BJA

British Journal of Anaesthesia, 124 (2): 197–205 (2020)

doi: 10.1016/j.bja.2019.10.013
Advance Access Publication Date: 25 November 2019
Quality and Patient Safety

QUALITY AND PATIENT SAFETY

Patterns in medication incidents: A 10-yr experience of a cross-national anaesthesia incident reporting system

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Abstract

Background: Medication-related adverse events (MRE) in anaesthesia care are frequent and require a deeper understanding if we are to prevent medication harm.
Methods: We searched for reported MRE from the Spanish Anaesthesia Incident Reporting System (SENSAR) database over a 10-yr period. SENSAR is a cross-national, multicentre system focused on perioperative and critical care. A descriptive analysis of independent variables, phase of medication process, type of MRE, and medication group involved, and their relationships with morbidity was conducted.
Results: A total of 1970 MRE were identified from 7072 reported incidents. Patient harm was reported in 31% of the MRE. The administration phase was more frequent (42%) and showed the highest harm rate (44%) compared with other medication process phases. The most frequent types of MRE were wrong treatment regimen and wrong medication (55% of cases). The medication groups most commonly reported were those that alter haemostasis (18%), vasoconstrictor agents (13%), and opioids (10%). Vasoconstrictor agents, benzodiazepines, and neuromuscular blocking agents were the medication groups involved in patient harm four-fold more, and opioids three-fold more, than medications that alter haemostasis. The 1970 incidents were investigated and led to implementation of 4223 local corrective patient safety and quality improvement measures.
Conclusions: Patient harm in the perioperative setting from medications remains a major issue for patients, hospital leaders, and clinicians. We found patterns and specific causes that can be mitigated through proven systems solutions, and should be taken into consideration in designing sustainable solutions for safe perioperative care.
Clinical trial registration: NCT03615898.

Keywords: anaesthesia; medication errors; opioids; patient safety; quality improvement; risk management; vasoconstrictors

Received date: 11 February 2019; **Accepted:** 6 October 2019

Editor's key points

- Medication-related adverse events are a frequent cause of patient morbidity and mortality in perioperative care, and must be better understood in order to prevent medication harm.
- Data from a bi-national, multi-centre system focused on perioperative and critical care were analysed, in particular the incidence and characteristics of medication-related adverse events over a 10-yr period.
- Of 7072 incidents analysed, 1970 adverse events were identified, with 31% resulting in patient harm, most frequently in the administration phase.
- Patient harm was more likely in errors involving vasoconstrictor agents, benzodiazepines, and neuromuscular blocking agents.

Adverse events and patient safety assurance are global growing challenges to healthcare service delivery.[1] The epidemic of harm is estimated to cause 100 000–400 000 preventable deaths per yr and represents the third leading cause of death in the USA.[2,3] Even though some remain sceptical about these claims,[4] the Joint Commission reports that medication errors are involved in 5.4% of all severe injuries or patient deaths, and the economic impact is projected to cost up to €819 million/yr.[5–7]

Correct medication management in the perioperative environment continues to present a unique organisational and professional challenge for anaesthesiologists and hospital risk management. Anaesthesiologists prescribe, prepare, and administer high-risk medications estimated to be up to half a million drug doses throughout their professional career.[8,9] Anaesthesia providers are unique in that they work in a well-documented high-risk area, without independent oversight, which is standard in other areas of medicine and in high-risk industries.[10] Medication-related events in surgical patients are amongst the most frequent errors, occurring up to one in 20 errors per anaesthetic.[11] Importantly, most MRE are preventable, with as many as 79% amenable to prevention.[12,13]

Incident Reporting Systems (IRS) capture information that is often missed by other surveillance systems.[14,15] IRS, the backbone of a safety culture, offer important opportunities to harvest meaning from data and identify system issues underlying MRE, and can help identify and implement corrective strategies.[16] For example, the implementation of a barcode-based system and a medication safety bundle can reduce self-reported errors and intercepted error rates.[17] These, and other human factors-driven system solutions such as prefilled syringes could help reduce the cognitive workload on anaesthesia providers and the possibility for medication errors.[18] Standardisation of medication concentrations and equipment, redesigning the clinical work space,[19] or using electronically controlled smart pumps with standardised concentrations are other effective, evidence-based recommendations.[20] The aim of this study was to assess the characteristics and severity of MRE in the perioperative environment as reported to a cross-national IRS in order to inform on methods to reduce or prevent future similar events.

Methods

Adverse medication incidents were retrospectively collated from the interactive Spanish Anaesthesia and Reanimation Incident Reporting System (SENSAR) database.[21–23] The SENSAR is a cross-national, multicentre incident reporting system focused on the perioperative and critical care environments. The incidents were reported and analysed during a 10-yr period, from 1 January 2008 to 31 December 2017. We obtained ethics approval from the Spanish Agency for Medicines and Healthcare Products (AEMPS) and approval from the Ethics Committee from Hospital Universitari i Politécnic la Fe, Valencia, Spain. The study was registered in ClinicalTrials.gov (NCT03615898). We followed the recommendations of Good Clinical Practices conducted in compliance with the Declaration of Helsinki, and the recommendations of the STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) statement. The Standards for Quality Improvement Reporting Excellence (SQUIRE) were used to draft the manuscript.[24]

Anaesthesiologists, anaesthesia trainees, and anaesthesia and intensive care nurses reported incidents anonymously using a web form accessed through a generic code for each of the 104 SENSAR participating hospitals in Spain and Chile. Reports are recorded in an electronic database using a semi-structured form with drop-down menus and free text allowing a detailed narrative description of the incident (Supplementary Fig. S1). The provider that reports the IRS can choose to update the MRE details, such as patient outcome, until the MRE analysis is finalised. The existing IRS protocol has been described in greater detail in another study.[21] A local safety team at each hospital, made up of anaesthesiologists, nurses, and risk managers, conducted the incident analyses based on a validated structured investigation methodology adapted and translated into Spanish from the widely used London Protocol.[22,25]

We considered that the perioperative 'medication process' starts when a medication is chosen and requested or obtained from the anaesthesia cart and ends with appropriate monitoring and documentation after the medication has been administered to the patient.[26] We defined a 'patient safety incident' as any clinical event or circumstance in which there could be, or has been, unnecessary harm caused to a patient.[27] We included all consecutive preventable and non-preventable adverse events in the study. The reported incidents were classified using a classification system modified from the validated, Basel University Critical Incident Reporting System (CIRS).[28] Incidents classified as MRE were selected from the information included in the structured database at the time of reporting and during a subsequent analysis of the incident by the authors (ERG and YSO). Unclassified incidents that were missing the type of incident information were manually reviewed, and a consensus was achieved by two authors (ERG and YSO), with any disagreements resolved by a third author (DAV).

Study variables

We described MRE using the following independent variables: type of MRE, phase of medication process and type of medication involved. We treated patient morbidity related to MRE as the dependent variable. We categorised the type of MRE using the following categories: medication administration omission, expired products administration, error in the medication selection, and either wrong dose, dilution, or route of administration. In the analysis, we take into account the medication, dose, dilution, and administered route; phase of the medication process (e.g. prescribing, preparing,

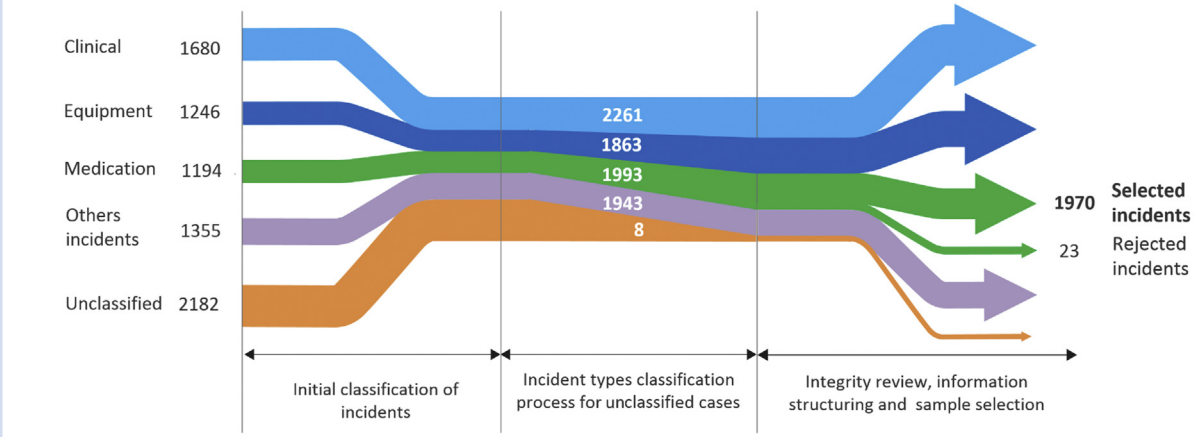

Fig 1. Sankey diagram selection process for the study population.

dispensing, administering, or medication monitoring), and other, if the previous steps are not applicable. The 'other' category includes incidents related to erroneous medication documentation (Supplementary Table S1).

We used the SENSAR classification system for the group of medications involved (Supplementary Table S2) and adapted the accepted WHO taxonomy for morbidity caused by the incident using the following categories: no harm, when patient outcome is not symptomatic; minor and intermediate morbidity, when any temporary deviation in physiologic parameters; and major morbidity, when this derangement is permanent, or leads to patient death (Supplementary Table S3).[27]

Statistical analysis

The results of the descriptive analysis are presented by the number and rate of reported MRE. The association of the three independent variables (e.g. type of MRE, phase of medication process, and type of medication involved) with patient morbidity was assessed using a multiple ordinal logistic regression model. These models are a simple extension of the binomial logistic regression model and are used when the dependent variable has more than two nominal (unordered) categories. Dummy coding of independent variables is common.

We selected the category with the highest observed MRE frequency as a reference category to improve the accuracy of the estimates. We used this category as a reference point to measure the probability of producing patient morbidity. The effects of the different variables in this model are presented as odds ratios (OR) with their corresponding 95% confidence intervals (CI) and *P*-values. We adjusted the *P*-values to reduce the chance of false positive inferences because of multiple comparisons between groups using the Holm–Bonferroni method and following a multiplicity corrected CI procedure.[29] Analyses were performed using R version 3.4.1 (R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was defined as $P<0.05$.

Results

A total of 7072 incidents were reported to SENSAR mainly by anaesthesia and critical care physicians during the 10-yr study period. Of these total incidents reported, 4898 cases were classified by the local patient safety analysis teams. Manual review of the unclassified incidents yielded another 2174 incidents. After reviewing the 7072 incidents, we found 6584 classified as a single type of incident (e.g. clinical, equipment, medication, other), 419 classified as two types, and 69 as three or more, with 2261 (32%) of these incidents related to clinical causes, 1863 (26%) related to equipment, and 1993 (28%) related to medications (MRE). Finally, 23 of the 1993 MRE were excluded from the analysis as the information provided did not allow a complete analysis even after an exhaustive review of the free text and drop-down menus by the authors (Fig 1).

The most frequent types of MRE involved a wrong treatment regimen (28%) or a wrongly administered medication (27%; Table 1). Most of the reported incidents occurred during the medication administration phase (42%) and the prescription phase (22%). The most prevalent medication groups involved were those that alter haemostasis (e.g. antithrombotic and anticoagulant drugs), vasoconstrictor agents, and opioids, together accounting for >40% of the reported MRE.

MRE were associated with harm in 31% of the reported incidents, of which 19% were minor, 9% were significant, and 3% life-threatening (Table 2). The harm distribution was not homogeneous between different types of MRE. Dosage (48%), wrong treatment regimen (34%), and no medication administration (32%) were the MRE most often associated with patient harm. Wrong dose presented more severe outcomes, with a higher rate of incidents with intermediate morbidity, major morbidity, or death compared with the other categories of MRE. The phase of medication process that showed the highest frequency of reported harm was also the administration phase (44% of the cases). The highest morbidity was associated with the intravenous and inhaled anaesthetics (46%), benzodiazepines and hypoglycaemic agents (45%), opioids (44%), and neuromuscular blocking agents (43%).

Overall, we identified medication administration as the most vulnerable moment in the medication administration process and with the highest risk for patient morbidity (Fig 2). The wrong dosage MRE, despite its low number of cases, stands out with its high morbidity rate. In contrast, dispensing an expired medication caused little to no harm. MRE related to

Table 1 Distribution table of medication related incidents classified by the phase of medication process, type of medication-related adverse event (MRE) and medication group involved.

	Number of incidents, *n* (%)	Clinical examples
Phase of medication process	**1970**	
Administration	835 (42)	Unintended epidural fentanyl administration instead of intravenous.
Prescription	425 (22)	Amoxicillin regimen prescription in a penicillin allergic patient.
Preparation	258 (13)	Incorrect epinephrine concentration labelling.
Dispensation	206 (11)	Incorrect medication (atropine vs adrenaline) given from one provider to the medication administering provider.
Monitoring	80 (4)	Absence of coagulation test in a patient under oral anticoagulant treatment.
Others	166 (8)	Preoperative medication administered is not registered in the clinical documentation of the patient, only oral information is recorded.
Type of MREs	**1970**	
Wrong treatment regimen	544 (28)	Continuous local epidural anaesthetic perfusion to 60 ml h^{-1} instead of 6 ml h^{-1}.
Wrong medication	534 (27)	Ceftazidime administration instead of the cefazolin prescribed.
No administration	184 (9)	Inadvertent loss of intravenous access during general anaesthesia, with a total intravenous anaesthesia impossible administration.
Wrong route of administration	112 (6)	Enteral nutrition connected to central intravenous access.
Wrong dosage	110 (6)	1000 μg ml^{-1} phenylephrine inadvertent administration instead of 100 μg ml^{-1}, with patient extreme bradycardia.
Expired medication	17 (1)	Expired epidural local anaesthetic bags storage in refrigerator.
Others	469 (24)	Anaphylaxis with amoxicillin.
Medication group involved	**1970**	
Medications that alter haemostasis	359 (18)	Low molecular weight heparin, sodium heparin, acetylsalicylic acid, acenocoumarin, protamine, clopidogrel, tranexamic, phytomethadione.
Vasoconstrictor agents	253 (13)	Atropine, noradrenaline, phenylephrine, adrenaline, ephedrine, dopamine, isoproterenol.
Opiates	204 (10)	Remifentanil, morphine chloride, fentanyl, tramadol, methadone, sulfentanil, alfentanil, meperidine.
Antimicrobial agents	163 (8)	Vancomycin, cefazolin, amoxicillin, clindamycin, gentamicin, teicoplanin, meropenem, ciprofloxacin.
Local anaesthetics	137 (7)	Bupivacaine, lidocaine, ropivacaine, levobupivacaine, mepivacaine, prilocaine.
Inhalation/intravenous anaesthetics	103 (5)	Sevoflurane, protoxide, desflurane, propofol, etomidate, dexmedetomidine, ketamine, thiopental.
Neuromuscular blocking agents	97 (5)	Rocuronium, cisatracurium, succinylcholine, atracurium.
Minor analgesics	93 (5)	Metamizole, dexketoprofen, paracetamol, diclofenac.
Reversal agents/ antidotes	67 (3)	Sugammadex, neostigmine, flumazenil, naloxone.
Fluid therapy/blood products	59 (3)	Physiological/glucose intravenous solution, hydroxyethyl starch, Hartmann solution, plasmalyte, parenteral nutrition, albumin, blood, platelets
Hypoglycaemic agents	47 (2)	Insulin, oral antidiabetic.
Benzodiazepines	44 (2)	Midazolam, clonazepam, diazepam.
Antihypertensive agents	43 (2)	Urapidil, nitroglycerine, enalapril, propranolol, sodium nitroprusside, carvedilol, bisoprolol.
No Information	196 (10)	No information about medication involved.
Other medications	105 (5)	Potassium chloride, iron sucrose, ranitidine, sodium bicarbonate, ondansetron, pantoprazole, calcium, metoclopramide, droperidol, mannitol.

medications that alter haemostasis were frequent but caused low morbidity.

The probability of harm for each phase of the medication process was lower in comparison with the reference category which we choose as the drug administration phase with the most important differences found during medication dispensation (OR, 0.26; 95% CI, 0.14–0.47; P<0.001) and during the drug preparation phase (OR, 0.39; 95% CI, 0.25–0.63; P<0.001) (Table 3). The wrong medication dosage and the wrong treatment regimen are the two types of MRE associated with the greatest risk of patient harm.

In comparison with medications that alter haemostasis, all medication groups except antimicrobial agents, reversal agents/antidotes, fluid therapy/blood products, and antihypertensive agents had higher reported rates of patient harm. Vasoconstrictor agents, benzodiazepines, and neuromuscular blocking agents showed harm rates four-fold than medications that alter haemostasis (OR, 4.10; 95% CI, 2.25–7.5; *P*<0.001; OR, 4.08; 95% CI, 1.60–10.43; *P*=0.001; and OR, 3.79; 95% CI, 1.79–8.03; *P*=0.012, respectively), whereas, opioids showed three-fold more harm (OR, 3.46; 95% CI, 1.91–6.28; *P*<0.001).

The analysis of 1970 medication incidents yielded 4223 local corrective safety management measures, of which 3086 were reported to be implemented by the local teams. All of these measures were grouped into different predetermined

Table 2 Medication-related adverse event (MRE) distribution by degree of reported morbidity for every analysed category. The three columns on the right display the reported severity degree of the MRE with any harm. Percentages are calculated based on the total cases of the analysed category. Data are presented as *n* (%).

	Unknown harm	No harm	Any harm	Minor morbidity	Intermediate morbidity	Major morbidity or death
Phase of medication process	**94 (5)**	**1260 (64)**	**616 (31)**	**375 (61)**	**176 (29)**	**65 (11)**
Administration	31 (4)	438 (52)	366 (44)	224 (61)	101 (28)	41 (11)
Prescription	40 (9)	296 (70)	89 (21)	51 (57)	30 (34)	8 (9)
Preparation	3 (1)	183 (71)	72 (28)	51 (71)	17 (24)	4 (6)
Dispensation	7 (3)	165 (80)	34 (17)	20 (59)	10 (29)	4 (12)
Monitoring	5 (6)	54 (68)	21 (26)	10 (48)	8 (38)	3 (14)
Others	8 (5)	124 (75)	34 (20)	19 (56)	10 (29)	5 (15)
Type of MREs	**94 (5)**	**1260 (64)**	**616 (31)**	**375 (61)**	**176 (29)**	**65 (11)**
Wrong treatment regimen	32 (6)	328 (60)	184 (34)	106 (58)	57 (31)	21 (11)
Wrong medication	15 (3)	363 (68)	156 (29)	101 (65)	41 (26)	14 (9)
No administration	19 (10)	106 (58)	59 (32)	38 (64)	15 (25)	6 (10)
Wrong route of administration	4 (4)	74 (66)	34 (30)	19 (56)	13 (38)	2 (6)
Wrong dosage	3 (3)	54 (49)	53 (48)	36 (68)	14 (26)	3 (6)
Expired medication	0 (0)	16 (94)	1 (6)	1 (100)	0 (0)	0 (0)
Others	21 (4)	319 (68)	129 (28)	74 (57)	36 (28)	19 (15)
Medication group involved	**94 (5)**	**1260 (64)**	**616 (31)**	**375 (61)**	**176 (29)**	**65 (11)**
Medications that alter haemostasis	24 (7)	275 (77)	60 (17)	29 (48)	20 (33)	11 (18)
Vasoactive medications	6 (2)	144 (57)	103 (41)	60 (58)	28 (27)	15 (15)
Opiates	8 (4)	107 (52)	89 (44)	60 (67)	24 (27)	5 (6)
Antimicrobial agents	19 (12)	107 (66)	37 (23)	22 (59)	11 (30)	4 (11)
Local anaesthetics	2 (1)	85 (62)	50 (36)	32 (64)	14 (28)	4 (8)
Inhalation/intravenous anaesthetics	1 (1)	55 (53)	47 (46)	27 (57)	14 (30)	6 (13)
Neuromuscular blocking agents	1 (1)	54 (56)	42 (43)	30 (71)	10 (24)	2 (5)
Minor analgesics	6 (6)	59 (63)	28 (30)	16 (57)	8 (29)	4 (14)
Reversal agents/antidotes	0 (0)	59 (88)	8 (12)	3 (38)	4 (50)	1 (13)
Fluid therapy/blood products	3 (5)	39 (66)	17 (29)	13 (76)	1 (6)	3 (18)
Hypoglycaemic agents	3 (6)	23 (49)	21 (45)	12 (57)	5 (24)	4 (19)
Benzodiazepines	3 (7)	21 (48)	20 (45)	13 (65)	7 (35)	0 (0)
Antihypertensive agents	0 (0)	29 (67)	14 (33)	11 (79)	3 (21)	0 (0)
Missing information	11 (6)	137 (70)	48 (24)	29 (60)	14 (29)	5 (10)
Others	7 (7)	66 (63)	32 (30)	18 (56)	13 (41)	1 (3)

categories in the database. The most frequent measures were communication through departmental clinical, morbidity, or patient safety feedback meetings, coordination meetings, and e-mail alerts. The most frequent implemented corrective measures of the three measures (1289, 1155, and 456, respectively), were modification or implementing new local clinical safety protocols, a change of material or supplier, and more training (456, 245, and 220 proposed corrective measures, respectively) (Supplementary Table S4).

Discussion

This study confirms the high prevalence of adverse perioperative medication incident reports. We found that MRE accounted for 28% of all incidents registered in the Spanish Anaesthesia IRS. MRE resulted in significant patient harm in 31% of the reported cases. The number of MRE we found are in accordance with other retrospective reports. Khan and Hoda[30] reported that 21% of critical incidents were related to medication errors in the operating theatre, and the Spanish ENEAS study found that 37.4% of adverse events in hospitalised patients were related to medications.[6] However, Cousins and colleagues,[31] over a 5 year period of medication incidents in England and Wales, reported only 9.68% of MRE. These differences might be explained by study heterogeneity, variable definitions, unique characteristics of the IRS, including the type of incident reporting from the hospital or primary care, and the reporting culture including the level of employee psychological safety.[32]

Prospective studies use different definitions for MRE and describe a significant variability in the rate of occurrence of anaesthesia medication errors.[33] Webster and colleagues[34] reported one in 133 (0.75%) medication errors per anaesthetic in their incident monitoring study. Similar results were found in different countries with a similar methodology (between 0.22% and 0.75%).[35] However, Nanji and colleagues[11] found that one in 20 anaesthetics included an error, or up to 10 times higher than other comparable, albeit retrospective studies. Different error definitions might account for the different results,[36] whereas direct observational studies usually detect higher error rates than self-reported incident studies.

We found that reported MRE have a heterogeneous distribution with the majority of the incidents found in a few categories. The most frequently reported types of medication incidents relate to the wrong medication treatment and wrong medication administration. Medications that alter haemostasis, vasoconstrictor agents, and opioids represented more than 40% of MRE.

Cooper and colleagues[12] reported 61.5% of incidents in their study as wrong medication treatment regimen and wrong medication incidents, whereas they accounted for 54.7% of our

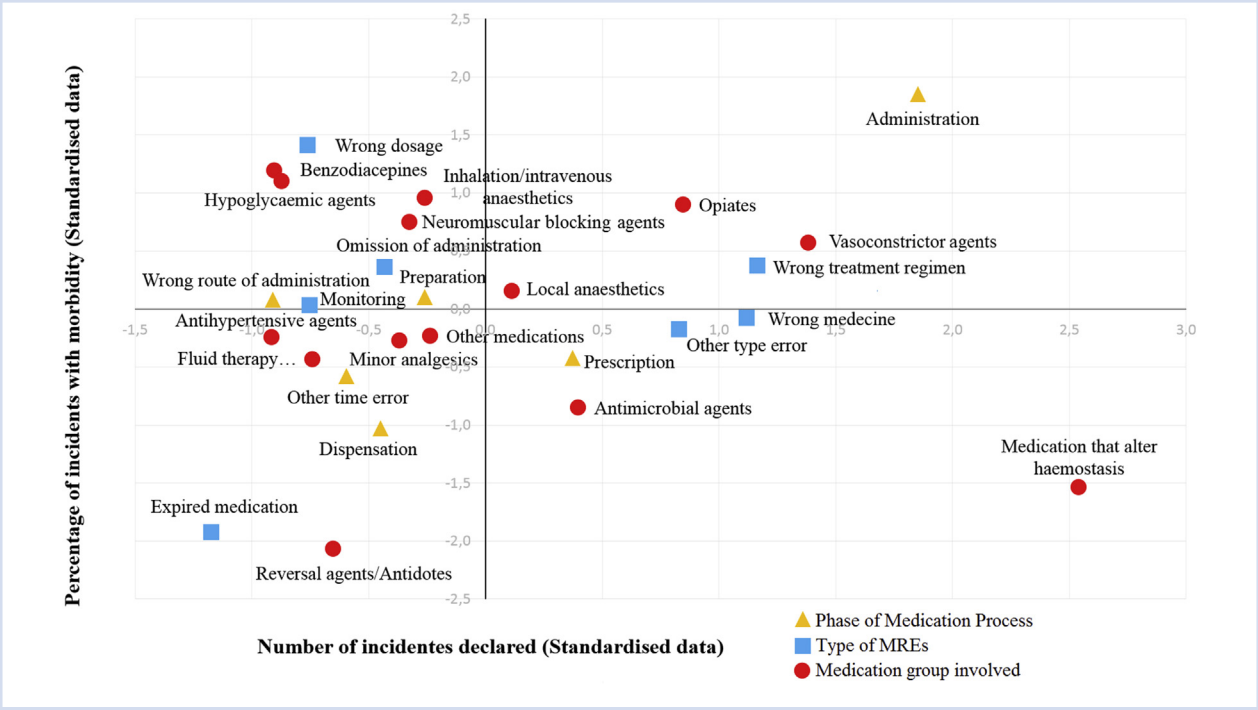

Fig 2. Rate of occurrence of incidents and related morbidity. In the normalisation process, the average distribution has been subtracted from each amount and divided by its standard deviation. This display shows the four quadrants that classify the descriptive variables by incident in a relative way according to the risk of producing harm to the patient. The division is by the medication incident type, phase of treatment process, and medication groups categories showing a higher morbidity and frequency than the average in the upper right quadrant; more frequent but associated with lower incident morbidity in the lower right quadrant; higher morbidity but infrequent appearance in the upper left quadrant; and lower frequency and morbidity in the left lower quadrant.

reported MRE. The authors describe sedatives and opioids were involved in 47% of wrong dose errors, whereas corticosteroids and vasoconstrictor agents accounted for 42% of wrong medication errors.[12] Khan and Hoda[30] found that neuromuscular blocking agents were the main medications contributing to MRE. Our MRE were drawn from the general population, in contrast with Gariel and colleagues,[37] who reported that in a paediatric population wrong dose selection occurred in two-thirds of cases, a two-fold higher frequency of reported MRE.

In contrast, a recent retrospective cross-sectional study of the Dutch National Registration System for Medication Error Reports found that anticoagulants and low molecular weight heparin were involved in 8.3% of the medication error reports, whereas they represented 18% of MRE in our study.[38] The study's surgical population case mix might explain the higher prevalence of anticoagulant use in comparison with the general population mix.

Our data show a higher reported MRE related harm, with almost 31% in contrast with the 16% rate previously identified.[31] This significantly higher rate may point to differences in voluntary reporting rates and reporting cultures, which impact reporting rates.[39] In the Cousins and colleagues study,[31] MRE resulted in severe injury or death in 0.9% of cases, and up to 10% of opioid-involved incidents were associated with severe harm. In our study, the type of MRE, the medication process phase, or the medication group involved were associated with different morbidity rate and harm severity. A number of different reasons might explain why the administration medication phase is the highest harm risk to patients in the perioperative settings. Often, one person, the anaesthesiologist, is in charge of prescribing, preparing, administering, monitoring, and treating the medication effects of potentially dangerous medications relying on personal judgement and verification routines. Large concentration/dose variations in this setting might contribute to the reported association between wrong dosage MRE and the highest reported morbidity. In contrast, conservative regulations with wide safety margins and proper storage might explain the lack of harm associated with the expired date MRE. Medications administration in the anaesthesia environment usually involve dangerous intravenous medications with large concentration dose variations, which might explain why wrong dosages were associated with the highest morbidity rates, whereas the expired medications administration reportedly caused no harm. The latter could be explained by the well-recognised wide medication safety margins and proper storage conditions.[40] Reported MRE with benzodiazepines (mainly midazolam), hypoglycaemic agents (insulin), and inhalation/intravenous anaesthetics (propofol) have shown the highest morbidity, whereas the vasoconstrictor agents and opioids combined both a high frequency and increased harm risk severity. Administration of wrongly diluted vasoconstrictor agents was associated with the highest likelihood of patient harm.

Despite not being the main goal of this study, the retrospective study of the reported MRE in our decentralised, locally administered, and cross-nationally coordinated patient safety

Table 3 Results of the ordinal logistic regression model. The category with the highest observed frequency in each variable was taken as the reference category. Categories with positive statistical significance for an alpha of 5% are highlighted in bold. The medication groups in bold font were found to be statistically significant. CI, confidence interval; SE, standard error.

	Estimate	SE	Odds ratio	95% CI (crude)	P-value (crude)	95% CI (adjusted)	P-value (adjusted)
Phase of medication process							
Administration	Reference category						
Prescription	**−0.68**	**0.15**	**0.50**	**(0.37−0.68)**	**<0.001**	**(0.33−0.77)**	**<0.001**
Preparation	**−0.94**	**0.17**	**0.39**	**(0.28−0.54)**	**<0.001**	**(0.25−0.63)**	**<0.001**
Dispensation	**−1.36**	**0.21**	**0.26**	**(0.17−0.38)**	**<0.001**	**(0.14−0.47)**	**<0.001**
Monitoring	−0.63	0.28	0.53	(0.30−0.91)	0.024	(0.26−1.07)	0.194
Others	**−1.10**	**0.23**	**0.33**	**(0.21−0.52)**	**<0.001**	**(0.17−0.63)**	**0.036**
Type of MREs							
Wrong treatment regimen	Reference category						
Wrong medication	**−0.52**	**0.15**	**0.59**	**(0.43−0.80)**	**0.001**	**(0.40−0.89)**	**0.007**
No administration	−0.09	0.19	0.91	(0.62−1.33)	0.644	(0.61−1.38)	1.000
Wrong route of administration	**−0.77**	**0.24**	**0.46**	**(0.29−0.74)**	**0.001**	**(0.25−0.88)**	**0.017**
Wrong Dosage	0.34	0.22	1.40	(0.90−2.16)	0.132	(0.85−2.31)	0.528
Expired medication	−2.40	1.05	0.09	(0.01−0.47)	0.022	(0.01−1.31)	0.201
Others	−0.02	0.16	0.98	(0.71−1.34)	0.883	(0.71−1.34)	1.000
Medication group involved							
Medications that alter haemostasis	Reference category						
Vasoconstrictor agents	**1.41**	**0.21**	**4.10**	**(2.72−6.22)**	**<0.001**	**(2.25−7.50)**	**<0.001**
Opiates	1.24	0.21	3.46	(2.30−5.23)	<0.001	(1.91−6.28)	<0.001
Antimicrobial agents	0.49	0.25	1.64	(1.01−2.65)	0.045	(0.92−2.91)	0.225
Local anaesthetics	**1.07**	**0.25**	**2.93**	**(1.80−4.77)**	**<0.001**	**(1.48−5.81)**	**<0.001**
Inhalation/Intravenous anaesthetics	**1.23**	**0.25**	**3.42**	**(2.08−5.60)**	**<0.001**	**(1.69−6.94)**	**<0.001**
Neuromuscular blocking agents	**1.33**	**0.27**	**3.79**	**(2.24−6.38)**	**<0.001**	**(1.79−8.03)**	**0.012**
Minor analgesics	**0.87**	**0.27**	**2.39**	**(1.38−4.08)**	**0.002**	**(1.16−4.94)**	**0.019**
Reversal agents/antidotes	0.01	0.42	1.00	(0.41−2.18)	0.990	(0.51−2.00)	0.990
Fluid therapy/blood products	0.87	0.34	2.38	(1.20−4.59)	0.010	(0.99−5.72)	0.105
Hypoglycaemic agents	**1.15**	**0.33**	**3.16**	**(1.64−5.98)**	**<0.001**	**(1.29−7.70)**	**0.007**
Benzodiazepines	**1.41**	**0.34**	**4.08**	**(2.06−7.95)**	**<0.001**	**(1.60−10.43)**	**0.001**
Antihypertensive agents	0.77	0.35	2.15	(1.05−4.23)	0.030	(0.92−5.03)	0.179
Missing information	0.51	0.23	1.66	(1.06−2.59)	0.025	(.96−2.90)	0.172
Others	**0.83**	**0.27**	**2.30**	**(1.36−3.85)**	**0.002**	**(1.15−4.59)**	**0.019**

learning system, also provides a glimpse of its improvement potential. The 4000 recorded local corrective safety management measures, plus the cross-national recommendations and alerts, are the founding purposes of our IRS. This study is an effort to take a different approach to identifying specific MRE patterns, and those with the highest reporting rates and risk to patients. We believe that this dataset endorses the importance of IRS as a powerful learning tool for continuous improvement and as a cornerstone of a safety culture.

Our study has several limitations. Firstly, the voluntary nature of IRS does not allow the calculation of the true incidence rates or the degree of under-reporting and selective reporting, known to be present in both passive and active information collection systems. The inherent IRS limitations prevent measurement of all MREs because of the lack of a denominator. We simply do not know the rate of the event types, only the rates which these MRE were reported.

Secondly, reporting rates can be affected by several factors, such as the medication type, use frequency and reporting pattern, degree of repetition of certain incidents, feedback obtained from the system, fear of reputation loss, safety awareness campaigns, and the safety culture at each hospital; all potentially could threaten the external generalisability of our conclusions.[41,42]

Thirdly, the specific characteristics of the SENSAR IRS may have influenced our findings. The SENSAR system heavily relies on local team leadership, buy-in, and institutional support, contributing to potential variability in how MRE are reported and analysed, support actions taken, and feedback is given. The analyses of the incidents carried out by the local SENSAR safety team can lead to heterogeneity in the findings, although all data analysts underwent a standardised training programme and we regularly audit the incident reporting quality assurance across all participating SENSAR hospitals. Our IRS incident taxonomy may be different to other studies, for instance the documentation errors included in the 'other' subcategory.

Fourthly, physicians reported most of the incidents in our study, as compared with other IRS where reporting is dominated by nurses.[43] These characteristics may have favoured the reporting of more severe and detailed incidents than in other IRS, thus allowing a better classification of the MRE and their causes.

Finally, the lack of complete incident characteristics and standardised medication names could have influenced our results. We addressed this by a manual review of all incident reports searching for missing information by two trained analysts. In a review of the British IRS, only 40% of the incidents in 2010 had specified the name of the involved MRE medication.[31]

Conclusions

Patient harm from medications in the perioperative setting remains a major safety concern for patients, hospital leaders

and clinicians. We found, through reported medication-related adverse events, a high prevalence of perioperative incident reports and describe their patterns and potential causes. The causes of these events were subsequently mitigated through systems solutions and should be taken into consideration in designing sustainable solutions for safe perioperative care.

Authors' contributions

Conception and design: YSO, JVC, ERG, ODC, DAV
Acquisition of data: YSO, JVC, ERG
Analysis of data: all authors
Drafting the article: YSO, JVC, ERG, ODC, DAV
Critical revision of the article: ODC, PB, DAV
All authors approved the final version to be published and agree to be accountable for all aspects of the work thereby ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Acknowledgements

We thank the SENSAR community for their commitment to improve patient safety, and their heartfelt commitment through the notification and analysis of incidents related to patient safety. Without this collaboration lasting learning and improvement would not be possible. We also thank the Data Science and Biostatistics Unit of Biomedical Research Institute La Fe for its collaboration in the design of the statistical analysis, and the Statistical Studies Service of the FISABIO Foundation for its help reviewing and interpreting the results.

Declarations of interest

YSO is a member of the Board of Directors of SENSAR since October 2018. JVC, ODC, and PB declare that they have no conflicts of interest. ERG is president of SENSAR since October 2018. DAV was president (from 2013 to October 2018) and vice president of SENSAR (from October 2018). He has received payments and travel funding from MSD, Aguettant and Philips for lectures. He is also chair of the ESA Patient Safety and Quality Committee and was member of Aguettant SAS European Scientific Board.

Funding

Grünenthal Pharma S.A.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2019.10.013.

References

1. World Health Organization (WHO). *Global action on patient safety (WHA72.6). Seventy-second world health assembly*. Geneva: World Health Organization; 2019. http://apps.who.int/gb/ebwha/pdf_files/WHA72/A72_R6-en.pdf. [Accessed 22 September 2019]
2. Wahr JA, Abernathy JH, Lazarra EH, et al. Medication safety in the operating room: literature and expert-based recommendations. *Br J Anaesth* 2017; **118**: 32–43
3. James JT. A new, evidence-based estimate of patient harms associated with hospital care. *J Patient Saf* 2013; **9**: 122–8
4. Shojania KG, Dixon-Woods M. Estimating deaths due to medical error: the ongoing controversy and why it matters. *BMJ Qual Saf* 2017; **26**: 423–8
5. Sentinel Data of Sentinel Events Reviewed by The Joint Commission. 1 Available from, https://www.jointcommission.org/sentinel_event_statistics_quarterly. [Accessed 9 July 2019]
6. Aranaz-Andrés JM, Aibar-Remón C, Vitaller-Murillo J, et al. Incidence of adverse events related to health care in Spain: results of the Spanish National Study of Adverse Events. *J Epidemiol Community Health* 2008; **62**: 1022–9
7. Antoñanzas-Villar F. Aproximación a los costes de la no seguridad en el Sistema Nacional de Salud. *Rev Esp Salud Publ* 2013; **87**: 283–92
8. Donaldson LJ, Kelley ET, Dhingra-Kumar N, Kieny M-P, Sheikh A. Medication without harm: WHO's third global patient safety challenge. *Lancet* 2017; **389**: 1680–1
9. Orser BA, Chen RJB, Yee DA. Medication errors in anesthetic practice: a survey of 687 practitioners. *Can J Anesth* 2001; **48**: 139–46
10. Joyce MF, Careskey HE, Barach P, Azocar RJ. The science of delivering safe and reliable anesthesia care. In: Sanchez JA, Barach P, Johnson J, Jacobs JP, editors. *Surgical patient care: improving safety, quality and value. cham: springer nature*; 2017. p. 327–47
11. Nanji KC, Patel A, Shaikh S, Seger DL, Bates DW. Evaluation of perioperative medication errors and adverse drug events. *Anesthesiology* 2016; **124**: 25–34
12. Cooper L, DiGiovanni N, Schultz L, Taylor AM, Nossaman B. Influences observed on incidence and reporting of medication errors in anesthesia. *Can J Anesth* 2012; **59**: 562–70
13. Cooper L, Nossaman B. Medication errors in anesthesia. *Int Anesthesiol Clin* 2013; **51**: 1–12
14. Macrae C. The problem with incident reporting. *BMJ Qual Saf* 2016; **25**: 71–5
15. Barach P, Small SD. Reporting and preventing medical mishaps: lessons from non-medical near miss reporting systems. *BMJ* 2000; **320**: 759–63
16. Kleinman L, Barach P. Towards a learning system for pediatric outcomes: harvesting meaning from evidence. *Prog Pediatr Cardiol* 2018; **49**: 20–6
17. Bowdle TA, Jelacic S, Nair B, et al. Facilitated self-reported anaesthetic medication errors before and after implementation of a safety bundle and barcode-based safety system. *Br J Anaesth* 2018; **121**: 1338–45
18. Litman RS. How to prevent medication errors in the operating room? Take away the human factor. *Br J Anaesth* 2018; **120**: 438–40
19. Grigg EB, Martin LD, Ross FJ, et al. Assessing the impact of the anesthesia medication template on medication errors during anesthesia: a prospective study. *Anesth Analg* 2017; **124**: 1617–25
20. Eichhorn JH. The Anesthesia Patient Safety Foundation at 25: a pioneering success in safety, 25th anniversary provokes reflection, anticipation. *Anesth Analg* 2012; **114**: 791–800
21. Bartolome A, Gómez-Arnau JI, Arnal-Velasco D, et al. *El Sistema Español de Notificación en Seguridad en Anestesia y Reanimación (SENSAR). Ministerio de Sanidad, Política Social e Igualdad*. Available from: 2010. accessed July 2019,

https://www.seguridaddelpaciente.es/resources/documentos/informesensar.pdf
22. Arnal D, Gomez-Arnau JI, Bartolome A, Puebla G, Santa-Ursula JA, Marzal JM. Como aprender de los errores: tres incidentes del Sistema Español de Notificación en Seguridad en Anestesia y Reanimación (SENSAR). *Rev Esp Anest Reanim* 2011;(58): S22–7. Available from: https://www.sensar.org/wp-content/uploads/2012/05/Suplemento-REDAR-Seguridad-del-paciente_Dic-2011.pdf. [Accessed 9 July 2019]
23. Reed S, Arnal D, Frank O, Gomez-Arnau JI, et al. National critical incident reporting systems relevant to anaesthesia: a European survey. *Br J Anaesth* 2014; **112**: 546–55
24. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007; **147**: 573–7
25. Taylor-Adams S, Vincent C. Systems analysis of clinical incidents: the London protocol. *Clin Risk* 2004; **10**: 211–20
26. Nebeker JR, Barach P, Samore MH. Clarifying adverse drug events: a clinician's guide to terminology, documentation, and reporting. *Ann Intern Med* 2004; **140**: 795–801
27. World Health Organization. *The conceptual framework for the international classification for patient safety (ICPS)*. Geneva: Final Technical Report; 2010
28. Staender S, Davies J, Helmreich B, Sexton B, Kaufmann M. The anaesthesia critical incident reporting system: an experience based database. *Int J Med Inform* 1997; **47**: 87–90
29. Ludbrook J. Multiple Inferences using confidence intervals. *Clin Exp Pharmacol Physiol* 2000; **27**: 212–5
30. Khan FA, Hoda MQ. Drug related critical incidents. *Anaesthesia* 2005; **60**: 48–52
31. Cousins DH, Gerrett D, Warner B. A review of medication incidents reported to the national reporting and learning system in England and Wales over 6 years (2005–2010). *Br J Clin Pharmacol* 2012;(74): 597–604
32. Rosenbaum L. Cursed by knowledge — building a culture of psychological safety. *N Engl J Med* 2019; **380**: 786–90
33. Cooper L, Fogarty-Mack P, Kroll H, Barach P. Medication safety in anesthesia: epidemiology, causes, and lessons learned in achieving reliable outcomes. *Int Anesthesiol Clin* 2019; **57**: 78–95
34. Webster CS, Merry AF, Larsson L, et al. The frequency and nature of drug administration error during anaesthesia. *Anaesth Intensive Care* 2001; **29**: 494–500
35. Webster CS. Estimating and reporting error rates, and detecting improvements. *Eur J Anaesthesiol* 2018; **35**: 60–1
36. Bowdle TA, Jelacic S, Nair B. Evaluation of perioperative medication errors. *Anesthesiology* 2016; **125**: 429–31
37. Gariel C, Cogniat B, Desgranges FP, Chassard D, Bouvet L. Incidence, characteristics, and predictive factors for medication errors in paediatric anaesthesia: a prospective incident monitoring study. *Br J Anaesth* 2018; **120**: 563–70
38. Diepstraten J, Bukkems VE, Mol PGM, Leebeek FWG, Kruip MJHA, van den Bemt PMLA. Anticoagulant medication errors in hospitals and primary care: a cross-sectional study. *Int J Qual Health Care* 2019; **31**: 346–52
39. Flemons WW, McRae G. Reporting, learning and the culture of safety. *Healthc Q* 2012; **15**: 12–7
40. Zilker M, Sörgel F, Holzgrabe U. A stability-study of expired ampoules manufactured more than 40 years ago. *J Pharm Biomed Anal* 2018; **150**: 318–26
41. Bognar A, Barach P, Johnson JK, et al. Errors and the burden of errors: attitudes, perceptions, and the culture of safety in pediatric cardiac surgical teams. *Ann Thorac Surg* 2008; **85**: 1374–81
42. Mitchell I, Schuster A, Smith K, Pronovost P, Wu A. Patient safety incident reporting: a qualitative study of thoughts and perceptions of experts 15 years after 'To Err is Human'. *BMJ Qual Saf* 2016; **25**: 92–9
43. Leistikow I, Mulder S, Vesseur J, Robben P. Learning from incidents in healthcare: the journey, not the arrival, matters. *BMJ Qual Saf* 2017; **26**: 252–6

Handling editor: Hugh C Hemmings Jr