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# Salty broth for salicylate poisoning? Adequacy of overdose management advice in the 2001 *Compendium of Pharmaceuticals and Specialties*

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## Abstract

**Background:** The *Compendium of Pharmaceuticals and Specialties (CPS)* is a collection of monographs written by pharmaceutical companies and published by the Canadian Pharmacists Association. The *CPS* is widely available and is consulted frequently by Canadian physicians. We examined overdose management advice contained in the *CPS* to see whether it reflects current standards.

**Methods:** We restricted our review to 10 classes of medication for which an overdose is frequently fatal: acetaminophen,  $\beta$ -blockers, calcium-channel blockers, digoxin, lithium, opioids, salicylates, tricyclic antidepressants, theophylline and valproic acid. A panel of 3 toxicologists arrived at a consensus on indicated, contraindicated and futile interventions for each of these classes of drug. Monographs were then rated for their inclusion of essential interventions as excellent (listed all interventions and unique supportive care issues and gave correct and complete indications), good (listed the key interventions and gave correct and complete indications), fair (listed the key indications but failed to give proper indications) or poor (failed to list the key interventions). Monographs were also rated on how well they warned against contraindicated interventions as excellent (did not advocate any futile or contraindicated treatments and warned against contraindicated treatments), good (did not advocate any futile or contraindicated treatments), fair (did not advocate any contraindicated treatments but did list some simple futile treatments) or poor (advocated contraindicated or complicated futile treatments, such as unnecessary hemodialysis). We also considered whether the monograph would allow a clinician to manage an overdose, whether it served to refresh one's memory and whether it was simply misleading or dangerous.

**Results:** We reviewed 119 monographs, of which 25 (21%) were adequate to allow a clinician to manage an overdose. Another 25 monographs were not adequate to allow a clinician to manage an overdose but would serve to refresh the memory regarding key management points. Sixty monographs (50%) contained misleading or dangerous advice. Nine monographs (8%) did not fall into any of these categories. In terms of listing essential interventions, 61 monographs (51%) were poor, 35 (29%) were fair, 22 (18%) were good, and 1 (1%) was excellent. For warning against contraindicated interventions, 57 monographs (48%) were poor, 9 (8%) were fair, 51 (43%) were good, and 2 (2%) were excellent.

**Interpretation:** Overdose management advice in the *CPS* is inadequate in most cases and is misleading or dangerous in half of the monographs examined. These sections should be omitted or rewritten to reflect current standards of care. Physicians should refer to authoritative sources (e.g., current toxicology texts, computerized databases or local poison control centres) for poisoning management advice.

Intentional and unintentional incidents of poisoning continue to cause illness and death. Physicians caring for poisoned patients must be aware of current management guidelines. Such information can be found in current toxicology texts and computerized databases or by telephone consultation with local poison control centres. Another readily available source of information is the *Compendium*

of *Pharmaceuticals and Specialities (CPS)*,<sup>1</sup> published annually by the Canadian Pharmacists Association and distributed to practising physicians. It can be found in emergency departments and physicians' offices across the country. The *CPS* is a compilation of product monographs on many of the medications sold in Canada. The monographs are written by pharmaceutical companies according to guidelines published by the Health Protection Branch of Health Canada.<sup>2</sup> These guidelines require that the monograph contain a description of pharmacologic properties, indications and dosage as well as information on the "signs and symptoms and current recommended management of overdose" with the medication. The manufacturers voluntarily submit monographs for publication in the *CPS*. According to *CPS* editorial policy, "editorial changes are limited to those required for consistency of style, clarity and presentation."<sup>3</sup> Manufacturers are responsible for keeping the monographs current, and the Health Protection Branch has the authority to request that the monograph be updated if "it is considered to be false, misleading, or incomplete in any respect."<sup>4</sup> In addition to the product-specific monographs submitted by pharmaceutical companies, the *CPS* contains general monographs developed by the *CPS* editors based on current literature. These contain information about an entire class of medication.

In 1979 Parker<sup>5</sup> surveyed 70 family physicians and found that the majority (90%) consulted the *CPS* as their first resource when treating a patient with a suspected drug overdose. He examined the overdose information for tricyclic antidepressants in the *CPS* and found major deficiencies and a lack of consistency from monograph to monograph. He recommended that *CPS* overdose information be updated frequently and that the date of revision be included in the monograph. In 1997 Mullen and colleagues<sup>6</sup> reviewed overdose management advice contained in the 1994 *Physician's Desk Reference*,<sup>7</sup> a US publication similar to the *CPS*. They found that management advice was often inadequate, misleading or even "potentially hazardous."

We looked at the accuracy of overdose management advice contained in the 2001 *CPS*. We limited our review to 10 classes of medication for which an overdose is frequently fatal: acetaminophen,  $\beta$ -blockers, calcium-channel blockers, digoxin, lithium, opioids, salicylates, tricyclic antidepressants, theophylline and valproic acid.<sup>8-12</sup>

## Methods

For each of the 10 classes of medication, 3 clinical toxicologists (J.R.B., R.P. and D.A.K.) independently reviewed overdose management guidelines from the following current toxicology texts and databases: the Poisindex System (Micromedex Inc., Denver), *Goldfrank's Toxicologic Emergencies*,<sup>13</sup> *Poisoning and Drug Overdose*<sup>14</sup> and *Clinical Management of Poisoning and Drug Overdose*.<sup>15</sup> We also referred to the management guidelines contained in the *Poison Management Manual*,<sup>16</sup> published by the British Columbia Drug and Poison Information Centre. We then met as a group and, for each class of medication, arrived at an

agreement on the essential indicated, contraindicated and futile management interventions. Given the brief space allotted in the *CPS* for management advice, we decided to limit our review to essential interventions and to not fault monographs for missing fine points of management.

We manually searched the 2001 *CPS* to find all monographs containing overdose management advice for each class of medication. Each reviewer independently evaluated each monograph and rated it as excellent (it listed all essential interventions with correct and complete indications and included a discussion of important supportive care issues unique to that class of medication), good (it listed the key interventions and gave correct and complete indications), fair (it listed the key indications but failed to give proper indications) or poor (it failed to list the key interventions). For warning against contraindicated interventions, a monograph was rated as excellent (it warned against contraindicated treatments and did not list any futile interventions), good (it did not advocate any futile or contraindicated treatments), fair (it did not advocate any contraindicated treatments but did list some simple futile treatments) or poor (it advocated contraindicated treatments or complicated futile treatments, such as unnecessary hemodialysis).

During our independent review of the monographs, we compared each monograph with the standard of care extracted from the current toxicology texts and answered the following 3 questions: Does the monograph allow a typical clinician to manage an overdose of this drug? Could the monograph safely "refresh the memory" with key management points? Is the monograph simply misleading or dangerous? For the third question, monographs could be considered "misleading or dangerous" if they advocated contraindicated interventions or if they misled the reader by focusing on futile interventions or discussing key interventions as if they were optional or experimental. These categories are not inclusive: a monograph may be insufficient to refresh one's memory or to fully manage an overdose without being dangerous. Similarly, the categories are not exclusive: a monograph that allows a clinician to manage an overdose will also be sufficient to refresh one's memory.

Since the monographs were written for the Canadian market, we felt that they should use Système international (SI) units rather than traditional units when discussing drug levels. Failure to use SI units may cause clinicians to misinterpret the significance of a given drug level and to make inappropriate management decisions. This is particularly important for salicylates, where 1 mmol/L = 13.8 mg/dL, and for theophylline, where 1  $\mu$ g/dL = 5.55  $\mu$ mol/L. We also felt that acetaminophen monographs should reflect Canadian practice and discuss *N*-acetylcysteine for intravenous rather than for oral use. Using these criteria, the reviewers rated the monographs as good or poor for "Canadian content." The issue of Canadian content did not apply to  $\beta$ -blockers, calcium-channel blockers, opioids or tricyclic antidepressants, because drug levels are not helpful in cases of overdose with these classes of medication and because there are no differences in management between Canada and the United States for overdose with these classes.

At a final series of meetings we compared our ratings and arrived at an agreement on the rating for each monograph. Rating discrepancies were recorded and classified as minor (a change of 1 level [e.g., from fair to good]) or major (a change of more than 1 level [e.g., from poor to excellent]). During these meetings we also recorded some of the more bizarre, misleading or dangerous management advice.

## Results

There were 119 monographs containing management advice for overdose with the classes of medication studied. In terms of listing essential interventions, 61 monographs (51%) were rated as poor, 35 (29%) as fair, 22 (18%) as good and 1 (1%) as excellent (Table 1). For warning against contraindicated interventions, 57 (48%) were rated as poor, 9 (8%) as fair, 51 (43%) as good and 2 (2%) as excellent (Table 2).

Half of the monographs contained advice that was misleading or dangerous (Table 3). Only 25 (21%) were sufficient to manage an overdose. Another 25 monographs (21%) were insufficient to manage an overdose but could serve to refresh the memory of a clinician concerning key management points. Nine monographs (8%) were insufficient to refresh one's memory but did not contain misleading or dangerous advice.

There were no major discrepancies in ratings between the reviewers. There were 6 minor rating discrepancies.

In terms of Canadian content, 12 of the 22 acetaminophen monographs were rated as poor because they used traditional units only or failed to discuss *N*-acetylcysteine for intravenous use. Ten of the 12 salicylate monographs, the single digoxin monograph, 1 of the 5 lithium monographs, 2 of the 7 theophylline monographs and both valproic acid monographs also used traditional rather than SI units.

## Interpretation

Half of the product monographs in the *CPS* that we examined contained misleading or dangerous advice for managing a drug overdose. The major problems included providing outdated or potentially dangerous advice regarding gastrointestinal decontamination, unnecessarily recommend-

ing potentially harmful interventions (especially hemodialysis) and failing to mention or to give appropriate indications for an essential antidote or life-saving intervention.

Gastrointestinal decontamination advice contained in the *CPS* often fell short of current recommendations. Ipecac is less effective than activated charcoal in preventing absorption of most poisons, and its use may cause protracted vomiting and delay the administration of activated charcoal. Furthermore, ipecac may result in aspiration when given to patients who are obtunded or who could become obtunded within the next hour or 2. For these reasons, ipecac syrup should not be used in the management of adults who present

**Table 2: Ratings of the monographs in terms of warning against contraindicated interventions for overdose management**

Drug (no. of monographs)	Rating;* no. (and %) of monographs			
	Excellent	Good	Fair	Poor
Acetaminophen (22)	0	14	1	7
ASA (12)	0	2	4	6
β-Blockers (19)	0	0	0	19
Calcium-channel blockers (13)	0	7	2	4
Digoxin (1)	0	0	1	0
Lithium (5)	0	0	0	5
Opioids (32)	1	26	0	5
Tricyclic antidepressants (6)	1	0	1	4
Theophylline (aminophylline) (7)	0	0	0	7
Valproic acid (2)	0	2	0	0
Total	2 (2)	51 (43)	9 (8)	57 (48)

\*Excellent = did not advocate any futile or contraindicated treatments and warned against contraindicated treatments, good = did not advocate any futile or contraindicated treatments, fair = did not advocate any contraindicated treatments but did list some simple futile treatments, poor = advocated contraindicated or complicated futile treatments, such as unnecessary hemodialysis.

**Table 1: Ratings of 119 product monographs for 10 classes of medication in the *Compendium of Pharmaceuticals and Specialties*<sup>1</sup> in terms of listing essential interventions for overdose management**

Drug (no. of monographs)	Rating;* no. (and %) of monographs			
	Excellent	Good	Fair	Poor
Acetaminophen (22)	0	1	12	9
ASA (12)	0	0	2	10
β-Blockers (19)	0	0	4	15
Calcium-channel blockers (13)	0	0	2	11
Digoxin (1)	0	0	1	0
Lithium (5)	0	0	5	0
Opioids (32)	1	20	7	4
Tricyclic antidepressants (6)	0	1	0	5
Theophylline (aminophylline) (7)	0	0	0	7
Valproic acid (2)	0	0	2	0
Total	1 (1)	22 (18)	35 (29)	61 (51)

\*Excellent = listed all interventions and unique supportive care issues and gave correct and complete indications, good = listed the key interventions and gave correct and complete indications, fair = listed the key indications but failed to give proper indications, poor = failed to list the key interventions.

following an intentional overdose.<sup>17</sup> Nevertheless, many of the monographs inappropriately recommended induced emesis. Emesis was even recommended in several of the opioid monographs and 1 of the tricyclic antidepressant monographs. Gastric lavage was also often advocated unnecessarily. Gastric lavage carries a risk of traumatic complications and should be reserved for patients with a potentially life-threatening poisoning who present early after ingestion and have not already vomited.<sup>18</sup> We were surprised to find that 4 of the acetaminophen monographs suggested gastric lavage to remove activated charcoal before oral administration of *N*-acetylcysteine. This addresses a theoretical concern regarding the binding of orally administered *N*-acetylcysteine to activated charcoal. However, standard dosages of *N*-acetylcysteine for oral use (as used in the United States) are so large that the interaction with activated charcoal is not considered to be of clinical importance.<sup>19,20</sup> Furthermore, this recommendation may cause confusion in Canada, where *N*-acetylcysteine is administered intravenously. Mention was also made of archaic modalities, such as “universal” antidote, fuller’s earth and continuous gastric suction.

Invasive techniques to enhance elimination were sometimes recommended unnecessarily. We were surprised to find that 2 of the acetaminophen monographs recommended hemodialysis. Dialysis may reduce acetaminophen levels but is not indicated because *N*-acetylcysteine is so effective. The Abenol monograph, for example, stated: “Hemodialysis, if it can be initiated within the first 12 hours, has been advocated for all patients with a plasma concentration of acetaminophen greater than 120 µg/mL 4 hours after drug ingestion.”<sup>21</sup> A person with an acetaminophen level under 150 µg/mL (1000 µmol/L) 4 hours after ingestion requires no treatment. Three of the 13 monographs for calcium-channel blockers recommended hemoperfusion or plasma-

pheresis. These invasive interventions are ineffective in severely hypotensive patients, are theoretically futile given the large volumes of distribution of most calcium-channel blockers and are not supported by clinical experience.

Other potentially dangerous or contraindicated interventions included acetazolamide and forced alkaline diuresis for salicylate poisoning, physostigmine as first-line therapy for tricyclic antidepressant toxicity and digoxin for β-blocker overdose. Conversely, many monographs omitted or failed to stress the importance of key interventions. This was true of hemodialysis for salicylates, lithium and theophylline, glucagon for β-blockers, calcium salts for calcium-channel blockers, and sodium bicarbonate for tricyclic antidepressants.

Several monographs contained advice that was archaic if not bizarre. The Entrophen (salicylate) monograph stated:<sup>22</sup>

Treatment is essentially symptomatic and supportive. Administer water, universal antidote and remove by gastric lavage or emesis. Force fluids (e.g., salty broth) to replace sodium loss. If the patient is unable to retain fluids orally, the alkalosis can be treated by hypertonic saline i.v. If salicylism acidosis is present, sodium bicarbonate i.v. is preferred because it increases the renal excretion of salicylates. Vitamin K is indicated if there is evidence of hemorrhage. Hemodialysis has been used with success.

This monograph went on to state that central nervous system depressants should not be used for convulsions and “external cooling with cool water *or alcohol* [our italics] should be provided quickly to any child who has a rectal temperature over 40°C.” We hope that no physician would actually prescribe salty broth while looking for “universal” antidote, but after reading this monograph a clinician may fail to recognize the importance of hemodialysis. The Elavil (amitriptyline) monograph recommended that continuous cardiac monitoring be “maintained for several days after the cardiac rhythm has returned to normal,”<sup>23</sup> and the Norpramin (desipramine) monograph stated that “prolonged observation of at least a week is strongly recommended.”<sup>24</sup> Monitoring of this duration is unnecessary and costly. The Tofranil (imipramine) monograph discussed paraldehyde for seizures. Paraldehyde is not readily available, and benzodiazepines or barbiturates are far better choices for treating tricyclic antidepressant-induced seizures.

The *CPS* contains a compilation of monographs written by pharmaceutical companies, approved by Health Canada’s Health Protection Branch and edited for style by the *CPS* editorial staff. The poison management sections in the *CPS* monographs are seldom sufficient to guide management decisions and often contain potentially misleading or dangerous advice. Pharmaceutical companies should revise the overdose sections of their monographs to reflect current standards. This could be done voluntarily or following review by the Health Protection Branch. Alternatively, overdose management sections could be eliminated from the *CPS*. Physicians should consult definitive sources for overdose management advice.

**Table 3: Numbers of monographs considered sufficient to allow a typical clinician to manage an overdose and numbers considered to be misleading or dangerous\***

Drug (no. of monographs)	No. (and %) of monographs	
	Sufficient for managing an overdose	Misleading or dangerous
Acetaminophen (22)	1	9
ASA (12)	0	7
β-Blockers (19)	0	19
Calcium-channel blockers (13)	0	2
Digoxin (1)	0	0
Lithium (5)	0	5
Opioids (32)	23	6
Tricyclic antidepressants (6)	1	5
Theophylline (aminophylline) (7)	0	7
Valproic acid (2)	0	0
Total	25 (21)	60 (50)

\*See Methods for details.



Competing interests: None declared.

**Contributors:** All authors were involved with the conception and design of the study. The task of extracting “standards of care” from the standard textbooks was divided equally among the authors, and the final standards of care were then derived by all 3 authors during meetings. Each author independently evaluated all 119 monographs, and these evaluations were discussed during another series of meetings. Dr. Brubacher tabulated the data and was responsible for writing the paper. All authors read the manuscript and gave input for the final version submitted.

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