PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

SFINX—a drug-drug interaction database designed for clinical decision support systems

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Abstract

Objective The aim was to develop a drug-drug interaction database (SFINX) to be integrated into decision support systems or to be used in website solutions for clinical evaluation of interactions.

Methods Key elements such as substance properties and names, drug formulations, text structures and references were defined before development of the database. Standard operating procedures for literature searches, text writing rules and a classification system for clinical relevance and documentation level were determined. ATC codes, CAS numbers and country-specific codes for substances were identified and quality assured to ensure safe integration of SFINX into other data systems. Much effort was put into giving short and practical advice regarding clinically relevant drug-drug interactions.

Results SFINX includes over 8,000 interaction pairs and is integrated into Swedish and Finnish computerised decision support systems. Over 31,000 physicians and pharmacists are receiving interaction alerts through SFINX. User feedback is collected for continuous improvement of the content.

Conclusion SFINX is a potentially valuable tool delivering instant information on drug interactions during prescribing and dispensing.

Keywords Drug-drug interaction database ·
Clinical decision support system · Drug interactions

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Introduction

Adverse drug reactions continue to be a significant source of illness, and also a cause of death, in Western societies [1]. Drug-drug interactions represent a common cause of adverse drug reactions [2, 3]. Drug-drug interactions may also cause therapeutic failure—a complication that is less well characterised and also less recognised in health care. Irrespective of the outcome, an important feature of drug-drug interactions is that they are often preventable. The various drugs within a therapeutic group may act differently with regard to their risk of causing drug-drug interactions. This is well known for commonly used drugs such as statins, macrolide antibiotics, serotonin re-uptake inhibitors, antifungal agents and hypnotics [4–8]. When an alternative drug is not available or a change is not feasible, the interaction may often be handled by dose adjustments or by intensified monitoring of the treatment outcome.

The medical literature contains a vast amount of information regarding drug-drug interactions that would benefit everyday clinical work. Every year, hundreds of new reports are published, adding to our understanding of drug-drug interactions. In addition, the U.S. and European regulatory authorities have given clear guidelines which state that relevant interaction studies are to be performed prior to marketing authorisation [9–11]. The problem for a practising clinician today is not a lack of information. On the contrary, there is an overload of information, which is difficult to retrieve, sort and digest into clinical decision making. For example, already in the early 1990s, it was discovered that reduced CYP2D6 activity would diminish the analgesic effect of codeine [12, 13]. Yet, in a hospital setting 10 years later, every fifth patient receiving codeine was also being treated with a CYP2D6 inhibitor [14].

A recent review concluded that various clinical decision support systems improve practitioner performance [15]. In particular, systems embedded into electronic health-record systems that automatically prompt the users to action seemed the most effective. However, such systems put special requirements on the database to be used. Data must be of high quality and sorted and presented in a premeditated way to assure the accuracy and safety of the system. Even more important, the system should not be over-alerting. In the case of drug-drug interactions, the system should warn of inappropriate new prescriptions in relation to the patient's present medication with a focus on warnings of definite clinical relevance, avoiding any uncertainty with regard to administration routes, indication or dose range [16]. Practical advice on how to handle, monitor for, or circumvent a certain risk will hopefully also increase the compliance of prescribers.

One of the major sources of drug information for healthcare professionals is the summary of product characteristics (SPCs) provided by drug companies and approved by regulatory authorities. A recent study comparing SPC information on drug-drug interactions with several interaction databases revealed that information is neither complete nor consistent among various SPCs of a given generic drug [17]. Additionally, the SPC texts often deliver information on drug-drug interactions in generalised terms, such as 'avoid all concomitant use of strong enzyme inhibitors', which may not be very helpful to the physician at the moment of prescribing. Other systematic and highly reliable sources of information on drug-drug interactions also contain such a large amount of information that, if coupled to an automated warning system without further consideration of the clinical context in which co-prescribing could occur, they would soon exhaust the end user and counteract their purpose.

Given this situation, it is our firm belief that a decision support system providing carefully sorted, structured and evaluated information on drug-drug interactions as well as clinically based recommendations, integrated into the physician's workflow and available at the point of care, would improve prescribing performance. The aim of this project was to develop and implement such a high quality drug-drug interaction database, specifically designed for use in clinical decision support systems.

Materials and methods

The content and structure of the database were defined in repeated workshops including pharmacists, physicians, clinical pharmacologists and software developers.

The following processes and properties were identified as important for the successful development of the database:

1. All working processes within the project should be standardised and documented.
2. The database should be structured according to individual substance names (and not e.g. to therapeutic groups or ATC codes) to ensure correct linkage to preparations containing more than one substance.
3. Drug formulation should be taken into account (in order to avoid unnecessary warnings related e.g. to topically administered drugs).
4. Substance properties (e.g. inducer, inhibitor of a certain CYP450) should be registered to ensure consistency within the database.
5. Information texts should be structured.
6. Interactions should be classified with regard to clinical relevance and level of documentation.
7. References should be included and linked to PubMed whenever possible.
8. English should be the working language of the database.

Working processes

A standard operating procedure (SOP) with rules and guidelines for literature searches and reference management was defined. Texts were written by pharmacists or residents in clinical pharmacology and approved by a specialist in clinical pharmacology. A 'shared text' function, used whenever applicable, minimises both the size of the database and the work load and ensures that texts are consistent within groups of drugs with similar interactions. After approval, the medical consequences and recommendation texts are translated into national languages.

Literature searches

Important drug-drug interaction literature sources were defined and tested using different search strategies and

three randomly chosen drug pairs. Based on experiences from the evaluation of the literature, seven information sources were included in the SOP: Medline, Drugline, DRUGDEX, Stockley, Hansten & Horn, SPC texts and EPARs (European public assessment reports) [18-26]. Embase [23] was excluded as a literature source, due to the low number of articles not covered by other sources. Each drug pair was searched by generic names in all sources. In Medline and Drugline, generic names were searched as text words. Whenever the Medline search resulted in an excessive number of hits (150 or more), adequate limitations were used to focus the search. All relevant reports or articles were entered into the reference database, connected to the relevant interaction and linked to PubMed whenever possible.

Inclusion criteria

1. Pharmacokinetic interactions, described in scientific publications or by the manufacturer, with a probable or definitive clinical consequence
2. Pharmacodynamic interactions, described in scientific publications or by the manufacturer, with a possible or definitive clinical consequence, including interactions involving an increased risk of bleeding
3. Interactions that have not been described in clinical studies or from cases, but that can be assumed to occur and be of clinical relevance, based on knowledge of the properties of the substances involved (classified as documentation level 0)
4. Pharmacokinetic interactions involving significant changes in drug exposure, but where no clinical consequences are expected (classified as clinical relevance A)

Exclusion criteria

1. Pharmacodynamic interactions evident from the pharmacological profile of the substances (e.g. antidotes, most evident agonist–antagonist interactions)
2. Natural products lacking the relational properties that characterise drugs (e.g. ATC code)
3. Activated charcoal
4. Pharmacodynamic interactions not proven to be of clinical relevance

Formulations

Since the outcome of drug interactions differs depending on the route of administration, drug formulations were taken into account for each substance in each interaction pair. As there is a large variety of drug formulations, different formulation classes were formed in terms of what is relevant for drug interactions. Each existing formulation was related to one of four groups: enteral (oral), enteral (non-oral), parenteral or topical.

Structured texts

Structured texts guarantee that the users can navigate more easily through the information. In order to make the information easy to handle in a busy clinical situation, we defined four headings:

– Consequence
– Recommendation
– Mechanism
– Background

These headings were sorted into four text fields. Phrase lists were developed to ensure the use of the same terms (e.g. beta blockers, ACE inhibitors) and expressions for the same recommendations (e.g. 'no dose adjustment is usually needed') or descriptions of medical conditions. The recommendation was to be short, practical from a clinical point of view, and specific as to how the interaction effect could be monitored, what kind of dose change would be needed or what alternative drugs could be used to avoid the interaction. The mechanism, when known, might include e.g. which enzymes or transporters are involved in a pharmacokinetic interaction. The background text gives a short summary of the publications referenced. The original language of all information is English. The consequence and recommendation texts are kept short and concise to aid functionality when integrated into clinical decision support systems and other applications and to enable easy translation of these 'clinical parts' to different languages.

Classification

To support prescribers in their interpretation of the information, and to enable electronic health-record systems to adjust the sensitivity of drug-drug interaction alerts, all interactions are classified regarding their clinical relevance and level of documentation (Table 1). A zero level of documentation was introduced for inclusion of potentially dangerous interactions that have not, and probably never will be, documented in clinical studies (e.g. voriconazole with cisapride would create a potentially life-threatening QT prolongation). A colour code (A: green, B: grey, C: yellow, D: red) was developed for the clinical relevance to aid end users and harmonise the outlook in various portal and medical-record system applications.

Database structure

A substance register formed the basis of the drug-drug interaction database. Different salts of the same substance

Table 1 Classification categories in SFINX for clinical relevance (A-D) and level of documentation (0-4), derived from an earlier Swedish interaction classification system by Sjöqvist [27]

Classification	Definition
A	Minor interaction of no clinical relevance.
B	Clinical outcome of the interaction is uncertain and/or may vary.
C	Clinically relevant interaction that can be handled e.g. by dose adjustments.
D	Clinically relevant interaction. The combination is best avoided.
0	Data derived from extrapolation on the basis of studies with similar drugs.
1	Data derived from incomplete case reports and/or in vitro studies.
2	Data derived from well-documented case reports.
3	Data derived from studies among healthy volunteers and/or pilot studies among patients.
4	Data derived from controlled studies in relevant patient populations.

were connected to the 'mother' substance whenever these were considered to behave identically with respect to drug interactions. Mother-child relationships were formed, and this hierarchy was even further expanded (mother-child-grandchild) when considered necessary. Substance properties, such as cytochrome P450 or transporter substrate, inducer or inhibitor, could be entered for each mother substance. The mother-child system could be used to connect all drugs on the market to the substance register. Other possibilities for relating drugs to the database were created by integrating ATC codes or Chemical Abstract Service (CAS) numbers to each substance, allowing the connection of the database to local drug registers in different countries. Mother-child relationships were utilised to avoid text duplication and minimise the size of the database. Interactions could be formed with any combination of mother substances. Different classifications could be chosen for each interaction depending on the formulation of each substance. Structured texts were connected to an interaction and could be shared between different interactions. References which resulted from literature searches were added to each interaction.

The theoretical working process determined the database structure and the development of the editorial tool for entering data into the database. Continuous literature searches resulted in database updates which could be traced in so-called audit trails. Those could be used to support the translation function of texts which had been translated earlier and were changed during the update process. The database was implemented using established techniques such as SQL database. The approved and translated content of the database can be exported to third-party systems on a regular basis. The export file is an XML (Extensible Mark-up Language) file specified by an XSD schema (XML Schema Definition). The editorial tool supports the possibility that several physicians and pharmacists could collaborate and enter texts simultaneously.

Results

Before the release of SFINX (December 2005 in Finland), 4,380 interaction pairs had been entered into the database.

For the development of the database, approximately seven full-time equivalents were employed for 2.5 years. The subsequent updating procedures, including quality assurance, improvements and technical support, have required about five full-time equivalents. Today, SFINX contains approximately 1,030 'mother' substances (not including the child or grandchild substances) and more than 8,000 drug-drug interaction pairs, based on information from 5,225 references. All substances registered in Sweden and/or Finland are included in the database. The proportion of texts in the different classification groups of clinical relevance (A-D) has been relatively stable over time (proportion of A interactions 6%, B 28%, C 50% and D 16%), with a dominance of the C group, i.e. combinations that are not contraindicated, but that may be of clinical concern (Fig. 1).

SFINX was first released in Finland on 1 December 2005 and published in the largest medical portal for health-care professionals. There are about 15,000 Finnish physicians and about 8,000 pharmacists who made almost 700,000 portal searches in SFINX in 2007 (Fig. 2). In Sweden, the portal solution was launched in March 2007 and now has 9,600 registered users, a figure that is steadily rising. In Finland, SFINX is a commercial product, and in Sweden it is publically funded and thus delivered free of charge.

SFINX has been embedded into medical-record systems in Finland and Sweden. In Finland, some 6,000 general practitioners and hospital doctors get automatic alerts on drug interactions when prescribing. In Sweden, SFINX is integrated directly into various electronic health record systems of 300 primary health-care centres and 10 hospitals. In Sweden about 8,000 users receive drug-drug interaction alerts daily through this application (Janus Web-based alert system). In addition, in Finland over 90% of the pharmacies have SFINX embedded into their electronic prescription delivery systems.

SFINX is updated four times a year. Literature searches are continuously performed according to standard operating procedures to identify new published interaction articles concerning both established drugs and novel substances. A

Fig. 1 Number of drug-drug interactions in SFINX
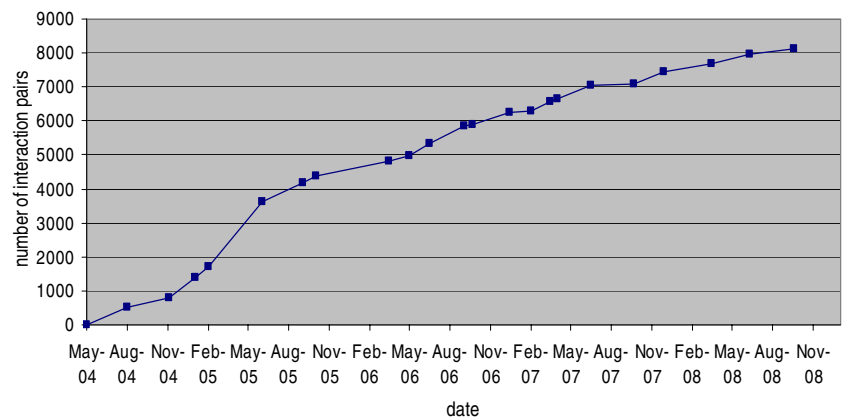
systematic follow-up of drugs coming out on the market is performed. Additionally, end-user feedback is collected from different applications (e.g. direct comment link from the website) and handled by experts to improve the content.

Discussion

A drug-drug interaction database, like any other knowledge database or evidence-based guidelines, should be developed by organisations independent of the pharmaceutical industry and with highly credible expertise, while software developers should focus on the usability of the system and the proper implementation into clinicians' workflow [28]. For the development of SFINX, the Department of Clinical Pharmacology at Karolinska Institutet and the Drug Interaction Unit at the Turku University Hospital, both of which are centers of excellence for clinical pharmacology, joined forces with the Department of Drug Management and Informatics at the Stockholm County Council, which is well-known as a provider of clinical decision support systems in Stockholm and throughout Sweden [29, 30].

Drug-drug interaction databases integrated into electronic health-record systems are useful tools to support general practitioners and improve drug-prescribing performance [15]. The main drawback or possible weakness of any such automated system is the risk of inappropriate alerts, a low signal-to-noise-ratio, and thus low specificity. Almost any degree of 'over-alerting', especially in the screening situation when information about drug-drug interactions is not actively sought to solve a clinical problem, will soon result in 'alert fatigue' and frequent overriding of the interaction warnings or may even prompt the user to shut down the system [16, 31]. The information overload generated by non-selective inclusion will conceal the important clinical message in the database.

In the development of SFINX, we tried to tackle these problems in different ways. The classification of clinical relevance allows the user to limit automated (screening)

alerts e.g. to those classified as C or D, meaning that the clinical relevance of the information has been well established. Interactions classified as B may be of interest in the investigation of an unexpected treatment outcome or in the vulnerable patient and in these cases can easily be retrieved. Taking drug formulations into account is a way to eliminate irrelevant warnings in relation to topically applied drugs (and sometimes, when bioavailability is the problem, in relation to parenteral administration) and to increase the specificity of the database, as has been suggested [32, 33]. Furthermore, by separating acetylsalicylic acid into low- and high-dose use, a substantial number of unnecessary warnings (related to the anti-inflammatory action of high doses) could be avoided in relation to antithrombotic, low-dose treatment. A remaining problem to solve is how to handle possible interactions that clearly depend on patient-specific characteristics, such as dose, renal function or enzyme or receptor variants. A future and interesting development of the system would be to connect the warnings to such information, whenever available in the patient records.

Another important issue in the development of a drug-drug interaction database is the availability of alternative treatment recommendations [34]. The aim of the SFINX
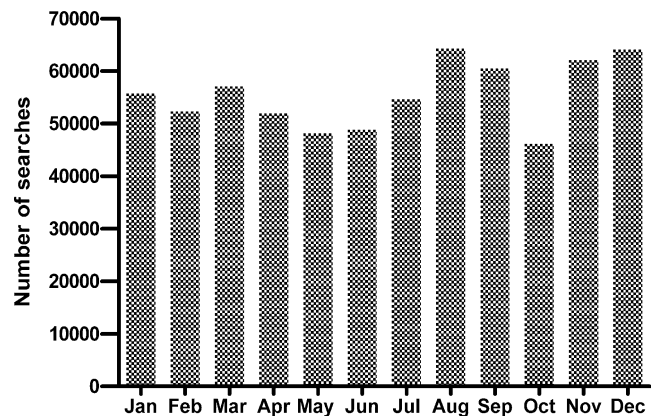
Fig. 2 Number of portal searches in SFINX in Finland in 2007

project has been to give short and practical recommendations on how to handle each potential drug interaction. Often, an interaction risk can be circumvented by choosing an alternative drug. The knowledge of the clinical situation in which a given combination may be prescribed is essential for deciding which drug in any given pair can be conveniently altered. Also, one must bear in mind that one drug may be given for different indications, meaning that alternative treatment options may also differ. A calcium-channel blocker given to treat hypertension can possibly be changed to an ACE inhibitor, whereas this would not be a valid option in the treatment of angina. For antibiotics, the sensitivity of the microorganism treated is of course essential for the choice of drug. Also, available alternatives may differ over time and regionally or nationally. The act of balancing the length of the recommendation text while still keeping it valid and informative has been a constant basis for discussions within the project. The collaboration between pharmacists and clinical pharmacologists has been essential to the development of the recommendation texts.

Another focus for discussion has been the inclusion and exclusion criteria: What drug pairs should be entered into the database? How far should the results from one well-performed and clinically relevant interaction study be extrapolated to other drugs? What pharmacodynamic interactions should be warned against? SPC texts very often contain warnings against combining two drugs that may both cause a lengthening of the QTc interval, despite the fact that there is no solid evidence that such combinations do actually increase the risk of cardiac arrhythmia. There have been several fatal cases of Torsade des Pointes arrhythmia and sudden death in relation to drug interactions, but these are actually pharmacokinetic interactions, e.g itraconazole inhibiting the metabolism of terfenadine and causing a several-fold increased exposure and adverse effects [35]. To warn against all possible and theoretical risks of drug combinations is not helpful to clinicians, who still have to treat patients with more than one symptom or disease everyday. The main aim of SFINX has been to include well-established and documented interaction risks, and to extrapolate theoretical risks only when judged to be of evident clinical value.

For clinical usefulness and for medical safety, the integration of a drug-drug interaction database into a medical-record system has to be tested and controlled. Systems should allow for customisation by the user. Frequently shown alerts may result in learning effects and should be possible to turn off. Even premeditated risks may result in unnecessary warnings (e.g. combining low-dose aspirin with an oral anticoagulant in patients suffering a stroke while on oral anticoagulation therapy) and should be possible to turn off by an individual end user. The alert information should be presented concisely to enable fast and easy understanding. We recommend displaying the consequence and recommendation text parts only, keeping all additional information available on demand. Also, colour codes (e.g. coloured boxes showing when an alert is generated) describing the clinical relevance are useful to avoid misinterpretations and to harmonise the function in different applications. Interaction warnings in the case of drug renewal should preferably not be shown, whereas a warning in relation to stopping a certain drug treatment, e.g. a strong enzyme inducer such as carbamazepine or rifampicin, may be very relevant. Based on our experience so far, we conclude that SFINX, if implemented as recommended, is a potentially useful tool when integrated into a clinical decision support system. Further studies on the effects of SFINX on prescribing habits of physicians and on patient outcome will be performed.

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