J. Med. Toxicol. (2010) 6:398–402
DOI 10.1007/s13181-010-0086-6

TOXICOLOGY INVESTIGATION

Benzonatate Ingestion Reported to the National Poison Center Database System (NPDS)

Mark L. Winter · Henry A. Spiller · Jill R. K. Griffith

Published online: 20 May 2010
© American College of Medical Toxicology 2010

Abstract Little has been published on benzonatate ingestion, with the few case reports suggesting significant risk of seizures after poisoning. A 7-year retrospective review of all single substance ingestion of benzonatate reported to the National Poison Center Database System (NPDS) from 2000 to 2006. In this review, there were 2,172 patients, of which 1,280 (58%) were female. Mean age was 20 years, with 676 (30%) <6 years. Serious outcomes occurred in 116 (moderate, n=81, 4%; major, n=31, 1%; and death, n=4, 0.2%). Mean age of those with serious outcome was 21 years, with 41 (35%) in children less than 6 years old. Forty-nine percent (1,084) patients were treated in a healthcare facility (HCF) of which 148 (7%) were admitted for medical care. Clinically significant effects that were documented included tachycardia (n=31, 1%), agitation (n=30, 1%), seizure (n=23, 1%), coma (n=14, 0.6%), ventricular dysrhythmia (n=9, 0.4%), cardiac arrest (n=8, 0.3%), hypotension (n=7, 0.3%), and asystole (n=6, 0.2%). Of patients with seizures reported, eight patients (0.4%) had multiple/discrete seizures and two had status epilepticus documented. Dysrhythmias but not seizures occurred in all fatalities in this review. Significant CNS and cardiac effects occurred in a small subset of this study (<1%), while half the patients received direct medical care in an HCF. No correlation between age and severity of medical outcome was detected by statistical analysis. A prospective study to better evaluate potential HCF triage criteria such as dosage, age, or preexisting conditions may be warranted. The fatalities from this study were due to dysrhythmias rather than seizures as previously reported in previous case reports. There were no clinical correlations between severity of outcomes and dose ingested. A median dose of 200 mg or greater suggests a potential for producing serious outcomes in a benzonatate exposure.

Keywords Benzonatate · Poisoning · Dysrhythmia · National database

Introduction

Benzonatate 4-(butylamino) benzoic acid, Tessalon® [1], (Fig. 1) is structurally related to the local anesthetic tetracaine (Fig. 2), with the addition of a polyethylene glycol moiety. It is a non-narcotic antitussive approved by the Food and Drug Administration for cough. The antitussive effect of benzonatate appears to be mediated by an action on both central and peripheral respiratory mucosal stretch receptors. In the treatment of cancer patients with cough refractory to centrally acting opioids, benzonatate, as a peripherally acting non-opioid, is used as second-line therapy [2–4].

There is limited published information on the toxicity from benzonatate ingestion. A total of four cases have been reported in the peer review literature with three of these cases presenting in full arrest with limited clinical details [5, 6]. The three fatalities (two infants and one adult) were in full arrest upon arrival of EMS and resuscitation efforts were unsuccessful. The fourth patient was a 39-year-old

Part of this work was presented as a poster at the 2008 North American Congress of Clinical Toxicology, Toronto, Canada, on September 14, 2008.

M. L. Winter · H. A. Spiller (✉)
Kentucky Regional Poison Center,
PO Box 35070, Louisville, KY 40232-5070, USA
e-mail: Henry.spiller@nortonhealthcare.org

J. R. K. Griffith
Mount Carmel West Medical Center,
Columbus, OH, USA

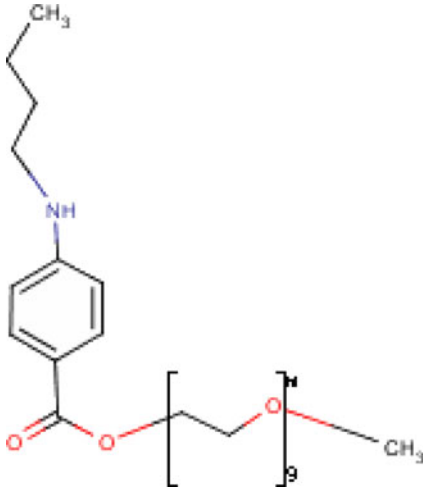

Fig. 1 Benzonatate

male who suffered a seizure and unstable ventricular tachycardia, which responded to cardioversion. He received oxygen, lavage, and activated charcoal and was discharged the following day after an uneventful hospital course. Two additional cases have been reported in abstract form and included one death and one child with a brief episode of seizures [7, 8]. A publishing bias towards severe or unusual cases may lead to overestimation of the prevalence of severe toxicity of this substance. In the case of benzonatate, a fatality rate of 67% from these published cases could potentially overestimate the true prevalence of severe outcomes.

Two abstracts have been published on retrospective studies from poison center data with only 3-6% of cases reported to have severe effects documented [9, 10]. These data suggest the possibility of this overestimation of the prevalence of severe outcomes. In an effort to elucidate the prevalence of toxicity and clinical picture associated with benzonatate toxicity, we reviewed 7 years of nationwide poison center data involving benzonatate ingestion.

Methods

We performed a 7-year retrospective study of all single substance ingestions of benzonatate reported to the National Poison Center Database System (NPDS) for the years 2000 through 2006. The NPDS database was searched using the American Association of Poison Control Centers product specific codes for benzonatate: 3106154, 5872216, 5472339, 5881309, 6449717, 5307453, 5331296, 5345586, 2339839, 2339847, 5881390, 3006602, and 3687914. Inclusion criteria included ingestion of benzonatate in humans. Exclusion criteria were animal exposures and poly substance ingestion. After initial search of the NPDS database, it was determined that the case selection included 25 cases of probable miscoding. In 25 of the 2,197 cases (1%) originally selected by the search, the reason for exposure was recorded as environmental or an adverse reaction to food suggesting the possibility of miscoding of the data in a small minority of the reported cases. These 25 cases were excluded from the study database prior to analysis, leaving 2,172 cases for analysis.

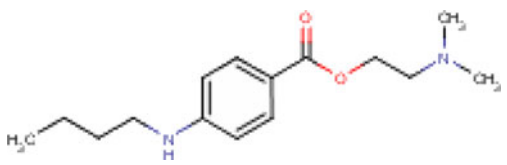

Fig. 2 Tetracaine

Once cases were identified, all personal identifiers, except patient age and date of occurrence, were removed. These cases were loaded into SPSS for Windows 11.5.0 for statistical analysis. The data collected included age, gender, weight, dose ingested, reason for exposure, clinical effects, treatment site, treatment, and medical outcome. Definition for reason for exposure, clinical effects, and medical outcome categories were standards used by all poison centers submitting data to the NPDS and have been published elsewhere [11].

Dose ingested was obtained by patient history and documented in the electronic record. The individual case notes were not available for review to verify history of documented dose The ingested dose was recorded in NPDS as estimate, maximum possible, or unknown. Only cases with the dose recorded as estimate or maximum possible were used when evaluating dose response. Patients were followed by telephone periodically following the ingestion, with inquiries about the occurrence of symptoms and the overall condition of the patient. This retrospective chart review was approved by the Institutional Review Board and meets the Human Subjects Research Committee requirements for minimal risk to loss of patient confidentiality information.

Results

The database search returned records of 2,172 patients that met the inclusion criteria (mean 272 per year), of which 1,280 (59%) were female. The mean patient age was 20 years with a range of 1-93 years old. Thirty percent of patients (n=676) were less than 6 years old. Fifty percent of patients (n=1,084) were treated in healthcare facilities (Table 1) of which 7% (n=148) were admitted for medical care.

Serious outcomes were reported in 116 patients (5%), who included 81 moderate effect patients (4%), 31 major effect patients (1%); and four deaths (0.2%) as shown in Table 1 and Table 4. Mean age of those with serious

Table 1 Management site and medical outcome

	Frequency of all patients	Frequency of patients managed on site Non-HCF	Frequency of patients managed at other	Frequency of patients already in (in route to) HCF when PCC called	Frequency of patients referred by PCC to a HCF	Frequency of patients receiving activated charcoal
Confirmed non-exposure	34 (2)	27 (3)	0	2 (1)	5 (1)	NA
Death	4 (0.2)	0	0	3 (1)	1 (0)	0 (0)
Major effect	31 (1)	0	1 (5)	25 (6)	5 (1)	8 (28)
Moderate effect	81 (4)	21 (2)	1 (5)	34 (8)	25 (4)	21 (26)
Minor effect	373 (17)	198 (19)	4 (22)	74 (17)	97 (15)	61 (16)
No effect	864 (39)	261 (24)	3 (17)	241 (55)	359 (56)	266 (31)
Not followed, judged as nontoxic exposure (clinical effects not expected)	103 (5)	100 (9)	0	3 (1)	0	NA
Not followed, minimal clinical effects possible (no more than minor effect possible)	493 (23)	442 (41)	5 (28)	21 (5)	25 (4)	NA
Unable to follow, judged as a potentially toxic exposure	138 (7)	0	4 (22)	19 (4)	115 (18)	NA
Unrelated effect, the exposure was probably not responsible for the effect(s)	51 (2)	24 (2)	0	12 (3)	15 (2)	NA
Total (percent of the total)	2,172	1073 (49)	18 (1)	434 (20)	646 (30)	

Definitions for medical outcome categories are standardized and used by all US poison centers (11). In each column, the percentage listed in parenthesis is calculated for the total number of patients in the column. Percentages listed in parenthesis are rounded to significant numbers and may not total 100%

HCF healthcare facility, *PCC* Poison Control Center

outcome was 21 years, with 41 (35%) less than 6 years old. An intentional exposure to benzonatate suggested a significantly increased risk for a serious outcome ($p<0.01$, OR 3.56, 95% CI 2.23-5.66). Thirty-three of the 285 patients with an intentional exposure (12%) developed a serious outcome versus 62 of the 1,740 patients with an unintentional exposure (4%) as shown in Table 4. Patients receiving activated charcoal as a decontamination therapy by medical outcome are listed in Table 1.

Reported clinically significant effects were infrequent (≤1%) and are listed in Table 2. Specifically, 23 patients experienced seizures (1%). In addition, eight patients (0.4%) had multiple/discrete seizures and two had status epilepticus documented (0.1%). Dysrhythmias but not seizures occurred in all fatalities in this review. When the dose was documented, the dose ingested versus outcome severity is presented in Table 3. Table 4 depicts the reason for exposure and medical outcome for 2,172 benzonatate exposures.

Thirty-one of 648 patients (5%) of the patients that were referred into a HCF by the PCC developed moderate or major symptoms during the course of their hospitalization with one fatality in this subset of benzonatate exposures. Ninety-three of these 648 patients (14%) that were referred into a HCF were intentional ingestions. In addition, 29 exposures (5%) in this group were referred into a HCF secondary to adverse drug reactions

Discussion

Reports of significant cardiac and CNS effects occurred in a small subset of this study. While the clinical effects reported (seizures, dysrhythmias) are similar to those reported in the few available cases reports, the prevalence of these effects was very low (≤1%) when reviewing the nationwide database over the last 7 years. Additionally, the prevalence of patients with any medical outcome that would denote systemic effect was low (5%). This is similar to two previously reported studies with fewer patients [9, 10]. These data suggest a risk of

Table 2 Clinical significant effects that would constitute either moderate or major effects by the definitions for medical outcome categories that are standardized and utilized by all US poison centers (11)

Clinical effects	Number of patients (% of total)
Tachycardia	31 (1%)
Agitation	30 (1%)
Seizure	23 (1%)
Coma	14 (0.6%)
Ventricular dysrhythmia	9 (0.4%)
Cardiac arrest	8 (0.3%)
Hypotension	8 (0.3%)
Asystole	6 (0.2%)

Table 3 Medical outcome by dose ingested when reported in NPDS

Outcome	Number of patients with recorded dose	Mean (median) dose in mg
Death	1	3,000
Major	20	1,410 (1,000)
Moderate	68	629 (200)
Minor	329	415 (100)

major outcome of 1.4% (31 of 2,172) for this review of benzonatate exposures.

There was no difference in percentage of patient who received activated charcoal based on medical outcome. This may reflect either a very rapid absorption of the benzonatate, producing significant toxicity prior to intervention or limited of efficacy activated charcoal after benzonatate ingestion.

Despite the low prevalence of significant clinical effects approximately half the patients received direct medical care in a healthcare facility. This high healthcare facility utilization rate may reflect an overly cautious triage approach from the poison center due to uncertainty of the prevalence of severe toxicity from benzonatate ingestion. Overall, these data show that the poison control center referred 30% of the benzonatate exposures in this study into a healthcare facility.

Our study found no correlation between age and severity of medical outcome. However, history of intentional ingestion did suggest an increased risk. This increased risk is not unexpected as intentional exposures are likely to ingest larger doses of benzonatate. From this review, when evaluating dose ingested as a potential triage threshold, a median dose 200 mg (one 200 mg capsule) or greater may suggest a potential for producing serious outcomes in children less than 6 years old. One previous smaller study suggested 600 mg in adults and greater than 10 mg/kg in children [10]. Our study is in agreement that ingestion of a single benzonatate Pearle is unlikely to cause a severe medical outcome. A prospective study to better evaluate potential healthcare facility triage criteria such as dosage, age, or pre-existing conditions may be warranted.

Although our study provides useful information regarding ingestion of benzonatate, a number of limitations should be considered. The retrospective nature of the data limits our ability to control for confounding factors. The data itself were derived from self-reported calls and reflected only information provided when the public or healthcare professionals reported an actual or potential exposure to a substance. Since this is a voluntary reporting system, there are several inherent biases (e.g., selection bias, misclassification bias). Also, this reporting system cannot capture all ingestions since reporting is voluntary. Due to the recall nature of the data, elements of histories such as dose ingested could be incomplete or inaccurate. Finally, benzonatate serum concentration data were not available for evaluation for this review.

Conclusions

In summary, severe medical outcome after ingestion of benzonatate was uncommon. The four fatalities reported in this study were due to dysrhythmias rather than seizures. A median dose of benzonatate of 200 mg or greater may suggest a potential for producing serious outcomes in a benzonatate exposure.

Table 4 Reason for exposure and medical outcome

	Frequency All patients	Frequency moderate outcome	Frequency of major outcome	Frequency of fatal outcome
Adverse reaction—drug	144 (7)	20 (25)	1 (3)	0
Intentional—abuse	12 (1)	1 (1)	2 (7)	0
Intentional—misuse	49 (2)	2 (3)	0	0
Intentional—suspected suicide	206 (9)	15 (19)	11 (35)	1 (25)
Intentional—unknown	17 (1)	0	0	1 (25)
Unintentional—general	1227 (56)	28 (35)	16 (52)	2 (50)
Unintentional—misuse	36 (2)	3 (4)	0	0
Unintentional—therapeutic error	477 (22)	12 (15)	1 (3)	0
Unknown reason	4 (0.2)	0	0	0
Total	2,172	81	31	4

In each column, the percentage listed in parenthesis is calculated for the total number of patients in the column. Percentages listed in parenthesis are rounded to significant numbers and may not total 100%. Definitions for medical outcome categories are standardized and used by all US poison centers (11)

Declaration of Interest The authors report no conflict of interest. The authors alone are responsible for the content and writing of the manuscript.

References

1. Product Information. Tessalon (benzonatate). St. Louis, MO: Forest Pharmaceuticals, July 2007.
2. Estfan B, LeGrand S (2004) Management of cough in advanced cancer. J Supp Oncol 2:523–7
3. Homsi J, Walsh D, Nelson KA (2001) Important drugs for cough in advanced cancer. Support Care Cancer 9:565–74
4. Doona M, Walsh D (1998) Benzonatate for opioid-resistant cough in advanced cancer. Palliat Med 12:55–8
5. Cohan JA, Manning TJ, Lukash L et al (1986) Two fatalities resulting from Tessalon™ (Benzonatate). Vet Hum Toxicol 28:543–4
6. Crouch BI, Knick KA, Crouch DJ et al (1998) Benzonatate overdose associated with seizures and arrhythmias. J Toxicol Clin Toxicol 36:713–8
7. Sheen S, Osterhoudt K, Birenbaum D (1997) Seizures in a toddler associated with benzonatate ingestion (abstract 31). J Toxicol Clin Toxicol 35:493
8. Shropshire A, Clifton J II, Aks S et al (1999) Death from intentional IV administration of benzonatate (abstract 169). J Toxicol Clin Toxicol 37:652
9. Borys DJ, Morgan DL, Juan J, Vincent CB (2006) Pediatric benzonatate exposures: a six-year retrospective review of 67 patients (abstract 297). J Toxicol Clin Toxicol 44:768–9
10. Schwarz KA, Vohra R, Clark RF (2006) Retrospective evaluation of outcomes of benzonatate exposures: a statewide poison control system based study (abstract 317). J Toxicol Clin Toxicol 44:777
11. Bronstein AC, Spyker DA, Cantilena LR et al (2008) 2007 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. Clin Toxicol 46:927–1057