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Suspected adverse drug reactions in elderly patients reported to the Committee on Safety of Medicines

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1 Spontaneous reports of suspected adverse drug reactions (ADRs) reported to the Committee on Safety of Medicines (CSM) have been studied in relation to patient age.
2 The proportion of reports received for the elderly increased between 1965 and 1983.
3 There was a correlation between the use of drugs and the number of ADR reports. Thus age-related prescription figures for two non-steroidal anti-inflammatory drugs (NSAI) and co-trimoxazole matched ADR reports for each drug in each age group.
4 The reported ADR was more likely to be serious or fatal in the elderly.
5 The commonest ADRs reported for the elderly affected the gastrointestinal (GIT) and haemopoietic systems, where more reports were received than would be expected from prescription figures.
6 The drug suspected of causing a GIT reaction was a NSAI in 75% of the reports.
7 Ninety-one per cent of fatal reports of GIT bleeds and perforations associated with NSAI drugs were in patients over 60 years of age.

Keywords adverse drug reactions elderly drug prescriptions

Introduction

Since the late 1960s, several centres have individually shown a positive correlation between the number of ADRs and age (Hurwitz, 1969; Koch-Weser *et al.*, 1982; Smith & Haber, 1970). Although several possible explanations exist (Royal College of Physicians, 1984), the apparent propensity of the elderly to develop ADRs may be due to the numbers and types of tablets they take. If this is so, it is necessary to accept the risk when the drug is mandatory for control of their disease. In order to examine whether ADRs in elderly patients are related to drug prescription, yellow card adverse reaction reports submitted to the CSM were compared with prescription data supplied by the Drug Surveillance Research Unit in Southampton and others (Inman, 1985).

Methods

The CSM runs a register of spontaneous adverse reaction reports received on yellow cards (Spiers *et al.*, 1984). The adverse reaction information presented here was obtained from the CSM database between June, 1964 and April, 1985. Full data for each complete year were only available between 1965 and 1983 at the time of writing. Reports of serious gastrointestinal reactions, bleeding or perforations, included all yellow cards received between June, 1964 and April, 1985. All reports were used where the patient's age was known. In every case, information was sought only about the suspect drug. Thus, each report was attributed to only one drug, even for a patient on multiple therapy. Fatal reactions were those where the chief adverse reaction led to death of the patient. Serious adverse reactions

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were those where the reaction was potentially life threatening, but does not include fatal reactions.

Information on the use of co-trimoxazole was obtained from surveys of drug use in the UK from 1968 to June, 1984 (Committee on Safety of Medicines, 1985). Information on the age/sex of users of fenbufen and Osmosin was obtained from the Drug Surveillance Research Unit in Southampton and reflected the usage pattern of these drugs when studied by prescription event monitoring in January to March, 1981.

Results

The proportion of adverse reaction reports received by the CSM for the elderly has risen from 24% of the total yellow cards in 1965 to 35% in 1983, since when it had remained constant over the next 2 years (Table 1). During this time, the elderly as a proportion of the population had risen by only about 1%. Although the total number of yellow cards peaked in those aged 55–64 years, the percentage that reported serious events rose with each decade after 35 years. The rise in fatal reactions was even more dramatic and was progressive from birth (Table 2). For example, the total number of reactions in those aged 55–64 years was almost 23,000 compared with 1,600 in those over 84 years, but the proportions that were serious and fatal were 18.5 and 41.9% respectively.

Systems principally involved in increased ADR in the elderly

a) *Gastrointestinal system*: 3,258 out of 4,598 serious GIT haemorrhages and perforations occurred in the over sixties (71%), and this group accounted for 82% of the fatal GIT reaction reports out of a total of 1,241 (Figure 1). The drug suspected of causing the reaction was a non-steroidal anti-inflammatory drug in 3/4 of the reports. Serious GIT bleeds and perforations associated with NSAI drugs were reported particularly in the elderly with 89% of the fatal reports being for the over-sixties (Table 3). Women accounted for 64% of the patients who bled and 70% of those with perforations. The only other type of drug regularly associated with these reactions was corticosteroids, for which there were 427 reports, 71% being in the elderly.

Table 1 Age distribution of yellow card reports to CSM 1965–1983 (young 0–65 males, 0–60 females; old 66 and over males, 60 and over females).

	1965		*1974*		*1983*	
	Number	%	*Number*	%	*Number*	%
Young	2800	76	3059	71	7453	65
Old	891	24	1256	29	4074	35

Table 2 Total number (%) of suspected ADRs reported to the CSM 1964 to June, 1984, for each age group and the number (%) of these which were serious or fatal.

Age (years)	*Total number*	*Serious*		*Fatal*		*Serious and fatal*	
		Number	%	*Number*	%	*Number*	%
0–4	5363	1045	19.5	119	2.2	1164	21.7
5–14	4156	547	13.6	108	2.6	655	16.2
15–24	10405	934	9.0	306	2.9	1240	11.9
25–34	15959	1259	7.9	490	3.1	1749	11.0
35–44	15644	1296	8.9	627	4.0	1923	12.9
45–54	18437	2086	11.3	750	4.1	2836	15.4
55–64	22858	2990	13.1	1242	5.4	4232	18.5
65–74	19758	851	4.3	1540	7.8	4391	12.1
75–84	8808	1677	19.0	979	11.1	2656	30.1
85+	1656	416	25.1	278	16.8	694	41.9
Age not known	9057	1162	12.8	209	2.3	1371	15.1
Total	132103	16263	12.3	6648	5.0	22911	17.3

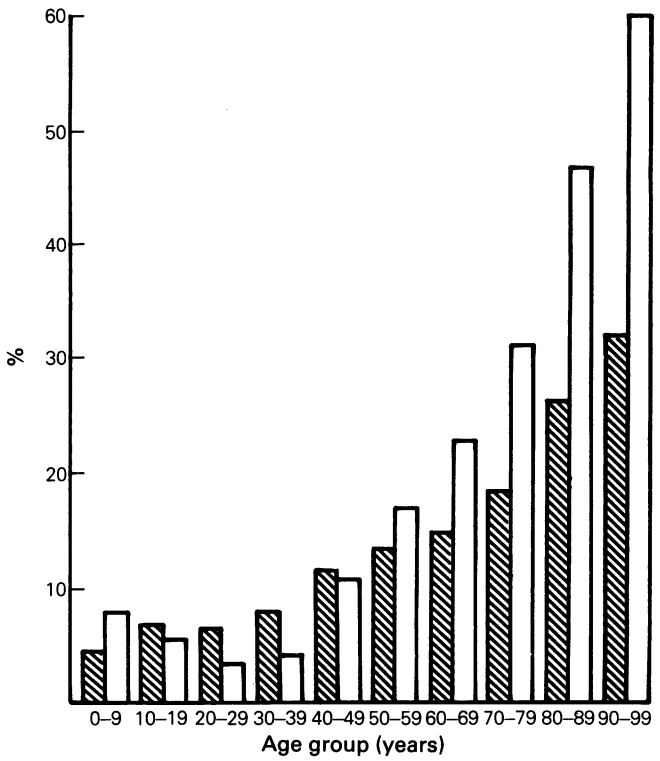

Figure 1 The age distribution of all cases of all gastrointestinal reactions (total $n = 4,598$ (▨) and fatal $n = 1,241$ □)) reported to the CSM. (There were an additional 955 reports, 23 fatal reactions, where the patient age was not given).

Table 3 Age and sex distribution from yellow card reports of serious and fatal GIT bleeds and perforations associated with four NSAI drugs (flurbiprofen, ibuprofen, ketoprofen and piroxicam).

	Age									
	< 60 years				*> 60 years*				*All*	
	Serious		*Fatal*		*Serious*		*Fatal*		*Serious*	*Fatal*
	Number	%	*Number*	%	*Number*	%	*Number*	%	*Number*	*Number*
Haematemesis and/or melaena	745	29	40	9	1786	71	428	91	2531	468
Perforation	102	30	16	11	235	70	125	89	337	141
Both	1	30	1	11	8	89	8	89	9	9

b) *Haemopoietic system*: Blood dyscrasias were infrequently reported, but 27% were fatal and these were more frequent in the older population (Figure 2). There were 378 out of 1,917 (20%) reports of fatal blood dyscrasias for the under-sixties compared with 764 out of 2,221 (34%) for the over-sixties.

Correlation between the number of ADR reports and prescription figures for various drugs

The age distribution of the cases with reported adverse reactions correlated reasonably well with the age distribution of prescriptions in the sample population for those drugs studied. The large number of reports in the elderly for

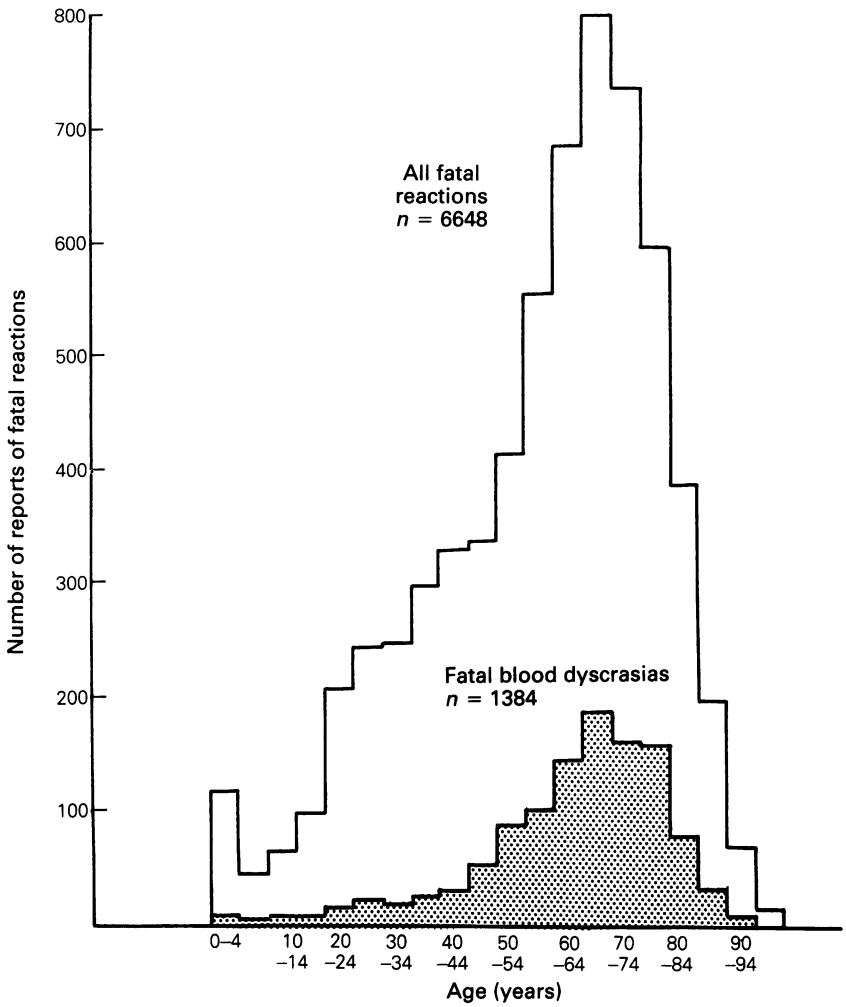

Figure 2 Age distribution of reported cases of fatal reactions; all reactions and blood dyscrasias.

fenbufen (Figure 3) and Osmosin (Figure 4) was no greater than might be expected from their widespread use of these drugs. Indeed, a rather smaller proportion of ADR reports than prescriptions was found for the drugs in the elderly. However, exceptions existed: 932 (37%) suspected ADRs to co-trimoxazole occurred in those aged 40–64 years compared with 511 (20%) in those above 65 years. However, 62% (n = 31) fatal blood reactions occurred in the latter group compared to 26% (n = 13) in the former. Further, the 74% of reported cases of GIT bleeding and perforation associated with NSAI drugs in the elderly was higher than would be suggested by their share of prescriptions during that time.

Discussion

The present evidence suggests that in general the number of ADRs reported in the elderly may be proportional to their use of drugs. The same conclusion has been reached recently using the same ADR database, but prescription figures from a different source (Weber & Griffin, 1986). Pickles (1986) also reported an association between yellow card reports and prescriptions for atenolol, alprazolam, zomepirac and benoxaprofen at various ages. Such arguments assume that the number of tablets in each prescription is similar at all ages and that compliance does not vary with ageing. Whilst there is no information on the former, evidence suggests

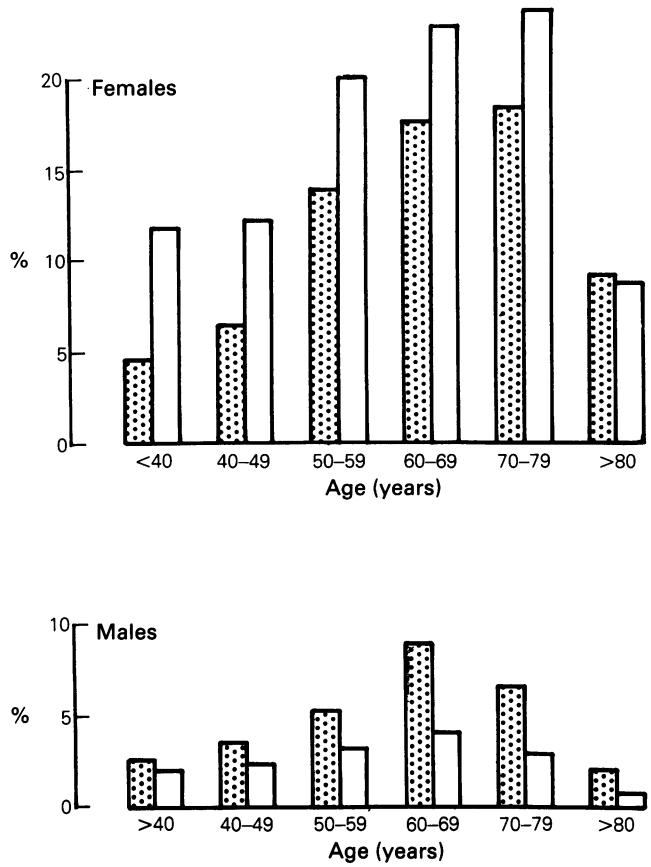

Figure 3 Age and sex distribution of prescriptions and ADRs reported for fenbufen. ⊡ prescriptions (from a sample of 3208 patients studied for prescription event monitoring), □ all ADR reports to CSM.

that compliance in elderly patients is no worse than that in the young, except in the confused, when the commonest problem is omission (Castleden & George, 1984). If the prescription rate figures are an accurate reflection of tablets taken and this accurately reflects ADR occurrence rates, it follows that a reduction in ADRs in the elderly may be achieved relatively easily by questioning whether to prescribe another drug to any patient.

Williamson & Chopin (1980) found that the greatest number of adverse reactions occurred with those drugs most frequently used, and diuretics were therefore responsible for the highest number of ADRs with psychotropics a close second. There may well be a true increase in certain specific ADRs in the elderly as has been suggested for the blood dyscrasias in patients on phenylbutazone (Inman, 1977), co-trimoxazole (Committee on Safety of Medicines, 1985) and with serious gastrointestinal bleeds in patients on non-steroidal anti-inflammatory drugs. The lack of a general excess of ADR reports for these drugs in the elderly suggests that the basic problem is not kinetic and that drug accumulation cannot be blamed. Apart from these important exceptions (Pickles, 1986), younger patients may well have the same ADR rate as older ones if they were given the same types of drugs as the elderly in the same numbers.

The present suggestion that serious gastrointestinal bleeds and perforations reported to the CSM most frequently involved elderly patients and the use of NSAI drugs is in line with the previous reports of these associations (Somerville *et al.*, 1986; Walt *et al.*, 1986). Whilst the prescribing of non-steroidal anti-inflammatory drugs is so common in the elderly that false associations of drug use and adverse events are particularly likely, the number of reports received by the CSM suggest that this is a major and genuine drug-related problem.

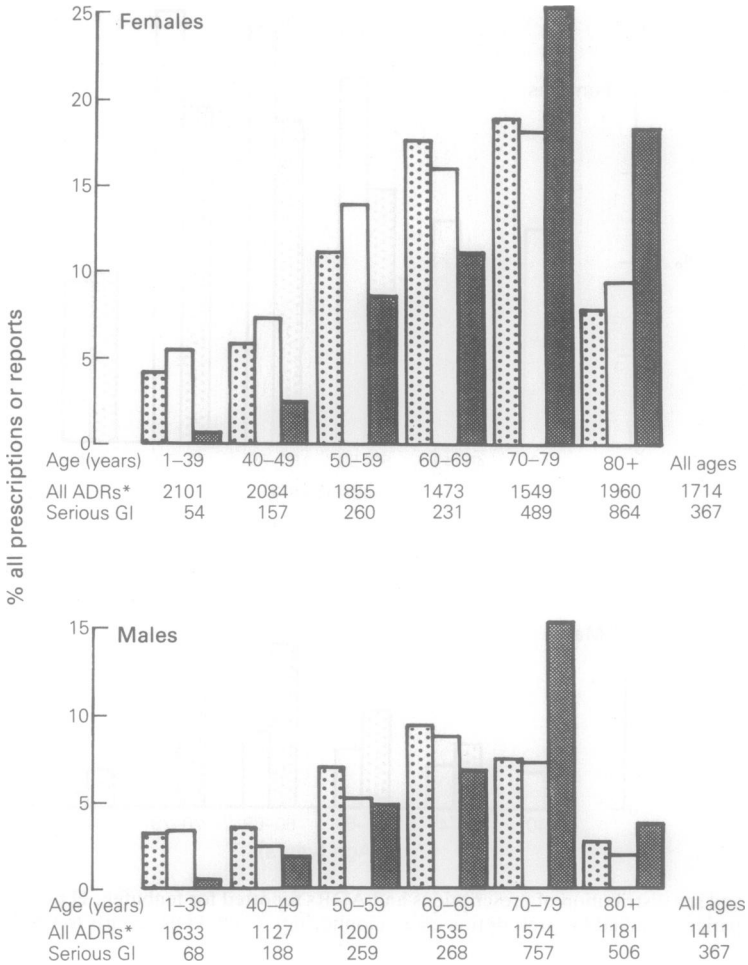

Figure 4 Age and sex distribution of prescriptions (⊡) and ADR reports (all (□, n = 713) reports and serious GIT bleeds and perforations (▨, n = 162)) for Osmosin brand of indomethacin.* Reports per million prescriptions.

Nevertheless, serious under-recognition or under-reporting is probably common, if the experiences of the Nottingham area are typical (Somerville *et al.*, 1986). There should be around 3,000 cases of upper gastrointestinal bleeding in patients on non-aspirin NSAI drugs annually in the UK, and only 409 (around 13%) were reported to the CSM in 1984. Women have more suspected reactions reported, but they also receive more NSAI drugs. Overall, prescribers would be wise to question carefully the need for a non-steroidal anti-inflammatory drug before prescribing such to the elderly, most particularly to the very elderly.

Analysis of spontaneous ADR reports can give only an indirect estimate of the true ADR rates. On the one hand, there is under-reporting of ADRs, and on the other, doctors are asked to report suspected associations of adverse events and drug therapy, not all of which may be true drug ADRs. In making comparisons between the reporting rates for various groups, the interpretation of yellow card reports is particularly difficult without adequate information on drug use. Detailed age-related prescription data are regarded as commercially confidential and are

not published. The limited prescription figures made available for this study may not in fact reflect accurately drug use, even during the periods of sampling. Nevertheless, this study does suggest no more, and perhaps fewer, reports were received for the elderly than might be expected.

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