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Evaluation of community pharmacists' knowledge about drug–drug interaction in Central Saudi Arabia

Ziyad Alrabiah *, Abdulaziz Alhossan, Sultan M. Alghadeer, Syed Wajid, Salmeen D. Babelghaith, Mohamed N. Al-Arifi

Department of Clinical Pharmacy, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia

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ABSTRACT

Introduction: Although all implemented and ongoing initiatives, drug-drug interactions (DDIs) are still a global problem. Most published studies about DDIs in Saudi Arabia are carried out in hospital settings. In addition, assessing the knowledge of drug interactions in Saudi Arabia is limited. The aim of our study is to evaluate the knowledge of potential common drug-drug interactions among community pharmacists particularly in Saudi Arabia.

Methodology: A crosses-sectional study utilizing a self- administered questionnaire was conducted among community pharmacy in Riyadh city Saudi Arabia. DDIs' knowledge was assessed by 26 drug pairs. Community pharmacists were asked to select the DDIs as "contraindication", "may be used together with monitoring", "no interaction" and "not sure".

Results: A total of 283 of community pharmacists completed the survey with response rate of 80.9%. Among the 26 drug pairs only 5 of them were identified correctly by most of the participants. To add more 3 out of the 5 pairs had a cutoff of less than 10% between the correct and wrong answer, meaning there still a majority that couldn't identify the correct answer. All the 26 pairs had a statistically significant difference between the correct and incorrect answer.

Conclusion: The results of this study showed that knowledge of community pharmacists about DDIs was inadequate. Community pharmacist should have specific courses in drug interactions to cover the most possible interactions that can be seen in this setting.

1. Introduction

Although of the tremendous advance in technology and health sciences, drug interaction is still vexatious for the national health system, and it may lead to deleterious sequelae (Wong et al., 2010). It's estimated that approximately 5% of the adverse effects in hospitals, and around 11% of the prescribed medications in the out-patient settings are attributed to potential drug interactions (Classen et al., 1997; Toivo et al., 2016). Nationally, about 0.6% of all hospital admissions were accounted for drug-drug interactions (DDIs) while in Saudi Arabia almost 7% of all hospital admissions due to drug-related problems were attributed to DDIs, most of these interactions happened among elderly population (Al-Arifi et al., 2014; Becker et al., 2007). The physiological changes that affect pharmacokinetics and pharmacodynamics, and the high incidence of polypharmacy make elderly population vulnerable subjects for potential impact of drug interactions (Hohl et al., 2001).

Beside the DDIs, drug interactions can manifest as drug-disease, or drug-dietary/herbal supplement interactions (Food and Administration, 2011). St. John's wort, a widely used herbal supplement as an antidepressant, is associated with numerous drug interactions (Zhou and Lai, 2008). Also, drug interactions can be dose or time dependent interactions (Cohen et al., 2008; Schachter, 2005). For example, it's highly recommended to limit the dose of simvastatin to 20 mg per day when co-administered with amlodipine or diltiazem to halt the incidence of myopathy (Schachter, 2005). It's also recommended to separate the administration time of oral fluoroquinolones and oral divalent or trivalent cation-containing compounds to prevent the antibiotic failure (Cohen et al., 2008).

* Corresponding author.
E-mail address: zalrabiah@ksu.edu.sa (Z. Alrabiah).

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Many national clinical practical guidelines such as Centers for Disease Control and Prevention, American Headache Society, American Heart Association, American College of Cardiology, American College of Gastroenterology and others provide recommendations regarding some of common drug interactions (Becker et al., 2007; Bhatt et al., 2008; Evans et al., 2010). In addition, several epidemiologic studies have shown the risk of harm with specific drug interactions and discussed the intensity of those kinds of interactions (Antoniou et al., 2010,2011a,2011b; Delaney et al., 2007; Fischer et al., 2010; Fralick et al., 2014; Juurlink et al., 2003). However, the knowledge and attitude towards drug interactions don't appear to be studied sufficiently. The published studies were either evaluated the knowledge among only prescribers or interns (Hincapie et al., 2012; Ko et al., 2008). Pharmacists, especially in the community settings, are in the front lines to detect DDIs, but unfortunately, they were not the main target in these published studies. In addition, assessing the knowledge of drug interactions in Saudi Arabia seems missing. Evaluating and then improving the knowledge of potential common DDIs among community pharmacists (CPs) by implementing useful programs will limit the incidence of deleterious adverse effects, emergency visits, hospital admissions, and certainly health cost. The aim of our study was to evaluate the knowledge of potential common DDIs among community pharmacists particularly in Saudi Arabia.

2. Methods

2.1. Design

A cross-sectional study was conducted using a self-administered questionnaire. The questionnaire was carried over a period of 6 months from November 2014 to May 2015. This study involved all community pharmacy outlets (including chain and independent pharmacies) in Riyadh city, Saudi Arabia.

2.2. Sample selection

The online calculator (Raosoft Inc) was used to estimate the study sample size. According to a previous study, number of community pharmacies in Riyadh city in August 2013 reached 1700 pharmacies (Al-Arifi, 2013). This study used the rate tolerates of 5%, and 95% confidence levels to give 314 pharmacies. This study involved 350 community pharmacies by a stratified random sampling.

2.3. Survey questionnaire

The questionnaire used was consisted of two sections; the first section was related to demographic data and included age, length of experience and country of graduation. The second section was about assessing the knowledge of CPs about DDIs. The DDIs questionnaire was designed and developed from previous studies that assessed the knowledge of health care professionals about DDIs (Gilligan et al., 2011; Ko et al., 2008; Momo et al., 2006). The questionnaire consisted of 26 drug pairs, those pairs were the most common DDIs found in published literature (Gilligan et al., 2011; Ko et al., 2008; Momo et al., 2006). CPs were asked to classify the DDIs as "contraindication", "may be used together with monitoring", "no interaction" and "not sure". Among the 26 drug pairs, nine were contraindicated (warfarin with cimetidine, sildenafil with isosorbide mononitrate, pimozide with ketoconazole, itraconazole with quinidine, methotrexate with probenecid, amiodarone with fluconazole, meperidine with phenelzine, alprazolam with itraconazole, and cprofloxacin with tizanidine). It also contained eleven drug pairs that can be used with monitoring and six drug pairs that had no known interactions. Any correct answer for the DDIs questions was given 1 point. Then scores were calculated by counting all the corrected answers with the maximum score of 26.

2.4. Ethical approval

The ethical approval was optioned from The King Saud University's institutional review broad.

2.5. Data analysis

The data were entered into SPSS software version 24 for analysis. Both descriptive and analytic statistics were applied. For descriptive analysis, results were presented as numbers, percentages, and mean (±SD). The Kruskal-Wallis test was used to determine differences between CPs demographic data in knowledge scores at a significance level of 0.05.

3. Results

A total of 283 CPs returned the survey with response rate of 80.9%. About two-third of the participants were between 25 and 35 years old. About half of respondents have an experience in the field of pharmacy for less than 10 years. More than one-third of respondents have been graduated from schools of pharmacy in Egypt (Table1).

3.1. Knowledge of community pharmacist of DDIs

The responses of the 26 DDIs knowledge questions are summarized in Table 2. The study found that the lowest correct response of DDIs was between amiodarone and fluconazole (16.3%) and the highest was between sildenafil and isosorbide mononitrate (74.6%). In most of incorrect responses "may be used together with monitoring" were chose more by 8 times followed by "shouldn't be used together" by 6 times.

Unfortunately, among the 26 drug pairs, only five of them were identified correctly by most of the participants. To add more 3 out of the 5 pairs had a cutoff of less than 10% between the correct and wrong answer, meaning there still a majority that couldn't identify the correct answer. All the 26 pairs had a statistically significant difference between the correct and incorrect answer (Table 3).

There were no significant differences were found between age groups, years of practice and country of graduation in knowledge score of DDIs ($p > 0.05$) as showed in Table 4.

Table 1
Demographic characteristics of the study participants (n = 283*).

Demographic data	Number of participants	Percentage (%)
Age		
25–35	182	64.3
36–45	80	28.3
46–55	12	4.2
Years of practice		
less than 10 years	142	51.8
11–20	120	43.8
21–30	9	3.3
31–40	3	1.1
Country of graduation		
Egypt	191	67.5
Sudan	7	2.5
Yemen	48	17
Saudi Arabia	11(3.9)	3.9
Others	8(2.8)	2.8

* Numbers and percentage don't add up to total (100%) due to missing data.

Table 2
Frequencies and percentages of respondents to potential DDIs*

Drug –drug combinations	Shouldn't be used together Contra indication) n(%)	May be used together with monitoring n(%)	No interactions n (%)	Not sure n (%)
Warfarin and cimetidine	**169 (59.7)**	81 (28.6)	21(7.4)	12(4.2)
Sildenafil and isosorbide mononitrate	**211(74.6)**	64(22.6)	6(2.1)	2(0.7)
Conjugated estrogens and raloxifen	66(23.3)	112(39.6)	**77(27.2)**	28(9.9)
Fexofenadine HCL and metoprolol	38(13.4)	84(29.7)	**124(43.8)**	37(13.1)
Theophylline and ciprofloxacin	113(39.9)	**99(35)**	53(18.7)	18(6.4)
Pimozide and ketoconazole	**92(32.5)**	127(44.9)	21(7.4)	43(15.2)
Methyldopa and phenobarbital	127(44.9)	80(28.3)	**50(17.7)**	26(9.2)
Phenytoin and cimetidine	148(52.3)	**87(30.7)**	23(8.1)	25(8.8)
Itraconazole and quinidine	**107(37.8)**	105(37.)	28(9.9)	42(14.9)
Amiodarone and simvastatin	72(25.4)	**122(43.1)**	63(22.3)	26(9.2)
Methotrexate and probenecid	**60(21.2)**	120(42.4)	54(19.1)	47(16.7)
Diphenhydramine and warfarin	45(15.9)	122(43.1)	**87(30.7)**	29(10.2)
Raloxifene and alendronate	30(10.6)	120(42.4)	**91(32.2)**	39(13.8)
Warfarin and diflunisal	82(29.0)	**106(37.5)**	31(11.0)	64(22.6)
Amiodarone and fluconazole	**46(16.3)**	96(33.9)	74(26.1)	67(23.7)
Theophylline and omeprazole	64(22.6)	77(27.2)	**97(34.3)**	45(15.9)
Sulfinpyrazone and warfarin	110(38.9)	**89(31.4)**	26(9.2)	58(20.5)
Meperidine and phenelzine	**125(44.2)**	54(19.1)	39(13.8)	65(23.0)
Fluconazole and phenytoin	109(38.5)	**107(37.8)**	44(15.5)	23(8.1)
Warfarin and nortriptyline	74(26.1)	**146(51.6)**	32(11.3)	31(11)
Amoxicillin and acetaminophen with codeine	18(6.4)	52(18.4)	**197(69.6)**	16(5.7)
Digoxin and clarithromycin	94(33.2)	**113(39.9)**	54(19.1)	22(7.8)
Alprazolam and itraconazole	**72(25.4)**	107(37.8)	60(21.2)	44(15.5)
Dopamine and phenytoin	76(26.9)	**114(40.3)**	36(12.7)	57(20.1)
Ciprofloxacin and tizanidine	**70(24.7)**	91(32.2)	57(20.1)	65(23.0)
Cyclosporine and rifampicin	102(36.0)	**88(31.1)**	39(13.8)	54(19.1)

* Bold numbers are the corrected answers.

Table 3
Comparison of correct rate in DDIs knowledge.

Drug – drug combinations	Correct answer (%)	Incorrect answer (%)	P value
Warfarin and cimetidine	59.7	40 0.3	<0.0001
Sildenafil and isosorbide mononitrate	74.6	25.4	<0.0001
Conjugated estrogens and raloxifen	27.2	72.8	<0.0001
Fexofenadine HCL and metoprolol	43.8	56.2	<0.0001
Theophylline and ciprofloxacin	35	65	<0.0001
Pimozide and ketoconazole	32.5	67.5	<0.0001
Methyldopa and phenobarbital	17.7	82.3	<0.0001
Phenytoin and cimetidine	30.7	69.3	<0.0001
Itraconazole and quinidine	37.8.	62.2	<0.0001
Amiodarone and simvastatin	43.1	56.9	<0.0001
Methotrexate and probenecid	21.2	78.8	<0.0001
Diphenhydramine and warfarin	30.7	69.3	<0.0001
Raloxifene and alendronate	32.3	67.8	<0.0001
Warfarin and diflunisal	37.5	62.5	<0.0001
Amiodarone and fluconazole	16.3	83.7	0.0004
Theophylline and omeprazole	34.3	65.7	<0.0001
Sulfinpyrazone and warfarin	31.4	68.6	<0.0001
Meperidine and phenelzine	44.2	55.8	<0.0001
Fluconazole and phenytoin	37.8	62.2	<0.0001
Warfarin and nortriptyline	51.6	48.4	<0.0001
Amoxicillin and acetaminophen with codeine	69.6	30.4	<0.0001
Digoxin and clarithromycin	39.9	60.1	<0.0001
Alprazolam and itraconazole	25.4	74.6	<0.0001
Dopamine and phenytoin	40.3	59.7	<0.0001
Ciprofloxacin and tizanidine	24.7	75.3	<0.0001
Cyclosporine and rifampicin	31.1	68.9	<0.0001

Table 4
differences between knowledge scores of CPs with their demographic characteristics.

Variables	Mean (median)	P value
Age		
25–35 years	8.12(7.5)	0.74
36–45 years	9.0(9.0)	
46–55 years	9.8(9.5)	
Practice		0.12
Less than 10 years	8.8(9)	
11–20	9(9.5)	
21–30	9.8(9)	
31–40	13.(11)	
Country graduation		0.874
Egypt	8.7(8)	
Sudan	9(9)	
Yemen	9.3(9)	
Saudi Arabia	9.1(10.5)	
Others	9.4(9)	

4. Discussion

Despite all implemented and ongoing initiatives, DDIs are still an international problem. Identifying any DDIs is varied based on the practice setting. In an inpatient setting for example, there are different tools that can help in identifying drug interactions and preventing their harm such as electronic systems and accessible scientific resources (Hazlet et al., 2001; Indermitte et al., 2007; Magnus et al., 2002). These tools are not available in most community pharmacies in Saudi Arabia. In addition, many medication safety standards are also not available in this setting yet in the country such as look-alike sound-alike and high alert medications list. The lack of electronic systems in community pharmacy setting has a serious impact on both medication and patient safety. Therefore, most of these medication safety standards are carried out by pharmacists' knowledge only.

Based on this study findings, there is a significant lack of information about the major DDIs and other minor interactions. Despite the fact that most of these included medications in this study are available in community pharmacies, most of participated pharmacists could not identify these interactions nor prevent their potential harmful risk. An intervention study was conducted in United

States among future health care professionals including pharmacists and medical students reported that they still did not identify potential DDIs after an educational session (Hincapie et al., 2012). Another cross-sectional study carried out in United States aimed to explore the impact of educational program on DDIs knowledge of health care professionals (medical students, pharmacy and nursing). It revealed that their knowledge scores before educational program were low where students did not classify all DDIs, but after intervention their knowledge scores significant improved (Harrington et al., 2011). Moreover, Yu et al. did survey in Singapore among prescribers to assess their knowledge about DDIs. The researchers concluded that prescribers did not identify potential DDIs. However, the lowest percentage was 18.2% for warfarin with cimetidine and the highest percentage of correct answer was 81.2% for paracetamol with amoxicillin (Ko et al., 2008). In addition, most of these medications can be dispense without a prescription, which diminishes the first safety line (the physician).

The need for an electronic system that can detect any DDIs or allergies is essential in the community pharmacy setting. By exploring the country's transformation plan, e-prescription system will be introduced soon and along with that community pharmacies should have electronic systems that can provide different safety tools (Indermitte et al., 2007; Patel et al.; Stock et al., 2008). In addition, community pharmacies should have specific courses in drug interactions to cover the most possible interactions that can be seen in this setting. Also, community pharmacists should complete specific number of continuous education hours in patient and medication safety in this setting annually. Furthermore, available and accessible scientific databases and resources should be available for all community pharmacists to check for interactions or any other safety or efficacy measurements. Further studies to investigate the impact of electronic systems and other safety requirements implementation in community pharmacies in Saudi Arabia are required to help improving patient and medication safety in this setting.

In conclusion, the results of this study showed that knowledge of community pharmacists about DDIs was inadequate. Further continues education and electronic systems can help CPs in detecting such interactions easily.

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