DOI:10.1111/j.1365-2125.2006.02809.x

Comparative assessment of four drug interaction compendia

Agnes I. Vitry
Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia, GPO Box 2471, Adelaide SA 5001, Australia

Correspondence
Dr A. I. Vitry, Pharm. D., Ph. D., Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, University of South Australia, GPO Box 2471, Adelaide SA 5010, Australia.
Tel.: + 61 8 8302 2392
Fax: + 61 8 8302 1087
E-mail: agnes.vitry@unisa.edu.au

Keywords
drug information, drug interaction

Received
12 October 2005
Accepted
19 September 2006
Published *OnlineEarly*
7 December 2006

Aims
To assess the consistency of inclusion and grading of major drug interactions for 50 drugs in four leading international drug interaction compendia.

Methods
Four international drug interaction compendia were compared: the drug interactions appendix of the British National Formulary, the interaction supplement in the French drug compendium Vidal, and two US drug interaction compendia, Drug Interaction Facts and the Micromedex (Drug-Reax) program. Major interactions were defined as potentially hazardous in BNF or with the warning 'contraindication' or 'avoid' in Vidal or with the significance grading 1 or 2 in DIF. Major interactions for a list of 50 drugs were searched in all four compendia.

Results
A total of 1264 interactions meeting the inclusion criteria were identified for these 50 drugs. After deletion of 169 duplicates, 1095 interactions were included in the analysis. Of the drug interactions classified as major in any one compendium between 14% and 44% were not listed in the other compendia. The grading systems used for the severity and the quality of the supporting evidence in Micromedex and DIF were inconsistent.

Conclusions
There is a lack of consistency in the inclusion and grading of drug interactions of major significance for 50 drugs across the four drug compendia examined. This may reflect the lack of standardization of the terminology used to classify drug interactions and the lack of good epidemiological evidence on which to base the assessment of the clinical relevance of drug interactions.

Introduction

Medication incidents are a significant problem for all health systems in the world [1–3]. Drug interactions are one cause of medication incidents. In a Danish study of 26 337 elderly patients, 4.4% received drug combinations carrying a risk of severe interactions [4]. In a recent prospective study in the United Kingdom, drug interactions accounted for 16.6% of adverse drug reactions causing hospitalization [5]. Wide implementation of computerized prescribing and dispensing with clinical decision support systems is recognized as a priority to reduce medication incidents [3, 6]. However, several studies have shown that there is a considerable and potentially clinically important variability in the performance of dispensing and prescribing computer programs in detecting drug interactions [7–9]. Drug interaction compendia can be used to populate clinical decision support systems. There has not been any

comprehensive assessment of the validity of the severity classification used in the international drug interaction compendia. This study aimed to assess the consistency of four leading international drug interaction compendia for the inclusion and the severity grading of major drug interactions.

Methods

Four international drug interaction compendia were compared: the drug interactions appendix of the British National Formulary (BNF, update September 2003) [10], the interaction supplement in the French drug compendium Vidal (update 2003) [11], and two US drug interaction compendia, Drug Interaction Facts (DIF, update January 2003) [12] and the Micromedex (DrugReax) program (updates 2003) [13]. These compendia were selected because they are commonly used by health professionals to obtain information on drug interactions in countries where they are published. The Vidal interaction supplement was edited and reviewed by an expert committee at the French drug agency. The BNF is a joint publication of the British Medical Association and the Royal Pharmaceutical Society of Great Britain. It is the most highly regarded source of drug information in the United Kingdom. DIF and Micromedex are among the compendia most commonly used to identify drug interactions in the United States. These resources are also commonly used by drug information services internationally.

The terminology and the grading systems used to classify the clinical significance of drug interactions differed between the four compendia (Table 1). For the purpose of the study, the definition of interactions of major significance was based on the categorization provided in the compendia and included:

- drug interactions with the mention 'contraindication' or 'avoid' in Vidal, or
- drug interactions identified as hazardous in BNF, or
- drug interactions with the significance rating 1 or 2 in DIF.

An overall significance rating was not provided for Micromedex and so could not be used in the definition. All drug interactions listed as major were searched in all compendia. Data on severity of outcome and quality of documentation listed in Micromedex and DIF were extracted and tabulated when available.

Major interactions were identified for 50 drugs available in the three countries where the compendia are published (France, United Kingdom and United States) (Table 2). These drugs were selected for their known high potential for interactions (e.g. warfarin, digoxin, theophylline) or because they were representative of a major therapeutic class (e.g. atenolol). No more than one drug of a given therapeutic class was included because many drug interactions may be common to members of the same class. Compendia were compared on a two by two basis. When a drug interaction was not listed in the compared compendium, the compendium index was checked to ascertain whether the interacting drug was marketed in the country. Drug interactions involving a drug not marketed in the country of publication of the compendium were not included in the specific analysis. Discrepancies in the inclusion of major interactions among the four compendia and correlation of the grading systems used in DIF and Micromedex were assessed using descriptive statistics and Spearman correlation tests performed on SPSS for Windows version 11.5.

Table 1
Categories used to classify drug interactions in the four compendia

Vidal
There are four levels of seriousness that are based on the clinical management which is recommended: 'contraindication' (absolute), 'avoid' (relative contraindication), 'precaution for use' (combination possible if recommendations are followed), and 'to take into account' (no specific recommendation).

BNF
BNF uses a bullet to mark interactions that are potentially hazardous and where combined administration of the drugs involved should be avoided (or only undertaken with caution and appropriate monitoring). BNF may also state specifically whether a drug combination must be avoided or whether a drug combination is contraindicated by the manufacturer.

DIF
DIF classifies the severity of drug interactions into three categories (major, moderate and minor) and the documentation level in five categories (established, probable, suspected, possible and unlikely). A significance rating from 1 to 5 is assigned to each drug interaction based on the severity and the documentation gradings: 1 (major severity and documentation suspected or more), 2 (moderate severity and documentation suspected or more), 3 (minor severity and documentation suspected or more), 4 (major or moderate severity and documentation possible), 5 (minor severity and documentation possible or any severity and documentation unlikely).

Micromedex
Micromedex classifies the severity of drug interactions into three categories (major, moderate and minor) and the documentation level in five categories (excellent, good, fair, poor and unlikely). There is no overall significance rating.

Table 2
Drugs selected for analysis

allopurinol	ciprofloxacin	fluoxetine	metformin	sibutramine
amiloride	clozapine	furosemide	methadone	sildenafil
amiodarone	co-trimoxazole	gentamycin	methotrexate	spironolactone
atenolol	cyclosporine	glibenclamide	nevirapine	sumatriptan
azathioprine	diclofenac	hydrochlorothiazide	omeprazole	theophylline
bromocriptine	digoxin	imipramine	pethidine	tramadol
captopril	disulfiram	itraconazole	phenobarbital	valproate
carbamazepine	erythromycin	lamotrigine	phenytoin	verapamil
cefamandole	ethinyloestradiol	lithium	pravastatin	vincristine
cimetidine	flecainide	isocarboxazid*	ritonavir	warfarin

**There was no nonselective monoamine-oxidase inhibitor (MAOI) marketed in all countries. Isocarboxazid is marketed in the UK and in the USA but not in France. However, as all interactions are common to all nonselective MAOIs in Vidal, it was assumed that these interactions were also relevant for isocarboxazid.*

Table 3
Drug interactions classified as 'contraindication' or 'to avoid' in Vidal: how they were classified in other compendia

	BNF (%)			DIF (%)				Micromedex (%)			
Vidal	NI	H	NH	NI	S1	S2	OS	NI	Maj	Mod	Min
Contraindication	29.5	67.0	3.5	44.6	35.6	11.9	7.9	27.9	61.5	10.6	0
Avoid	21.7	65.7	12.6	43.3	14.7	30.8	11.2	23.5	40.9	34.9	0.7
Total	24.7	66.2	9.1	43.9	23.4	22.9	9.8	25.3	49.4	94.9	0.4

NI = not included. H = hazardous. NH = nonhazardous. S = significance rating. OS = other significance ratings. Maj = major severity. Mod = moderate severity. Min = minor severity.

Results

Overall, 1264 drug interactions meeting the inclusion criteria were identified (range 3–87 per drug). After deletion of 169 duplicates, 1095 interactions were included in the analysis.

Of the interactions classified as 'contraindication' or 'avoid' in Vidal, 57 (24.7%) were not included in BNF, 107 (43.9%) were not included in DIF and 64 (25.3%) were not included in Micromedex (Table 3). Twenty-five drug interactions classified as 'contraindication' or 'to avoid' in Vidal were not included in any other compendium.

Of the interactions classified as 'hazardous' in BNF, 282 (42.2%) were not included in Vidal, 259 (40.2%) were not included in DIF and 182 (27.4%) were not included in Micromedex (Table 4). Eighty drug interactions classified as 'hazardous' in BNF were not included in any other compendium. Eighteen drug interactions which were specifically highlighted as 'avoid' or 'contraindicated by the manufacturer' in BNF were not included in any other compendium.

Of the interactions classified with a significance rating 1 or 2 in DIF, 176 (38.6%) were not included in Vidal, 120 (26.5%) were not included in BNF and 70 (14.6%) were not included in Micromedex (Table 5). Thirty-four drug interactions with the rating 1 or 2 in DIF were not included in any other compendium.

Eighty major interactions were included in all compendia.

Among the interactions common to Micromedex and DIF, 53 (33%) of the 161 interactions classified as major in Micromedex were classified as moderate in DIF and 44 (29%) of the 150 interactions classified as major in DIF were classified as moderate in Micromedex. There was a weak correlation between these two compendia for the grading of the severity and the quality of the supporting evidence (respective Spearman correlation coefficients 0.546 and 0.430).

	Vidal (%)				DIF (%)				Micromedex (%)			
BNF	NI	CI	A	O	NI	S1	S2	OS	NI	Maj	Mod	Min
Hazardous	42.2	8.8	14.0	35.0	40.2	15.6	26.2	18.0	24.4	24.0	44.8	3.8
Avoid	39.5	31.2	17.4	11.9	41.8	32.7	16.4	9.1	20.4	61.1	16.8	1.7

NI = not included. CI = contraindication. A = avoid. O = other categories including 'to take into account' and 'precautions'. S = significance rating. OS = other significance ratings. Maj = major severity. Mod = moderate severity. Min = minor severity.

Table 4
Drug interactions classified as 'hazardous' or 'avoid' in the BNF: how they were classified in other compendia

	Vidal (%)				BNF (%)			Micromedex (%)			
DIF	NI	CI	A	O	NI	H	NH	NI	Maj	Mod	Min
S1	25.9	26.7	17.8	29.6	17.7	77.7	4.6	6.0	66.2	24.8	0
S2	43.9	5.0	14.6	36.5	30.0	18.3	51.7	18.5	12.1	64.6	4.8
Total	38.6	11.4	15.6	34.4	26.5	35.3	38.2	14.6	29.1	53.0	3.3

NI = not included. CI = contraindication. A = avoid. O = other categories including 'to take into account' and 'precautions'. S = significance rating. Maj = major severity. Mod = moderate severity. Min = minor severity.

Table 5
Drug interactions classified with significance rating 1 and 2 in the DIF: how they were classified in other compendia

Discussion

This study shows that there are important discrepancies among four of the leading international drug interaction compendia for the identification and classification of major interactions. Between 14% and 44% of the drug interactions classified as major in any one compendium are not listed in other compendia. Only 80 major interactions are common to the four compendia for the 50 drugs in this analysis. The grading systems used for the severity and the quality of the supporting evidence in DIF and Micromedex are inconsistent.

Three previous studies have examined the concordance among American drug interaction compendia. Fulda *et al.* [14] compared the inclusion of drug interactions for five drug classes in five American drug interactions compendia. Individual interactions were rarely listed in more than one or two of the compendia. Chao & Maibach [15] found considerable discrepancies among four American drug compendia for the inclusion of drug interactions on selected at-risk dermatologic drugs. Abarca *et al.* [16] assessed the agreement of four American drug interaction compendia for major drug interactions. Overall, 406 major drug interactions were listed in one or more of the four compendia. Only nine (2.2%) of the major drug interactions were listed in all four compendia.

This study confirms and expands the results of these studies as it compares leading compendia published in different countries. BNF is regarded as the main independent source of drug information in the United Kingdom. The Vidal interaction supplement was prepared by a committee at the French drug agency. Both DIF and Micromedex are among the most commonly used resources by US health professionals.

There are several limitations to this study. Only the major drug interactions listed for 50 drugs were examined. However, by including 1095 drug interactions, about one fifth of the estimated 5000 known drug interactions have been assessed [17]. There is little reason to think that this selection could bias the comparisons as the drugs selected are well known for their interactive potential or are representative of a major therapeutic class. Furthermore, many interactions with drugs not included in the list were included in the analysis as they were drug interactions described for other drugs of the list (for example there were 15 interactions with

quinidine and 16 interactions with rifampicin included in the dataset). Only four compendia have been included in this study but it seems unlikely that increasing the number of compendia compared would decrease the variability of the findings. Stockley's drug interactions [18], which is a well-known British drug interaction compendium, was not included in the study as it did not provide an explicit ranking system in terms of the clinical significance or severity of the drug interaction or quality of the supporting evidence. Subtle differences between compendia were not taken into account, for example a drug interaction may be classified as a drug–drug interaction in one compendium and as a drug–class interaction in another compendium.

Reasons for discrepancies

This study does not attempt to provide explanations for the discrepancies observed between the compendia. However, a number of factors may explain the differences observed. First, each compendium uses different inclusion criteria. For example, Vidal includes interactions between drugs of the same therapeutic class (e.g. interaction between amiloride and other potassium–sparing diuretics), interactions between drugs with antagonist pharmacological properties (e.g. pethidine with nalbuphine) that other compendia have decided not to include. DIF includes interactions with food and non-medicinal drugs (e.g. cocaine). Second, discrepancies may partly be due to different information sources, for example, publications in a language other than English (e.g. French), unpublished reports released by drug companies, spontaneous drug interaction reports collected through national post-marketing surveillance systems, and information provided in summaries of product characteristics. The latter may differ between countries and may include undiscriminatory class labellings [19, 20]. In many cases the original and complete evidence supporting this information is not published and its clinical relevance is unknown. Furthermore, there are only few epidemiological studies which have focused on drug interactions. Most of these studies have limitations as they relied on a single drug interaction compendium to identify potential drug interactions or did not provide enough details to identify which drug interactions are most problematic or analyses were not adjusted for potential confounders [16].

Third, compendia do not always make the same assumptions when extrapolating from a drug interaction observed with one drug to the other drugs in the therapeutic class. Inappropriate class labelling was recently criticized in an evaluation of the BNF [17].

Fourth, there is no consensus on the severity classification of drug interactions and the best way to assess their clinical relevance. Hansten *et al.* [21] considered that the criteria used in the classification of drug interactions by several compendia, such as the severity and quality of the supporting evidence, were inadequate and too limited. They proposed additional criteria such as the biological plausibility, the likely frequency of the concurrent use of the two drugs in the general patient population and the existence of warnings in the product information. More recently, the Partnership to Prevent Drug–Drug Interactions (PP-DDIs) tried to define a list of serious drug interactions using a 16-item instrument which included evidence supporting the interaction, severity, probability of the interaction and probability of co-administration of two drugs [22]. However, the relevance of this list for clinical practice has been questioned [23].

In conclusion, there is a lack of consistency in the inclusion and grading of interactions of major significance for the 50 drugs across the four drug compendia examined. This may reflect the lack of standardization of the terminology used to classify drug interactions and the lack of good epidemiological evidence on which to base the assessment of the clinical relevance of drug interactions. A concerted effort is needed to identify better clinically relevant interactions and communicate relevant information to health professionals.

I thank the Drug Information Association Foundation for funding this research. I thank those who have commented on this project, Ms Simone Rossi, Assistant Professor Libby Roughead and Dr Nick Buckley.

References

1 Kohn LT, Corrigan JM, Donaldson MS, eds. To err Is human: Building a safer health system. Washington DC, National Academy Press, 1999.

2 Expert Group on Learning from Adverse Events in the NHS. An organisation with a memory. London, Stationery Office, 2000. http://www.doh.gov.uk/orgmemreport/index.htm.

3 Australian Council for Safety and Quality in Healthcare. Second national report on patient safety: improving medication safety. Canberra, Australian Council for Safety and Quality in Healthcare, 2002.

4 Rosholm JU, Bjerrum Hallas J, Worm J, Gram LF. Polypharmacy and the risk of drug–drug interactions among Danish elderly. Danish Med Bull 1998; 42: 210–3.

5 Pirmohamed M, James S, Meakin S, Green C, Scott A, Walley T, Farrar K, Park B, Breckenridge A. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ 2004; 329: 15–9.

6 Shojania KG, Duncan BW, McDonald KM, Wachter RM, eds. Critical analysis of patient safety practices. Evidence Report/Technology Assessment No. 43. AHRQ Publication No. 01-E058. Rockville, MD, Agency for Healthcare Research and Quality, 2001.

7 Hazlet TK, Lee TA, Hansten P, Horn J. Performance of community pharmacy drug interaction software. J Am Pharm Assoc 2001; 41: 200–4.

8 Mukasa D, Hughes, J. Drug interactions in the elderly: frequency, significance and differences among standard reference resources. Australian Pharmacist 2002; 21: 603–8.

9 Chen YF, Neil KE, Avery AJ, Dewey ME. Prescriptions with potentially hazardous/contraindicated drug combinations presented to community pharmacies. Int J Pharm Pract 2002; 10(Suppl): R29.

10 Joint Formulary Committee. British National Formulary, 46th edn. London, British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003.

11 Vidal. Interactions medicamenteuses. Paris, Vidal, 2003.

12 Tatro D, ed. Drug interaction facts. Facts and Comparisons. Wolters Kluwer, St Louis. MO: 2003.

13 Klasko RK, ed. Drug-Reax system [database on CD-ROM]. Greenwood Village, Thomson Micromedex, 2003.

14 Fulda TR, Valuck RJ, Vander Zanden J, Parker S, Byrns PJ. Disagreement among drug compendia on inclusion and ratings of drug–drug interactions. Curr Ther Res 2000; 61: 540–8.

15 Chao S, Maibach, H. Lack of drug interaction conformity in commonly used drug compendia for selected at-risk dermatologic drugs. Am J Clin Dermatol 2005; 6: 105–11.

16 Abarca J, Malone D, Armstrong E, Grizzle AJ, Hansten PD, Van Bergen RC, Lipton RB. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc 2004; 44: 136–41.

17 Aronson JK. Drug interactions–information, education, and the Brtish National Formulary. Br J Clin Pharmacol 2004; 57: 371–2.

18 Stockley IH. Drug Interactions, 6th edn. London, The Pharmaceutical Press, 2006.

19 Saito M, Hirata-Koizumi M, Miyake S, Hasegawa R. Comparison of information on the pharmacokinetic interactions of Ca antagonists in the package inserts from three countries (Japan, USA and UK). Eur J Clin Pharmacol 2005; 61: 531–6.

20 Bergk V, Haefeli W, Gasse C. 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 2000; 61: 327–35.

21 Hansten PD, Horn JR, Hazlet TK. ORCA: Operational classification of drug interactions. J Am Pharm Assoc 2001; 41: 161–5.

22 Malone DC, Abarca J, Hansten, PD, Grizzle AJ, Armstrong EP, Van Bergen RC, Duncan-Edgar BS, Solomon SL, Lipton RB. Identification of serious drug–drug interactions: results of the partnership to prevent drug–drug interactions. J Am Pharm Assoc 2004; 44: 142–51.

23 Juurlink DN. Drug–drug interactions: where do we go from here? J Am Pharm Assoc 2004; 44: 128–34.