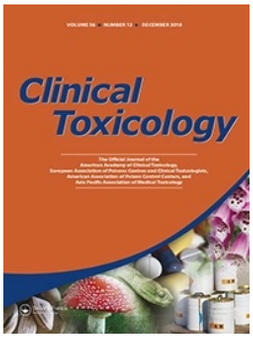

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CLINICAL RESEARCH

Fatalities in poisoned patients managed by medical toxicologists

Nir Friedman[a,b,c], Mirit Shoshani-Levy[a], Jeffrey Brent[d], Paul Wax[e], Sharan L. Campleman[f], and Yaron Finkelstein[a,g]; for the Toxicology Investigators Consortium

[a]Department of Paediatrics, Division of Emergency Medicine, Hospital for Sick Children, Toronto, Canada; [b]Department of Pediatric Emergency Medicine, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Tel Hashomer, Israel; [c]Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel; [d]Departments of Medicine and Emergency Medicine, School of Medicine, University of Colorado, Aurora, CO, USA; [e]University of Texas Southwestern Medical School, Dallas, TX, USA; [f]American College of Medical Toxicology, Phoenix, AZ, USA; [g]Department of Paediatrics, Clinical Pharmacology and Toxicology, Hospital for Sick Children, Toronto, Canada

ABSTRACT

Background: Poisoning is a leading cause of injury-related death in the United States. The Toxicology Investigators Consortium (ToxIC) Case Registry, established by the American College of Medical Toxicology, prospectively captures patients who were directly cared for and managed at the bedside by medical toxicology services. We sought to describe exposure cases who presented to Emergency Departments (EDs) across ToxIC sites, received direct bedside care by medical toxicologists; however, the intoxication resulted in fatality.

Methods: We identified all cases in the ToxIC Case Registry that resulted in fatality after hospital presentation over the 6-year study period. We collected data on patient demographics and clinical information including age group, sex, circumstances of exposure, route of exposure, substances involved, presenting signs and symptoms and management prior to death.

Results: Of 44,567 recorded cases in the registry over the study period, 268 (0.6%) fatalities met the inclusion criteria and comprise the study cohort. There was no sex predominance (138 females; 51.5%) and 27 (10.1%) were pediatric fatalities. In 195 (72.7%) patients, exposure was intentional. In 175 (65.3%) patients, fatality was associated with exposure to pharmaceuticals. The leading substances resulting in death were non-opioid analgesics, followed by opioids (72% prescription opioids), cardiovascular medications, sedatives, antipsychotics, antidepressants, and sympathomimetics. At time of consult, the central nervous system was the most common system affected in both fatal and non-fatal cases. Compared with non-fatal ToxIC cases ($n = 44,299$), fatal cases involved significantly less children (27.7% vs. 10.1%, respectively; $p < .001$), and were managed more aggressively (e.g., mechanical ventilation 8.3% vs. 69.8%, $p < .001$). Both non-opioid analgesics (25.3% vs. 14.7%; $p < .001$) and opioids (17.8% vs. 7.5%; $p < .001$) were significantly more likely to be ingested in fatal compared with non-fatal cases, although analgesics, opioids, and non-opioids, were the most common agents implicated in both groups.

Conclusions: Most ToxIC registry exposures resulting in death involve intentional exposure, without sex predominance. One in 10 fatalities involved a child. Analgesics, non-opioids, and opioids are the most commonly implicated agents in both fatal and non-fatal intoxications, which highlights the centrality of these agents as major sources of both morbidity and mortality.

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Poisoning; fatalities; Toxicology Investigators Consortium (ToxIC)

Introduction

Poisoning is a major global public health concern and the leading cause of injury-related death in the United States (US) [1]. It is also one of the most common reasons for Emergency Department (ED) visits [2–4]. In the US, death rates from drug overdose have been increasing annually since 1979 and the overall drug overdose mortality rate manifests an exponential growth curve [5]. The age-adjusted rate of drug overdose deaths in the US in 2015 (16.3 per 100,000) was more than 2.5 times higher than the rate in 1999 [6]. According to the 2016 Report of the American Association of Poison Control Centers (AAPCC) National Poison Data System (NPDS), the top most implicated agent classes in exposure-related fatalities were analgesics including opioids followed by cardiovascular drugs and stimulants/street drugs [7]. Data from the NPDS are collected from poison centers across the US and provide information about a large number of cases. However, NPDS information is usually communicated to poison centers over the phone by individuals with varying degrees of medical training, if any. To complement that, the Toxicology Investigators Consortium (ToxIC), a broad network of medical toxicology services prospectively captures all cases that their members have directly cared for at the bedside. Thus, determinations of exposure substances and circumstances implicated in ToxIC are made by highly trained physicians (medical toxicologists) directly caring for those patients, and intimately involved in their management.

We sought to explore the exposures reported to the ToxIC registry, which resulted in patient deaths. The main

CONTACT Yaron Finkelstein yaron.finkelstein@sickkids.ca Pediatrics, Pharmacology and Toxicology, University of Toronto, Hospital for Sick Children, Toronto, ON M5G1X8, Canada

goal was to identify common substances in the US leading to fatalities, despite direct medical toxicology care.

Methods

In 2010, the American College of Medical Toxicology established the ToxIC. The ToxIC registry catalogues patients who were consulted on and managed at the bedside by medical toxicology services across the US. The decision whether to consult the medical toxicology service is made at the discretion of the frontline physician caring for the patient, and by nature, tends to capture more serious exposures, in which the treating physician feels a consult is warranted and may benefit the patient. In 2016, ToxIC had 46 sites, comprising 79 unique medical facilities, that include 83% of all medical toxicology fellowship training programs in the US [8]. These constitute the majority of medical toxicology services and teaching programs in the US. The distribution of ToxIC sites is described on the ToxIC website (https://ToxICRegistry.org). As medical toxicology is highly specialized, most ToxIC sites are at academic and tertiary care medical centers in urban areas.

We collected data from the ToxIC Case Registry to identify all confirmed overdose cases of patients who presented to affiliated EDs between 1 April 2010 and 31 March 2016, and resulted in overdose-related fatality. We collected demographic and clinical information on each patient including, but not limited to, age group, sex, circumstances of exposure, type of exposure, substances involved, route of exposure, presenting signs and symptoms and management prior to death. Exclusion criteria were cases with no identified exposure and patients that presented with signs or symptoms that were unlikely or unknown to be toxin-related. The ToxIC registry functions under the Western IRB approval, and each participating site is pursuant to their institution's IRB approval, policies, and regulations. Descriptive statistics were conducted using Pearson's Chi-square test with Yates' correction, as appropriate.

Results

Among 44,567 patients who received bedside medical toxicology consultation across ToxIC sites over the 6-year study period, 268 (0.6%) died from the exposure, of whom 138 (51.5%) were female. Similarly, among the 44,299 non-fatal ToxIC cases, 22,249 (50.2%) were female. Significantly more fatalities (241; 89.9%) involved adults, compared with 32,002 (72.3%) adults in non-fatal ToxIC cases ($p < .001$); those between 19 and 65 years of age comprised the majority of fatalities (200; 74.6%). Among 27 children who died, adolescents (13–18 years) were the most frequent age category (20; 7.5%) (Table 1). Similarly, adolescents were the most frequent age group among non-fatal pediatric cases ($n = 7152$; 16.1%), followed by 2–6 year-old preschoolers ($n = 2183$; 4.9%).

Table 1. Demographics of fatal cases in the ToxIC registry.

	N (%)
Gender	
Female	138 (51.5)
Male	130 (48.5)
Age (years)	
<2	5 (1.9)
2–6	2 (0.7)
7–12	0 (0)
13–18	20 (7.5)
19–65	200 (74.6)
66–89	38 (14.2)
>89	3 (1.1)
Total	268 (100)

Exposure route and intent

The most common route of substance exposure was oral ingestion (152; 56.7%). Other routes included parenteral exposures (11; 4.1%), inhalation of gas/vapor (10; 3.7%). Three (1.1%) cases involved intranasal route administration. The rest involved combined routes or exposure route was not reported. Exposure to a single substance accounted for 135 (50.4%) fatalities, similar to 22,838 (51.6%) cases in non-fatal exposures ($p=.7$). Most fatal exposures were intentional, i.e., with deliberate intent of self-harm (195; 72.7%), of which 141 involved pharmaceutical and 54 involved non-pharmaceutical substances. Of the 91 deceased patients who were exposed to a single agent intentionally – non-opioid analgesics, opioids, sympathomimetic and toxic alcohols constituted the most commonly encountered classes, collectively accounting for 62 cases (68.9%). An unintentional exposure leading to fatality accounted for 39 (14.5%) cases, 29 pharmaceutical and 10 non-pharmaceutical substances. Among all (single and polypharmacy exposures) non-fatal intentional cases, the following drug classes were the most commonly reported exposures: analgesics ($n = 9341$), sedative hypnotics/muscle relaxants ($n = 7921$), antidepressants ($n = 6717$), and opioids ($n = 6648$).

Substance classes

Most fatalities (175; 65.3%) were associated with pharmaceutical agents; the latter were involved in 16,102 (70.5%) of 22,838 non-fatal, *single* agent exposure cases ($p=.06$). From the 135 single agent fatal cases, the most commonly encountered substance class was non-opioid analgesics (34; 25.2%, 32 of those involved acetaminophen), followed by opioids (24; 17.8%), toxic alcohols (11; 8.2%), gases/vapors (11; 8.2%), and sympathomimetics (10; 7.4%). Table 2 summarizes the top 10 exposure classes in the single agent group for fatal vs. non-fatal cases. Non-opioid analgesics and opioids were both significantly more likely to be ingested in fatal compared to non-fatal cases ($p < .001$; Table 2). A total of 505 individual substances involved in fatalities were listed in the registry. Non-opioid analgesics, opioids, cardiovascular medications, and sedatives including muscle relaxants were the most common categories comprising over a half of all reported agents leading to death (Table 3).

Exposure to more than one agent was reported in 133 (49.6%) fatal cases, similar to 21,461 (48.4%) non-fatal cases ($p=.7$): among fatal cases, exposure to two substances in 61 (22.8%), three in 19 (7.1%), four in 13 (4.9%), and five or more in 40 patients (14.9%). The most commonly encountered substance classes were opioids and cardiovascular (each with 57/370 (15.4%)) in the polypharmacy group),

Table 2. Top 10 fatal vs. non-fatal single agent exposures.

	Fatal cases ($n = 135$)		Non-fatal cases ($n = 22{,}838$)	
Rank	Agent classes	*N* (%)	Agent classes	*N* (%)
1	Non-opioid analgesics	34 (25.3)	Non-opioid analgesics	3349 (14.7)
2	Opioid	24 (17.8)	Opioid	1722 (7.5)
3/4	Toxic alcohols	11 (8.2)	Sed-hypnotic/muscle relaxants	1695 (7.4)
3/4	Gases/vapors/irritants/dusts	11 (8.2)	Ethanol	1694 (7.4)
5	Sympathomimetic	10 (7.4)	Antidepressant	1538 (6.7)
6	Cardiovascular	9 (6.7)	Cardiovascular	1195 (5.2)
7	Diabetic med	8 (5.9)	Envenomation	1189 (5.2)
8	Ethanol	7 (5.2)	Sympathomimetic	1163 (5.1)
9	Caustic	3 (2.2)	Antipsychotic	1010 (4.4)
10	Anticonvulsant	2 (1.5)	Anticholinergic/antihistamine	993 (4.3)

Table 3. Agent classes recorded in fatal cases in the ToxIC registry.

Agent classes	*N* (%)
Analgesic	84 (16.6)
Opioid	81 (16)
Cardiovascular	66 (13.1)
Sed-hypnotic/muscle relaxant	49 (9.7)
Antidepressant	34 (6.7)
Sympathomimetic	30 (5.9)
Gases/vapors/irritants/dusts	26 (5.2)
Ethanol	21 (4.2)
Anticholinergic/antihistamine	18 (3.6)
Diabetic med	17 (3.4)
Antipsychotic	15 (3)
Toxic alcohols	14 (2.8)
Anticonvulsant	12 (2.4)
Herbals/dietary supplements/vitamins	6 (1.2)
Psychoactive	5 (1)
Cough and cold	4 (0.8)
Caustic	3 (0.6)
Gastrointestinal	3 (0.6)
Anticoagulant	3 (0.6)
Herbicide/rodenticide/insecticide	3 (0.6)
Antimicrobials	3 (0.6)
Hydrocarbon	2 (0.4)
Plants and fungi	2 (0.4)
Anesthetic	2 (0.4)
Chemotherapeutic and immune	1 (0.2)
Household	1 (0.2)
Total	505 (100)

Table 4. Antidotal treatment in fatal cases.

Antidote	*N* (total = 242)[a]
NAC	82
Sodium bicarbonate	65
Naloxone/nalmefene	46
Lipid resuscitation therapy	35
Hyperinsulinemia-euglycemia therapy	23
Calcium	19
Fomepizole	18
Atropine	16
Vitamin K	15
Glucagon	12
Flumazenil	10
Hydroxocobalamin	9
Methylene blue	8
Thiamine	6
Fab for digoxin	4
Factor replacement	4
Folate	4
Physostigmine	3
Octreotide	2
Thiosulfate	1
Pyridoxine	1
Anticoagulant reversal therapy	1
Pralidoxime	1

[a]Total exceeds 242, because some patients received ≥2 antidotes.

followed by analgesics (50 cases, 13.5%), sedative-hypnotics/muscle relaxants (47 cases, 12.7%), and antidepressants (32 cases, 8.7%). Among the 81 cases of opioids involved (either single or polypharmacy), 58 cases (71.6%) were prescription opioids. The most commonly used opioids documented in fatal cases were heroin ($n = 21$, 25.9%), oxycodone ($n = 20$, 24.7%), hydrocodone ($n = 13$, 16.0%), methadone ($n = 11$, 13.6%), and tramadol ($n = 6$, 7.4%).

Signs and symptoms

The central nervous system was the most common system affected at time of consult, followed by metabolic disturbances and pulmonary involvement. The most common central nervous sign was coma/CNS depression ($n = 198$; 73.9%). Other CNS effects were agitation ($n = 22$; 8.2% of all cases), seizures ($n = 22$; 8.2% of all cases), delirium or toxic psychosis ($n = 20$, 7.5% of all cases), and hyperreflexia/myoclonus/tremor ($n = 15$, 5.6% of all cases). In non-fatal cases, the most common system affected was also the nervous system ($n = 12{,}555$) and the most common signs reported were coma/CNS depression, agitation, and/or delirium/psychosis.

Treatment

Specific toxicologic treatment was reported in 242 cases (90.3%). There were 199 antidote administrations, accounting for 82% of all treatments reported; 34% of all cases received two or more antidotal therapies for a given encounter. N-acetyl cysteine (NAC) comprised 41% of all antidotal treatments (Table 4).

Among non-fatal cases, the most commonly administered antidote was NAC given in 4547 cases (16.5% of patients receiving any treatment). Naloxone was the second most commonly used antidote provided to non-fatal cases, representing one-third of all cases receiving an antidote. In contrast, among fatal cases, sodium bicarbonate was the second most commonly toxicologic treatment administered. Overall, the most common medications provided to non-fatal cases were benzodiazepines ($n = 11{,}916$; 26.9%), antipsychotics ($n = 1772$; 4.0%), and vasopressors ($n = 1639$; 3.7%).

Non-antidotal pharmacotherapy was administered to 176 patients in the fatal group (65.7%). Vasopressors were administered most frequently, accounting for 84.1% of all pharmacological support. Mechanical ventilation was provided to 169 (69.8%) of 242 patients with reported specific therapy, a much larger ventilation rate compared with 3673 (8.3%) non-fatal cases ($p < .001$). Fifty-eight (24.0%) patients in the fatal

group were managed by enhanced elimination techniques, including 38 who received continuous renal replacement therapy and 20 underwent hemodialysis. Fourteen patients (5.2%) underwent therapeutic hypothermia, eight (3%) were managed with cardiac pacemaker and five (1.9%) were put on extracorporeal membrane oxygenation (ECMO).

Pediatric cases

Twenty-seven children (10.1% of all fatal cases) died. Eleven (40.7%) were exposed to polypharmacy, most commonly involving combinations of sympathomimetics, opioids, and cardiovascular medications. Opioids were the most common class involved in fatal pediatric cases by a single agent.

Discussion

During a 6-year study period, 268 patients presented to participating ToxIC sites with an overdose, were consulted by medical toxicology services and subsequently died. Half of all deaths involved females, one in 10 were children, and two thirds of all deaths were due to exposure to pharmaceuticals. In almost three out of four fatalities, exposure was intentional. The leading substances resulting in death were non-opioid analgesics, followed by opioids, 72% of the later were prescription opioids. About half of fatalities involved a single agent exposure. Interestingly, we found many clinical similarities between fatal vs. non-fatal cases; however, few differences stand out: first, proportionally, the former had involved less children. Second, there were dissimilarities in the top single agents involved in both categories (Table 2). However, analgesics, both opioid and non-opioid, were the most common agents implicated in both groups. This highlights the importance of these agents as major sources of both morbidity and mortality. Third, and more intuitive, there were differences in management intensity and proportions of mechanical ventilation.

The 2017 Annual Report [9] of the AAPCC NPDS reported on 2682 exposure-related fatalities. Several striking differences exist in fatal cases between the two registries: In ToxIC, 93 of 268 (34.7%) deaths were attributed to non-pharmaceuticals compared to only 368 of 2682 (13.7%) non-pharmaceuticals fatalities in the NPDS report ($p < .0001$). We found that the leading substance categories in the single substance exposure fatalities were non-opioid analgesics, followed by opioids, toxic alcohols, toxic gases/vapors, and sympathomimetic. In contrast, the 2017 NPDS report [9] ranked the top category in the single substance exposure fatalities as street drugs/stimulants, followed by non-opioid analgesics, opioids, and fumes/gasses/vapors.

Our data corroborate the US Centers for Disease Control and Prevention (CDC) reports [1], emphasizing the role of medications as the cause of most poisoning deaths. According to the CDC, misuse or abuse of prescription drugs, including opioid analgesic pain relievers, is responsible for much of the increase in drug related deaths [1].

Several limitations of our study merit mention. As often is the case in large database research, we had no access to patients' full medical records, which prevents us from exploring full details regarding the circumstances that led to exposure, especially specific personal motivations in intentional cases [10]. However, the ToxIC registry has an important advantage – since all case data are collected by medical toxicologists who cared for the patient directly at the bedside, it systemically collects high-quality data regarding various factors including volition (i.e., exposure intent, deliberate vs. non-deliberate) [10]. Regarding missing data, ToxICs data Quality Assurance program has become progressively more rigorous over the study period. Currently, all cases are fully reviewed, and if there are any incongruities in the data or missing fields, the respective ToxIC investigator is contacted for clarification and data completion. Any rare instance of a case with significant missing data that cannot be clarified with the investigator results in the case being excluded from the ToxIC database.

In summary, roughly one in 165 patients consulted by ToxIC medical toxicology services at the bedside dies. Three out of four fatalities involve intentional exposures, primarily to pharmaceuticals, most commonly analgesics (opioids and non-opioids). Fatalities affect both sexes equally, and one in 10 deaths is a child.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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