Important New Evidence Service

In Partnership with The Centre for Medicines Optimisation at Keele University

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Medicines optimisation: what is the incidence of drug-related deaths in hospital inpatients?

Adverse drug reactions (ADRs) are an important cause of morbidity and mortality. While many studies have assessed the incidence of ADRs in hospitalised patients, less is known about the rate of deaths related to ADRs in hospitals. A new retrospective cohort study has examined the incidence, risk factors and characteristics of drug–related deaths in a tertiary care hospital in Spain. Around 1 in 15 inpatient deaths were related to an ADR, with more cases reported in males, the 'younger elderly' and in those taking a greater number of drugs. This study provides further evidence for ADRs as an important cause of death in hospitalised patients.

Reference: Montané E, Arellano AL, Sanz Y *et al*. (2018) Drug-related deaths in hospital inpatients: A retrospective cohort study. Br J Clin Pharmacol, 84: 542–552. doi: 10.1111/bcp.13471

What do we know already?

- It is estimated that about 5% (1 in 20) of hospital admissions are medicines-related, and about half of these are thought to be preventable (ref: WeMeRec bulletin on medicines-related hospital admissions).
- Despite many studies assessing the incidence of ADRs in hospitalised patients, fatalities related to ADRs are often secondary outcomes, and therefore data are more limited.
- In the few studies that are available, there is wide variability in the incidence of drug-related deaths, ranging from 0.02% to 0.95% for incidences of hospital admissions and from 3% to >18% for incidences of patient deaths in hospital (Montané *et al*, 2018).
- A 2004 study conducted in two large NHS hospitals found that over 2% of patients admitted with an ADR died, suggesting that adverse events may be responsible for the deaths of 0.15% of all patients admitted to these hospitals. Aspirin, non-steroidal anti-inflammatory drugs and diuretics were the drugs most commonly implicated, consistent with the results of other studies.

What does this evidence add?

- Whilst its single-centre, retrospective design is a limitation, this new study provides additional evidence for the major role that medicines have as a cause of death in hospitalised patients, with 7% (1 in 15) of all inpatient deaths at this hospital associated with medicines.
- Drug-related deaths were more common in men, younger patients (median age 72 years) and in patients receiving more drugs compared with deaths from other causes. This is contrary to previous data where ADRs were more frequent in women, the elderly and patients with high co-morbidity. Possible explanations for these findings may be the methods used to assess fatal ADRs in this study and differences in the characteristics of patients attending this tertiary hospital (and its available medical specialities) compared with other 'general' hospitals.
- Most ADRs are predictable from the known pharmacology of the drug and are therefore likely to be preventable. This is demonstrated in the study, which reported that about half of the drug-related deaths were potentially preventable. Haemorrhages and infections occurred in the majority of drug-related deaths in this study, with antithrombotic drugs and antineoplastics combined with glucocorticoids being implicated in most of the events.

Study details

Population:

- This retrospective cohort study was performed in 2015 in a tertiary care hospital in Barcelona with 511 beds for a population of 850,000 people.
- From the database of all patients who died at the hospital during 2015 (excluding deaths in the emergency room), patients were selected for further review if their death diagnosis was included in a predefined list of diseases and syndromes considered potentially to have been caused by drugs.

Intervention:

- All potential cases were reviewed by the Drug Safety Committee of the hospital to determine whether death was related to drugs by applying World Health Organization-Uppsala Monitoring Centre (WHO-UMC) criteria, which applies one of six categories (*certain, probable/likely, possible, unlikely, conditional/unclassified and unassessable/unclassifiable*). The Naranjo algorithm (*link to web tool*) was also used to score causal probability (definite [9-12 points], probable [5-8 points], possible [1-4 points] and doubtful [0 points]).
- An ADR was defined as per the EU Directive 2010/84/EU as 'a response to a medicinal product that is noxious and unintended effects resulting not only from authorised use of a medicinal product at normal doses, but also from medication errors and uses outside the terms of the marketing authorisation, including the misuse, off-label use and abuse of the medicinal product'.
- Schumock and Thornton criteria were applied to identify preventable drug-related deaths. The seven criteria checklist (*link to web tool*) assesses mainly the appropriateness of the drug according to the patient's condition and to pharmacokinetic characteristics of the drug, drug monitoring and drug-drug interactions. Co-morbidity was measured using the Charlson comorbidity index - a validated method of estimating risk of death from co- morbid disease in longitudinal studies (range 0-8, with a higher score indicating worse prognosis).

Outcomes and results:

- The study aimed to determine the incidence and risk factors for drug-related deaths. Secondary objectives were to identify the drugs involved and to describe the characteristics of the associated ADRs, to assess drug-drug interactions and to identify preventable ADRs.
- Of the 21,483 patients admitted to the hospital, there were 1,135 inpatient deaths (18.9%), with diagnosis of death available for 1,036 of these patients (91.3%).
- After drug causality assessment, 73 patients were considered as drug-related death cases (0.34% of all hospital admissions and 7.05% of all inpatient deaths). All deaths were classified as ‘probably’ or ‘possibly’ related to drugs, irrespective of the assessment method used.
- For the cases of drug-related death, the median age was 72 (range 19-94 years) and 72.6% were men. Median Charlson score was 2 points, median number of drugs during an ADR episode was 7 (range 2-14) and median hospital stay was 5 days (range 0-57).
- The ADR was the cause for hospital admission in 67 out of the 73 drug-related deaths (91.8%), with the ADR having started in hospital for the remaining 6 patients.
- In the 6 patients whose ADR started during their hospital stay, four had received cytotoxic and/or immunosuppressant drugs for haematological malignancies and developed respiratory infections or sepsis. One patient developed haemorrhagic shock following intravenous dexketoprofen and one patient developed a retroperitoneal haematoma following the use of enoxaparin for atrial fibrillation. The incidence of hospital-acquired fatal ADR calculated from all admissions was 0.03% (6/21,483) and the incidence of hospital-acquired fatal ADR was 0.58% of patients who had died (6/1,036).
- The most frequent drug-related deaths were as a result of haemorrhage (34 cases, 46.6%), followed by sepsis or infections in drug-immunosuppressed patients (32 cases, 43.3%).
- In 41 (56.2%) of drug-related deaths, there was only one drug involved, with two drugs in 23 cases (31.5%), three drugs in eight cases (11%) and four drugs in one case (1.4%). In 32 cases, a drug-drug interaction was present, all of which were pharmacodynamic and synergistic interactions.
- In total, 116 drugs were implicated. The most commonly involved drugs were aspirin (20 cases, 17.2%), prednisone (15 cases, 12.9%), acenocoumarol (11 cases, 9.5%), dexamethasone (6 cases, 5.2%), ciclosporin (5 cases, 4.3%) and clopidogrel (4 cases, 3.4%).
- The medical indications for the drugs were atrial fibrillation and solid tumours (15 cases for each indication, 20.5%).
- The related drug was started within a week before the ADR in eight patients (11%), one week to 6 months before the ADR in 27 patients (37%) and greater than 6 months in 36 patients (49.3%).
- Drugs were considered the cause of death in 38 (52.1%) cases and ‘contributed’ to death in 35 (47.9%) patients. The main contributive causes for intracranial haemorrhages were falls and hypertension.
- Drug-related deaths were potentially preventable in 34 cases (46.6%) according to Schumock and Thornton criteria – a finding similar to previous studies.
- Male gender, age (younger elderly patients) and greater number of drugs were risk factors for drug-related deaths.

Level of evidence: Level 2 according to the SORT criteria.

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