Availability And Characteristics Of Information On Drug-Durg Interactions In The Drug Package Inserts: An Experience From Bangladesh

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Abstract

Package insert is an essential part of the drug packaging that contains important safety information including drug-drug interactions (DDIs) of a particular drug. This exploratory study was conducted to determine the extent and nature of information on DDIs presented in the drug package inserts in Bangladesh. The study found that more than half (56%) of the package inserts did not include any information on DDIs. Package inserts of many common drugs had no information on DDIs. None of the selected inserts mentioned any rate of occurrence or morbidity of DDIs. None of the package inserts specified any DDI as clinically significant. In most of the cases, no mechanisms were stated to avoid or to reduce the incidences of common DDIs. Many of the potential drug-drug interactions were found to be omitted in those package inserts.

INTRODUCTION

Package insert is an essential feature of drug packaging present in most of the medicinal and pharmaceutical products as a piece of paper with information pertaining to that particular product [1]. It is considered as the primary source of information for health care providers about drugs [2]. In practice, package insert is a legally required document intended to inform the user of the approved and off label uses of the drug, its dose and any contraindications or adverse effects [1]. Mostly, it is an effective mean to communicate about the risks of drugs [3], and it has an important impact on patients compliance and thus on the ultimate effectiveness of drug use [4]. To achieve its goals, the drug insert must clear and comprehensible to convey the intended use of the product, provide adequate directions for its use, warn against potential harmful effects and provide instructions for appropriate length of treatment and when to seek medical advice [5].

On the other hand, drug interactions present a growing concern in the health care settings all over the world. Drug-drug interactions (DDIs), one of the most common forms of adverse drug related events but widely under-recognized source of medical errors [6,7,8,9]. Although, some drug interactions can also be beneficial, they can be harmful either by increasing the toxicity of a drug or by reducing its efficacy [9,10]. Thus, the consequences of being exposed to an interaction are not trivial. Rather it has enormous impact on total patient care including the risk of increased hospitalization [11,12]. Preventable drug interactions account for about one third of adverse drug effects but incur about one half of the total adverse effect costs [6,9].

The exact prevalence of drug interactions are not yet known. Several studies found between 2.2% and 70.3% patients may be affected by potential drug interactions [10]. Other studies have reported that the incidence of drug interactions ranges from 3% to 30% [6]. Again, a number of studies have also estimated the incidence of potential drug-drug interactions in 20-30% of patients with clinically relevant interactions at 4-10% [7,13,14]. Although, not all drug interactions are clinically significant, it is important to be alert for those that are. But, it is impossible to remember all the known important drug interactions; however, knowledge of the main types of drug interactions will act as a useful alert when prescribing [10]. To treat patients in a competent and safe manner, some awareness of the DDI issue and some means of detecting DDIs are essential [12].

No information on drug interactions is available as no such studies have been conducted in Bangladesh till date. Apparently, drug package inserts are likely to be of great importance in the developing countries like Bangladesh, where electronic drug alert systems, especially computer-

assisted detection of drug interactions are virtually absent. From healthcare professionals to the patients, drug inserts provide most of the information relating to adverse drug reactions, which can be lifesaving [15]. We conducted an analytical study to explore the extent and nature of information on DDIs presented in the drug package inserts of some highest selling drugs in Bangladesh. We particularly emphasized on 'drug-drug interactions' as they are the most common forms of drug interactions.

METHODS

SAMPLE SELECTION

Top ten highest selling drugs in Bangladesh were selected from IMS product index (Second Quarter 2006, Bangladesh Edition). Package inserts of the selected products were obtained from three locations (Dhaka, Kushtia and Chuadanga) of Bangladesh. Because of financial constraints and technical limitations, we could not perform randomization of samples. For this we gathered a small convenience sampling of 150 package inserts from different drug manufacturers during September 05 to October 06, 2006. Repeated inserts for the same drugs were excluded from the study.

DATA ANALYSIS

The collected package inserts of different brands were sorted out according to individual drug name. These are then analysed to obtain necessary information on DDIs by two graduate pharmacists. Drug inserts containing information on interactions were separated from those containing no information at all. The extracted DDIs information was enlisted in the pre-formulated table of a personal computer. The information was further cross-checked with the help of the available published and retrievable literatures to determine any substantial omission and consistency of information in the collected package inserts. Descriptive statistical analysis was performed using Microsoft® Excel 2002 version Windows XP Professional.

RESULTS

Of the total (n=150) package inserts, only 66 (44%) contained some information on DDIs while 84 (56%) did not include any. No information on DDIs was found in the package inserts of aluminum-magnesium containing antacids. Comparatively, higher number of package inserts of ranitidine, amoxicillin, paracetamol (acetaminophen) and omeprazole were found to carry no information on DDIs. Number of package inserts containing DDIs information was greater for calcium and ceftriaxone injection. A brief summary of drug-wise package inserts containing information on DDIs have been depicted in the table 1.

Figure 1

Table 1: Drug-wise number of package inserts with DDIs information

	With information	No information
Drugs	N (%)	N (%)
Ranitidine	9 (6.0)	12 (8.0)
Omeprazole	5 (3.3)	9 (6.0)
Ciprofloxacin	6 (4.0)	8 (5.3)
Cefradine	7 (4.7)	8 (5.3)
Amoxicillin	10 (6.7)	11 (7.3)
Calcium	9 (6.0)	7 (4.7)
Ceftriaxone inj.	5 (3.3)	1 (0.7)
Paracetamol	8 (5.3)	10 (6.7)
Aluminium-Magnesium Antacids	0 (0)	10 (6.7)
Diclofenac	7 (4.7)	8 (5.3)
TOTAL	66 (44.0)	84 (56.0)

Except the Aluminium-Magnesium antacid, drug inserts from all other products provided a number of events of DDIs. But none mentioned any rate of occurrence or morbidity of these incidences. Also, there were no statements specifying the DDIs as dangerous or potential or clinically significant in those package inserts. In most of the cases, no mechanisms were stated to avoid or to reduce the incidences of common DDIs. A short description of the information on DDIs extracted from the drug package inserts have been provided in the table 2.

Figure 2

Table 2: Types of drug interactions presented in the package inserts

Drugs	Characteristics of DDIs in the package inserts
Ranitidine	Can delay the elimination of diazepam, phenytoin and warfarin. No interaction with theophylline, propanolol or antacids.
Omeprazole	Absorption of ketoconazole is reduced. Omeprazole can delay the elimination of diazepam, phenytoin and warfarin. Monitoring of patients receiving warfarin or phenytoin is recommended and a reduction of warfarin or phenytoin dose may be necessary.
Ciprofloxacin	Interacts with theophylline and caffeine. Enhances effect of warfarin. Elevates serum creatinine in patients receiving cyclosporine concomitantly.
Cefradine	Enhances nephrotoxicity with aminoglycosides, furosemide and ethacrynic acid.
Amoxicillin	Probenecid may delay the excretion of amoxicillin.
Calcium	Reduces the absorption of tetracycline and fluoride preparations. Vitamin D increases absorption of calcium. Increases activity of digoxin. Hypercalcemia may result with thiazide diuretics.
Ceftriaxone	No significant drug-drug interactions have been observed.
Paracetamol	Interacts with alcohol, phenobarbital, phenytoin, anticoagulants and carbamazepine. Normal doses in such interactions may cause liver damage. Slows down excretion of chloramphenicol thus increases risk of toxicity. With zidovudine increases chance of neutropenia.
Diclofenac	Use with aspirin lowers the plasma concentration of each other. Increases the plasma concentrations of digoxin, methotrexate. Nephrotoxicity is caused with diuretics. Activity of sulfonylureas is increased.

DISCUSSION

Our study showed that more than half of the drug package inserts analysed did not include any information on DDIs. Most of the drugs having no information on DDIs came from drug classes including antiulcer, antibiotics and non-steroidal anti-inflammatory drugs (NSAIDs). Individually, large number of package inserts of ranitidine, omeprazole, amoxicillin, paracetamol and Aluminium-Magnesium containing antacids included no information on DDIs. Notably, more inserts of calcium supplements and ceftriaxone injection contained information on DDIs. But no detailed drug interactions were mentioned in all the inserts of ceftriaxone injection. Only the statement- “No significant drug-drug interactions have been observed” was reported.

Ethically and legally speaking drug package inserts should provide all the necessary information in correct and easily understandable form for safe and effective use. The information should be unbiased, should not hide anything [1]. Unfortunately, evidence from underdeveloped countries shows that package inserts often contains minimised adverse drug reactions [16]. This fact was reflected in the present study. Drug package inserts in Bangladesh also contained either curtailed or no information on important drug-drug interactions.

No doubt that the potential for drug-drug interactions is an important aspect of overall drug safety [17]. The present study found incomprehensive records of potential DDIs in the inserts of the most common drugs in Bangladesh. It is evident that drugs consisting of divalent or trivalent (such as Aluminium-Magnesium antacids) can reduce the absorption of ciprofloxacin by 60%-75% when administered concomitantly and thus increase the possibility of therapeutic failures [17,18]. But this important information was not found in the package inserts of either ciprofloxacin or antacid available in Bangladesh.

Interactions between warfarin and acetaminophen may be clinically significant even at lower dosages [19,20]. Similarly, concomitant use of diclofenac and warfarin should be avoided as this combination increases the risk of bleeding [21]. These important facts were also not found in the package inserts of either paracetamol or diclofenac during the study. Studies reported that omeprazole is a potential inhibitor of CYP3A4, which can cause fatal torsades de pointes and QT-interval prolongation when used with some non-sedating antihistamines [9]. Though omeprazole was one of the most selling products in Bangladesh, this vital information was not found in the package inserts of omeprazole brands.

Quite a large number of inserts of ranitidine included no information on any DDIs as it is often considered as devoid of any potential drug interactions. But the possibility of potential DDIs of ranitidine cannot be ruled out completely [22]. Almost all antibiotics can potentiate the effects of warfarin by inhibiting intestinal flora that produce vitamin K. Simultaneous use of oral contraceptive pills and antibiotics produces potential interactions thereby decreasing effectiveness of oral contraception [21]. Except for ciprofloxacin, no package inserts of other antibiotics mentioned any possible interactions with warfarin. It was also reported that none of the antibiotic package inserts provided any information on possible interactions with contraceptive pills.

In Bangladesh, sources of drug information quite limited and drug companies are the vital sources of information here [23]. As with other countries in the world, drug package insert is also a legal document, which is mandatory to registration of any drug in Bangladesh. However, important drug safety information is not available in most of the package inserts. Package inserts in Bangladesh are mostly physician-oriented yet they may be the primary source of basic information particularly dosage schedules and safety matters for the patients as well. For this, drug inserts should be clear and comprehensible with adequate directions of drug uses and

warnings of potential and preventable harmful drug effects. In addition, regular upgrading by the drug manufacturers and initiating awareness programs for both patients and healthcare professionals to comply with the information provided definitely will help to attain the eventual objectives of drug package inserts. The drug regulatory authorities should monitor more carefully to ensure important drug adverse events in the package inserts of Bangladesh.

LIMITATIONS

The present study is associated with certain methodological limitations. Being cross-sectional in nature, the study design fails to measure any concrete outcomes or any cause and effect. The study samples do not represent the entire population because of non-random sample selection method used. There is a potential for selection bias in the samples due to non-probabilistic sample selection process.

CONCLUSION

Our study showed a large number of drug package inserts in Bangladesh did not contain any information on drug-drug interactions. Many of the potential drug interactions were found omitted in the package inserts. Comprehensive studies are required to determine the actual characteristics and prevalence of DDIs information in the package inserts. Further studies are also needed to find out the usefulness and awareness of drug inserts among the potential clients in Bangladesh.

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