ORIGINAL ARTICLE

Adverse drug events as a cause of hospital admission in the elderly

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Abstract

Background: Previous studies of adverse drug events (ADE) as a cause of hospital admission in the elderly have often been limited in their ability to assess fully the impact and potential for prevention because they either did not include all categories of ADE and/or did not assess severity and preventability.

Aims: To assess the frequency, severity and preventability of ADE causing emergency medical admissions in the elderly.

Methods: Cross-sectional survey of 219 patients aged 75 years and over who were consecutive unplanned admissions to acute medical units of the Royal Hobart Hospital in an 8-week period during August and September 1998.

Results: Seventy-three of 240 (30.4%) admissions may have been a result of ADE. Patients admitted because of ADE were taking more drugs than those admitted for other reasons. Most ADE were adverse drug reactions to a single (46%) or multiple drugs (25%). Non-compliance, omission or cessation of indicated treatment accounted collectively for 26% of admissions. Of all ADE admissions 53.4% were considered definitely preventable. The commonest causative drugs were cardiovascular drugs (48.4%), and the commonest manifestations were falls and postural hypotension (24.1%), heart failure (16.9%) and delirium (14.5%). ADE categories in which a high proportion of admissions was both severe and definitely preventable were non-compliance and omission of indicated treatment.

Conclusions: Adverse drug events are a common preventable cause of unplanned medical admissions in the elderly. Non-compliance and omission of indicated treatment are causes of ADE-related admissions that are both preventable and frequently associated with severe ADE. (Intern Med J 2001; 31: 199–205)

Key words: adverse drug events, elderly, emergency admissions.

INTRODUCTION

Medication-related illness is a significant problem, particularly among the elderly. The proportion of elderly emergency admissions that were drug-related hospital admissions (DRHA) varied between 15 and 22% in Australian studies that were recently reviewed1 and up to 31% in an earlier study.2 This is considerably higher than in studies that also included younger patients.1 Predisposing factors in the elderly include physiological changes associated with ageing, multiple pathological conditions and the resulting need for multiple drug treatment.

While some of the variability in previous studies confined to the elderly may be because of differences in age range, admitting wards and study design, it is likely that a significant contributor is the differing criteria and classification systems used for adverse drug events (ADE). Some studies included only adverse drug reactions (ADR)3,4 and assessment of the impact and potential for prevention was limited because many studies did not assess severity or preventability.

The limitations of previous studies and the need for continuing assessment of drug-related admissions to hospital in the elderly in the face of continual changes
in prescribing practices were the reasons for this study.

METHODS

A prospective, cross-sectional study was carried out over a consecutive 8-week period in August and September 1998 at the Royal Hobart Hospital (RHH), which is the major public acute care hospital for Southern Tasmania (population approximately 250 000, bed capacity approximately 500). The study was approved by the RHH Research and Ethics Committee.

The subjects in the study were all acute, unplanned, emergency admissions to medical wards of patients who were 75 years or older. The records of all subjects were reviewed within 24 h of admission and subjects were interviewed as soon as practical after admission. The information collected included age, sex, comorbidities, living circumstances, function in activities of daily living, social supports, medications and medication changes prior to admission, previous ADE, medication changes during admission, details of presenting complaint, admission diagnosis, and examination and investigation findings. Patients and/or their relatives who consented to interview were asked to provide information regarding any recent changes to drug therapy, compliance, alcohol consumption and previous ADE. Then, to determine if cognition was impaired, the standard Mini Mental State Examination (MMSE) was performed. If the MMSE was lower then 25/30 this was assessed against a relative’s assessment of patient cognition prior to the recent illness, the patient was assessed again later in the admission to see if an improvement had occurred, and the medical record was checked for documentation of improvement in mental state.

Classification of ADE

We used the WHO classification for ADR, with additional categories using the definitions of Strand et al. Non-compliance was defined as a deviation from the prescribed medication regimen because of choice, non-comprehension or forgetfulness producing an exacerbation of symptoms of the patient’s condition. A drug interaction was defined as the modification of one drug by the prior administration of another producing loss of therapeutic effect or toxicity. Dosage decrease or cessation was defined as a decrease or cessation of a prescribed therapy by a doctor causing an exacerbation of symptoms. An overdose was defined as a deliberate or inadvertent ingestion of drug in excess of the prescribed amount causing toxicity. Omission of indicated treatment was when a patient had an indication for a medication because of a prior medical condition or risk factor but was not receiving it, resulting in symptoms of the condition. Inadequate medication was when the prescribed dose was less than the recommended dose leading to an exacerbation of symptoms. Multiple drugs causing ADE was when the patient was taking more than one drug that shared the same adverse effect that resulted in the presentation.

We defined one ADE as occurring if one drug caused one or more adverse manifestations or if two or more drugs contributed to one adverse manifestation.

Criteria for causality of ADE

In cases of suspected ADE because of ADR, drug interactions (DI), excessive dose and multiple drugs, causality was classified as definite, probable or possible. ‘Possible/possible’ causal relationship was added because of the potential situation where despite strong suspicion of an ADE by the investigators it was not recognized by the treating doctor and the criteria for improvement after drug withdrawal could not be tested.

For non-compliance or inadequate treatment, causing an exacerbation of the patient’s condition, the following criteria were used:

1. The symptoms of the disease are known to reappear at insufficient dosages.
2. The symptoms were not likely to have been caused by a progression of the disease.
3. Presence of a reasonable temporal relationship between the start of inadequate treatment and the appearance of symptoms.
4. The symptoms resolved upon adjustment to an adequate dosage.
5. No other condition present could explain the symptoms.
6. Drug levels were clearly below the therapeutic range or there was clear evidence of intake of insufficient dosage.

For a ‘definite’ causal relationship, all criteria were satisfied; for a ‘probable’ causal relationship, criteria 1–5 were satisfied; for a ‘possible’ causal relationship, criteria 1–4 were satisfied; and for a ‘possible/possible’ causal relationship, criteria 1–3 were satisfied.

Preventability or avoidability was assessed as below:

1. Definitely avoidable: the drug event was a result of
a drug-treatment procedure inconsistent with present-day knowledge of good medical practice or was clearly unrealistic, taking the known circumstances into account.

2 Possibly avoidable: the prescription was not erroneous, but the drug event could have been avoided by an effort exceeding obligatory demands.

3 Not avoidable: the drug event could not have been avoided by any reasonable means, or it was an unpredictable event in the course of a treatment fully in accordance with good medical practice.

Where a combination of drugs was involved but preventability varied for each drug, the preventability of the admission was assessed as that for the drug scoring the highest grade of preventability.

Severity was assessed as severe, moderate or mild and definitions were modified from a previously reported classification. Severe was defined as life-threatening; causes permanent damage or requires intensive care. Moderate was defined as requiring hospital admission, change in therapy or specific treatment. Mild was defined as not requiring hospital admission or therapy.

All cases of suspected ADE mixed with a random sample of cases without a suspected ADE were independently reviewed blindly by a consultant physician for the presence of an ADE. Those judged as having ADE were also assessed blindly by the physician for causality, severity and preventability.

Statistical methods

Descriptive statistics were expressed as mean and 95% confidence intervals. Differences in proportions were tested using Fisher’s exact test. Group comparisons were made using unpaired Students t-tests. Tests were two-sided and comparisons were considered statistically significantly different if \( P < 0.05 \).

RESULTS

There were a total of 240 acute unplanned admissions to the medical units of patients aged 75 years and over during the study period. Of these, 21 were re-admissions. Demographic details of admissions are outlined in Table 1.

There were 76 different ADE resulting in a total of 73 admissions. Thus, up to 30.4% of admissions were as a result of drug-related problems. Among the 219 patients admitted once during the study there were 67 admissions directly related to ADE. Of these, three patients had two different adverse events contributing to their admission resulting in 70 ADE. Among the 21 re-admissions during the study there were six drug-related admissions, each a result of one ADE. Table 2 provides a comparison of ADE and non-ADE admissions.

The different groups and classes of drugs causing DRHA are shown in Table 3. Table 4 summarizes the manifestations of the ADE. There were 32 (46%) admissions because of ADR caused by 35 different drugs resulting in 43 manifestations. Almost all ADR were ‘type A’ predictable reactions that can be pharmaco-logically explained, while only one was ‘type B’ non-predictable/idiosyncratic reaction (rash related to ticlopidine). Falls and falls associated with postural

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Patient demographics</th>
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<tbody>
<tr>
<td>Characteristic</td>
<td>Mean (95% CI, range)</td>
</tr>
<tr>
<td>Age all (( n = 240 ))</td>
<td>81.8 years (81.2–82.4, 75–94)</td>
</tr>
<tr>
<td>Females (( n = 132 ))</td>
<td>82.7 years (81.8–83.6)*</td>
</tr>
<tr>
<td>Males (( n = 108 ))</td>
<td>80.7 years (79.9–81.5)</td>
</tr>
<tr>
<td>Number of comorbidities</td>
<td>4.2 (4.0–4.4, 0–11)</td>
</tr>
<tr>
<td>Number of medications</td>
<td>5.8 (5.4–6.2, 0–18)</td>
</tr>
<tr>
<td>Hospital stay (days)</td>
<td>9.3 days (5.4–6.2, 0–18)</td>
</tr>
</tbody>
</table>

*\( P < 0.0015 \) comparison of mean age of females and males. CI, confidence interval.

| Table 2 | Comparison between ADE and non-ADE admissions |
|-----------------|------------------|------------------|---|
| Characteristic   | ADE admissions (95% CI) | Non-ADE admissions (95% CI) | \( P \) |
| Age              | 81.8 years (80.6–83.0) | 81.9 years (81.1–82.7) | NS |
| Sex ratio male/female | 26/47 | 108/132 | NS (0.07) |
| Comorbidities    | 4.3 (3.9–4.7) | 4.1 (3.9–4.3) | NS |
| Medications      | 6.7 (5.9–7.5) | 5.4 (5.0–5.8) | 0.004 |
| Past history ADE| 47.8% (35.4–60.2) | 44.2% (36.4–52.0) | NS |
| Hospital stay    | 10.0 days (7.3–12.6) | 9.0 days (7.6–10.5) | NS |

ADE, adverse drug events; NS, not significant; CI, confidence interval.
There were 19 (25%) admissions with 21 ADE as a result of multiple drugs. The most common manifestations were falls and falls associated with postural hypotension ($n = 5$). The drugs contributing most commonly to postural hypotension were diuretics ($n = 5$). Other manifestations were confusion ($n = 4$) and renal failure ($n = 4$).

There were nine (12%) patients admitted because of non-compliance. The common reasons for non-compliance were poor social circumstances ($n = 3$) and cognitive impairment ($n = 3$). Other causes of ADE were omission of indicated treatment either because of cessation or failure to prescribe ($n = 10$, 14%), drug interactions, overdose and inadequate dose (each $n = 1$).

Overall, there were six deaths that were related directly to an ADE. The four deaths judged preventable included: two as a result of embolic strokes secondary to chronic atrial fibrillation in patients not receiving thrombosis prophylaxis, although it was indicated according to accepted criteria; one as a result of digoxin toxicity leading to bradycardia and cardiac failure; and one deliberate drug overdose.

Causality of ADE was rated as definite in 20.0%, probable in 41.4%, possible in 31.4% and
possible/possible in 7.1% of cases. Severity was rated moderate in 84.3% and severe in 15.7% of cases. The ADE were considered definitely preventable in 53.4% of cases, possibly preventable in 23.3% and not preventable in 23.3%.

The proportions of admissions in the different ADE categories that were judged definitely preventable were ADR to a single drug 12/35 (34%), ADR because of multiple drugs 9/19 (47%), NC 9/9 (100%) and omission of indicated treatment or drug cessation 7/10 (70%). For the various categories of ADE, the proportions in which the manifestations were rated as severe were ADR 2/35 (6%), multiple drugs 3/19 (16%), non-compliance 3/9 (33%) and omission or cessation of drug treatment 3/10 (30%). The proportion of ADE that were rated severe and definitely preventable was greater in those ADE categories in which treatment was indicated but not taken (non-compliance and omission/cessation of indicated treatment) as compared to ADR because of single or multiple drugs (6/19 vs 5/54, \( P = 0.029 \) for severe rating; and 16/19 vs 21/54, \( P < 0.001 \) for definitely preventable).

**DISCUSSION**

We have found that a high proportion of emergency medical admissions in elderly people in our hospital resulted from ADE. The most common mechanism was ADR to a single drug, however, the categories in which a high proportion of the ADE were both severe and preventable were those in which drug treatment was indicated but not taken either because it was not prescribed or because of non-compliance.

The incidence of DRHA in the elderly we observed was higher than most but not all previous studies.\(^2,9\) Reasons may include our broad definition of ADE, the prospective design of our study allowing most patients to be interviewed and the age range we studied. Several studies have included patients aged 65 and over.\(^9-12\) Notably, the two other studies that used an older cut-off had incidence figures close to ours.\(^2,1\) We, however, did not demonstrate an association between age and DRHA or number of comorbidities or number of medications, which suggests that within a restricted very old age range in which multiple comorbidities and multiple medications are the norm, age per se is not an important risk factor for ADE. This is consistent with other studies confined to the geriatric age group.\(^3,7,10,13\) Positive relationships between age and DRHA have been found in studies without age restrictions.\(^11,14,15\) We were not able to substantiate the previously reported finding that the ADE incidence drops in the very very old.\(^7,13\)

Patients with ADE were taking significantly more medications than non-ADE patients, which is consistent with other studies.\(^3,10,12\) Although the number of comorbidities in ADE and non-ADE patients was not different, analysis of specific comorbidities may have been a more useful indicator of ADE risk. A previous finding that people with ADE are more likely to have a previous ADE history\(^10\) was not substantiated by this study. The trend for female gender to be associated with ADE is in keeping with previous studies.\(^14,16\)

The manifestations of ADE we observed are similar to those of other studies in this age group.\(^2,11\) Falls and falls associated with postural hypotension, heart failure and acute confusion were the most common presentations. These are commonly unrecognized presentations of ADE in the elderly.\(^17\)

The high proportion with causality classed as possible or possible/possible was not surprising given that ADR are often difficult to prove in the elderly. The criteria used were limiting first because drug levels are not measured routinely for the vast majority of the suspected culprit drugs and re-challenge poses particular hazards in this patient group and not surprisingly was almost never performed. Second, offending drugs had to be withdrawn to see if there was improvement, which posed problems in some cases where ADE were suspected by the investigators but not accepted by the doctor managing the case, and as the drug was not withdrawn this made it impossible to even reach possible status. The decision to include all possible cases in the overall incidence of DRHA was to avoid providing an unrealistically low estimate. However, if only probable and definite cases were included the incidence is still quite high at 18%. The assessment of causality is difficult to compare with many other studies as it was often not assessed in them. However, this could be a reason for a lower incidence in some if only ADE with definite causality were used.

Cardiovascular medications were implicated in almost half of the cases of DRHA, which is similar to some\(^2,10\) but higher than other studies.\(^9\) Given that approximately 60% of patients over 75 have cardiovascular disease it is not surprising that it is the most common medication group taken by this age group.\(^18-20\) Cardiovascular disease is problematic because treatment often requires more than one
medication, which may be one of unavoidable reasons for multiple drug use in the elderly.

The neurological drugs were the next highest ranking group of medications implicated but were responsible for a lower proportion than some but not all earlier studies. In our study, neurological drugs contributed to 9.6% of single medications causing ADE, but when the drugs from multiple drugs group were included they contributed to 20.5% of the offending drugs, indicating that neurological drugs often caused problems when given in combination with other drugs.

Adverse drug events as a result of multiple drugs were the second most important cause (25%) of ADE admissions. This compares to the 25% in a previous study. This suggests that in the elderly prescribing additional drugs requires careful consideration, particularly when new drugs have the potential to have additive adverse effects with existing drugs.

As all ADE in this study caused or contributed to hospital admission, they were all considered to be at least moderate or severe. Severity could not be assessed in relation to other studies as it was not analysed. The highest proportion of severe ADE was associated with omission of treatment and non-compliance. This is partly explained because the latter two included omission or non-compliance with anti-coagulant prophylaxis resulting in fatal or severe strokes. These were also the categories in which a high proportion of ADE were rated definitely preventable.

Strategies and further research to reduce elderly admissions resulting from ADE should therefore focus on these causes, encouraging treatment for conditions for which therapy is indicated and addressing causes of poor compliance in the elderly. However, it is also necessary to take care in combining drugs that share the same adverse effects and choose and monitor drugs carefully in the individual elderly person to avoid ADR. In particular, checking for postural hypotension, and avoiding drugs that predispose to falls, delirium and aggravate heart failure.

In our study, 53.4% of ADE were classed definitely avoidable, which translated to 15% of all acute medical admissions in this age group that potentially could have been prevented. The cost of these admissions was calculated to be A$157 700 based on a cost of A$332 per bed day (based on bed day charges for privately insured patients at the RHH, as at November 1998) for the 475 bed days of the 39 preventable admissions. This extrapolates to A$946 200 per year.

If the results from this study reflect experience more generally then this suggests that ADE are responsible for an alarming number of preventable hospital admissions in patients aged 75 years and over.

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REFERENCES