EDITORIALS

IATROGENESIS - STILL A GERIATRIC GIANT

"Show me a drug without side-effects, and I'll show you a drug without any effect!" Professor Derrick Dunlop, Edinburgh.

"At the beginning of the twentieth century syphilis was the great mimic of systemic disorders. Later, tuberculosis took over this role. Both of these diseases have been lamed by chemotherapy and now 'drugs' head the list of disease simulators." Committee on Safety of Medicines [1].

The prevalence and significance of drug-induced illness in old age have been well described [2-10]. Studies in different countries have shown that hospitalized elderly patients are two to three times more likely to experience an adverse drug reaction(ADR) than patients aged 20 to 30 years [6]. The prevalence rates for ADRs among elderly people in hospital and community settings have been reported as 15%-42% [2,9,10]and 2.5-50.6% [3,7]respectively. ADRs is an important cause of hospital admission in old age [2,5,9]. A recent study [2] shows that two of five patients aged over 70 years admitted to a general medical ward experience ADRs, half of which are severe. However, adverse drug reactions in old age frequently remain unrecognized by doctors or patients. Very often, "iatrogenesis" masquerades as incontinence, immobility, instability, falls, intellectual impairment, and geriatric failure to thrive [11-13]. Like the other geriatric giants, iatrogenesis afflicts a gigantic number of old people and makes a gigantic onslaught on the independence of their victims.

Prompt recognition of an iatrogenic aetiology for an illness will ensure the avoidance of unnecessary investigations and the early withdrawal of the offending drug, best exemplified by the case reports by Miu, *et al.*[14] in this issue of the *Journal*. Failure to detect and diagnose iatrogenic disease may lead to the phenomenon of prescribing cascade [15], as illustrated by the patient I encountered in an orthogeriatric assessment(Figure 1): a 77-year-old woman on 14 medications from 3 specialists separately caring for her heart, brain and mind ended up in a fall with hip fracture - "a pill for every ill" has become an "ill from every pill" [16].

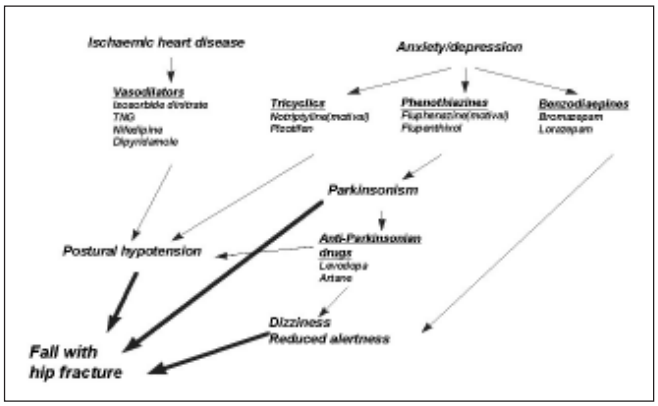

Figure 1. Prescribing cascade in a 77-year-old woman

How many of these ADRs in old age are predictable and avoidable? Studies have raised concern that elderly people are frequently prescribed contraindicated or inappropriate drugs [17,18]. Eighty percent of ADRs are dose-related [10]. Attention has been drawn to the frequent occurrence of allopurinol hypersensitivity syndrome among elderly patients in whom no reduction in the "standard" dose of allopurinol of 300 mg was made [19]. It is a type III hypersensitivity vasculitis triggered by allopurinol's principal metabolite, oxipurinol, which accumulates to toxic concentrations when there is reduced renal clearance. Renal function diminishes steadily with age, although serum creatinine does not rise to signal this decline because of reduced creatinine production in old age. Using an allopurinol dose appropriate to the estimated creatinine clearance in an elderly person can help to avoid this potentially fatal allopurinol hypersensitivity syndrome [19]. A better knowledge of the prescriber on the pharmacokinetics and pharmacodynamics in old age is important in reducing iatrogenesis. However, the magnitude of changes in pharmacokinetics and pharmacodynamics due solely to ageing is minor in comparison to that due to disease. Frailty may be important in determining decreases in metabolism of some drugs, possibly due to deficiency of cofactors. An example is that the clearance of salicylate from plasma(metabolised by aspirin esterase) while being similar in the young and fit elderly persons, is significantly reduced in frail elderly patients [20].

Elderly, and particularly frail elderly, people have often been excluded from clinical trials [21-23]. A recent study revealed that a third of the original research papers in four major medical journals excluded elderly people without justification [21]. In the US, 60% of the 214 clinical trials of drug therapy for acute myocardial infarctions excluded elderly patients [23]. Despite the increasing prevalence of tuberculosis in old age in Hong Kong, anti-tubercu-

losis chemotherapy trials have excluded people aged over 75 years [24]. Few of our frail elderly Chinese can tolerate the recommended 4-drug anti-tuberculosis regime (rifampicin, isoniazid, pyrizinamide, ethambutol). This local experience is in accord with the finding by Mitchell, *et al.*,[25] who advised regular monitor of liver function test in elderly patients on anti-tuberculous chemotherapy, a caution not included in the guidelines of the British and American Thoracic Societies.

Much of the information on which treatment decisions are based in elderly patients is derived from studies involving younger adults. The benefit to risk ratio of any given intervention may be quite different in frail older patients with significant comorbidities, and the applicability of such study findings to routine geriatric medical practice is therefore limited [22]. "Evidence-based medicine" may turn into "evidence-biased medicine" if evidence is extrapolated from younger adults to older people, from fit elderly people to frail elderly people, from one country to another country, from the "average" to the individual, and if heterogeneous elderly people are being treated as a homogeneous biomass. Indeed, guidelines derived from such evidence-biased medicine, glorified in the name of evidence-based medicine, may cause harm in our elderly patients [26].

As the geriatric patient population has often been excluded from participation in pre-marketing studies of drugs; post-marketing surveillance, either as case reports of adverse drug events by alert doctors or in the form of more formal studies are important to provide information on the risk/benefit ratio of drugs in elderly patients. The medical profession has to be constantly reminded of such unfortunate lessons as the opren (benoxaprofen) scandal: a non-steroidal anti-inflammatory drug linked to 61 deaths (mostly elderly people) and 3500 adverse reactions 2 years after the drug was launched in 1980 [27,28].

In this issue, Hung, *et al* [29], reports glibenclamide -associated hypoglycaemia in a 78-year-old patient after anti-Helicobacter induced anorexia. Since 1983, there have been reports of serious hypoglycaemia associated with glibenclamide use in elderly diabetics with significant mortality and morbidity [30,31]. Of the 57 cases of glibenclamide-associated hypoglycaemia reported by Asplund, *et al*, [30] the median age was 75 years, the mortality 17%, and the morbidity significant, including permanent brain damage and acute myocardial infarction. A recent pharmacoepidemiological study [32] showed that the rates(per 1000 person-years) of severe sulphonylurea-associated hypoglycaemia among elderly(aged over 65 years) Tennessee from 1985 to 1989 were highest for glibenclamide(16.6), second highest for chlorpropamide(15.3), and lowest for tolbutamide(3.5). It is noteworthy that although the duration of action of glibenclamide(16-24 hours) is much shorter than chlorpropamide(60 hours), glibenclamide has a higher risk of hypoglycaemia in elderly diabetics. The protracted hypoglycaemic effects of glibenclamide has been attributed to the prolonged presence of active metabolites; and the delayed beta-cell response elicited by this drug in the absence of an early first phase peak of insulin release [33]. Both these factors are absent for tolbutamide and gliclazide, sulphonylureas that are thought to be safer and thus recommended in elderly diabetics [34-36]. Pharmacological, epidemiological and clinical data of an increased frequency of hypoglycaemia associated with glibenclamide led to guidelines recommending their avoidance in elderly diabetics [37]. An audit in UK on the geriatricians' and diabetologists' management of elderly diabetics from 1988 to 1992 showed a decreasing trend of glibenclamide use and an increasing preference for shorter-acting hypoglycaemic agents [38]. However, glibenclamide is widely prescribed to our elderly diabetics locally.

To reduce drug-related iatrogenic disease, doctors should heed of the recommendations from a recent report of the Royal College of Physicians [39]: think carefully before prescribing; prescribe with maximum knowledge about the patient and about therapeutics; monitor the patient for the efficacy and side-effects of medication; help the patient make better use of their medication; and agree responsibility for prescribing across the primary/secondary interface. Using computers to store prescribing information can be helpful, though the role of the intracranial computer still remain paramount [16,40].

The focus on iatrogenic illness in old age caused by prescribed medication should not divert attention from other non-drug related iatrogenic conditions: ageism, inadequate assessment, sick-role induction, regimentation for staff convenience, disabling environment/equipment and diagnostic/therapeutic procedure-related complications [8,41]. Much knowledge has been accumulated for the better care of our elderly people, as can be seen from the articles devoted to ageing in the October 1997 issues of 100 journals from 33 countries to commemorate the "Ageing: a global theme" [42,43]. Hopefully, with improved attitude, knowledge and skills among doctors caring for old people, the geriatric giant "iatrogenesis" will be tamed.

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