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PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Impact of the drug-drug interaction database SFINX on prevalence of potentially serious drug-drug interactions in primary health care

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Abstract
Purpose To investigate the impact of the integration of the drug-drug interaction database SFINX into primary health care records on the prevalence of potentially serious drug-drug interactions.
Methods The study was a controlled before-and-after study on the prevalence of potential drug-drug interactions before and after the implementation of SFINX at 15 primary healthcare centres compared with 5 centres not receiving the intervention. Data on dispensed prescriptions from health care centres were retrieved from the Swedish prescribed drug register and analysed for September–December 2006 (pre-intervention) and September–December 2007 (post-intervention). All drugs dispensed during each 4 month period were regarded as potentially interacting.
Results Use of SFINX was associated with a 17% decrease, to 1.81×10^{-3} from 2.15×10^{-3} interactions per prescribed drug-drug pair, in the prevalence of potentially serious drug-drug interactions ($p=0.042$), whereas no significant effect was observed in the control group. The change in prevalence of potentially serious drug-drug interactions did not differ significantly between the two study groups. The majority of drug-drug interactions identified were related to chelate formation.
Conclusion Prescriptions resulting in potentially serious drug-drug interactions were significantly reduced after integration of the drug-drug interaction database SFINX into electronic health records in primary care. Further studies are needed to demonstrate the effectiveness of drug-drug interaction warning systems.

Keywords Drug-drug interactions · Clinical decision support systems · Database management systems · Medical order entry systems · Medication errors/prevention and control

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Introduction

Drug-drug interactions may cause serious adverse effects and increase the risk of hospitalisation [1–3]. Many drugs have been withdrawn from the market due to their potential to give rise to fatal drug-drug interactions. Some examples are terfenadine and cisapride, both of which may cause Torsade de Pointes when used in combination with drugs that inhibit the cytochrome P450 isoenzyme CYP3A4 [4].

The average number of drugs used by each patient has increased over time, and this dramatically increases the risk for drug-drug interactions. Becker et al. have shown that the prevalence of drug-drug interactions among patients 55 years or older in the Netherlands increased to 19.2 from 10.5% between 1992 and 2005 [5]. In Sweden the prevalence of polypharmacy, i.e. the proportion of the population dispensed ≥5 drugs over a 3 month period, increased by 8.2% in only 3 years, and the frequency of excessive polypharmacy (≥10 drugs) increased even more [6]. There are several thousand substances registered in Europe, many of which can give rise to drug-drug interactions. Several studies have shown that physicians are only aware of a minority of serious drug-drug interactions [7, 8].

Various drug-drug interaction alerting software programmes are used throughout the world, and many of them

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are integrated into clinical decision support systems (CDSSs). An optimal drug-drug interaction database implemented into a decision support system could result in decreased costs and suffering for the patients [9]. The major pitfall for drug-drug interaction alerting programmes is that they tend to over-alert the prescribers, leading to alert fatigue and decreased use of the system [10].

SFINX (Swedish Finnish Interaction X-referencing) is a drug-drug interaction knowledge base produced as a collaboration between Sweden and Finland. It is designed especially for integration into electronic health record systems. Three features in SFINX that are aimed at increasing the usefulness are a classification system based on clinical relevance, drug formulation sensitivity and interaction handling recommendations. Classification of severity makes it easier for the prescriber to evaluate the relevance and the documentation of the interaction. The SFINX classification system is presented in Table 1. Formulation-specific classification results in fewer irrelevant warnings e.g. for topical preparations. In addition, SFINX gives clear recommendations to the prescriber on how to handle specific drug-drug interactions [11]. This ought to increase the user friendliness and is regarded as a quality criterion for a useful drug-drug interaction database [12, 13].

For several years, SFINX has been integrated into CDSSs in Sweden and Finland. In February 2007 SFINX was implemented into electronic health record systems through the CDSS Janus toolbar [14] in most primary health care centres in the north-western part of Stockholm. Some of the centres received education on how to use the toolbar whereas others only received a pamphlet. The toolbar generates warnings if the patient drug list or the newly prescribed drug would interfere with one of the drugs from the list or the patient status. In February 2007, SFINX also became available online to all Swedish prescribers through http://www.janusinfo.se [15].

The aim of the present study was to test the hypothesis that integration of SFINX into the CDSS would decrease the prescribing of drug combinations that lead to potentially serious drug-drug interactions in primary health care. This study focused on primary health care, and data on dispensed drugs were retrieved from the Swedish Prescribed Drug Register [16].

Table 1 Severity classification according to SFINX

Grade	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 by for example dose adjustments
D	Clinically relevant interaction that is best avoided

Materials and methods

The study was designed as a controlled before-and-after study. All 26 primary health care centres in the north-western part of Stockholm County were invited to participate in the study. The health care centres were divided into two groups, one consisting of all centres that received SFINX in February 2007 and one comprising centres without any warning system for drug-drug interactions integrated in the medical record system. The health care centres starting to use SFINX did so because it was automatically introduced in their medical record system. Thus, study group allocation was not influenced by the preference of the participating centres. Health care centres with only one employed physician, a change in the number of prescriptions of 30% or more and those that had been privatised during the years 2006 or 2007 were excluded. In total 13% of the health care centres in the north-western region were excluded based on these criteria.

Inclusion

Data on dispensed prescriptions from all patients attending the participating health care centres and receiving at least one prescription in September–December 2006 and/or 2007 were included. A 3 month period has been shown to be useful to study concomitant drug use in drug dispensing databases in Denmark [17]. We applied a similar methodology since the Swedish prescribed drug register is similar to the Danish registers [18]. According to the Swedish legislation, all prescriptions are valid up to 1 year after they are issued and may be repeatedly dispensed until the prescribed amount is reached. Medication for 3 months is the maximum amount that patients can be dispensed at any occasion if they want their drugs to be subsidised. We chose to include a fourth month to study concomitant use since some patients with chronic medications redeem their drugs in longer intervals than every third month [19].

Exclusion

Patients prescribed only one drug were excluded because they can not be exposed to any drug-drug interaction. Patients receiving drugs in a specific multidose drug dispensing system (ApoDos) were excluded since the prescriber does not have access to SFINX when prescribing in ApoDos. Among the most severe interactions, i.e. D-interactions, the interaction between low dose acetylsalicylic acid and warfarin was excluded because this combination is frequently prescribed intentionally.

Data collection

Anonymised data on all prescribed drugs from the participating health care centres were retrieved from the Swedish Prescribed Drug Register held by the National Board of Health and Welfare. All prescription data for the two time periods, September 1 to December 31, 2006 and September 1 to December 31, 2007, were analysed regarding possible drug-drug interactions by linking the prescription file to the DDI database SFINX through an especially developed SAS application. The SAS application reduced patient-specific prescription data to unique substances to avoid multiplication of interactions. This was achieved through several steps: (1) reduction to unique registration numbers, (2) then to unique substance IDs, and (3) finally to unique ATC codes. The remaining substance IDs per patient were then linked to the SFINX database to check for the prevalence of possible drug-drug interactions. Output data included number of patients, number of unique drugs prescribed, number of D-interactions (Table 1) and which drugs were involved in all interaction pairs.

The study was approved by the Regional Ethics Committee at Karolinska Institutet, Stockholm (2011/926-31/1)

Data analysis

The primary outcome was the change in the prevalence of potential D-interactions (highest severity; see Table 1) from the pre-intervention period to the post-intervention period in the SFINX group. A potential D-interaction was defined as the dispensing of two interacting drugs within the same time window of 4 months. The number of possible interaction pairs per patient (i.e. the total number of two-drug combinations that could be derived from all drugs used concomitantly during a 4 month period by an individual patient) was calculated. The prevalence was calculated by dividing the number of D-interactions by the number of possible interaction pairs. The number of possible interaction pairs was chosen rather than interaction per patient or interactions per prescription because the latter two are very sensitive to quantitative changes in drug use since the number of interactions is expected to increase exponentially with the number of prescriptions to each patient. The change was analysed using Fisher's exact test.

Due to the small number of eligible health care centres in the control group, the change in the proportion of drug interactions in the SFINX group was compared to the change in proportion in the control group as a secondary outcome. The changes in the prevalence of D-interactions in the SFINX group and the control group were compared by logistic regression (group-time interaction). In a subgroup analysis we determined the change in drug interaction prevalence in centres that had received SFINX together with an education on the system and in centres who had received only a pamphlet. The subgroup analyses were performed using the same methods as in the main analysis.

Due to the risk of overestimating the prevalence of drug interactions when using all prescriptions from a 4 month period, a sensitivity analysis using only prescriptions from a 3 month period (September–November) was performed. The same statistical methods were used as in the main analyses.

All statistical analyses were performed using R version 2.10.1 [20].

Results

Study population

A total of 15 centres out of 18 using SFINX and 5 centres out of 8 without SFINX agreed to participate in the study. All prescriptions issued during September–December 2006 (n=90,806) (pre-intervention, baseline) and during September–December 2007 (n=91,489) (post-intervention) were included in the analysis. Patient and health care centre characteristics are presented in Table 2.

Table 2 Patient and health care centre characteristics

	SFINX group, pre-intervention	SFINX group, post-intervention	Control group, pre-intervention	Control group, post-intervention
Health care centres (n)	15	15	5	5
Patients (n)	19,932	20,088	5,009	4,988
Median age (IQ range)	58 (40–70)	58 (41–71)	58 (40–71)	58 (40–71)
Gender % (M/F)	39/61	39/61	39/61	40/60
Median drugs, n (IQ range)	3 (2–4)	3 (2–4)	3 (2–4)	3 (2–4)
Prescriptions (n)	73,133	73,776	17,673	17,713
D-interactions[a]	314	267	48	44

IQ Interquartile

[a]SFINX level of drug-drug interaction severity. See Table 1 for more information

Impact on prescribing

We found a significant 17% decrease, to 1.81×10^{-3} from 2.15×10^{-3} interactions per drug pair, in the prevalence of D-interactions (p=0.042) in the SFINX group (RR 0.81; 95% CI: 0.60–0.99) while no significant change, to 1.35×10^{-3} from 1.47×10^{-3} interactions per drug pair, was observed in the control group (RR 0.91, 95% CI: 0.32–1.29). The prevalence of D-interactions was significantly lower in the control group than in the SFINX group at baseline: OR 0.70, 95% CI: 0.51–0.95. In the logistic regression analysis the reduction in prevalence of D-interactions did not differ significantly between the two groups (p >0.05 for group-time interaction) (Fig. 1). The frequency of D-interactions per patient decreased to 1.3 from 1.5% within the SFINX group and to 0.88 from 0.96% within the control group. There was a trend towards a more pronounced decrease in D-interactions per possible interaction pairs in the four health care centres who had received education (21%, p= 0.24) compared to the other health care centres in the SFINX group (16%, p=0.06), but the difference between the two subgroups was not statistically significant for group-time interaction.

The change in D-interactions differed greatly between health care centres and ranged from a decrease of 58% to an increase of 68% within the group using SFINX.

In the sensitivity analysis, based on 3 months of prescription data, the prevalence of D-interactions decreased non-significantly (p=0.27) by 12%, whereas the prevalence in the control group increased non-significantly (p=1) by 0.6%. The results from the regression showed a non-significant (p=0.67) difference between the groups. A majority of the most common serious drug-drug interactions found were between antibiotic agents and chelating agents such as calcium and magnesium. The 14 most common drug-drug interactions in the SFINX group and their change between pre- and post-intervention can be found in Table 3. The contribution of the four drugs most commonly involved in the drug-drug interactions (calcium, iron, norfloxacin, and ciprofloxacin) to the total prescription volume did not differ significantly between the two study groups (data not shown).

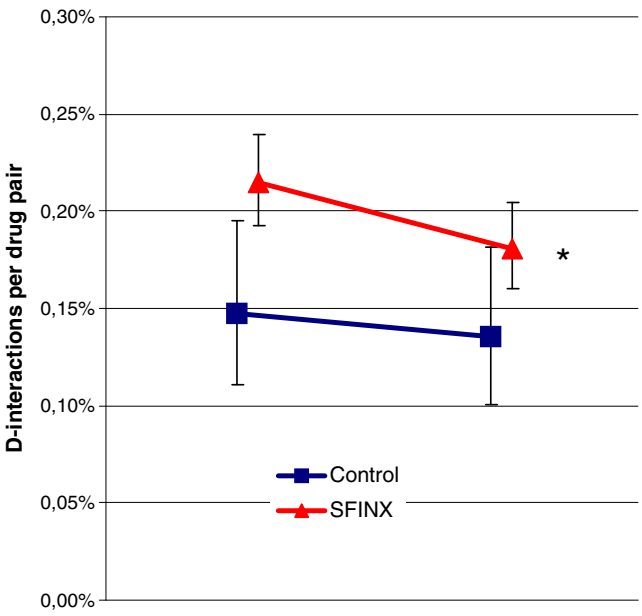

Fig. 1 Change in the prevalence of drug-drug interactions from pre-intervention to post-intervention. *p<0.05

Discussion

The results from this study indicate that integration of SFINX into an electronic health record system through the Janus toolbar is associated with reduced prescribing of high severity drug-drug interactions. We found a 17% decrease in the prevalence of potentially serious interactions. There was also a trend towards a larger decrease in the health care centres which had received education about usage of the Janus toolbar system during the implementation compared to those which had not. This difference was not statistically significant but supports the idea that emphasis on education increases the adherence to CDSS [21]. By qualitative investigation of the results from an expert meeting, discussing success factors when implementing a computerised physician order entry system in hospitals, Ash et al. found that training during implementation and especially support after implementation were of major importance for successful implementation.

The clinical benefits of drug-drug interaction systems are still to be proven. In a meta-analysis Wong et al. analysed studies investigating the effects of drug-drug interaction warning systems [22]. Four studies were good enough to be included in the meta-analysis and the result of the meta-analysis was a non-significant decrease in the relative risk by 0.66 (95% CI 0.33–1.18). Two more studies [23, 24] have been published since then, one where the frequency of drug interactions decreased by 43% [23] and one where it decreased by 30% [24]. Direct comparison between different interaction warning systems is difficult since the classification of interaction severity differs markedly across different systems, with some giving severe warnings for only a few interactions, while others give severe warnings for almost all possible interactions. Even inclusion of interactions into databases differs among different vendors [25]. However, there is a need for concise and product-independent information about drug-drug interactions, since information in the product SPC differs for each drug, and information about an interaction included in the SPC for

Table 3 The change in the prevalence of the 14 most common serious drug interactions after implementation of SFINX

Interacting drugs	Interaction mechanism	Change in prevalence (%)	Number of interactions pre-intervention	Number of interactions post-intervention
Doxycycline-calcium	Chelate formation	−8.5	39	36
Doxycycline-iron	Chelate formation	−19.2	27	22
Amiloride-potassium	Additive effect on potassium levels	−48.0	21	11
Bupropion-ethylmorphine	Decreased efficacy of ethylmorphine	−66.9	15	5
Calcium-norfloxacin	Chelate formation	−64.6	14	5
Duloxetine-tramadol	Decreased efficacy of tramadol	−46.6	13	7
Spironolactone-potassium	Additive effect on potassium levels	−23.7	13	10
Ciprofloxacin-calcium	Chelate formation	+9.1	10	11
Diltiazem-metoprolol	Additive effect on SA- and AV-nodes	−0.8	10	10
Ciprofloxacin-iron	Chelate formation	−11.8	9	8
Norfloxacin-iron	Chelate formation	−38.0	8	5
Doxycyline-magnesium	Chelate formation	−17.3	6	5
Fluoxetine-tramadol	Decreased efficacy of tramadol	−0.8	6	6
Gemfibrozil-simvastatin	Inhibition of the hepatocellular transport of simvastatin	−17.3	6	5

drug A might not be mentioned in the SPC for the interacting drug B [26].

The Swedish Prescribed Drug Register is an excellent source for studying drug exposure in Swedish patients [18]. All drugs that are dispensed at Swedish pharmacies are registered, and every patient and prescribing unit can be identified making it possible to study for example drug interactions. However, we found that using the prescribed drug register is not an optimal way of studying the adherence of prescribers to a decision support system including a drug-drug interaction knowledge base. Some of the actions taken by the physicians due to an interaction alert cannot be detected in the register data. For example changes in drug dosing cannot be extracted from this source since dosage texts in the electronic health record systems are free text fields, thereby delivering non-extractable information. Additionally, almost one-third of the D-interactions found in this study are interactions that can usually be avoided by temporary stopping of one of the drugs (e.g. iron supplementation) during treatment with an antibiotic. You could also separate the intake in time so that the impact of the interaction would be minimal. These actions may be documented in the electronic health care records but cannot be identified in the prescribed drug register. By using data from a 4 month period and studying all interactions during that period, we may have overestimated the number of drug interactions because the patient may not have used the drugs at the same time. To address this issue, we performed a sensitivity analysis based on a shorter time period of 3 months, arriving at similar results. On the other hand, the D-interactions are few and could be considered the "tip of the iceberg" while the actual number of clinically relevant drug-drug interactions is likely to be much larger. Assuming that the proportion of relevant interactions being identified in the study is similar in both study groups and before/after the intervention, the relative changes would still be valid for the true frequency of drug-drug interactions. Another study option would have been to look at all drugs purchased at the same time, but then the drug interaction prevalence would have been underestimated, and we would have observed fewer interactions with drugs for treatment of chronic diseases.

In this study a significant difference between study and control group in reduction of serious drug-drug interactions could not be demonstrated. One explanation is that the control group was small. A larger control group may have made it possible to find a difference between the two groups. Also, the high dropout rate in the control group, 38% of the centres contacted, increases the risk for selection bias with the health care centres with a larger interest in drug

therapy possibly being more prone to participate. Surprisingly, the baseline prevalence of drug interaction was significantly lower in the control group compared to the SFINX group. This indicates that the two studied groups are not truly comparable, possibly due to the abovementioned selection bias or some other difference. For example more of the centres in the control group were privately run, which may have influenced the results. Importantly, the lower baseline prevalence of drug interactions in the control group may theoretically have influenced the results of the study, by reducing their potential for further improvement as compared to the intervention group. The choice of gaining access to SFINX was not made by the health care centres but was instead a consequence of which medical record system they were using at the time (SFINX was introduced in some systems, but not in others). Hence, the prescribers' willingness to gain access to SFINX should not be an important source of bias in this study.

Between the pre- and post-intervention period, the prevalence of drug interactions decreased both in the SFINX group and the control group, although non-significantly in the latter. A possible explanation is that the prescribers in the control group actually used SFINX through the Janus website, which was made available in 2007. The SFINX database was updated at the same time both in the Web solution and within the toolbar, making it possible for the prescribers in the control group to access the same information about interactions as the prescribers in the SFINX group. Another explanation may also be that the time between intervention and follow-up was relatively short, and it may take a while for prescribers to get used to the new decision support system.

In this study 1.5% of the patients taking more than one drug were exposed to a potential serious drug interaction, which is lower than the prevalence found in Sweden in 2003–2004 of 2.9% [27]. The prevalence in this study is expected to be lower because the data used only show the prescriptions for a given patient from one health care centre and not any other drugs used by the included patients. The exclusion of patients receiving Apo-Dos and exclusion of the warfarin–low dose acetylsalicylic acid interaction may also have reduced the prevalence further. Apo-Dos (unit-dose dispensing) is rather commonly used in Sweden to facilitate drug use among patients with polypharmacy and is also used more frequently among elderly people. Bergkvist et al. [28] showed that medication errors are almost six times more common among patients receiving Apo-Dos.

Interestingly, approximately two-thirds of the serious drug interactions found in our data were interactions resulting in decreased effect of one of the drugs due to chelate formation or inhibited formation of active metabolites. Frequently, these interactions are not recognised [29] despite often being as severe as interactions caused by a moderately increased effect of another drug. Further investigations about the clinical importance of these "silent" drug-drug interactions are warranted.

In conclusion, our study supports the potential usefulness of SFINX in reducing the number of serious drug interactions. Still, more studies are needed, and using data from electronic health record systems would be an optimal way to study prescribers' adherence to the warnings. Additionally, our findings should be confirmed in a randomised controlled trial using an education plan during the implementation of a clinical decision support system into the electronic health record system.

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Conflicts of interest M.L. Andersson and Y. Böttiger are, as employees of the Stockholm County Council, working with the quality and content of the SFINX database.

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