Drug-Related Deaths in a Department of Internal Medicine

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Background: Drug therapy is associated with adverse effects, and fatal adverse drug events (ADEs) have become major hospital problems. Our study assesses the incidence of fatal ADEs in a major medical department and identifies possible patient characteristics signifying fatal ADE risk.

Methods: During a 2-year period, a multidisciplinary study group examined all 732 patients who died—5.2% of the 13,992 patients admitted to the Department of Internal Medicine, Central Hospital of Akershus, Nordbyhagen, Norway. Decisions about the presence or absence of fatal ADEs were based on aggregated clinical records, autopsy results, and findings from premortem and postmortem drug analyses.

Results: In 18.2% of the patients (133/732) (95% confidence interval, 15.4%-21.0%), deaths were classified as being directly (64 [48.1%] of 133) or indirectly (69 [51.9%] of 133) associated with 1 or more drugs (this equals 9.5 deaths per 1000 hospitalized patients). Those with fatal ADEs (cases) were older, had more diseases, and used more drugs than those without fatal ADEs (noncases). In 75 of the 133 patients with fatal ADEs, autopsy findings and/or drug analysis data were decisive for recognizing the ADEs; in 62 of the remaining 595 patients, similar data proved necessary to exclude the suspicion of a fatal ADE. Major culprit drugs were cardiovascular, antithrombotic, and sympathomimetic agents.

Conclusions: Fatal ADEs represent a major hospital problem, especially in elderly patients with multiple diseases. A higher number of drugs administered was associated with a higher frequency of fatal ADEs, but whether a high number of drugs is an independent risk factor for fatal ADEs is unsettled. Autopsy results and the findings of premortem and postmortem drug analyses were important for recognizing and excluding suspected fatal ADEs.

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MATERIALS AND METHODS

The Central Hospital of Akershus, Nordbyhagen, Norway serves a population of 300,000, most of whom live in the residential area of Oslo, Norway. The Department of Internal Medicine covers all major subspecialties in internal medicine, covering mainly secondary care for its population. The present study is a joint project between the departments of internal medicine, pathology, and clinical chemistry, Central Hospital of Akershus; the Division of Clinical Pharmacology and Toxicology, Clinical Chemistry Department, Ullevaal University Hospital, Oslo; and the National Institute of Forensic Toxicology, Oslo.

The study, which started on October 3, 1993, and ended on November 21, 1995, covers 2 years (after accounting for 7 weeks of discontinuation because of construction work in the Department of Pathology, Central Hospital of Akershus). During the study, 13992 patients were admitted to the Department of Internal Medicine, 96% as emergency cases.

All in-hospital deaths (n=732) are included in the present study regardless of length of hospitalization.

PROTOCOL

For all patients who died, copies of relevant medical records, available biochemical and other test data, autopsy findings, and detailed information on drug use on hospital admission and during hospital stay were obtained.

Incomplete medication data obtained at hospital admission were thoroughly checked with relatives and the patients’ general practitioners.

In selected cases, drug analysis data were also provided. Plasma specimens were sampled and frozen on admission in the 13992 patients entering the hospital during the study period. However, the frozen samples were only stored for later analysis in the 732 patients who died. An autopsy was performed in 572 (78.1%) of these 732 patients. In these 572 subjects, postmortem blood specimens were also drawn with a standardized technique from the femoral vein at autopsy for possible later analysis. Among the remaining 160 subjects (21.9%), the next of kin declined autopsy in 59 (36.9%), autopsies were not done because of inadequate capacity in the Department of Pathology in 67 (41.9%). However, in 128 of these 160 patients not autopsied (including all 67 in the “inadequate autopsy group”), a definite diagnosis and cause of death were established, such as a metastasizing carcinoma, a large myocardial infarction (MI), and a computed tomographic-verified cerebral hemorrhage.

The classification of death with relation to suspected fatal ADEs (classification criteria described in Figure 1) followed 2 steps:

1. First, all members (J.E., I.B., J.E., O.B., T.H., and H.S.) separately reached a decision on whether drugs directly or indirectly might be connected to the fatal outcome after scrutinizing the following: (1) drug therapy and changes in therapy close to the time of death; (2) the clinical course, with emphasis on symptoms and signs preceding death; (3) cause of and mode of death; (4) laboratory and other test findings (including drug analysis data); and (5) autopsy findings.

2. At intervals, the group met for discussions. If all 6 group members had concluded that no suspicion of a fatal ADE existed in a particular patient, this conclusion was accepted as final. However, if one or more of the members had suggested a possible or probable fatal ADE, extensive discussions followed regarding all pros and cons for this suggestion. Four cases were finally defined as not classifiable, whereas a consensus was reached in the remaining 728.

IDENTIFICATION OF FATAL ADEs

Classification of ADEs included the World Health Organization’s definition of ADRs (a response to a drug that is noxious and unintended, and that occurs at doses normally used in humans for the prophylaxis, diagnosis, or therapy of disease or for the modification of physiological function), and adverse events related to intoxications and inappropriately prescribed or administered drugs. The identification of ADRs or ADEs was based on known drug actions and interactions, as described in the literature and drug monographs. An observed toxic drug value was not classified as causing death if the mode of death appeared to represent the natural course of their main disease or was not compatible with known drug actions.

Drugs used for necessary palliation were not classified as causing fatal ADEs even if a drug (eg, large doses of analgesics given for pain relief in patients with terminal cancer) may have shortened life slightly.

The classification criteria (Figure 1) were based on causality, as described by Wulf, and were subdivided into causal (subgroups a-d) and contributing (subgroups e-h) fatal ADEs, the subgroups indicating degrees of certainty in descending order.

REPRODUCIBILITY

Despite the fact that all members had participated in the pilot study and in finalizing the protocol, it was believed that a 2-year study might cause drift in the study technique. To test decision consistency, 1 in 8 cases was reclassified at random 3 months after the study was completed. The measure of agreement (κ) was 0.76, indicating good reproducibility. Divergent classifications almost exclusively occurred in patients among whom the weakest ADR classification had been registered.

STATISTICAL METHODS

Computations are based on the 728 consensus cases (unless otherwise noted). The disease classification followed the International Classification of Diseases, Ninth Revision, Clinical Modification.

With a 5% significance level, to have a test power of 80% to detect a mean difference of 1 in number of drugs administered—between cases (those with fatal ADEs) and noncases (those without fatal ADEs)—at least 700 patients must be included in the study. Thus, with 732 patients included, the power of the study is 80%.

Group differences between cases and noncases were tested with a 2-sided t test. When comparing frequencies, the χ² Fisher exact test was used. The test for trend was done with the Spearman rank correlation test. Each significance test was performed with a 5% significance level.
In 18.2% of the patients (133/732) (95% confidence interval, 15.4%-21.0%), deaths were classified as being directly (64 [48.1%] of 133) or indirectly (69 [51.9%] of 133) associated with 1 or more drugs (this equals 9.5 deaths per 1000 hospitalized patients) (Table 1). No sex difference was noted. Patients who died in the hospital were in general markedly older than those discharged from the hospital alive (70.5 vs 60.1 years; P < .001).

Men with fatal ADEs were significantly older than those without fatal ADEs, whereas no corresponding age difference was found among women (Table 1).

The number of drugs used on hospital admission was significantly higher in cases than in noncases, as was the number of concomitant diseases.

The proportion of fatal ADEs was highest among patients who died of gastrointestinal diseases (42.4%) (gastrointestinal ulcerations and hemorrhage caused by non-steroidal anti-inflammatory drugs or anticoagulants or antibiotic-associated pseudomembranous enterocolitis), approximately median among those with a cardiovascular cause of death, and significantly lower among those who died of cancer and respiratory diseases (Table 2). The median in-hospital time before death was similar in cases and noncases (3 days after hospitalization in both groups).

A significant association between the number of drugs used and the risk of drug-related death was seen (Table 3). As many as 202 patients used 12 or more drugs at the time of death, and 48 (23.8%) of these 202 deaths were classified as drug related compared with 85 (16.2%) among the remaining 526 patients using fewer than 12 drugs at the time of death (P < .01). A total of 495 different generic drugs were used in the last 2 days before death, and 792 different International Classification of Diseases, Ninth Revision, Clinical Modification, diagnoses were established in the total group.

A survey of the most commonly involved “culprit” drugs is given in Table 4, indicating that the most common drugs linked to fatal ADEs were antithrombotic agents, sympathomimetic drugs given for lung diseases, and cardiovascular drugs (angiotensin-converting enzyme inhibitors, calcium channel blockers, and diuretics).

Serum drug analyses were performed in 306 (41.8%) of the 732 patients, mostly taking digitalis, xanthines, and psychotropic drugs; when performed, they usually included more than 1 drug. Sixty-nine patients (22.5% of all drug analysis cases) of 728 deaths (9.5% of all study deaths) had 1 or more toxic drug concentrations on this analysis. Of these 69 patients, 29 (42.0%) were classified as having a fatal ADE related to the toxic drug value and 40 (58.0%) were not.

The group also discussed whether suspected drugs had been applied appropriately. In slightly less than half of the fatal ADE cases, it was concluded that various degrees of inappropriateness were seen in drug choice, route of administration, and/or drug dose. These conclusions were, however, only reached after considering all data made available after the patient had died—including data from the drug analyses and autopsy findings.

Few fatal ADEs were registered in the patient records, and only 8 were reported to the health authorities according to official regulations. In general, bleeding

Table 1. Characteristics of the 728 Patients Who Died in the Hospital During the 2-Year Study Period*  

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (n = 133)</th>
<th>Noncases (n = 595)</th>
<th>P Value</th>
<th>95% Confidence Interval†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>55 (41)</td>
<td>231 (39)</td>
<td>.59‡</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>78 (59)</td>
<td>364 (61)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (range), y</td>
<td></td>
<td></td>
<td>.74</td>
<td>-3.4 to 4.7</td>
</tr>
<tr>
<td>Female</td>
<td>72.5 (30-96)</td>
<td>71.8 (14-96)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>72.1 (27-89)</td>
<td>69.1 (25-94)</td>
<td>.02</td>
<td>0.4 to 5.4</td>
</tr>
<tr>
<td>Comorbidity§</td>
<td>5 (0-8)/4.7</td>
<td>4 (0-8)/3.9</td>
<td>&lt;.001†</td>
<td>0.4 to 1.2</td>
</tr>
<tr>
<td>No. of drugs</td>
<td></td>
<td></td>
<td>.01</td>
<td>0.2 to 1.8</td>
</tr>
<tr>
<td>On hospital admission</td>
<td>5 (0-12)/5.0</td>
<td>4 (0-12)/4.0</td>
<td>&lt;.001</td>
<td>0.4 to 1.5</td>
</tr>
<tr>
<td>In the past 48 h</td>
<td>9 (0-15)/9.5</td>
<td>8 (0-15)/8.5</td>
<td>.01</td>
<td>0.2 to 1.8</td>
</tr>
<tr>
<td>Length of stay, d</td>
<td>3 (0-59)/5.9</td>
<td>3 (0-76)/6.1</td>
<td>.85</td>
<td>1.7 to −1.4</td>
</tr>
</tbody>
</table>

*Data are given as the median (range)/mean unless otherwise indicated. Cases represent patients in whom 1 or more drugs supposedly caused or contributed to the fatal outcome; and noncases, all others.
†Level of significance of the differences between cases and noncases, using a 2-sided t test.
‡Measured with the χ² Fisher exact test.
§Number of diagnoses in addition to main diagnoses.
||Significant trend (Spearman rank correlation). P = .001 is the cutoff between 0 and 1 comorbidity.
complications related to the use of antithrombotic or anticoagulant agents and nonsteroidal anti-inflammatory drugs were readily recognized, whereas most others were not.

Autopsy findings and/or the results of drug analyses were judged decisive for identifying fatal ADEs in 75 of the 133 patients who were found to have fatal ADEs, and for excluding suspicions of fatal ADEs in 62 of the remaining 595 patients (Figure 2).

Three case histories may illustrate pertinent classifications.

Table 2. Main Cause of Death Among the 728 Patients Who Died in the Hospital During the 2-Year Study Period

<table>
<thead>
<tr>
<th>Causes of Death</th>
<th>Total No. of Patients</th>
<th>Cases, No. (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circulatory disorders</td>
<td>320</td>
<td>67 (20.9)</td>
</tr>
<tr>
<td>Respiratory diseases</td>
<td>183</td>
<td>21 (11.5)</td>
</tr>
<tr>
<td>Cancer</td>
<td>106</td>
<td>4 (3.8)</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>33</td>
<td>14 (42.4)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>86</td>
<td>27 (31.4)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>728</strong></td>
<td><strong>133 (18.3)</strong></td>
</tr>
</tbody>
</table>

*Main group classification according to the International Classification of Diseases, Ninth Revision (ICD-9).
†Cases represent patients with fatal adverse drug events. The number (percentage) is given for each group of diagnoses.

Table 3. Number of Drugs Administered in 728 Patients Who Died in the Hospital During the 2-Year Study Period

<table>
<thead>
<tr>
<th>No. of Drugs*</th>
<th>Total No. of Patients</th>
<th>Cases, No. (%)†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before Hospital Admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>128</td>
<td>17 (13.3)</td>
</tr>
<tr>
<td>2-3</td>
<td>214</td>
<td>31 (14.5)</td>
</tr>
<tr>
<td>4-5</td>
<td>165</td>
<td>34 (20.6)</td>
</tr>
<tr>
<td>≥6</td>
<td>221</td>
<td>51 (23.1)</td>
</tr>
<tr>
<td>Last 48 h Before Death</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-5</td>
<td>176</td>
<td>23 (13.1)</td>
</tr>
<tr>
<td>6-8</td>
<td>183</td>
<td>34 (18.6)</td>
</tr>
<tr>
<td>9-11</td>
<td>167</td>
<td>28 (16.8)</td>
</tr>
<tr>
<td>≥12</td>
<td>202</td>
<td>48 (23.9)</td>
</tr>
</tbody>
</table>

*Grouped by quartiles.
†Cases represent patients with fatal adverse drug events. The number (percentage) is given for each quartile. The test for trend was significant (P = 0.01, Spearman rank correlation).

Table 4. Groups of Administered Drugs Found to Be Associated With Fatal ADEs*

<table>
<thead>
<tr>
<th>Class of Drugs</th>
<th>No. of Times Involved</th>
<th>Types of Fatal ADEs Observed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>61</td>
<td>Cardiodepression, hypotension, dehydration, AV block, bronchial obstruction, β-blocking withdrawal effect, and renal failure</td>
</tr>
<tr>
<td>Antiasthmatic</td>
<td>55</td>
<td>Arrhythmias, myocardial infarction, and cardiac arrest</td>
</tr>
<tr>
<td>Antithrombotic</td>
<td>45</td>
<td>Cerebral hemorrhage, gastrointestinal hemorrhage, and cardiac tamponade</td>
</tr>
<tr>
<td>Anti-infective</td>
<td>14</td>
<td>Pseudomembranous enterocolitis, renal failure, hepatic failure, pancreatitis, and bone marrow depression</td>
</tr>
<tr>
<td>Antipsychotic or anxiolytic</td>
<td>12</td>
<td>Respiration depression and severe sedation</td>
</tr>
<tr>
<td>Analgesic</td>
<td>12</td>
<td>Respiratory depression, hepatorenal syndrome, and severe sedation</td>
</tr>
<tr>
<td>NSAID</td>
<td>6</td>
<td>Hemorrhagic gastrointestinal ulceration</td>
</tr>
<tr>
<td>Other</td>
<td>32</td>
<td>Miscellaneous</td>
</tr>
</tbody>
</table>

*The total number of drugs involved in fatal ADEs was 237. Some cases involve more than 1 drug. ADE indicates adverse drug event; AV, atrioventricular; and NSAID, nonsteroidal anti-inflammatory drug.
disease, with marked exacerbation necessitating relevant treatment. He died during infusion of a β₂-agonist, probably precipitating further coronary ischemia, extension of his MI, and arrhythmia. Autopsy data and the association between the infusion of terbutaline and clinical deterioration/death indicated that terbutaline might have contributed to his death. This case was classified as fatal ADE category g (contributing).

CASE 3

This patient was a 72-year-old woman with long-standing bronchial asthma, epilepsy, and rheumatoid arthritis. She was treated with low-dose furosemide for mild symptoms of heart failure. A secondary low serum potassium level was treated with potassium tablets. She was admitted with pneumonia, which was treated with intravenous cephalothin sodium (Cefalotin). During hospitalization, she developed pseudomembranous enterocolitis, for which metronidazole was administered. All other medication was continued, including potassium tablets and furosemide. After partial recovery, she was discharged from the hospital for 2 days; however, she was then readmitted with possible septic shock and, therefore, was admitted to the intensive care unit. Despite conventional treatment, including vasopressors and antibiotics, she died 19 hours after readmittance to the hospital. Autopsy results revealed a large bleeding esophageal ulcer, which had perforated to the mediastinum. A remnant of potassium tablets was also found in the ulcer, as was massive aspiration of blood to both lungs. The pseudomembranous enterocolitis was in remission. Serum analysis of phenobarbital showed therapeutic concentrations. The patient had not reported chest pain.

In conclusion, cephalothin sodium given for pneumonia caused pseudomembranous enterocolitis, causing dehydration due to massive diarrhea, which was worsened by not discontinuing treatment with furosemide. This patient died of a large bleeding esophageal ulcer, which was linked to the use of potassium tablets given while she was dehydrated and had difficulties in swallowing. Without an autopsy, this case would have been missed.

This case was classified as fatal ADE categories a (direct—potassium tablets) and f (contributing—cephalothin sodium causing pseudomembranous enterocolitis and furosemide increasing dehydration).

The use of potassium tablets and furosemide should have been avoided, and the fatal ADE might have been prevented.

COMMENT

The high incidence of fatal ADEs observed underscores the validity of the concern expressed recently about a possible increasing incidence of drug-related fatalities. Considering the extremely complex array of possible drug-drug and drug-disease interactions in subjects taking the high number of drugs observed in this study, serious ADEs may even have been overlooked.

The fatal ADE incidence of 9.5 per 1000 hospitalized patients in the present study is higher than that given in earlier reports, whereas the in-hospital death rate of 5.2% (732/13392) is similar to that reported in comparable departments of internal medicine. The differences in the reported incidence of fatal ADEs are difficult to compare because of differences in materials, methods, and criteria for classification of deaths as drug related. Whereas some use the World Health Organization’s definition of ADR/fatal ADR, we have included all deaths in which a drug might have caused or contributed to death. By definition, this implies that inappropriately chosen or administered drugs were included. To the patient and the clinician, this should probably be the desired approach because the total hazard of drug therapy is what matters to the patient. However, apparently our criteria for “drug-related death” are at least as strict as those applied in the literature. To our knowledge, autopsy findings have not been applied routinely in previously published studies, nor have we found studies in which premortem and postmortem blood specimens have been drawn for later drug analyses. As previously noted, these data appeared decisive for recognizing fatal ADEs in 75 of the 133 patients who were found to have fatal ADEs and for excluding suspected fatal ADEs in 62 of the remaining 595 patients, and, therefore, appear to be of major importance for identifying fatal ADEs.

The multidisciplinary approach may also have contributed to the high recognition rate compared with previous studies; the 2-step approach may have done so as well. Thus, a case was often suggested by only 1 or a few group members, even when readily recognized and accepted by all the other members after having been brought forward. Whereas unanimous agreement on the presence or absence of fatal ADEs was reached in all, the subclassification was somewhat more ambiguous, and occasionally had to be decided by a majority vote. The hospital clinicians, as judged by the patient records, only recognized a few cases, and only 8 had been reported to the health authorities despite regulatory demands.

Drift in the technique during the 2-year period was probably small, as demonstrated by a k of 0.76 in the random sample of 85 reclassified patients. Moreover, the differences in classification were mostly seen in cases initially classified as indirectly drug related.

There were problems using commonly used algorithms for establishing causality concerning ADRs in the present study, partly because these algorithms require drug...
withdrawal and rechallenge to achieve a high probability score on the ADR, which of course is impossible in patients who die.\textsuperscript{27,28} Moreover, these algorithms do not add scores for postmortem drug analyses’ or autopsy findings, variables often of decisive importance in our study.

Men with assumed fatal ADEs—but not women—were significantly older than those without assumed fatal ADEs. The differences between cases and noncases were, however, hardly of diagnostic importance because the age differences were small.

Most patients who died had multiple diseases, and patients with fatal ADEs had significantly more diseases than those without fatal ADEs.

The median number of drugs used on hospital arrival was 4, but this increased dramatically during hospitalization (Table 1). In a US study,\textsuperscript{29} it was found that the risk of an ADR increased from 13% among patients taking 2 drugs to 82% for patients taking 7 or more drugs.

Considering differences in the pharmacokinetics of most drugs seen in a senescent diseased population compared with a healthy adult population, considerable caution should be exercised when dosing and adding new drugs to complex medical regimes in elderly patients.\textsuperscript{29-34}

Computer software programs have been introduced and recommended as a drug treatment quality assurance tool, aiming at reminding prescribers of potential important drug-drug and drug-disease interactions.\textsuperscript{35-38} However, this approach is only applicable in hospitals with direct computer entry of medication orders.

Our study has some limitations, such as being a one-site study and using only one investigator group. Moreover, autopsy data were lacking in 22% of the cases, and the investigators were by definition not blinded to the outcome. However, the prospective approach following a half-year pilot study to refine the study techniques, the multidisciplinary approach, and the retesting of a randomized group of cases may to some extent meet the criticisms following these limitations.

In the present study, 96% of all patients admitted to the department were emergency cases, were often critically ill, and had complex drug regimens and clinical presentations that make rapid correct assessment difficult.\textsuperscript{13,29} It is, therefore, hardly surprising that inappropriate drug regimens may be introduced as a result of misinterpretation of the clinical picture, as also demonstrated by autopsy findings.

Although the consensus group made an effort to decide if the drugs given were given for a correct indication, preventability as such is hard to judge retrospectively. However, misinterpretation of symptoms and signs, especially in the emergency department; lack of monitoring drug concentrations; and inadequate adjustment of drug doses according to age, body dimensions, metabolism, and pharmacokinetics have resulted in several fatal ADEs that ought to have been preventable.\textsuperscript{30-43}

Fatal ADEs were mainly early hospital events (median time to death, 3 days), suggesting the importance of exercising considerable caution in therapy choice when encountering elderly patients with complex diseases in an emergency situation.

By definition, this study has only dealt with ADEs, and cannot suggest the possible magnitude of years lost or gained by drug therapy. It does, however, actualize the old proverb: Do not harm your patient.

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