS and electronic prescribing should be encouraged, but when problems do occur, the professional responsibility of health professionals to report suspected ADEs and ADRs to the relevant national bodies should continue to be highlighted.

The literature shows that elderly patients are exposed to more medicines and have an increased risk of type A (and of some type B) adverse reactions, and that many of these are avoidable. Knowledge of pharmacological principles and how ageing affects drug kinetics and response is essential if we are to promote safe prescribing. The occasional unavoidable occurrence of ADRs in the elderly should be set against the knowledge that dose-related failure of existing therapy to manage the condition adequately may be one of the most important reasons for admission of the elderly to hospital [52]. Thus, age is not a reason for withholding effective therapies since, although the risk of death due to several common diseases (e.g. coronary heart disease, stroke, and cancer) is greater with increasing age, the proportional reduction in mortality is often as great or greater in the elderly than in younger people. The predicted percentage growth in the number of individuals aged 60 or more over the next 20 years varies from 20% in Italy to as high as 67% in Australia [53]. This continued world-wide expansion of the elderly population means that geriatric clinical pharmacology will continue to be an important area of research, and that the challenge to improve the risk–benefit ratio for existing and newly introduced medicines in the clinical setting should not be shirked. After all, the French composer Auber (1782–1871) once observed that despite its associated problems and shortcomings, he had come to the conclusion that 'ageing seems to be the only available way to live a long time'.

References

1 Cunningham G, Dodd TRP, Grant DJ, Murdo MET, Richards RME. Drug-related problems in elderly patients admitted to Tayside hospitals, methods for prevention and subsequent reassessment. Age Ageing 1997; 26: 375–82.

2 Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Adverse drug reactions in elderly patients as contributing factor for hospital admission: cross sectional study. Br Med J 1997; 315: 1057–8.

3 Mannesse CK, Derkx FH, de Ridder MA, Man in 't Veld AJ, van der Cammen TJ. Contribution of adverse drug reactions to hospital admission of older patients. Age Ageing 2000; 29: 35–9.

4 Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. JAMA 1998; 279: 1200–5.

5 Wiffen P, Gill M, Edwards J, Moore A. Adverse drug reactions in hospital patients. Bandolier Extra 2002; 1–15 http://www.bandolier.com

6 Anon. A spoonful of sugar; medicines management in NHS hospitals. London: Audit Commission, 2001.

7 Gurwitz JH, Avorn J. The ambiguous relation between aging and adverse drug reactions. Ann Intern Med 1991; 114: 956–66.

8 Cooper JW. Probable adverse drug reactions in a rural geriatric nursing home population: a four-year study. J Am Geriatric Soc 1996; 44: 194–7.

9 Williamson J, Chopin JM. Adverse reactions to prescribed drugs in the elderly: a multicentre investigation. Age Ageing 1980; 9: 73–80.

10 Davidsen F, Haghfelt T, Gram LF, Brosen K. Adverse drug reactions and drug non-compliance as primary causes of admission to a cardiology department. Eur J Clin Pharmacol 1988; 34: 83–6.

11 Carbonin P, Pahor M, Bernabei R, Sgadari A. Is age an independent risk factor of adverse drug reactions in hospitalized medical patients? J Am Geriatr Soc 1991; 39: 1093–9.

12 Lassila HC, Stoehr GP, Ganguli M et al. Use of prescription medications in an elderly rural population: the MoVIES Project. Ann Pharmacother 1996; 30: 589–95.

13 Straand J, Rokstad KS. Elderly patients in general practice: diagnoses, drugs and inappropriate prescriptions. A report from the More & Romsdal Prescription Study. Fam Pract 1999; 16: 380–8.

14 Gholami K, Shalviri G. Factors associated with preventability, predictability, and severity of adverse drug reactions. Ann Pharmacother 1999; 33: 236–40.

15 Bordet R, Gautier S, Le Louet H, Dupuis B, Caron J. Analysis of the direct cost of adverse drug reactions in hospitalised patients. Eur J Clin Pharmacol 2001; 6: 935–41.

16 Dormann H, Krebs S, Muth-Selbach U et al. Adverse drug reactions in patients with gastroenterological diseases: does age increase the risk? Aliment Pharmacol Ther 2001; 15: 171–80.

17 Rawlins MD, Thompson JP. Pathogenesis of adverse drug reactions. In Textbook of adverse drug reactions, ed Davies DM. Oxford: Oxford University Press, 1977; 44.

18 Moore N, Lecointre D, Noblet C, Mabille M. Frequency and cost of serious adverse drug reactions in a department of general medicine. Br J Clin Pharmacol 1998; 45: 301–8.

19 Lagnaouie R, Moore N, Fach J, Longy-Boursier M, Begaud B. Adverse drug reactions in a department of systemic diseases-oriented internal medicine: prevalence, incidence, direct costs and avoidability. Eur J Clin Pharmacol 2000; 56: 181–6.

20 Green CF, Mottram DR, Rowe PH, Pirmohamed M. Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study. J Clin Pharm Ther 2000; 25: 355–61.

21 McDonnell PJ, Jacobs MR. Hospital admissions resulting from preventable adverse drug reactions. Ann Pharmacother 2002; 36: 1331–6.

22 Beijer HJ, de Blaey CJ. Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies. Pharm World Sci 2002; 24: 46–54.

23 Suh DC, Woodall BS, Shin SK, Hermes-De Santis ER. Clinical and economic impact of adverse drug reactions in hospitalized patients. Ann Pharmacother 2000; 34: 1373–9.

24 Bowman L, Carlstedt BC, Hancock EF, Black CD. Adverse drug reaction (ADR) occurrence and evaluation in elderly inpatients. Pharmacoepidemiol Drug Saf 1996; 5: 9–18.

25 Olsson R, Wiholm BE, Sand C, Zettergren L, Hultcrantz R, Myrhed M. Liver damage from flucloxacillin, cloxacillin, and dicloxacillin. J Hepatol 1992; 15: 151–4.

26 Devereaux BM, Crawford DH, Purcell P, Powell LW, Roeser HP. Flucloxacillin associated cholestatic hepatitis. An Australian and Swedish epidemic? Eur J Clin Pharmacol 1995; 49: 81–5.

27 Larrey D, Vial T, Micaleff A et al. Hepatitis associated with amoxycillin–clavulanic acid combination: report of 15 cases. Gut 1992; 33: 368–71.

28 O'Mahony MS, Woodhouse KW. Age, environmental factors and drug metabolism. Pharmacol Ther 1994; 61: 279–87.

29 Routledge PA. Therapeutics and toxicology. In Textbook of medicine, 4th edn, eds Souhami RL, Moxham J. Edinburgh: Churchill Livingstone, 2002.

30 Lackner TE. Strategies for optimizing antiepileptic drug therapy in elderly people. Pharmacotherapy 2002; 22: 329–64.

31 Nobili A, Tettamanti M, Frattura L et al. Drug use by the elderly in Italy. Ann Pharmacother 1997; 31: 416–22.

32 Onder G, Pedone C, Landi F et al. Adverse drug reactions as cause of hospital admissions: results from the Italian Group of Pharmacoepidemiology in the Elderly (GIFA). J Am Geriatr Soc 2002; 50: 1962–8.

33 Stewart RB, Cooper JW. Polypharmacy in the aged. Practical solutions. Drugs Aging 1994; 4: 449–61.

34 Hudson RP. Polypharmacy in twentieth century America. Clin Pharmacol Ther 1968; 9: 2–10.

35 Hogerzeil HV. Promoting rational prescribing: an international perspective. Br J Clin Pharmacol 1995; 39: 1–6.

36 Willmore LJ. Management of epilepsy in the elderly. Epilepsia 1996; 37 (Suppl 6): S23–33.

37 Griffin MR, Piper JM, Daugherty JR, Snowden M, Ray WA. Nonsteroidal anti-inflammatory drug use and increased risk for peptic ulcer disease in elderly persons. Ann Intern Med 1991; 114: 257–63.

38 Piper JM, Ray WA, Daugherty JR, Griffin MR. Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991; 114: 735–40.

39 Shorr RI, Ray WA, Daugherty JR, Griffin MR. Concurrent use of nonsteroidal anti-inflammatory drugs and oral anticoagulants places elderly persons at high risk for hemorrhagic peptic ulcer disease. Arch Intern Med 1993; 153: 1665–70.

40 Halsey JP, Cardoe N. Benoxaprofen: side-effect profile in 300 patients. Br Med J 1982; 284: 1365–8.

41 Bedell SE, Jabbour S, Goldberg R et al. Discrepancies in the use of medications: their extent and predictors in an outpatient practice. Arch Intern Med 2000; 160: 2129–34.

42 Atkin PA, Veitch PC, Veitch EM, Ogle SJ. The epidemiology of serious adverse drug reactions among the elderly. Drugs Aging 1999; 14: 141–52.

43 Seymour RM, Routledge PA. Important drug–drug interactions in the elderly. Drugs Aging 1998; 12: 485–94.

44 Routledge PA, Hutchings AD. Therapeutic Drug Monitoring (TDM). In The immunoassay handbook, 2nd edn. ed Wild D. London: Nature Publishing Group, 2001.

45 Hamilton RA, Briceland LL, Andritz MH. Frequency of hospitalization after exposure to known drug–drug interactions in a Medicaid population. Pharmacotherapy 1998; 18: 1112–20.

46 Tamblyn RM, McLeod PJ, Abrahamowicz M et al. Do too many cooks spoil the broth? Multiple physician involvement in medical

management of elderly patients and potentially inappropriate drug combinations. CMAJ 1996; 154: 1174–84.

47 Weideman RA, Bernstein IH, McKinney WP. Pharmacist recognition of potential drug interactions. Am J Health Syst Pharm 1999; 56: 1524–9.

48 Shorr RI, Bauwens SF. Effects of patient age and physician training on choice and dose of benzodiazepine hypnotic drugs. Arch Intern Med 1990; 150: 293–5.

49 Levy AR, Tamblyn RM, Mcleod PJ, Fitchett D, Abrahamowicz M. The effect of physicians' training on prescribing beta-blockers for secondary prevention of myocardial infarction in the elderly. Ann Epidemiol 2002; 12: 86–9.

50 Anonymous. Reducing and preventing adverse drug events to decrease hospital costs. Rockville, MD: Agency for Healthcare Research and Quality, 2000.

51 Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes. A systematic review. JAMA 1998; 280: 1339–46.

52 Raschetti R, Morgutti M, Menniti Ippolito F et al. Suspected adverse drug events requiring emergency department visits or hospital admissions. Eur J Clin Pharmacol 1999; 54: 959–63.

53 Martin U, George CF. Drugs and the elderly. In Pharmacovigilance, eds Mann R, Andrews E. Chichester: Wiley, 2002.