Retained drugs in the gastrointestinal tracts of deceased victims of oral drug overdose

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Context. The extent of non-absorbed drug burden in the GI tract following overdose is unknown. Patients who present with clinical signs of toxicity may not undergo decontamination due to assumption that the drug has already been completely absorbed and because of limited scientific evidence of benefit for routine GI decontamination in poisoned patients. Objective. The goal of this study was to assess whether people who die of an oral overdose have unabsorbed drug present in the GI tract. The secondary goal was to analyze pharmacologic characteristics of retained drugs when present. Materials and methods. Retrospective review of autopsy reports from 2008 to 2010, whose cause of death was determined as “intoxication” or “overdose,” was performed at the Office of Chief Medical Examiner of the City of New York (OCME NYC). Decedents of all ages were identified via electronic OCME database. Inclusion criteria were as follows: 1) cause of death was determined as “intoxication” or “overdose” noted by forensic autopsy, 2) ingestion of a solid drug formulation. Results. 92 out of 1038 autopsies (9%) that met inclusion criteria had documentation of retained pill fragments, granules, paste, sludge, slurry, or whole pills in the GI tract. The most common drugs found were opioids and anticholinergics. Ninety-eight percent (98%) of the retained drugs were either modified-release preparations or drugs known to slow GI transit. Most decedents were dead on arrival; there were twelve in-hospital deaths and eleven patients died in the Emergency Department. Bupropion and venlafaxine were responsible for four deaths in those who received medical care. One person died in the ICU following bupropion ingestion. Discussion and conclusion. Overdose of an oral drug that either has modified-release properties or slows GI tract motility may result in substantial unabsorbed drug burden remaining in the GI tract.

Keywords GI decontamination; Autopsy; Retained drugs

Introduction

Fatalities from drug overdose have been on the rise for several decades. The United States Centers for Disease Control and Prevention (CDC) reported 38,329 drug overdose fatalities in 2010, of which, approximately 60% were related to pharmaceuticals.¹ Recently, poisoning became the leading cause of unintentional injury-related fatality in people between 25 and 64 years of age.²

Gastrointestinal (GI) decontamination remains a controversial topic in the management of a poisoned patient. The goal of GI decontamination is to prevent the absorption of drug from the GI tract into the systemic circulation following an overdose and thereby reduce the severity of the clinical effects. Although GI decontamination is no longer routinely recommended in clinical practice,³–⁵ there still are instances in which a benefit can be realized.⁶–⁹

GI decontamination is controversial once the patient demonstrates clinical signs of toxicity and benefits are difficult to prove given the heterogeneity of the studied populations. Overt toxicity signifies at least some drug absorption. Although the pharmacokinetics of most drugs change following overdose, the persistence of undigested drug in the GI tracts of patients who are manifesting clinical effects is not studied. A study using gastric scintigraphy in patients following demonstrated markedly delayed passage into the duodenum of the ingested drug following confirmed overdose of tricyclic antidepressants, acetaminophen, opioid–acetaminophen preparation, carbamazepine, and phenytoin.¹⁰

The main objective of this study was to assess the presence of undigested or partially digested tablets in the GI tract in oral overdose fatalities. A secondary objective was to discern the unique pharmacologic characteristics of these drugs when present, such as their capacity to alter absorption of the drug or to slow GI motility. The presence of tablets or fragments in the GI tracts of the decedents might support the potential utility for more aggressive decontamination in select cases.
Methods

This study is a retrospective review of data collected prospectively. The study was approved by the Office of Chief Medical Examiner of the City of New York (OCME NYC). Death certificates of decedents of all ages where the cause of death was determined to be “intoxication” or “overdose” were identified through an electronic record search of OCME NYC database for the years 2008–2010. The OCME NYC record of each relevant decedent with a unique identifying code was reviewed and abstracted by the lead researcher, who was at the time of the study a medical toxicology fellow. The autopsy report, all toxicology results, supplemental information gathered by medico-legal investigators, and hospital documentation, when appropriate, were collected. Inclusion criteria were as follows: (1) cause of death “intoxication” or “overdose” determined following a forensic autopsy and (2) ingestion of a solid drug formulation. Exclusion criteria were as follows: (1) cause of death other than “intoxication” or “overdose”, (2) forensic autopsy not performed, (3) route of ingestion other than oral (e.g., injection, inhalation, and insufflation), and (4) a non-solid drug ingestion.

Table inscriptions, if noted in the autopsy report, were queried by the lead author via Epocrates® tablet identification tool. There was no routine testing or identification of retained whole tablets. Postmortem toxicology testing, when available, provided identification of a drug when not directly identifiable, such as when in the form of a paste or slurry.

Results

A total of 1,038 medical examiner cases from years 2008 to 2010 were identified and reviewed (see Fig. 1). 694 cases were excluded, 180 of which did not have an autopsy performed. The remaining 514 excluded cases consisted mostly of decedents who died of either the isolated or combined effects of cocaine, heroin, methadone, and/or ethanol. There were four body packers (drug smugglers), one with 101 effects of cocaine, heroin, methadone, and/or ethanol. There were 92 out of 1,038 decedents (9%) who had whole pills, pill fragments, pill granules, paste, sludge, or slurry in the GI tract. Among these 92 cases, 98% had drugs in their GI tract that are known to slow GI tract motility, delay gastric emptying, or were in a modified-release preparation. Table 1 contains a comprehensive list of these drugs. Among these drugs, anticholinergics, some sedative–hypnotics such as barbiturates, and opioids reduce peristalsis. Salicylates delay gastric emptying. Modified-release preparations often have delayed absorption and delayed clinical effects following overdose. The most common class of drug found on autopsy was anticholinergic agents (30%). The combination of opioid and anticholinergic drugs was also prevalent (22%), followed by opioids (16%) and non-opioid modified-release preparations (10%).

There were two decedents (2%) with retained drugs that did not have a known effect on GI transit. The cause of death was determined to be intoxication by the following agents: benzodiazepines in one case, and a combination of lamotrigine and citalopram in the other.

A single drug was the cause of death in 17 out of 92 autopsies. Bupropion, quetiapine, and diphenhydramine accounted for a total of nine fatalities (three fatalities [17%] per each drug) when ingested as a single agent in a decedent with whole pills found in GI tract. The identifiable bupropion tablets were in the form of extended-release preparation based on the tablet markings or medication list available in the medico-legal chart. One decedent with combined extended-release bupropion and ethanol ingestion had 10–20 tablets with intact markings confirming bupropion in the stomach. Oxycodone was responsible for 2 of 17 fatalities as a single agent. The remainder of single drug fatalities (one case per drug) resulted from ingestion of clozapine, pentobarbital, morphine, venlafaxine, nortriptyline, and amitriptyline.

Most decedents were dead upon arrival of Emergency Medical Services. There were twelve in-hospital fatalities that are further described in Table 2. Eleven out of these twelve died in the Emergency Department, with bupropion toxicity determined to be a cause of death in three of these patients, and venlafaxine in three other patients. One person with bupropion ingestion died in the Medical Intensive Care Unit (MICU).

Fig. 1. Data selection.

Discussion

The present study suggests that overdose of medications with either modified-release properties or that slow GI transit time may be associated with a significant GI tract burden of unabsorbed pills and pill fragments. Medications identified in this study with this property include anticholinergic agents, opioids, barbiturates, and salicylates. The absorption of modified-release preparations may be significantly altered following overdose, and their effect on the GI tract may alter the absorption of other drugs as well.

Perhaps the most compelling findings were retention of multiple undigested pills in the GI tracts of decedents who died of bupropion and venlafaxine overdoses. This was noted in patients who died of a bupropion overdose prior to...
Retained drugs in the deceased

Arriving at health care facility as well as several who survived to reach the Emergency Department. The patient who died in the MICU had 15–20 tablets of bupropion retained in the stomach. Another patient who died in the ED following a venlafaxine overdose had 71 retained whole pills in the GI tract (Table 2). There was no documentation of GI decontamination in the brief medical chart scanned into the OCME database, and time from ingestion to death was not known. It is unclear whether patients had physical or historical evidence of having received GI decontamination. Although there is little known about the lethality of these drugs following overdose, findings suggest that select cases with significant bupropion or venlafaxine overdose may warrant more aggressive approaches to GI decontamination.

GI decontamination is no longer routinely recommended in the management of the acutely poisoned patients. The American Academy of Clinical Toxicology (AACT) and European Association of Poisons Centres and Clinical Toxicologists (EAPCCT) recommend administration of activated charcoal only up to one hour post ingestion in a patient with intact airway following ingestion of a toxin that is known to be adsorbed by activated charcoal. Whole-bowel irrigation is recommended for patients who have ingested a modified-release or enteric-coated preparation, a large dose of iron, or who are internally concealing illicit drugs (“body packer”). Gastric lavage is no longer routinely recommended, although it is routinely practiced in many places. Furthermore, the presence of clinical signs and symptoms of toxicity often precludes

Table 1. Retained drugs.

<table>
<thead>
<tr>
<th>Classes of drugs</th>
<th>Specific drugs</th>
<th>Percent of autopsies with retained drug in the GI tract*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticholinergic only</td>
<td>Antihistamine:  • Diphenhydramine  • Doxylamine</td>
<td>30% (26 of 92 autopsies)</td>
</tr>
<tr>
<td></td>
<td>Antipsychotic:  • Chlorpromazine  • Clozapine  • Olanzapine  • Quetiapine  • Trifluoperazine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Antidepressant:  • Amitriptyline  • Doxepin  • Imipramine  • Nortriptyline  • Paroxetine</td>
<td></td>
</tr>
<tr>
<td>Muscle relaxants:</td>
<td>• Cyclobenzaprine</td>
<td></td>
</tr>
<tr>
<td>Opioid only</td>
<td>• Codeine  • Hydrocodone  • Morphine  • Oxycodone  • Oxymorphone  • Propoxyphene  • Tramadol</td>
<td>16% (15 of 92 autopsies)</td>
</tr>
<tr>
<td>Non-opioid modified-release preparations only</td>
<td>• Bupropion  • Venlafaxine</td>
<td>10% (9 of 92 autopsies)</td>
</tr>
<tr>
<td>Sedative-hypnotic only</td>
<td>Barbiturates:  • Butalbital  • Pentobarbital  • Phenobarbital</td>
<td>3% (3 of 92 autopsies)</td>
</tr>
<tr>
<td>Delay of gastric emptying only</td>
<td>Salicylates:  • Aspirin</td>
<td>2% (2 of 92 autopsies)</td>
</tr>
<tr>
<td>Combination of drugs</td>
<td>• Opioid and anticholinergic  • Opioid and modified-release preparation  • Opioid and sedative-hypnotic  • Opioid, sedative-hypnotic, and anticholinergic  • Opioid, anticholinergic, and modified-release preparation  • Anticholinergic and modified release preparation  • Anticholinergic and sedative-hypnotic</td>
<td>Total: 37% (34 of 92 autopsies)</td>
</tr>
</tbody>
</table>

GI, Gastrointestinal.

*Note that 2 autopsies (2%) contained drugs that did not affect GI transit and were not modified-release preparations.
### Table 2. Hospital fatalities.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hospital course*</th>
<th>Autopsy findings (GI tract)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bupropion</td>
<td>Family noted hallucinations, agitation, seizure, and unresponsiveness EMS: • Cardiac arrest • ACLS ED: • ACLS continued without ROSC • Death</td>
<td>The stomach contained two white pills</td>
</tr>
<tr>
<td>Bupropion</td>
<td>EMS: • Agitation ED: • Agitation - received midazolam • Head computed tomography (CT) without acute injury • Transfer to MICU MICU: • Hypotension • Dopamine started with transient blood pressure (BP) improvement • Cardiac arrest • ACLS without ROSC • Death</td>
<td>The stomach contained approximately 15–20 white, film-coated tablets bearing the markings WPI-3332.</td>
</tr>
<tr>
<td>Bupropion Venlafaxine</td>
<td>Decedent called son and admitted to overdose; son called 911 EMS: • Unresponsive to painful stimuli ED: • Seizure followed by asystole • ACLS • Initial return of spontaneous circulation • Cardiac arrest 40 min later • Death</td>
<td>The stomach contained approximately 100 mL of black, thick fluid and a small amount of white, granular sludge-like material.</td>
</tr>
<tr>
<td>Paroxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine</td>
<td>Seen the day prior to death EMS: • Heart rate (HR) 122 beats per min • Aphasic, jerking ED: • Agitation • Normal head CT • Unresponsive - ventricular fibrillation cardiac arrest • Defibrillation with return of spontaneous circulation • Intubation • Intravenous fluids • Amiodarone • Sudden decompensation with bradycardia cardiac arrest • Death</td>
<td>The stomach contained disintegrating pills and 71 white-colored intact pills</td>
</tr>
<tr>
<td>Ethanol</td>
<td></td>
<td></td>
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<tr>
<td>Venlafaxine Diphenhydramine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>End-to-end surgical anastomosis between distal esophagus and proximal jejunum; The esophagus and proximal small intestine contained white sphuerules and tan pasty material, proximally, and pink slurry distally</td>
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<td></td>
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<tr>
<td>Lamotrigine Paroxetine Zolpidem</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMS: • Unresponsive ED: • Intubated • Pulseless shortly after arrival • ACLS for 1 h 20 min • Death</td>
<td>The stomach contained approximately 150 mL of thick, tan liquid with dense mixture of white granular material is partially suspended in the liquid.</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
### Table 2. (Continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Hospital course*</th>
<th>Autopsy findings (GI tract)*</th>
</tr>
</thead>
</table>
| Amitriptyline         | Patient with history of cancer on hospice was discovered with empty medication bottles at the scene. ED:  
* Wide complex tachycardia unresponsive to sodium bicarbonate  
* DNR/DNI  
* Death | The gastric contents consisted of 330 cc of pink fluid slurry with apparent pill fragments and 14 intact orange tablets. |
| Atenolol Diltiazem Ethanol Nortriptyline | EMS:  
* Altered mental status  
* Cardiac arrest during transport to the hospital  
* Resuscitation efforts for approximately 2 h  
* Death | Stomach contained multiple granular blue pill fragments; small intestine contains numerous granular blue pill fragments. |
| Pentobarbital         | EMS:  
* Unresponsive  
* Intubation  
ED:  
* Cardiac arrest  
* ACLS without ROSC  
* Death | The stomach contained 100 cc of thick gray fluid |
| Quetiapine Cocaine    | Witnessed seizure  
ED:  
* Initial HR of 130 bpm, BP of 70 mmHg systolic  
* BP improved with IV fluids  
* Seizure followed by diazepam  
* Recurrent seizure  
* Wide QRS  
* Bradycardia  
* Asystole  
* ACLS for 30 min without ROSC  
* Death | The stomach contained fine white granular material |
| Morphine Methadone   | Shortness of breath and collapse  
EMS:  
* Cardiac arrest  
* ACLS  
ED:  
* ACLS without ROSC  
* Death | The stomach contained ¼ white pill without markings. |
| Morphine              | ED:  
* Apnea  
* ACLS without ROSC  
* Death | The stomach contained scant white granular particles and a partially dissolved white pill. |

*Information provided was taken directly from the OCME NYC chart.

GI, Gastrointestinal; EMS, Emergency Medical Services; ACLS, Advanced Cardiac Life Support; ED, Emergency Department; ROSC, Return of Spontaneous Circulation; MICU, Medical Intensive Care Unit; DNR, Do not Resuscitate; DNI, Do not Intubate.

GI decontamination with a generally incorrect assumption that the drug has been largely absorbed from the gut.
Retained drugs in the GI tract have been described in the literature in the form of pharmacobezoars, or concretions of drug(s) that are formed after ingestion. A comprehensive review cited enteric-coated aspirin, iron, nifedipine, clomipramine, meprobamate, quinidine, theophylline, venlafaxine, verapamil, aluminum hydroxide, bromides, magnesium oxide, and potassium chloride as potential concretion-forming drugs. Overdose of extended-release quetiapine resulted in a pharmacobezoar formation. The present study did not demonstrate the presence of any discrete pharmacobezoars.

The major limitations of our study are its retrospective nature and lack of direct evidence of the clinical course prior to death. Additionally, the total drug burden in either the gut or the body could not be determined. In some cases of the multidrug overdose cases, the identified pills may not have been the sole cause of death. Additionally, this study was not designed to assess clinical benefits of GI decontamination. Extrapolation of our findings to living patients following overdose is limited.

The time from ingestion to death could not be determined based on the available information. Most of the fatalities occurred outside the hospital setting. A formal laboratory analysis of the identified pills was not performed and
few tablets had markings. Finally, only a single abstrac-
tor reviewed the autopsy records introducing the potential
for systematic bias, although the vast majority of the data
collected were objective in nature.

Future directions would involve analysis of postmortem
retention of modified-release preparations such as bupro-
pion and venlafaxine in single drug overdose fatalities. Such
knowledge may provide important information in determining
the need for GI decontamination in patients with such
ingsestions.

Conclusion

A three-year retrospective analysis of autopsies of decedents
whose cause of death of “overdose” or “intoxication” with an
oral drug revealed that 9% of the deceased had pills, sludge,
slurry, paste, fragments, or whole tablets retained in the
GI tract. Ninety-eight percent of these drugs either had the
capacity to slow GI motility or were modified-release prepa-
ration. The most common classes of drugs were anticholin-
ergics (30%) or combination of opioids and anticholinergics
(22%). People who die of an overdose following ingestion
of drugs that either slow transit through the GI tract or have
modified-release preparations may have significant burden
of non-absorbed drug in the GI tract.

Declaration of interest

The authors report no declarations of interest. The authors
alone are responsible for the content and writing of the
paper.

References

1. Centers for Disease Control and Prevention (CDC). Drug overdose in
2. Centers for Disease Control and Prevention (CDC). 10 leading
causes of injury deaths by age group highlighting unintentional
wisqars/pdf/10cid_unintentional_deaths_2010-a.pdf. Accessed on
17 February 2014.
3. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of
Clinical Toxicology; European Association of Poisons Centres and
4. Seger D, Meulenbelt J, Lheureux P; American Academy of Clinical
Toxicology; European Association of Poisons Centres and Clinical
5. Benson BE, Hoppu K, Troutman WG, Bedry R, Erdman J, Höjer J,
et al.; American Academy of Clinical Toxicology; European Associa-
tion of Poisons Centres and Clinical Toxicologists. Position paper up-
date: gastric lavage for gastrointestinal decontamination. Clin Toxicol
(Phila) 2013; 51:140–146.
of acutely poisoned patients without gastric emptying. Ann Emerg
7. Pond SM, Lewis-Driver DJ, Williams GM, Green AC, Stevenson NW.
Gastric emptying in acute overdose: a prospective randomised
8. de Silva HA, Fonseka MM, Pathmeswaran A, Alahakone DG,
Ratnatileke GA, Gunatilake SB, et al. Multiple-dose activated
charcoal for treatment of yellow oleander poisoning: a single-
blind, randomized, placebo-controlled trial. Lancet 2003; 361:
9. Eddleston M, Juszczak E, Buckley NA, Senarathna L, Mohamed F,
Dissanayake W, et al. Multiple-dose activated charcoal in acute
self-poisoning: a randomized controlled trial. Lancet 2008; 371:
579–587.
10. Adams BK, Mann MD, Aboo A, Isaacs S, Evans A. Prolonged gas-
tric emptying half-time and gastric hypomotility after drug overdose.
in acute organophosphorus pesticide poisoning (GLAOP) – a ran-
domised controlled trial of multiple vs. single gastric lavage in unse-
lected acute organophosphorus pesticide poisoning. BMC Emerg Med
2006; 6:10.
Toxicol (Phila) 2011; 49:72–89.
Kupferschmidt H, Ceschi A. Gastric pharmacobezoars in quetiapine
51:937–940.