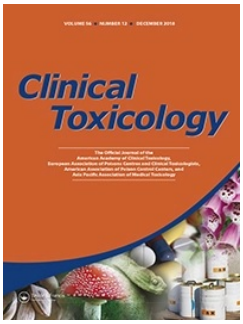

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POISON CENTRE RESEARCH

An analysis of fatal iatrogenic therapeutic errors reported to United States poison centers*

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ABSTRACT

Objective: This is a descriptive study evaluating fatal iatrogenic and in-hospital medication errors reported to United States poison centers.

Methods: A retrospective evaluation of the National Poison Data System from 2000–2017 of all therapeutic errors with a scenario coded as iatrogenic/healthcare professional or occurring in a healthcare facility. Death abstracts were reviewed for details of the exposure and therapeutic error scenarios were recoded or added to the case as appropriate. Cases, where death was considered not related to the exposure, were excluded. Additionally, we created one additional scenario (rate-related) and one additional route of administration (intrathecal) to better describe the cases.

Results: A total of 172 cases were evaluated. The majority of the patients were female (52.3%) with a median age of 58.5 years (range: 2 days to 96 years). The most commonly reported medication error was "other incorrect dose" (22.7%) followed by other/unknown error (15.1%). The route of exposure was primarily parenteral (54.9%), followed by ingestion (30.2%), then intrathecal (7.0%). The most common medications were cardiac drugs, chemotherapeutics, opioids, anticoagulants, and sedative-hypnotic/antipsychotics.

Conclusions: Iatrogenic and in-hospital medication errors have been studied extensively with goals to reduce their occurrence. Specific controls to prevent incorrect dosing routes, 10-fold overdoses, and incorrect intrathecal administration have been instituted. Despite interventions, all three of these therapeutic errors continued to occur in 2017, suggesting that more preventive controls should be instituted.

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Fatalities; iatrogenic; intrathecal; administration error

Introduction

Medication errors are a common occurrence in the healthcare setting [1]. The pivotal report *To Err is Human*: *Building a Safer Health System* highlighted the significant loss of life associated with medical errors and called for research to improve processes that result in errors [2]. Medication errors are a group of medical errors that involve medications rather than other care and interventions occurring in the healthcare system. They are defined by the National Coordinating Council for Medication Error Reporting and Prevention as "any preventable event that may cause or lead to inappropriate medication use or patient harm while the medication is in the control of the health care professional, patient, or consumer."

Systematic reviews of direct observation studies report medication error frequency of 10-25% in most studies but as high as 72% [1,3]. Fortunately, fatal medication errors are rare and none were reported in two systematic reviews [1,3]. In general, fatal medication errors are published as case reports, but this reporting may be limited due to concerns about legal ramifications of publication [4–6]. It is likely that a large number of fatal medication errors go unreported. This study sought to describe a large series of fatal medication errors reported to U.S. poison centers.

Methods

This was a retrospective study of fatal iatrogenic medication errors reported to United States poison centers from 2000 to 2017 using the American Association of Poison Control Center (AAPCC) National Poison Data System (NPDS). NPDS receives data from poison centers serving the entire U.S. population. When cases are reported to a poison center by the public or health professionals, the specialist in poison information (SPI) documents the information in one of several on-line data entry systems that submit data electronically in near-real-time to NPDS. An NPDS user manual provides definitions for all fields coded by SPIs. At the conclusion of the case, the SPI assigns one of 10 possible medical outcomes. When the medical outcome is "death" the poison center medical director enters additional coded information and a narrative abstract into the fatality module. The

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Supplemental data for this article can be accessed here.

NPDS fatality database includes more information on the case including pre-hospital cardiac/respiratory arrest, review of hospital management information, postmortem/coroner report review, and blood/tissue levels. The medical director assigns a relative contribution to fatality (RCF) and the hierarchy of substances (when there is more than one substance). Possible RCFs are undoubtedly responsible, probably responsible, contributory, probably not responsible, and clearly not responsible. Two independent medical/clinical toxicologist reviewers from the AAPCC Fatality Review Team review all deaths with special attention paid to RCF and the hierarchy of substances. Prior to 2006 and in indirect death cases, RCFs were not assigned. In these cases ($n = 92$), the RCF was determined by two authors independently with discussion to reach a consensus on inclusion. We required consensus for inclusion, but if there was a discrepancy in the RCF between the authors, the value closer to "contributory" was assigned (e.g., if one case had undoubtedly responsible and probably responsible assigned by each author, the case was assigned probably responsible). Additionally, all cases were reviewed and in cases where authors disagreed with the originally assigned RCF based on the review of the abstract, the RCF was changed from unknown or probably not responsible to "contributory" (see Supplementary material). Cases were included if the reason for exposure was coded as a therapeutic error with either one scenario coded as "health professional/iatrogenic error" or the location of exposure coded as "healthcare facility." Only therapeutic error cases with RCF of undoubtedly responsible, probably responsible, or contributory to the death were included. Therapeutic errors are defined according to the AAPCC's NPDS Coding Users' Manual [7] as "an unintentional deviation from a proper therapeutic regimen that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance." This definition includes the mistaken use of non-drug substance as a drug.

The first author read death abstract narratives provided by each poison center to the NPDS to ensure the correct error scenario was coded. Health professional/iatrogenic error is one of the sixteen error scenarios defined by NPDS. These include incorrect dosing route, dispensing cup error, 10-fold dosing error, inadvertently took/given someone else's medication, inadvertently took/given medication twice (double-dose), incorrect formulation or concentration given, incorrect formulation or concentration dispensed, wrong medication is taken/given, health professional/iatrogenic error, more than one product containing the same ingredient, confusing units of measure, other incorrect doses, drug interaction, other/unknown therapeutic error. When health professional/iatrogenic error is coded, a second scenario to describe the error should be also be coded. If a descriptive error was not coded and one could be determined from the narrative, the code was added. We added an additional error scenario that we termed "rate-related error" where medication was administered at an incorrect rate. We also added intrathecal administration as a route of exposure. Routes previously available to code include ingestion, parenteral, aspiration (with ingestion), bite/sting, dermal, inhalation/nasal, ocular, "other," otic, rectal, vaginal, and unknown. Where multiple errors or routes of administration were coded, a primary error scenario and the primary route of administration was added for each case based on the more descriptive error (e.g., 10-fold dosing error versus other incorrect doses) or for the most acute route of exposure (parenteral vs. oral). All multiple substance cases are presented in the Supplementary material. Drug-drug interactions that resulted in death were summarized together.

We summarized the following characteristics: age, gender, the substance of exposure, month/year of exposure, route of exposure, and exposure scenario. The primary objective was to describe the types of errors and agents reported over time. We described the specific errors each year to identify if any disappeared over time. Summary statistics were performed with Prism 8 (GraphPad Software, La Jolla, CA).

The review board at our institution deemed the study as not human subject research.

Results

A total of 231 cases were identified by the search. Original RCFs assigned by the Fatality Review Team were, undoubtedly responsible ($n = 37$), probably responsible ($n = 21$), contributory ($n = 37$), probably not responsible ($n = 17$), clearly not responsible ($n = 10$), unknown ($n = 17$), and not assigned ($n = 92$). After review of abstracts, RCFs were undoubtedly responsible ($n = 48$), probably responsible ($n = 43$), contributory ($n = 81$), probably not responsible ($n = 19$), clearly not responsible ($n = 12$), and unknown contribution ($n = 28$). Five cases were included due to a change in the RCF by the authors (4 originally unknown, 1 probably not responsible) and one case was excluded. The final number of cases included was 172. Majority of the patients were female ($n = 90$; 52.3%) with a median age of 58.5 years (range: 2 days to 96 years) (Table 1). Most of the cases occurred in adults, but age distribution was bimodal with peaks around <1 year and 75 years (Table 1).

The most commonly reported medication error was "other incorrect dose" (22.7%) followed by other/unknown error

Table 1. Demographics for iatrogenic error related fatalities.

	n (%)
Age group*	
0–5	20 (11.6)
6–12	4 (2.3)
13–19	5 (2.9)
20–29	7 (4.1)
30–39	9 (5.2)
40–49	15 (8.7)
50–59	26 (15.1)
60–69	20 (11.6)
70–79	32 (18.6)
80–89	25 (14.3)
>89	5 (2.3)
Gender	
Female	90 (52.3)
Pregnant	1 (0.6)
Male	80 (46.5)
Unknown	1 (0.6)

*Age unknown for 4 cases.

(15.1%; Table 2). The only error scenario that was not coded was "exposure through breast milk." All other scenarios occurred, along with the additional scenario of "rate-related error." The route of exposure was primarily parenteral (52.9%), followed by ingestion (30.2%), then intrathecal (7.0%). A total of 17 cases with more than one route had a primary route assigned (usually parenteral and oral assigned to parenteral) and 25 cases had the error changed. Of these 25 cases, 20 were changed due to the addition of rate-related error with others assigned primarily to drug interactions when both interaction and incorrect dose or doses are given/taken too close together were also assigned. Table 2 shows the number and percentage of each primary route and error that occurred. The chronicity of the exposures was primarily acute (58.1%), followed by acute-on-chronic (20.3%), chronic (19.8%), and unknown (1.7%).

Table 2. Error scenarios and routes of administration for iatrogenic error related fatalities.

	n (%)
Error	
Other incorrect dose	39 (22.7)
Other/unknown error	26 (15.1)
Incorrect dosing route	18 (10.5)
Rate related error	18 (10.5)
Wrong medication taken/given	16 (9.3)
10-fold dosing error	15 (8.7)
Interaction	12 (7.0)
Incorrect formulation given	7 (4.1)
Incorrect formulation or concentration dispensed	6 (3.5)
Doses given/taken too close together	5 (2.9)
More than 1 product containing same ingredient	3 (1.7)
Confused units of measure	2 (1.2)
Iatrogenic/healthcare professional error (i.e., contraindicated medication)	2 (1.2)
Took/given other's medication	2 (1.2)
Took/given medication twice	1 (0.6)
Primary route	
Parenteral	91 (52.9)
Ingestion	52 (30.2)
Intrathecal	12 (7.0)
Inhalation/nasal	5 (2.9)
Aspiration (with ingestion)	4 (2.3)
Other	4 (2.3)
Dermal	2 (1.2)
Rectal	1 (0.6)
Vaginal	1 (0.6)

Other/unknown error is frequently coded when either an unknown scenario occurs or a pre-defined scenario does not adequately describe the situation. Some examples of other/unknown errors in this dataset include bladder instillation and subsequent intravascularization of glycine solution, alum, and formaldehyde in three separate cases; inadequate cleaning of hemodialysis machine after sterilization with hydrogen peroxide, prolonged administration of sodium nitroprusside without sodium thiosulfate, drug contamination, alternative therapy with carbon dioxide, dual beta-blocker administration, excessive application and occlusion of lidocaine prior to hair removal, and aspiration of activated charcoal. When looking at the type of error by age group, it is difficult to identify any specific patterns (Figure 1). Of note, the age group of 0–5 years had over 1/3rd of the 10-fold dosing errors. Additionally, the 70–79 years group had about 1/3rd of the "wrong medication taken/given" errors.

Rate related errors occurred with 5-fluorouracil, nitroglycerin, lepirudin, nesiritide, diltiazem, vasopressin, drotrecogin alfa, midazolam, alteplase, propofol, amiodarone, fentanyl, nitroprusside, treprostinil, and heparin. These primarily consisted of a dose intended as infusion given as a bolus [5], administered as at an unknown faster rate than intended [7], a pump malfunction [3], the medication was removed from the pump and free-flowed [1], the rate for hourly administration set per minute [1], and the drug was administered at a rate intended for another medication [1].

Specific medications were known for 171/172 cases. The category with the highest number of cases was cardiac (42/

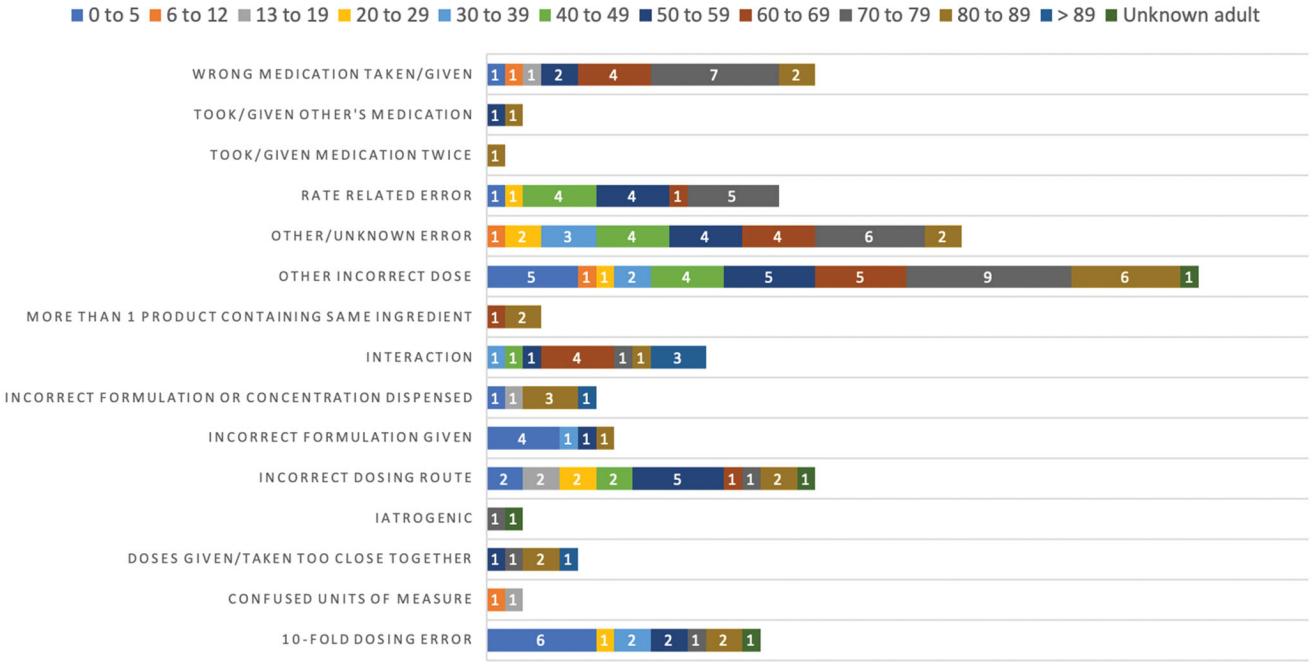

Figure 1. Distribution of primary errors broken down by age groups. Numbers in bar are number of cases per age group.

Table 3. First listed classes and drugs reported in fatal iatrogenic medication errors.

Other cardiac agents	21	Sedative-hypnotics, antipsychotics	15	Nutrition	6
Digoxin	7	Propofol	4	Total parenteral nutrition	1
Epinephrine	4	Baclofen	3	Enteral nutrition	1
Amiodarone	2	Midazolam	2	Intravenous fat emulsion	1
Nitroprusside	2	Clozapine	1	Glycine	1
Flecainide	1	Diazepam	1	L-arginine	1
Nesiritide	1	Haloperidol	1	Parenteral dextrose	1
Nitroglycerin	1	Phenobarbital	1	Electrolytes	5
Phenylephrine	1	Quetiapine	1	Phospho-soda	2
Treprostinil	1	Promethazine	1	Calcium	1
Vasopressin	1	Calcium channel blockers	12	Magnesium	1
Chemotherapeutics	20*	Diltiazem	8	Sodium bicarbonate	1
Colchicine	7	Amlodipine	2	Gases	5
Methotrexate	7	Verapamil	1	Nitrogen	4
Vincristine	3	Nifedipine	1	Carbon dioxide	1
5-fluorouracil	1	Local anesthetics	12	Hypoglycemic agents	2
Mitomycin	1	Lidocaine	7	Glyburide	2
Opioids	16	Bupivacaine	5	Antidotes	3
Morphine	7	Beta-blockers	9	Activated charcoal	2
Fentanyl	4	Metoprolol	3	Acetylcysteine	1
Meperidine	2	Carvedilol	2	Other chemicals	3
Hydromorphone	1	Labetalol	2	Formaldehyde	1
Nalbuphine	1	Propranolol	1	Hydrogen peroxide	1
Oxycodone	1	Timolol	1	Isopropyl alcohol	1
Anticoagulants	12	Metals	6	Imaging	3
Heparin	3	Lithium	2	Gadolinium	1
Enoxaparin	2	Alum	2	Iopamidol	1
Lepirudin	2	Iron dextran	1	Diatrizoate	1
Alteplase	1	Zinc	1	Other drugs	8
Dabigatran	1	Anti-infectives	5	Diphenhydramine	1
Eptifibatide	1	Amantadine	1	Cholestyramine	1
Reteplase	1	Azithromycin	1	Probiotics	1
Tenecteplase	1	Ciprofloxacin	1	Gemfibrozil	1
Anti-epileptic agents	9	Linezolid	1	Naltrexone	1
Phenytoin	5	Tobramycin	1	Neostigmine	1
Fosphenytoin	3			Tacrolimus	1
Topiramate	1			Drotrecogin alfa	1

*One unknown chemotherapeutic agent administered through IT route.

172), with a predominance of "other cardiac agents" over calcium channel blockers and beta-blockers (Table 3). Among the calcium channel blockers, diltiazem was the most frequently reported (8/12). Opioids accounted for 16 fatalities, of which 7 were due to morphine. Anticoagulants also made up a large proportion of the cases with large heparin boluses, administration of alteplase to a patient with an intracerebral hemorrhage, and administration of tenecteplase at a dose intended for alteplase. Other agents to note include the parenteral administration of cholestyramine and probiotics. In children less than 1 year of age, the specific agents included heparin [3], intravenous lipid emulsion [1], amiodarone [1], zinc [1], calcium salts [1], azithromycin [1], isopropyl alcohol 70% [1], and tacrolimus [1]. Figure 2 shows the classes of agents broken down by age groups. Of note, cardiac agents (beta-blockers, calcium channel blockers, and other cardiac agents) predominated in the 60 years and older groups.

Route of administration relative to the class of medication is presented in Figure 3. In about 1/3rd of the categories, parenteral administration made up more than 50% of the exposures. Notable exceptions include imaging, hypoglycemic agents, antidotes, calcium channel blockers, chemotherapeutic agents, and beta-blockers. Figure 4 shows the route of administration relative to specific errors. Rate related errors were made exclusively in parenteral administration.

Multiple medications were listed for 40 of the cases. The combination of a beta-blocker and calcium channel blocker or dual beta-blocker/calcium channel blocker was reported responsible for 10/40 cases (25.0%). Multiple sedating agents were the reason for 5 of the fatalities attributed to multiple medications.

Discussion

Medication errors in the hospital are common and potentially devastating. This study described the scenarios and routes of medication errors that resulted in fatalities reported to poison centers over an 18-year period. As expected, most of these errors occurred in older populations, but notably, ages showed a bimodal distribution at $<$ 1 year and around 75 years of age. The most commonly reported error was another incorrect dose and the most common route was parenteral, unlike a previous poison center study [8].

Almost every error and every category of agent had at least one parenteral administration involved. Only the categories in which the substance was a gas and errors of "took or given others medication" and "took or given medication twice" did not include the parenteral route. Parenteral administration was the primary route for almost every class of medication. Furthermore, notable incorrect dosing route errors included parenteral administration of enteral nutrition,

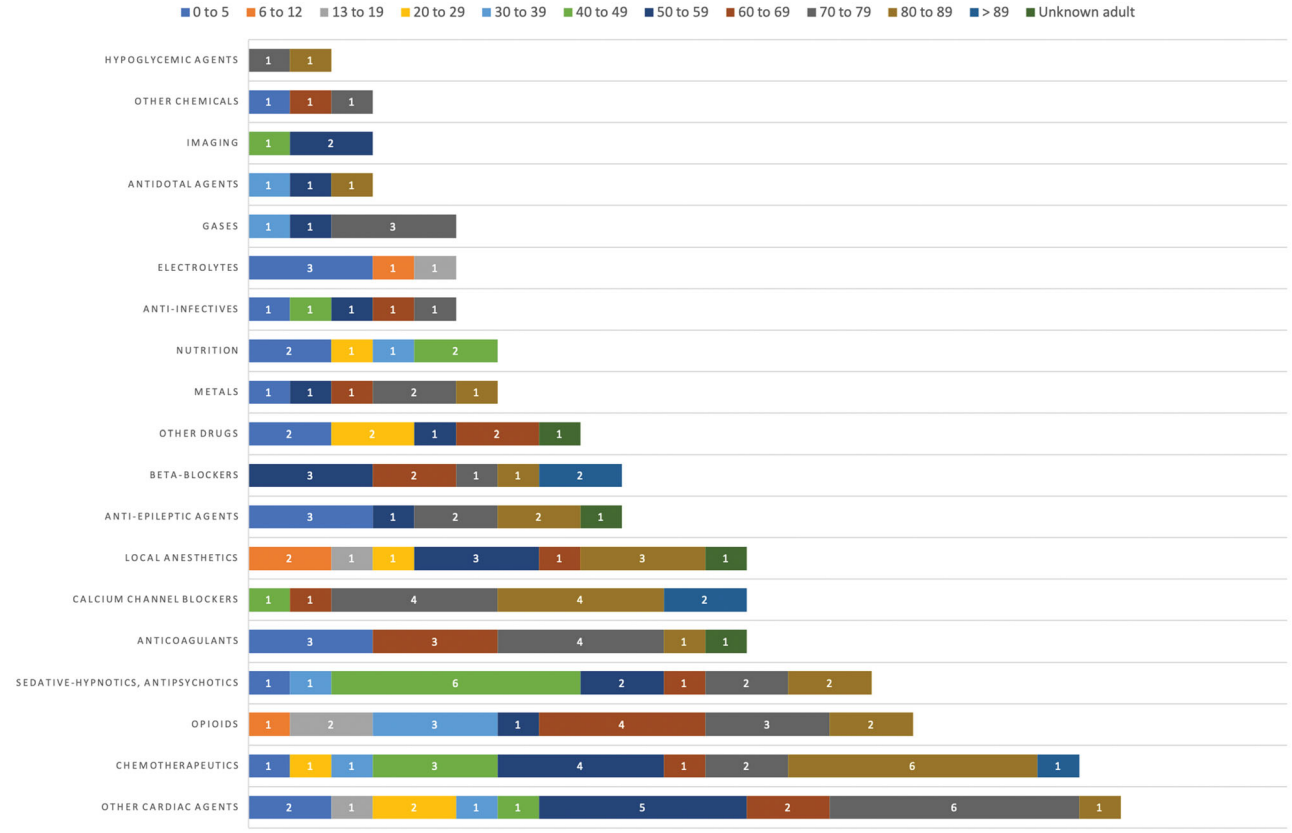

Figure 2. Distribution of first ranked agents broken down by age groups. Numbers in bar are number of cases per age group.

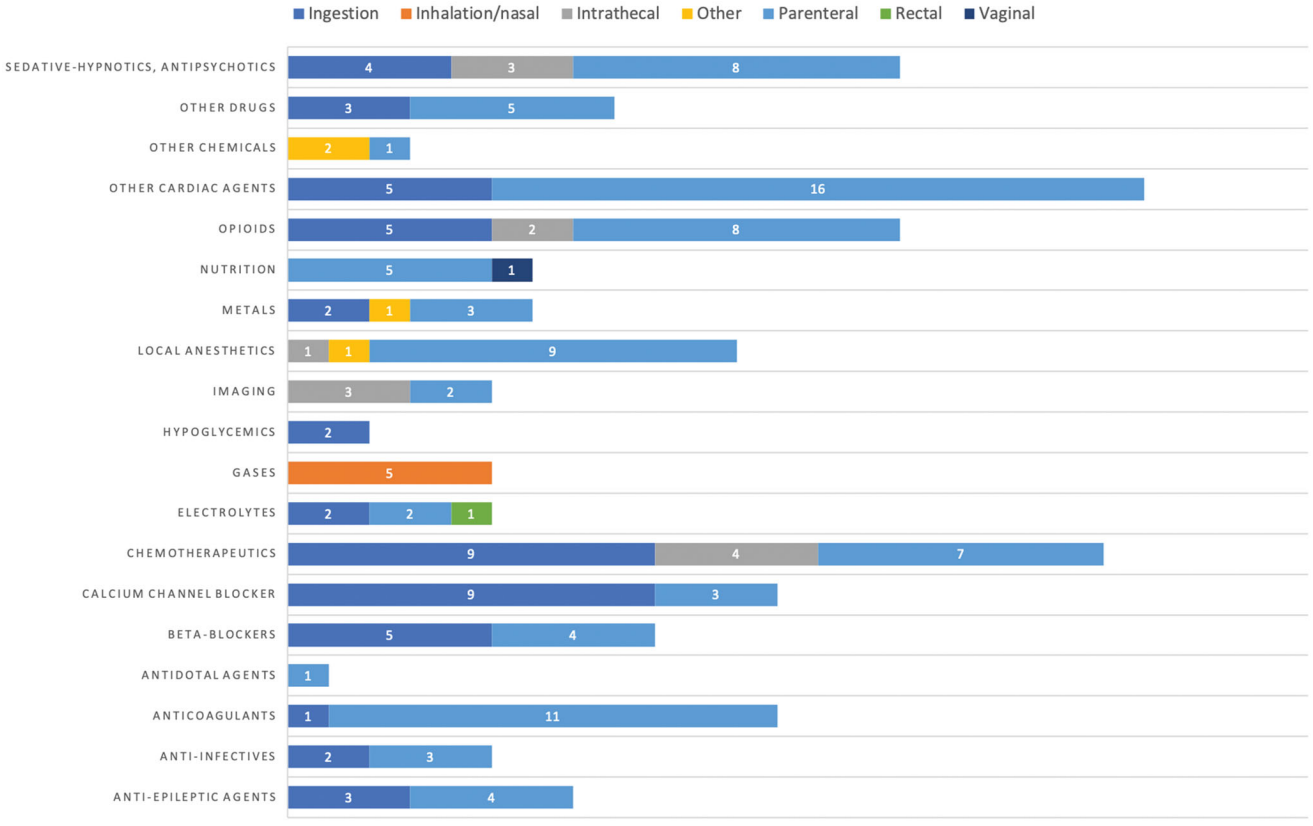

Figure 3. Distribution of first ranked agents broken down by primary route of administration. Numbers in bar are number of cases per route of administration group.

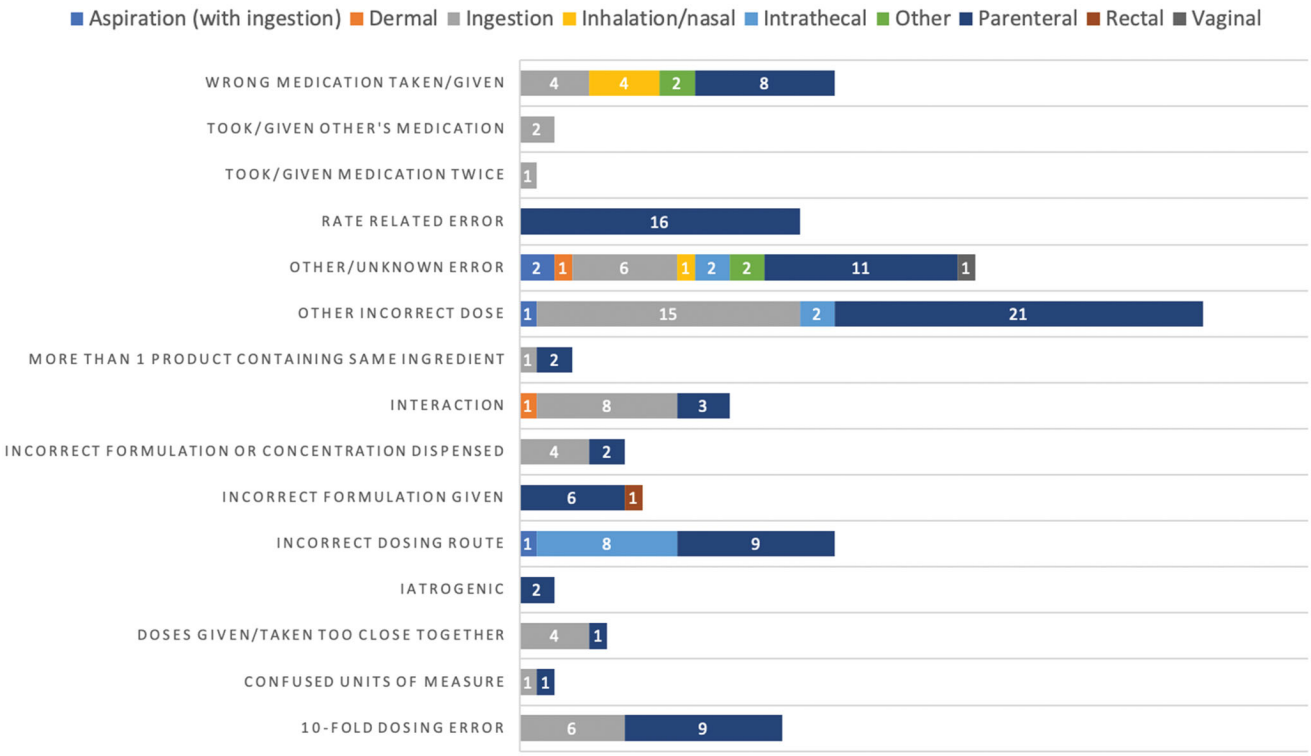

Figure 4. Distribution of primary error broken down by primary route of administration. Numbers in bar are number of cases per route of administration group.

cholestyramine, and probiotics. These cases are similar to previous reports including parenteral administration of enteral feeds which led to death in a 77-year old female [9]. Additionally, Shah-Momammadi reported on 20 inadvertent parenteral administrations of oral medications reported to the Pennsylvania Patient Safety Reporting System from 2004 and 2012. Four of the cases resulted in patient harm and one of resulted in death [10].

The agents included in this series are consistent with those considered high-risk [11]. In a large systematic review, the medications associated with the most fatal and non-fatal medication errors included methotrexate, warfarin, opioids, digoxin, theophylline, and other anticoagulants [11]. This is somewhat consistent with the most commonly reported medications in our series. Notably, the most common medications in our series were morphine, diltiazem, colchicine, local anesthetics, methotrexate, and digoxin. Morphine and other opioids were distributed evenly among all age groups, probably because of their ubiquitous use. Errors included multiple opioids, parenteral administration of oral formulations, and 10-fold errors. Calcium channel blocker errors were primarily in patients age 70–89 years. Inadvertent intravascularization of local anesthetics is a well-documented cause of mortality [12]. Fortunately, well-published errors and deaths after the administration of intravenous colchicine resulted in the removal of IV colchicine from the market [13]. Teasing out the cause of death in patients with elevated digoxin concentrations is incredibly difficult since many patients with digoxin toxicity die from multi-factorial reasons [14]. These agents are all commonly used in elderly patients, who are at higher risk of error due to polypharmacy and more susceptibility to adverse outcome of errors. Interestingly warfarin was only coded in one case and the patient did not have an abnormal INR and none of the cases included theophylline, two agents of concern in the elderly.

The combination of either two beta-blockers, two calcium channel blockers, or a beta-blocker and a calcium channel blocker was implicated in about 25% of the multi-substance cases. This combination is frequently used to control heart rate in patients but does increase the risk of complete bradycardia and hypotension [15,16]. Careful monitoring and selection of patients prior to the initiation of this combination is crucial. Additionally, medication reconciliation to confirm home medications prior to the administration of additional agents may reduce the rate of errors and adverse events [17].

Intrathecal administration of chemotherapy is a well-described potentially fatal medication error. In a systematic review published in 2014, Gilbar identified 32 cases of intrathecal vincristine administration, 25 of which resulted in death [4]. The risk of intrathecal vincristine administration has been described since 1968, but cases continue to occur with the cases in this series in 2002, 2008, and 2009 [18]. Importantly, in our series, other agents involved in intrathecal errors included imaging agents (diatrizoate meglumine and gadolinium), baclofen, and morphine. While baclofen and morphine are frequently used intrathecally, overdose has been described as complications with both, and these procedures are not without risk [19,20].

We added two additional descriptors to the dataset to more accurately describe these cases. Intrathecal administration is not a pre-defined route of administration in NPDS and

these cases are often coded as other route or parenteral administration. Additionally, we added rate-related administration errors. Since no error scenario in NPDS adequately describes this error, these are likely coded as other incorrect dose or other/unknown error. The addition of rate-related error improved the description of approximately 11% of cases. Intrathecal administration further clarified 6.4% of the cases. None of these cases overlapped, suggesting an overall clarification of close to 17% of cases by the addition of these two scenarios.

Multiple previous studies have addressed therapeutic errors reported to poison centers [8,21–23]. Most of these previous studies have focused on large coded datasets to describe the most common errors reported. Hodges and colleagues evaluated serious non-healthcare facility error reported to US poison center from 2000 to 2012 [8]. The distribution of errors and specific agents in our data are very consistent with theirs with a large proportion of cardiovascular agents among adults and less with children along with a fairly high proportion of 10-fold dosing errors in children. These consistencies in our small series relative to the poison center database as a whole suggest the patterns we showed are not due to chance.

There are several limitations to this series. Poison center data are passively collected and most medication errors are not reported to poison centers. Additionally, fatalities are often not reported to poison centers such that these data are inconsistent with other data sources such as vital statistics and medical examiners [24,25]. This is a retrospective database study of passively collected errors which cannot attempt to estimate the frequency and cannot be directly compared to direct observation style studies [1,3]. A large proportion of the errors were other incorrect doses or other/unknown therapeutic errors. While these were re-classified when possible to one of the pre-defined scenarios, there are too many other situations to be able to describe all of the cases with a separate descriptor code. The limitations of these scenarios have been previously described [26]. Coding is imperfect and some cases may have been missed due to coding of other reasons for exposure [6]. Finally, it is possible that other data were available to the abstract writer that was not included in the abstract that resulted in initial coding of the error or agent thought responsible [27]. In 6 cases, we changed the RCF (5 resulted in inclusion and 1 in exclusion). This was performed by two authors independently. We did not have access to the original poison center or hospital medical record that was used to originally determine the RCF, but each case had signs and symptoms consistent with the exposure and while the error did not directly cause the death, it likely contributed in already critically ill patients. The case that was excluded died in a house fire but there was an unclear error with sodium thiosulfate.

Conclusion

Medication errors continue to occur. Iatrogenic and in-hospital medication errors have been studied extensively with goals to reduce their occurrence. Specific controls to prevent incorrect dosing routes, 10-fold overdoses, and incorrect intrathecal administration have been instituted. Despite interventions for prevention, fatal medication errors continue to occur, suggesting that better preventive controls should be instituted.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Data availability statement

The American Association of Poison Control Centers (AAPCC) maintains the National Poison Data System (NPDS), which houses de-identified case records of self-reported information collected from callers during exposure management and poison information calls managed by the country's poison control centers (PCCs). NPDS data do not reflect the entire universe of exposure to a particular substance as additional exposure may go unreported to PCCs; accordingly, NPDS data should not be construed to represent the complete incidence of U.S. exposures to any substance(s). Exposure does not necessarily represent a poisoning or overdose and AAPCC is no able to completely verify the accuracy of every report. Findings based on NPDS data do not necessarily reflect the opinions of AAPCC.

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