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Clinically important drug–drug interactions in primary care

A. A. H. Dhabali PhD, R. Awang Pharm D and S. H. Zyoud MSc
WHO Collaborating Centre for Drug Information, National Poison Centre, Universiti Sains Malaysia (USM), Penang, Malaysia

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SUMMARY

What is known and Objective: **Drug–drug interactions (DDIs) cause considerable morbidity and mortality worldwide and may lead to hospital admission. Sophisticated computerized drug information and monitoring systems, more recently established in many of the emerging economies, including Malaysia, are capturing useful information on prescribing. Our aim is to report on an investigation of potentially serious DDIs, using a university primary care–based system capturing prescription records from its primary care services.**

Methods: **We retrospectively collected data from two academic years over 20 months from computerized databases at the Universiti Sains Malaysia (USM) from users of the USM primary care services.**

Results and Discussion: **Three hundred and eighty-six DDI events were observed in a cohort of 208 exposed patients from a total of 23 733 patients, representing a 2-year period prevalence of 876·4 per 100 000 patients. Of the 208 exposed patients, 138 (66·3%) were exposed to one DDI event, 29 (13·9%) to two DDI events, 15 (7·2%) to three DDI events, 6 (2·9%) to four DDI events and 20 (9·6%) to more than five DDI events. Overall, an increasing mean number of episodes of DDIs was noted among exposed patients within the age category ≥70 years ($P = 0·01$), an increasing trend in the number of medications prescribed ($P < 0·001$) and an increasing trend in the number of long-term therapeutic groups ($P < 0·001$).**

What is new and Conclusion: **We describe the prevalence of clinically important DDIs in an emerging economy setting and identify the more common potentially serious DDIs. In line with the observations in developed economies, a higher number of episodes of DDIs were seen in patients aged ≥70 years and with more medications prescribed. The easiest method to reduce the frequency of DDIs is to reduce the number of medications prescribed. Therapeutic alternatives should be selected cautiously.**

WHAT IS KNOWN AND OBJECTIVE

Drugs can be used in combination to achieve a preferred therapeutic goal or to treat coexisting diseases. Such combinations may result in undesired interactions of a pharmacodynamic or pharmacokinetic nature with consequential undertreatment or harmful effects.[1] The possibility of one drug influencing the safety or efficacy of another drug (a drug–drug interaction, DDI) is an additional variable when choosing pharmacotherapy.[2] In selecting the optimum therapy, factors like dose, route of administration, contraindications, the possibility of adverse drug reactions and cost are important.[2] DDIs cause considerable morbidity and mortality worldwide.[3–6]

Several studies using administrative databases have estimated the prevalence of DDIs among ambulatory patients in different countries.[7–10] Sophisticated computerized drug information and monitoring systems, more recently established in many of the emerging economies, including Malaysia, are capturing useful information on prescribing. Our aim is to report on an investigation of potentially serious DDIs, using a university primary care–based system capturing prescription records from its primary care services. Our hope is that the data reported would provide a useful baseline for follow-on or comparative studies, both nationally and internationally, particularly by those interested in prescribing quality in emerging economies.

METHODS

This is an observational retrospective case and prescription review of all patients who visited the primary care setting of the Universiti Sains Malaysia (USM). Data were collected from two academic years (i.e. 20 months: 1 July 2004–30 April 2005 and 1 July 2005–30 April 2006) from the university's computerized databases. USM offers primary health care to its beneficiaries through USM health centre (USMHC) and a panel of private clinics (USMPC). Healthcare utilization data of the beneficiaries are stored in computerized databases in USM's research and development unit. These computerized databases receive data of beneficiaries' visits to both USMHC and USMPC. Each visit is documented in these databases with a unique number and includes the beneficiary's biodata, the diagnosis and the treatment given. In the study period, there were 30 466 beneficiaries. Students, staff and dependants are the three identified categories of patients in this study. These three categories represented 68%, 10% and 22% of the number of beneficiaries, respectively.[11]

This research was carried out with the permission of the USM's respective authorities. To maintain confidentiality, information related to the identification of patients and healthcare providers was obscured prior to data collection. The data comprised of each patient's demographics (age, gender, ethnicity, marital status and type of beneficiary) and drugs prescribed. The prescribed medications were classified according to the disease or the body system. Medications for the same disease/

Correspondence: A. A. H. Dhabali, National Poison Centre, Universiti Sains Malaysia (USM), 11800 Penang, Malaysia. Tel.: +6046532090; fax: +6046568417; e-mail: dahbali@yahoo.com

body system were classified into groups called long-term therapeutic groups (LTTGs).[11] The number of LTTGs for each patient was a measure of the number and the severity of the long-term diseases he/she suffered from. A list of clinically significant DDIs was collected from the following sources: (i) MedFacts Pocket Guide of Drug Interactions,[12] (ii) clinically Significant Drug Interactions,[13] (iii) update on clinically significant drug interactions in dermatology,[14] (iv) clinically significant pharmacokinetic drug interactions with psychoactive drugs: antidepressants and antipsychotics and the cytochrome P450 system,[15] (v) clinically significant pharmacokinetic drug interactions with benzodiazepines[16] and (vi) clinically significant drug interactions with agents specific for migraine attacks.[17] DDIs that could be controlled by scheduling and had recommended monitoring were excluded from the study. The DDIs had to meet further criteria according to a previous study[18]: (i) be mentioned in either two therapeutics books or one therapeutic book and two drug information books, (ii) have a recommendation to avoid the interaction; (iii) have a safer alternative drug. The purpose of these criteria was to ensure that there was an agreement between practice-based books.[19–24]

A DDI was considered if two drugs whose co-prescribing is to be avoided were prescribed for the same patient in the same visit, and safer alternatives were available. Drugs in injection dosage forms were not considered as drug interaction events because they are usually given in emergency situations. The number of times each patient was exposed to these DDI events was calculated. A list of interacting drug pairs is given in Appendix S1. Drugs in Appendix S1 were classified into object medication or class (drug 1) and precipitant medication or class (drug 2). DDI events were summed up as episodes for each patient. Each patient's episode represents the number of times that patient was exposed to a clinically significant DDI. Clinically important DDI episodes were graded as grade I – one DDI episode, grade II – two DDI episodes, grade III – three DDI episodes, grade IV – four DDI episodes and grade V – five or more DDI episodes.

Data extracted from the USM's databases were imported into SPSS files (Statistical Package for Social Sciences; version 15, Chicago, IL, USA). For comparative analysis, variables were tested for normality using the Kolmogorov–Smirnov test. Statistical significance for intergroup differences was tested by the Student's t-test or ANOVA for continuous variables. One-way ANOVA with Tukey's *post hoc* test was used to test for differences in the means between categories. A *P*-value less than 0·05 was considered statistically significant.

RESULTS AND DISCUSSION

A total of 23 733 patients visited the USM's primary care clinics during the study period (Fig. 1). 377 155 medications were prescribed, with an average of 15·9 medications per patient. The prevalence of drug pairs causing DDI events is given in Appendix S2. During the study period, 12 760 patients had 41 502 drug 1 prescriptions. This represented 53·7% of all patients. Among these 41 502 drug 1 prescriptions, 386 clinically important DDI events were identified (2-year DDI period prevalence of 930·8 per 100 000 prescriptions). The 386 DDIs were observed among a cohort of 208 exposed patients, representing a 2-year period prevalence of 876·4 per 100 000 patients or 1% of all patients. Of the 208 exposed patients, 138 (66·3%) were exposed to one DDI event, 29 (13·9%) to two DDI events, 15 (7·2%) to three DDI events, 6 (2·9%) to four DDI events and 20 (9·6%) to five or more DDI events.

The prevalence of prescriptions with DDI events was 1%, representing a 2-year period prevalence of 876·4 per 100 000 patients. This is a relatively low prevalence compared to other

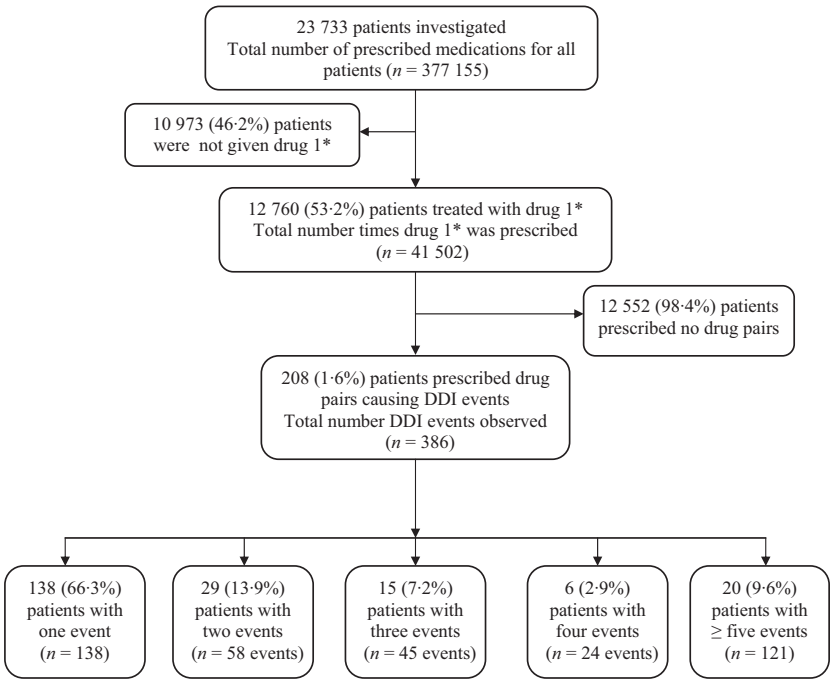

Fig. 1. Flow chart showing the identification of clinically important drug–drug interactions (DDIs). *Drug 1 from Appendix S1.

studies.[7, 18, 25, 26] Limiting the definition of drug interaction events to the co-prescription of interacting drug pairs might have been the main reason for this relatively low figure. An outpatient study in a university hospital in Thailand found that DDI events were higher across visits than those within the same visit.[9] Another outpatient study in the United States found that the DDI rate differed with different definitions of co-prescription time frames.[25] Another explanation for the low prevalence of DDIs in the current study might have been the over-representation of young healthy individuals. These individuals usually visited the clinics with a single acute illness. This was expected to result in prescribing fewer drugs and consequently a lower risk of DDI. Previous studies have found that patients on multiple medications are more susceptible to prescriptions with DDIs.[27, 28]

The most commonly identified interacting medication pairs were NSAIDs with thiazide diuretics (133 events, 34·5%), and statins with diltiazem (101 events, 26·2%) followed by theophylline with erythromycin (18 events, 4·7%); (see Appendix S2). More than 81% of the DDI events were attributed to NSAIDs (34·5%), statins (35·8%) and theophylline (10·9%). The high share of NSAIDs was attributed to its high prescribing frequency rather than to the high prevalence of DDI events. NSAIDs were prescribed 23 666 times, of which only 0·6% were associated with DDI events. Theophylline had a lower prescription volume (719 prescriptions) than the other two groups, but it was associated with a higher prevalence (5·8%) of DDI events, which increased its share of DDI events. The share of statins in DDI events was similar to that of NSAIDs, despite its low prescription volume. This was attributed to the high prevalence of DDI events associated with statins (3·2%). Warfarin and methotrexate had high prevalence, but their contribution to DDI events was negligible because of the small number of patients and small number of prescriptions. These small values might have been due to the presence of other sources of these medications, mainly the government general hospital. A study in the United States reported that visits with warfarin-involving drug interactions constituted 92% of all visits with drug interactions.[28]

The DDI events associated with NSAIDs were with thiazide diuretics; those associated with statins were mostly with diltiazem and, to a lesser extent, with macrolide antibiotics, whereas those associated with theophylline were mainly with macrolide antibiotics. NSAIDs can decrease the diuretic effect of thiazides dramatically. Macrolides have the potential to inhibit the metabolism of theophylline even if co-administered for a few days. This effect can increase the blood level of theophylline, leading to adverse drug events such as arrhythmia and seizure. It would have been safer to prescribe frusemide instead of the thiazide diuretic and to replace the macrolide antibiotic with a suitable β-lactam antibiotic or a tetracycline, depending on the infection being targeted and the susceptibility of the most likely infecting micro-organism.

The prevalence of exposure to DDIs was 7% at the primary care level of a managed care organization in the United States.[18] Limiting interactions to severe/moderate drug interactions resulted in a prevalence of exposed patients of 3·5% in that study. The prevalence of exposed patients in our study was 1%, which is not different from 3·5% as reported in Solberg's study,[18] despite the differences between the two studies. First, 69% of patients in that study were 40 years of age or older, with 7·3 drugs per patient per year on average. The likelihood of prescriptions with DDIs increases in older patients and in patients on multiple drugs. Second, that study included interactions in which adverse outcomes could be avoided by scheduling the administration time of the two drugs (like lipid sequesterant interactions with warfarin and digoxin), whereas the current study did not consider such interactions because such scheduling could omit the potential adverse outcomes of the interaction. Additionally, that study included interactions with monitoring recommendations, whereas the current study did not include such interactions. Third, Solberg's study[18] considered overlapping of the supply days of the interacting drug pairs, whereas the current study considered only co-prescribing the interacting drug pair in the same visit. Fourth, the number of patients on drugs like phenytoin, carbamazepine, valproic acid, warfarin and rifampicin was negligible in the current study. For example, 0·4% of patients were on anti-epileptics in the current study, while the corresponding figure in the Solberg study was 3%. These drugs are well known for having interactions with many other drugs. Fifth, the US study[18] used different information sources to construct the interacting drug pairs. The sources used were Hansten and Horn's Drug Interactions: Analysis and Management, the DRUGREAX System of MICROMEDEX (Thompson, Greenwood Village, CO, USA) and Evaluations of Drug Interactions™ (EDI). The first reference is a textbook, whereas the second and the third references are drug information software programs. Research has shown that standard drug interaction references and software programs are suboptimal in judging the clinical relevance and the importance of drug interactions.[29, 30]

On the other hand, one study in an ambulatory care setting in the United States has reported that the rate of clinically significant DDIs detected by software programs was reduced by 81% after review of the clinical cases by clinical pharmacists.[7] Conversely, agreement between a computer program and a clinical pharmacologist was high in a DDI study in a Geneva hospital outpatient clinic.[26] However, the clinical pharmacologist who reviewed the computer decisions used the DDI compendia criticized above for being suboptimal in terms of judging the clinical relevance and importance of DDIs.

Overall, we noted an increasing mean number of DDI episodes among exposed patients within the age category ≥70 years ($P = 0{\cdot}01$), an increasing trend in the number of medications prescribed ($P < 0{\cdot}001$) and an increasing trend in the number of LTTGs ($P < 0{\cdot}001$). Other factors such as gender, ethnicity, marital status and beneficiary type did not have a statistically significant influence on the mean number of DDI episodes (Table S3). A previous study from Brazil reported that the odds of exposure to DDIs were higher in older patients and in those administered more drugs.[31] Other studies have reported increasing patient age as an important risk factor for DDIs.[9, 27, 28] It was observed in our study that the use of multiple medications is significantly associated with increasing episodes of clinically important DDIs, which is consistent with previous research.[27, 28, 32] Another previous study from Mexico reported that the factors significantly associated with having one or more DDIs included taking five or more medications, patient age 60 years or older and suffering from cardiovascular diseases.[33]

WHAT IS NEW AND CONCLUSION

We describe the prevalence of clinically important DDIs in an emerging economy setting and identify the more common potentially serious DDIs. In line with the observations in developed economies, a higher number of episodes of DDIs were seen in patients aged ≥70 years and with more medications

prescribed. The easiest method to reduce the frequency of DDIs is to reduce the number of medications prescribed. Therapeutic alternatives should be selected cautiously.

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CONFLICT OF INTERESTS

We would like to declare that there were no conflicts of interest in conducting this research.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Appendix S1 List of the proposed clinically important pairs of interacting drugs.

Appendix S2 Prevalence of drug pairs causing drug-drug interactions events (number of exposed patients = 208).

Table S1 The demographic data and characteristics related to the exposed patients according to the number of episodes of drug–drug interactions.

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