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RESEARCH LETTER TO THE EDITOR

Potential drug–drug interactions in deceased inpatients

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Dear Sir,

Drug–drug interactions (DDIs) are a common problem in patients with polypharmacy causing severe, or even fatal adverse drug reactions (FADRs) [1]; moreover, DDIs have increased significantly in the past two decades due to the increasing number of prescriptions per patient [2]. The prevalence of DDIs in hospitalized patients ranges from 15 to 45% [3]. A recently published meta-analysis [4] reports a prevalence of potential DDIs (pDDIs) ranging from 16.3 to 71.1% among general inpatients, and from 46.3 to 90.3% among intensive care unit (ICU) patients. According to a meta-analysis, DDIs cause 22% of the severe adverse drug reactions (ADRs) in hospitalized patients [5]. Due to the importance of the issue, the scarce bibliography on the prevalence of potential DDIs in cases of drug-related deaths in hospitalized patients, we carried out an observational cross-sectional study in a large sample of patients who died during admission to a university hospital to determine the prevalence of pDDIs among these inpatients, and to analyze the risk factors associated with drug-related deaths.

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For the purpose of this study, an observational cross-sectional study was conducted in consecutive inpatients who had died between 1 January 2009 and 31 October 2010 in San Cecilio University Hospital (Granada, Spain). The study inclusion criteria were: adult (≥ 18 years old) patients of either gender who had died in any hospital department, excluding the emergency department. Exclusion criteria were: patients with terminal illness included in oncologic palliative care; patients with FADRs due to drugs administered prior to admission to hospital; drug consumption in a suicide attempt; hospital stay < 24 h. This study shows the analysis of a subgroup of patients ($n = 925$), after exclusion of patients in oncologic palliative care ($n = 368$) and patients with FADRs due to drugs prescribed before admission ($n = 95$), belonging to a wider sample ($n = 1388$) whose analysis was previously reported [6]. From the clinical records of patients, data on gender, age, diagnosis, clinical evolution, cause of death, length of stay, department in which the death took place, and pharmacological treatment received during the hospital stay were gathered. The researchers independently reviewed all clinical records evaluating the association of drugs with the death of patients, and then met to decide on the degree of association of drugs with the death after an exhaustive case-by-case discussion. The database was reviewed by a computerized statistical software (STATA 13.0) based on Stockley´s drug interactions book [7] for detecting pDDIs through their anatomical therapeutic chemistry (ATC) [8] codes combination. Potential DDIs (pDDIs) were defined as drug pairs that could potentially interact and result in adverse reaction, which had been previously described in an interaction database, drug reference guides or drug compendia [4, 5]. The pDDIs were registered according to Stockley's Drug Interactions [7]. ADRs were defined as proposed by the WHO as "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." Assessment of the causality relationship between death and drug consumption was based on criteria applied by Ebbesen et al. [9] that were previously used and

described in a study by our research group [6]. No causality relationship could be established among pDDIs and drug-related deaths because no tool to assess this relationship has been reported yet. Diagnoses were encoded using the 10th revision of the international classification of diseases (ICD-10), [10] and drugs using the ATC classification [8]. The main outcome variable was the prevalence of pDDIs among inpatients included in the study; secondary variables were the drugs associated with pDDIs. Predictive variables for drug-related deaths included age, gender, number of drugs administered, number of diseases, length of stay, and hospital department. A descriptive statistical analysis was performed. The association of the presence or absence of drug-related death with the study variables was examined using the Chi square test for qualitative variables and the Student's *t* test for numerical variables. The independent effects of the different covariates on the presence/absence of ADRs-related death were studied by fitting a logistic regression model and estimating the odds ratio for each study variable. STATA 13.0 was used for the statistical analysis.

During the study period, 925 patients fulfilled the inclusion criteria. Their mean age was 76.5 ± 12.4 years, 43.5% were female, the mean length of hospital stay was 9.3 ± 10.2 days and the mean number of drugs per patient was 9.7 ± 3.3 (Table 1). A total of 2653 pDDIs were detected in 765 (82.7%) patients of the global sample. The most frequently detected pDDIs (Table 2) were opiate/opiate in 333 (36%) of the patients in the global sample; corticosteroid/potassium-depleting diuretic in 240 (25.9%) patients; and low molecular weight heparin (LMWH)/angiotensin-converting enzyme inhibitor (ACEI) in 162 (17.5%). A total of 21 drugs were involved in pDDIs, and NSAIDs were the most common in 603 cases (65.2% of patients in global sample), followed by potassium-depleting diuretics in 538 cases (58.2%), and opiates in 505 (54.6%). The main causes of hospital death in the global sample were multiple organ failure (14.8%); respiratory failure (13.1%); septic shock (12.5%); heart failure (8.9%); and acute renal failure (8.1%).

A total of 143 deaths (15.5%) were suspected to be drug related (Table 1). Out of these 143 deaths, 135 (94.4%) cases had, at least, one pDDI. Among drug-related deaths (Table 2), the most frequent DDIs were opiate/opiate in 63 (44%) patients; corticosteroid/potassium-depleting diuretic in 49 (34.3%); and NSAID/NSAID in 42 (29.4%). The most frequent causes of death of patients with FADRs were cardiac dysrhythmia (19.7%); gastrointestinal bleeding (15.5%); and respiratory failure (12.7%).

As shown in Table 1, patients with a suspected drug-related death had a significantly longer length of stay ($P < 0.001$), received more drugs ($P < 0.001$) and had more pDDIs ($P < 0.001$) than patients without drug-related death. Multivariate logistic regression analysis reveal that the receipt of more than 12 drugs, the length of stay, and the presence of, at least, one potential drug–drug interaction (≥ 1 pDDI) are the independent risk factors for drug-related deaths in the study population (Table 3).

Our study finds a high prevalence of drug-related deaths (15.5%) that could be due to applying of a sensitive previously used methodology [6, 9] for detection of ADRs in deceased patients. In fact, our prevalence is similar to that reported by a Norwegian group [9] in an Internal Medicine Department (18.2%), and higher than reported (9.6%) in a recently published meta-analysis [11]. We also detect a prevalence of pDDIs (82.7%) in patients deceased in

Table 1 Characteristics of the patients included in the study

Variables/groups	All deaths	Drug-related deaths	Non-drug-related deaths	*P* value
Number of deaths	925	143	782	
Age[a]	76.5 ± 12.5	78.5 ± 10.1	76.2 ± 12.8	0.296
Females, *n* (%)	403 (43.5)	71 (49.6)	332 (42.5)	0.119
Comorbidities[a]	4.8 ± 1.8	4.9 ± 1.7	4.7 ± 1.8	0.317
Length of stay in days[a]	9.3 ± 10.2	12.1 ± 10.7	8.8 ± 10.0	< 0.001*
Number of drugs[a]	9.8 ± 3.3	11.4 ± 2.8	9.5 ± 3.3	< 0.001*
Potential interactions, *n* (%)	765 (82.7)	135 (94.4)	630 (80.6)	< 0.001*
Department				
Oncology, *n* (%)	42 (4.5)	6 (4.2)	36 (4.6)	
Intensive care, *n* (%)	160 (17.3)	13 (9.1)	147 (18.8)	< 0.001*
Internal medicine[b], *n* (%)	572 (61.8)	89 (62.2)	483 (61.8)	
Surgery[c], *n* (%)	151 (16.3)	35 (24.5)	116 (14.8)	

[a]Data expressed as mean ± SD

[b]Other medical specialties

[c]Other surgical specialties

*$P < 0.05$

Table 2 Most frequently detected potential drug–drug interactions in the global sample and in patients with/without drug-related death

Potential drug–drug interactions	All deaths ($n=925$)	Drug-related deaths ($n=143$)	Non-drug-related death ($n=782$)	P value
Opiate/opiate, *n* (%)	333 (36)	63 (44.0)	270 (34.5)	0.037*
Corticosteroid/diuretic, *n* (%)	240 (25.9)	49 (34.3)	191 (24.4)	0.017*
LMWH/ACEI, *n* (%)	162 (17.5)	31 (21.7)	131 (16.7)	0.153
NSAID/NSAID, *n* (%)	157 (17.0)	42 (29.4)	115 (14.7)	< 0.001**
LMWH/antiplatelet, *n* (%)	150 (16.2)	25 (17.5)	125 (16.0)	0.624
LMWH/NSAID, *n* (%)	120 (13.0)	33 (23.1)	87 (11.1)	< 0.001**
NSAID/diuretic, *n* (%)	108 (11.7)	30 (21.0)	78 (10.0)	0.001**
Antipsychotic/antipsychotic, *n* (%)	100 (10.8)	23 (16.1)	77 (9.9)	0.039*
Digitalis/diuretic, *n* (%)	99 (10.7)	24 (16.8)	75 (9.6)	0.018*
Opiate/BZD, *n* (%)	67 (7.2)	20 (14.0)	47 (6.0)	0.002**
NSAID/corticosteroid, *n* (%)	53 (5.7)	18 (12.6)	35 (4.5)	0.001**
Antipsychotic/BZD, *n* (%)	40 (4.3)	9 (6.3)	31 (4.0)	0.024*

LMWH low molecular weight heparin, *ACEI* angiotensin-converting enzyme inhibitor, *NSAID* non-steroidal anti-inflammatory drug, *BZD* benzodiazepine

*$P<0.05$

**$P<0.01$

Table 3 Logistic regression analysis of risk factors associated with drug-related deaths in the hospital

Variable	OR (95% CI)
Sex	
Male	1.00
Female	1.33 (0.91–1.94)
Age (years)	
18–68	1.00
69–78	0.99 (0.54–1.83)
79–84	1.20 (0.65–2.22)
> 84	1.12 (0.60–2.09)
Number of diseases	
≤ 4	1.00
> 4	0.89 (0.59–1.35)
Number of drugs	
0–5 drugs	1.00
6–9 drugs	0.63 (0.26–1.51)
10–12 drugs	2.08 (0.92–4.70)
> 12 drugs	2.54 (1.10–5.89)*
Department	
Internal medicine[a]	1.00
Oncology	0.95 (0.34–2.62)
Intensive care	0.57 (0.29–1.08)
Length of stay 1.35 (0.83–2.19) surgery[b]	1.02 (1.01–1.04)*
Potential drug–drug interactions	
0	1.00
≥ 1	2.68 (1.23–5.86)*

OR odds ratio, *CI* confidence interval

[a]Other medical specialties

[b]Other surgical specialties

*$P<0.05$

hospital that is higher than reported in general inpatients (44%) or in ICU patients (63%) [4].

In relation to inpatients with drug-related death, we find an even higher prevalence of pDDIs (94.4%), similar to that reported (90.3%) in a study performed with ICU patients [12]. Our study population consists of deceased inpatients, i.e., patients seriously ill who died in the hospital, and who remained for a long time in the hospital and simultaneously received several drugs. Our study suggests the harmful impact of the DDIs in the health of patients, even in those cases of potential DDIs without a previously reported clinical relevance, because the adjusted multivariate analysis shows that more than one potential DDI constitutes an independent risk factor for drug-related deaths.

As the multivariate analysis shows, the presence of, at least, one pDDI, the prescription of more than 12 drugs simultaneously, and the length of stay emerge as independent risk factors for drug-related death. The risk of fatal ADR has previously been associated with polypharmacy [6, 9, 11]. In relation to pDDIs as an independent risk factor for drug-related death, to our knowledge, only one study [13] has reported a significant association with an increased risk of mortality in patients exposed to, at least, two potentially severe DDIs. In our study, the presence of, at least, one potential DDI is associated to the almost threefold increased risk of drug-related death independently of the global number of drugs; we consider that this fact constitutes a novelty in the area of drug-related deaths in hospitalized patients. Moreover, we have not found any study that reports the length of stay as an independent risk factor for ADR-related death.

This study has the limitations associated with a single center observational design; retrospective data collection; the gathering of information from clinical records; besides, renal or liver failure were not included as independent conditions (we only included the total number of diseases) that could be related to drug-related death risk; and we did not consider the appropriateness of prescriptions. Study strengths include a wide sample, the application of a validated methodology for assessment of drug-related deaths, the computerized tool based on Stockley´s Drug Interactions book for detecting pDDIs, and the utilization of adjusted multivariate analysis to control confusion variables.

In conclusion, a high prevalence of pDDIs is detected among deceased inpatients, especially in patients with drug-related deaths. The independent risk factors for death related to ADR are the receipt of more than 12 drugs, the presence of one pDDI and length of stay. To ameliorate the risk of drug–drug interactions, and considering that NSAIDs and diuretics are the most involved drugs in pDDIs, we recommend using NSAIDs at the lowest dosages and for the shortest time, especially in poly-medicated inpatients; besides, we recommend a progressive reduction of the dosage of potassium-depleting diuretics as quickly as clinically possible in these patients, and to reassess their indication every day.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Statement on human and animal rights This study was approved by the Clinical Research Ethics Committee of San Cecilio University Hospital, Granada (Spain). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study formal consent is not required.

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