BJCP British Journal of Clinical Pharmacology

DOI:10.1111/j.1365-2125.2008.03322.x

Variability in the quality of overdose advice in Summary of Product Characteristics (SPC) documents: gut decontamination recommendations for CNS drugs

Andrew J. B. Wall, D. N. Bateman & W. S. Waring

Scottish Poisons Information Bureau, Royal Infirmary of Edinburgh, Edinburgh, UK

Correspondence
Dr W. Stephen Waring, Scottish Poisons Information Bureau, Royal Infirmary of Edinburgh, 51 Little France Crescent, Edinburgh EH16 4SA, UK.
Tel: + 44 131 242 1385
Fax: + 44 131 242 1387
E-mail: s.waring@ed.ac.uk

Keywords
gastric lavage, gut decontamination, overdose, poisoning management, toxicology

Received
21 August 2008

Accepted
2 October 2008

Published *Early View*
24 November 2008

WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- The Summary of Product Characteristics (SPC) is a legal document that gives healthcare providers information concerning each specific drug, including advice on the management of overdose.
- Clinical outcomes after drug overdose may be influenced by the appropriate use of gut decontamination procedures.
- The extent to which poisoning management advice in the SPC agrees with Poisons Centres recommendations is uncertain.

WHAT THIS STUDY ADDS

- Significant discrepancies exist between poisoning management advice contained in SPC documents and TOXBASE recommendations.
- SPC documents may include inappropriate recommendations for induced emesis and gastric lavage, or omission of oral activated charcoal as a potentially effective therapy.
- The SPC document cannot be relied on as a primary reference source for advice concerning drug overdose.

AIMS

Deliberate self-poisoning is a major cause of morbidity and mortality. The Summary of Product Characteristics (SPC) document is a legal requirement for all drugs, and Section 4.9 addresses the features of toxicity and clinical advice on management of overdose. The quality and appropriateness of this advice have received comparatively little attention.

METHODS

Section 4.9 of the SPC was examined for all drugs in the central nervous system (CNS) category of the British National Formulary. Advice concerning gut decontamination was examined with respect to specific interventions: induced vomiting, oral activated charcoal, gastric lavage, and other interventions. Data were compared with standard reference sources for clinical management advice in poisoning. These were graded 'A' if no important differences existed, 'B' if differences were noted but not thought clinically important, and 'C' if differences were thought to be clinically significant.

RESULTS

SPC documents were examined for 258 medications from 67 manufacturers. The overall agreement was 'A' in 23 (8.9%), 'B' in 28 (10.9%) and 'C' in 207 (80.2%). Discrepancies were due to inappropriate recommendation of induced emesis in 21.7% (95% confidence interval 17.1, 27.1), gastric lavage in 38.4% (32.7, 44.4), other gut decontamination in 5.8% (3.6, 9.4) and failure to recommend oral activated charcoal in 57.4% (51.1, 63.4).

CONCLUSIONS

Gut decontamination advice in SPC documents with respect to CNS drugs was inadequate. Possible reasons for the observed discrepancies and ways of improving the consistency of advice are proposed.

Introduction

Deliberate self-poisoning is one of the commonest reasons for acute medical admission to hospital, and is responsible for around 3000 deaths annually in the UK [1–3]. Recent guidelines and international consensus statements have improved the consistency of clinical advice in the management of poisoned patients, particularly with regard to gut decontamination strategies. For example, induced emesis is ineffective and a potentially hazardous strategy, and is not normally recommended [4, 5]. The role of gastric lavage is somewhat uncertain and, in view of the increased risk of aspiration pneumonia and oesophageal perforation, is generally reserved for ingestion of life-threatening quantities of certain agents [6–8]. Early administration of oral activated charcoal may minimize systemic drug exposure and is generally recommended within 1 h of drug ingestion [9, 10].

The risk of significant toxicity and death may be minimized by correct initial assessment and intervention. Optimal management strategies depend on the specific agents and extent of exposure [11]. Toxic effects might not be anticipated from the principal mechanism of action, and distinct effects may be observed after massive overdose [12–14]. The onset of toxicity may be more rapid or be delayed compared with the anticipated therapeutic effects [15, 16]. TOXBASE is the Department of Health approved source of information on poisons management in the UK and freely available to healthcare professionals. It is an internet-based resource that is provided by the National Poisons Information Service and is frequently reviewed to ensure that the content is accurate, up-to-date and consistent with authoritative guidelines [17, 18]. Advice in line with TOXBASE is produced in an abbreviated form in the British National Formulary (BNF).

The European Directive 2001/83/EC requires that a Summary of Product Characteristics (SPC) be included in all applications to obtain marketing authorization. The SPC informs health professionals on how to use the product safely and effectively, and section 4.9 is entitled 'overdose', and includes features of toxicity and clinical management advice.

Comparable documents are the Monthly Index of Medical Specialties (MIMS) and the Physicians' Desk Reference (PDR) in Australia and the USA, respectively, and around 25–50% of healthcare staff use these resources for poisoning management advice [19, 20]. Little is known about the extent to which SPC documents are used for poisoning management advice, but these are readily available to healthcare staff in the community and hospital Emergency Departments. Moreover, the SPC document has legal status and is relied on by the Courts as a standard dataset for individual drugs. The present study was designed to determine how closely the clinical management advice offered by the SPC agrees with that provided in current clinical guidelines.

Methods

Data collection

Drugs in the central nervous system (CNS) category of the BNF were examined because these agents are highly represented in drug overdose [21]. Generic and proprietary preparations were identified from the Electronic Medicines Compendium (eMC), an electronic source of up-to-date SPC documents (http://www.emc.medicines.org.uk). If a SPC document was not available via eMC, then the manufacturer was contacted directly. The study was conducted between February and June 2008, and comparison between the SPC and TOXBASE (http://www.toxbase.org) was made contemporaneously.

Data analysis

Gut decontamination advice was examined with respect to induced vomiting, gastric lavage, oral activated charcoal, and other methods including whole bowel irrigation. A score was assigned according to the advice in each category, and a composite grade was used to indicate the overall extent of agreement between the SPC and guidelines. Grade 'A' indicated close overall agreement or only minor discrepancies that were not deemed clinically important, e.g. no mention of gastric lavage *vs.* gastric lavage not indicated. Grade 'B' was applied for minor discrepancies that might be clinically relevant, e.g. administration of oral activated charcoal up to 4 h after ingestion *vs.* up to 1 h after ingestion. Grade 'C' was applied if clinically important and potentially hazardous discrepancies existed, e.g. advice in favour of induced emesis *vs.* do not induce vomiting, or gastric lavage indicated *vs.* contraindicated.

Identical SPC documents related to different formulations of a drug from a single manufacturer were considered as a single agent. The number assigned to each grade was expressed as a proportion of all SPC documents, and 95% confidence intervals were constructed using the modified Wald method.

Results

There were 167 drug preparations in eMC, but SPC data could not be obtained for four: Papaveretum (Roche, Basel Switzerland), Perphenazine (Goldshield, Thornton Heath UK), Sertindole (Lundbeck, Copenhagen, Denmark) and Zotepine (Orion, Espoo, Finland). At the time of the study, entries for four further drugs had not been placed on the main TOXBASE database: entacapone, tolcapone, palonosetron and riluzole. Therefore, the study included 159 drugs, which were associated with 258 separate preparations from 67 different manufacturers.

The overdose section of the SPC document corresponded closely with TOXBASE in 23 (8.9%), only minor

Table 1

Agreement between the Summary of Product Characteristics document and TOXBASE across individual drug categories as defined by the British National Formulary

Drug category	Drugs	Preparations	Grade 'A'	Grade 'B'	Grade 'C'
Hypnotics	18	33	1 (3.0%)	6 (18.2%)	26 (78.8%)
Antipsychotics	24	36	4 (11.1%)	6 (16.7%)	26 (72.2%)
Antidepressants	21	28	1 (3.6%)	6 (21.4%)	21 (75.0%)
CNS stimulants	4	8	0 (0.0%)	2 (25.0%)	6 (75.0%)
Antiobesity drugs	3	3	1 (33.3%)	0 (0.0%)	2 (66.7%)
Antiemetics	14	26	1 (3.8%)	3 (11.5%)	22 (84.6%)
Analgesics	25	55	5 (9.1%)	2 (3.6%)	48 (87.3%)
Antiepileptics	19	25	1 (4.0%)	1 (4.0%)	23 (92.0%)
Antiparkinson	19	29	7 (24.1%)	0 (0.0%)	22 (75.9%)
Substance misuse	8	11	0 (0.0%)	2 (18.2%)	9 (81.8%)
Dementia	4	4	2 (50.0%)	0 (0.0%)	2 (50.0%)
Total	159	258	23 (8.9%)	28 (10.9%)	207 (80.2%)
95% CI			6.0, 13.1	7.6, 15.3	74.9, 84.7

Grade 'A', minor or no discrepancy; Grade 'B', discrepancy of doubtful clinical importance; Grade 'C', a potentially hazardous discrepancy.

Table 2

Agreement between the Summary of Product Characteristics document and TOXBASE for specific aspects of gut decontamination recommendations

Treatment category	Grade 'A'	Grade 'B'	Grade 'C'
Induced vomiting	201 (77.9%)	1 (0.4%)	56 (21.7%)
Gastric lavage	151 (58.5%)	8 (3.1%)	99 (38.4%)
Oral activated charcoal	25 (9.7%)	85 (32.9%)	148 (57.4%)
Other gut decontamination	243 (94.2%)	0 (0.0%)	15 (5.0%)

Grade 'A', minor or no discrepancy; Grade 'B', discrepancy of doubtful clinical importance; Grade 'C', a potentially hazardous discrepancy ($n = 258$).

discrepancies existed in 28 (10.9%), and major discrepancies in 207 (80.2%) (Table 1). Discrepancies between the advice contained in the SPC and TOXBASE were noted for all aspects of gut decontamination (Table 2). Examples of inappropriate recommendations of alternative forms of gastric decontamination are shown in Table 3.

Discussion

Over recent years, evidence-based guidelines have sought to standardize the clinical management of poisoned patients, specifically with regard to means of gut decontamination [5, 6, 9, 22]. SPC documents presented gut decontamination advice that differed from current guidance, as a result of both omission of potentially effective oral activated charcoal administration, and inclusion of ineffective and potentially hazardous measures such as induced emesis and purgatives. Similar discrepancies have been noted between MIMS and PDR documents and prevailing clinical management advice after overdose. For example, a study of 25 drugs listed in MIMS included omission of antidote in 14 (56%) and inappropriate recommendation of treatment in one (4%) [19]. A study of 20 PDR entries found discrepancies involving omission of a recommended treatment in 13 (65%) and recommendation of a contraindicated treatment in three (15%) [20]. Previous research has addressed the structure and readability of SPC documents, but inadequacies have been identified concerning the adverse effects and drug interactions recommendations [23–25].

The SPC is a legal document that is submitted to the authorities in consideration of a marketing authorization, e.g. to the European Medicines Agency or the Medicines and Healthcare products Regulatory Agency. At the time of submission, only limited data will be available concerning the toxicity of novel drugs. Nonetheless, the general principles of poisoning management should be chosen to reflect current practices. Periodic updates would allow incorporation of data from clinical experience [26]. However, there is no requirement for this, and the content cannot be changed without approval by the originating authority. A more flexible system is needed to allow minor amendments without a costly and extensive review. Clearer indication of when the overdose data were more recently reviewed might allow more accurate interpretation, similar to the version control process that applies for TOXBASE entries. A formal mechanism for collaboration between the Pharmaceutical Industry and Poisons Control Centres does not exist, but might offer advantages for document review.

A limitation of the study is that only one category of drugs was examined, namely those acting on the CNS. Despite this, these included a range of drugs and 67 manufacturers, and the data are likely to be representa-

Table 3

Examples of discrepancies between Summary of Product Characteristics (SPC) documents and TOXBASE in specific categories of gut decontamination

Induced vomiting	TOXBASE: Syrup of ipecac should not be administered routinely in the management of poisoned patients. **SPC recommendations in contrast to TOXBASE:** 'vomiting should be induced if the patient is conscious' 'it is advisable to stimulate vomiting' 'stomach should be emptied by . . . induction of emesis' 'vomiting should be induced with syrup of ipecac'
Gastric lavage	TOXBASE: 'Gastric lavage should not be employed routinely, if ever, in the management of poisoned patients'. Consider if <1 h after ingestion of life-threatening quantities of specific agents, e.g. lithium, ethylene glycol. **SPC recommendations in contrast to TOXBASE:** 'advisable to perform gastric lavage' 'gastric lavage should be considered if co-ingestants are suspected' 'gastric lavage is useful if performed soon after ingestion' '0.02% solution of potassium permanganate may be used for lavage' 'stomach should be emptied immediately by lavage' 'gastric lavage . . . within the first 6 h after ingestion'
Activated charcoal	TOXBASE: 'Consider administration of activated charcoal if more than (stated dose) has been ingested within 1 h'. Generally recommended with specific exceptions: alcohols, iron, and lithium **SPC recommendations in contrast to TOXBASE:** Oral activated charcoal not mentioned 'has been shown to not significantly absorb . . . in an *in vitro* study'
Other measures	TOXBASE: For a small number of specific agents, additional gut decontamination procedures are recommended, e.g. whole bowel irrigation after lithium ingestion. The routine use of purgatives is not recommended **SPC recommendations in contrast to TOXBASE:** 'an osmotic laxative is also recommended' 'sorbitol may be as or more effective than emesis' 'a saline purge should be given' 'charcoal should be followed by magnesium sulphate 15%' 'saline cathartic may be used' 'a high enema is recommended'

tive of discrepancies in other therapeutic areas. A possible criticism is that many of the discrepancies concerned omission of activated charcoal administration. Robust outcome data in support of activated charcoal administration are lacking, and this omission might be less 'hazardous' than other discrepancies. Nevertheless, clinical management advice with respect to gut decontamination encourages a consistent approach based on consensus international expert opinion, supported by basic and clinical data [9].

In conclusion, SPC advice regarding gut decontamination after CNS drug overdose is unreliable and differs widely from prevailing guidelines due to omission of potentially effective treatments, and inclusion of interventions that are ineffective and potentially hazardous. The SPC alone cannot be viewed as a reliable source of poisoning management advice.

Competing interests

D.N.B. and W.S.W. participate in editing and updating of TOXBASE entries with colleagues on behalf of the National Poisons Information Service.

The authors gratefully acknowledge the contribution of staff from the NPIS Birmingham, NPIS Cardiff, NPIS Edinburgh and NPIS Newcastle units who are responsible for updating and supporting TOXBASE. The NPIS is part of the Chemical Hazards and Poisons Division of the Health Protection Agency in the UK.

REFERENCES

1 Camidge DR, Wood RJ, Bateman DN. The epidemiology of self-poisoning in the UK. Br J Clin Pharmacol 2003; 56: 613–9.

2 Deaths related to drug poisoning in England and Wales, 2002–06. Health Stat Q 2007; 36: 66–72.

3 Mortality statistics 2005: injury and poisoning. Health Stat Q 2007; 35: 72–7.

4 Krenzelok EP, McGuigan M, Lheur P. Position statement: ipecac syrup. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol 1997; 35: 699–709.

5 American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position paper: ipecac syrup. J Toxicol Clin Toxicol 2004; 42: 133–43.

6 Vale JA, Kulig K; for the American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position paper: gastric lavage. J Toxicol Clin Toxicol 2004; 42: 933–43.

7 Vale JA. Position statement: gastric lavage. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. J Toxicol Clin Toxicol 1997; 35: 711–9.

8 Heard K. The changing indications of gastrointestinal decontamination in poisonings. Clin Lab Med 2006; 26: 1–12.

9 Chyka PA, Seger D, Krenzelok EP, Vale JA; for American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. Clin Toxicol 2005; 43: 61–87.

10 LoVecchio F, Shriki J, Innes K, Bermudez J. The feasibility of administration of activated charcoal with respect to current practice guidelines in emergency department patients. J Med Toxicol 2007; 3: 100–2.

11 Wiener SW, Hoffman RS. Trends in clinical toxicology: advances that may change your practice. Basic Clin Pharmacol Toxicol 2005; 97: 1–7.

12 Pollak PT, Shafer SL. Teaching application of clinical pharmacology skills using unusual observations from clozapine overdoses. J Clin Pharmacol 2004; 44: 141–9.

13 Howell C, Wilson AD, Waring WS. Cardiovascular toxicity due to venlafaxine poisoning in adults: a review of 235 consecutive cases. Br J Clin Pharmacol 2007; 64: 192–7.

14 Waring WS, Good AM, Bateman DN. Lack of significant toxicity after mirtazapine overdose: a five-year review of cases admitted to a regional toxicology unit. Clin Toxicol 2007; 45: 45–50.

15 Lucas C, Christie GA, Waring WS. Rapid onset of haemodynamic effects after angiotensin converting enzyme-inhibitor overdose: implications for initial patient triage. Emerg Med J 2006; 23: 854–7.

16 Waring WS. Delayed cardiotoxicity in chronic lithium poisoning: discrepancy between serum lithium concentrations and clinical status. Basic Clin Pharmacol Toxicol 2007; 100: 353–5.

17 Bateman DN, Good AM. Five years of poisons information on the internet: the UK experience of TOXBASE. Emerg Med J 2006; 23: 614–7.

18 Thanacoody HK, Good AM, Waring WS, Bateman DN. Survey of cases of paracetamol overdose in the UK referred to National Poisons Information Service (NPIS) consultants. Emerg Med J 2008; 25: 140–3.

19 Mullen WH, Anderson IB, Kim SY, Blanc PD, Olson KR. Incorrect overdose management advice in the Physicians' Desk Reference. Ann Emerg Med 1997; 29: 255–61.

20 Mallows J, Chan B, Graudins A. Quality of poisoning management advice in the Monthly Index of Medical Specialties Annual. Emerg Med Australas 2005; 17: 511–9.

21 Joint Formulary Committee. British National Formulary, 55th edn. London: Pharmaceutical Press, 2008.

22 National Poisons Information Service. Annual Report 2006–2007, ISBN 978-0859516020. Available at http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1196942161917 (last accessed 1 August 2008).

23 Venot A, Duclos C. Methodology for the analysis and representation of the medical information about drugs in the Summary of Product Characteristics (SPC). Proc AMIA Symp 1999; 166–70.

24 Failings in treatment advice, SPCs and black triangles. Drug Ther Bull 2001; 39: 25–7.

25 Bergk V, Haefeli WE, Gasse C, Brenner H, Martin-Facklam M. Information deficits in the summary of product characteristics preclude an optimal management of drug interactions: a comparison with evidence from the literature. Eur J Clin Pharmacol 2005; 61: 327–35.

26 Arguello B, Fernandez-Llimos F. Clinical pharmacology information in summaries of product characteristics and package inserts. Clin Pharmacol Ther 2007; 82: 566–71.