Selected Topics: Toxicology

ARE ONE OR TWO DANGEROUS? DIPHENOXYLATE-ATROPINE EXPOSURE IN TODDLERS

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Abstract—Lomotil® (Pfizer Inc., New York, NY) (diphenoxylate-atropine) is said to be potentially toxic to toddlers with exposure to as little as one to two tablets. A review of the data on diphenoxylate-atropine poisonings from the American Association of Poison Control Centers annual reports, review articles, and case series disputes this view. Fatalities associated with diphenoxylate-atropine have been reported in toddlers after repetitive or incorrect dosages. Fortunately, trends in pediatric diphenoxylate-atropine ingestions are decreasing. We review the management, trends, and current concepts regarding pediatric diphenoxylate-atropine ingestions. © 2008 Elsevier Inc.

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INTRODUCTION

Diphenoxylate-atropine, commonly known as Lomotil® (Pfizer Inc., New York, NY), is an antidiarrheal agent. First introduced in 1960, it is a prescription medication due to its opioid component. Diphenoxylate-atropine exposure has been extensively reported in children under the age of 6 years, as this age group seems to be most susceptible to diphenoxylate-atropine toxicity. It is commonly believed that serious toxicity can result with ingestion of only one or two pills in the pediatric population. By reviewing the available literature, this article evaluates the basis for this belief. Furthermore, guidelines for triage and observation are provided based on these findings. Included are a short review of the pharmacology, pathophysiology, and management of diphenoxylate-atropine exposures.

CHARACTERISTICS OF DIPHENOXYLATE-ATROPINE

Diphenoxylate-atropine is an opioid-anticholinergic combination. Each tablet or 5 cc of syrup contains 2.5 mg of diphenoxylate hydrochloride and 0.025 mg of atropine sulfate (1). Diphenoxylate is a synthetic phenylpiperidine derivative closely related to meperidine (Demerol®). It decreases both the propulsive and non-propulsive smooth muscle contractions of the stomach and intestines and thus prolongs the transit time of intestinal contents. The atropine is added in the formulation to decrease the abuse potential (1). Commercial names for the diphenoxylate-atropine combination in the United States include Lomotil®, Diphenatol®, Elmotil®, Enoxa®, Lofene®, Lonox®, Lo-
trol®, and Lo-Quel®. The manufacturer states that diphenoxylate-atropine is not recommended for children below the age of 4 years (1). The recommended daily dosage of diphenoxylate in children older than 4 years of age is 0.3 to 0.4 mg/kg/24 h administered in four divided doses. The adult dose is 5 mg four times daily.

The pharmacokinetics of diphenoxylate are based upon studies in adults by Karin et al. from 1972 (2). There are no pharmacokinetic studies in children. After ingestion of diphenoxylate-atropine, the atropine and diphenoxylate are absorbed through the gastrointestinal tract. The absorption has been shown to be delayed in cases of overdose, due to delay in gastric motility. The diphenoxylate component of the drug is subsequently metabolized to difenoxine. This is important because difenoxine is more active and longer acting than diphenoxylate. Peak plasma concentrations of diphenoxylate and difenoxine are reached in 2–4 h (2). The half-life of difenoxine is 4.4 h compared to 2.5 h for diphenoxylate in therapeutic doses (2).

Serious toxicity, including respiratory depression, aspiration pneumonia, cerebral edema, and death have been reported (3–6). Clinical features of diphenoxylate-atropine toxicity are due to the combination of anticholinergic (atropine) and opioid (diphenoxylate) properties. Anticholinergic features include hyperpyrexia, tachycardia, flushing, dry skin, urinary retention, and central nervous system excitement. Opioid features include miosis, lethargy, respiratory depression, and coma. Symptoms of diphenoxylate-atropine can be prolonged for up to 24 h due to the delayed gastrointestinal (GI) motility properties from the anticholinergic effects and opioid properties (3).

### CASE REPORT

Several cases of pediatric diphenoxylate-atropine ingestions have been reported over the past 40 years. Deaths involving diphenoxylate-atropine have been reviewed and described. Most cases involve the ingestion of multiple tablets, or repetitive dosages of diphenoxylate-atropine. The 2000 annual report of the American Association of Poison Control Centers reported a 2-year-old boy who was given 8–16 drops of diphenoxylate-atropine over a 48-h period (7). This child subsequently developed lethargy and respiratory depression and died shortly after admission. Wasserman et al. described a 10-month-old who developed cyanosis and respiratory depression after ingestion of Emerset® and Lomotil® within a 12-h time frame (8). This infant was admitted after being found comatose.

### DIPHENOXYLATE-ATROPINE TOXICITY IN CHILDREN

The clinical manifestations of diphenoxylate-atropine overdose may vary. Initially, diphenoxylate-atropine toxicity was described as having two distinct phases of clinical symptoms (4,8–10). The first phase was an anticholinergic toxidrome lasting 2–3 h after exposure followed by a much longer opioid phase. These two distinct phases were challenged by McCarron et al., who extensively reviewed 36 cases of pediatric diphenoxylate-atropine ingestions (3). These authors found only four of 36 (11%) had the classic, previously described sequence of clinical symptoms. All patients manifested some opioid side effects and in nearly half, these were the only side effects reported. Toxic effects included miosis, lethargy, apnea, and respiratory depression. In seven cases, respiratory depression occurred 13–24 h after ingestion. Based upon these findings, McCarron et al. stated, “diphenoxylate-atropine intoxication should be considered a long acting opioid overdose that may include manifestations of atropine toxicity.”

Significant morbidity and mortality may result when there is delayed or absent GI decontamination. In McCarron’s review, eight patients had no or delayed (> 26 h) GI decontamination (3). All eight had significant complications, including aspiration pneumonia, cerebral edema, and death. Intact pill fragments have been found in some cases 15–27 h after ingestion (3,8,10). Based on this information, it seems reasonable to initiate gut decontamination as rapidly as possible.

### MINIMAL TOXIC DOSE OF DIPHENOXYLATE-ATROPINE

There is no known minimal toxic dose of diphenoxylate-atropine ingestion. The lowest reported dose of diphenoxylate-atropine ingestion associated with symptoms involved half a tablet (10). That case, reported by Rumack and Temple, described a 6-month-old who ingested 1.25 mg of diphenoxylate-atropine and subsequently developed miosis. The infant was given two doses of naloxone and did not develop any respiratory depression. McCarron’s review had a 24-month-old patient with drowsiness, miosis, flushing, dry appearance, and hyperthermia within 8 h after ingestion of 1 mg/kg of diphenoxylate-atropine (3). This patient later developed hyperactivity, tachycardia, ataxia, and vomiting. Wasserman reported toxicity after two tablets, however, this individual case was not described (8). Curtis and Goel reviewed 45 patients and found no consistent correlation between the dose of diphenoxylate-atropine ingested and the severity of symptoms (4). In fact, they found that the mean dose ingested was actually
greater in the group with mild symptoms then in those with more toxic symptoms.

Currently, the literature does not support the concept that “one pill can kill.” Prior series report that all fatalities occurred after repetitive or numerous dosages of diphenoxylate-atropine (3,4,8,10). Reports with one-half tab ingestion resulted in minor symptoms (e.g., miosis) but not mortality. Based on case reports, the smallest documented quantity resulting in coma and respiratory depression in young children is six to eight tablets (11–15) (Table 1). After extensive English literature review, the authors were unable to find any case that resulted in death after the ingestion of just one tablet or dose of diphenoxylate-atropine. A few cases reviewed, however, were of an “unknown” ingested amount.

## MANAGEMENT OF DIPHENOXYLATE-ATROPINE INGESTIONS

Patients with diphenoxylate-atropine overdose or suspected toxicity should be initially placed on a cardiac monitor. As with any ingestion, the vital signs should be monitored closely. The patients’ mental status should be closely observed and continually reassessed. Serum diphenoxylate levels are not useful towards the management of an acute overdose. Due to the delayed GI emptying properties of the drug, decontamination is paramount. GI decontamination can be achieved by charcoal administration or gastric lavage if necessary, and can be done several hours after ingestion. Activated charcoal can be given to alert patients or those with a protected airway. Administration of an emetic is not recommended.

Naloxone can be given to patients showing signs of altered mental status or respiratory depression. A continuous naloxone intravenous infusion can be started for those patients requiring frequent naloxone boluses. Patients showing signs and symptoms of diphenoxylate-atropine toxicity should be admitted to the pediatric intensive care unit for monitoring and treatment. We also believe that children with suspected significant ingestions (those ingestions above therapeutic guidelines), regardless of symptoms, require an observation period of at least 12–24 h. Those individuals with a certain history of isolated ingestion involving a single tablet or dose of diphenoxylated-atropine may be safely observed at home.

## TRENDS IN DIPHENOXYLATE-ATROPINE INGESTIONS

Recent diphenoxylate-atropine exposures and ingestions have decreased when compared to 10 years ago (7,16–24). In 2002, there were a total of 513 diphenoxylate-atropine ingestions, with 192 in the age group of 6 years and younger (22). This is comparatively less than 1995, when there were 1390 diphenoxylate-atropine ingestions, 720 being in the < 6-year age range (16). Table 2 illustrates a trend toward decreasing diphenoxylate-atropine exposures in children over the previous 10 years.

Although total diphenoxylate-atropine ingestions and pediatric exposures (< 6 years of age) have decreased since 2000 (513), ingestions over the past 3 years still range in number from 176–213. This does not represent a small number of potentially fatal ingestions. The last reported pediatric death from diphenoxylate-atropine occurred in 2000 in a 2-year-old child (7).

## CURRENT CONCEPTS: WHAT’S NEW IN DIPHENOXYLATE-ATROPINE POISONINGS

Currently, there are virtually no new data or information concerning diphenoxylate-atropine ingestions. After the

### Table 1. Minimal Toxic Dose of Diphenoxylate-Atropine by Case Report or Case Series

<table>
<thead>
<tr>
<th>Article/Author</th>
<th>Year Paper Published</th>
<th>Patient Age</th>
<th>Lowest Amount Ingested Diphenoxylate</th>
<th>Morbidity</th>
<th>Mortality</th>
<th>Individual Case Well Described</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rumack and Temple (10)</td>
<td>1974</td>
<td>6 months</td>
<td>1.25 mg</td>
<td>Miosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Wasserman et al. (8)</td>
<td>1975</td>
<td>Unknown</td>
<td>2 tablets</td>
<td>Somnolent</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Curtis and Goel (4)</td>
<td>1979</td>
<td>Unknown</td>
<td>2 tablets</td>
<td>Unknown</td>
<td>Unknown</td>
<td>No</td>
</tr>
<tr>
<td>Ginsburg and Angle (12)</td>
<td>1969</td>
<td>2 years</td>
<td>6 tablets</td>
<td>Coma/respiratory depression</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>King and Powell (11)</td>
<td>1965</td>
<td>5 months</td>
<td>15 mg</td>
<td>Coma</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Henderson/Psaila (13)</td>
<td>1969</td>
<td>2 years</td>
<td>6 tablets*</td>
<td>Respiratory arrest, CPR</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Canby (14)</td>
<td>1965</td>
<td>2 years</td>
<td>8 tablets</td>
<td>Apnea/cyanosis</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Snyder et al. (15)</td>
<td>1973</td>
<td>22 months</td>
<td>8-10 tablets</td>
<td>Respiratory depression</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Harris and Rossiter (25)</td>
<td>1969</td>
<td>2 years</td>
<td>12 tablets</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Referenced in the article as “might have ingested 6 tablets.” CPR = cardiopulmonary resuscitation.
introduction of diphenoxylate-atropine to the public in 1960, the first case report of toxicity was in 1965 (14). After that, the majority of case reports and reviews concerning poisonings of diphenoxylate-atropine were described in 1969 and the 1970s (4,8–15,25). The most recent case series is that of McCarron et al. (3). Excellent reviews and case series can also be found by Wasserman, and Curtis and Goel (4,8). Most of the current information on diphenoxylate-atropine ingestions comes from the American Association of Poison Control Centers annual report. It may be that the decreasing trends have resulted from improved physician and public knowledge concerning the dangers of diphenoxylate-atropine ingestions in the pediatric population.

**SUMMARY**

Diphenoxylate-atropine is a powerful prescription anti-diarrheal agent commonly used in adults. It is rarely, if ever, prescribed for pediatric patients. However, toddlers are still exposed to this potentially fatal medication. Children remain exposed to diphenoxylate-atropine through inadvertent ingestion or more rarely from treatment by unsuspecting parents. Diphenoxylate-atropine still remains a dangerous medication for the pediatric population for four important reasons: 1) repetitive or incorrect dosages, 2) symptoms may be delayed 24 h after ingestion, 3) there is no known minimal toxic dose, and 4) the clinical course is variable.

We believe that children younger than 6 years of age who have received repetitive or numerous dosages of diphenoxylate-atropine and are demonstrating signs of toxicity should be admitted and closely monitored. Children 6 years of age and younger who have an isolated ingestion of one tablet or dose of diphenoxylate-atropine may be safely observed at home.

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**REFERENCES**


