Latin American Journal of Pharmacy
(formerly *Acta Farmacéutica Bonaerense)*
Lat. Am. J. Pharm. **35** (5): 1051-5 (2016)

Short communication

Received: September 10, 2015
Accepted: January 5, 2016

Frequency and Levels of Potential Drug-Drug Interactions in Tuberculosis Patients of a Teaching Hospital in Pakistan

Fayyaz UDDIN [1], Nasar KHAN [2], Shamsul GHANI [3], & Saeed A. KHAN [4] *

[1] *Department of Pharmacy, University of Peshawar, Pakistan*
[2] *Department of Molecular Biology and Genetics, Izmir institute of Technology, Urla, Izmir 35000, Turkey*
[3] *Department of Bioinformatics and Biotechnology, International Islamic University, Islamabad, Pakistan*
[4] *Department of Pharmacy, Kohat University of Science and Technology, Kohat, Pakistan*

***SUMMARY*. Polypharmacy in tuberculosis is used to prevent occurrence of resistance to mycobacteria. However, drug-drug interaction is one of the undesirable consequences of polypharmacy, that may lead to ineffective medication or change in therapeutic response. The objective of the study was to identify prevalence, types and nature of potential drug-drug interactions in tuberculosis patients at Khyber Teaching Hospital, Peshawar Pakistan. Medical records of 409 randomly-selected patients were reviewed for pDDIs using Micromedex Database. Results show that total 304 interacting-combinations lead to 1437 potential drug-drug interactions. 87.5% of the these potential drug-drug interactions were of moderate and major severity (*i.e.,* 65.6% and 44.3% respectively). With regards to scientific-evidence, almost 50% of the potential drug-drug interactions were good documented while 34.7% had fair level of documentation. Furthermore, we have listed some of the interacting drug combinations, particularly most frequent major and moderate interactions, will help health care professionals to review their established therapeutic strategy for tuberculosis patients in their clinical settings.**

RESUMEN. La polifarmacia se utiliza en la tuberculosis para prevenir la aparición de resistencia a las micobacterias. Sin embargo, la interacción fármaco-fármaco es una de las consecuencias indeseables de la polifarmacia, que pueden conducir a medicamentos ineficaces o a cambios en la respuesta terapéutica. El objetivo del estudio fue identificar la prevalencia, tipos y naturaleza de las potenciales interacciones fármaco-fármaco en pacientes con tuberculosis en Khyber Teaching Hospital, Peshawar Pakistán. Los registros médicos de 409 pacientes seleccionados al azar fueron revisados para pDDIs utilizando la base de datos Micromedex. Los resultados muestran que el total de 304 que interactúan combinaciones conducen a 1437 potenciales interacciones farmacológicas. 87,5% de estas potenciales interacciones fármaco-fármaco eran de gravedad moderada y mayor (65,6% y 44,3% respectivamente). En cuanto a la evidencia científica, casi el 50% de las posibles interacciones entre fármacos fueron bien documentadas, mientras el 34,7% tenían buen nivel de documentación. Además, se ofrece una lista de algunas de las combinaciones de fármacos que interactúan, en particular las interacciones importantes y moderadas más frecuente, como ayuda a los profesionales de la salud para revisar la estrategia terapéutica establecida para pacientes con tuberculosis en sus entornos clínicos.

INTRODUCTION

Many drugs when co-administered may exhibit effects different from their individual pharmacological actions. The change in therapeutic response may be agonistic, antagonistic or synergistic in nature [1]. Drug-drug interactions are not always serious. In some patients severe reactions occur, while the other experience no effects [2]. Drug-drug interactions are more critical in case of drugs having severe toxicity and a low therapeutic index [3].

The first-line treatment of tuberculosis (TB) include rifampicin, isoniazid, ethambutol, pyrazinamide and streptomycin. Most of these agents are candidates of common drug interactions, *e.g.,* rifampicin is a potent liver enzyme inducer, hence increasing the metabolism and excretion of the drugs metabolized by microsomal enzymes [4,5]. Similarly, ethambutol and pyrazinamide can increase serum urate levels. Pyrazinamide inhibits the urate clearance, hence may interact with allopurinol and probenecid [6,7]. Likewise, streptomycin can be a potential risk of

KEY WORDS: drug-drug interaction, polypharmacy, tuberculosis.

* Author to whom correspondence should be addressed. *E-mail:* saeedkhan663@hotmail.com

ISSN 0326 2383 (printed ed.)
ISSN 2362-3853 (on line ed.)

oto- or nephrotoxicity in the presence of ototoxic or nephrotoxic drugs, and it can be a potential threat of fatal respiratory depression in the presence of anaesthetics and neuromuscular blocking drugs [8].

Polypharmacy is used in conditions where combination of many drugs are appropriate and useful, such as diabetes mellitus, Helicobacter pylori gastritis and tuberculosis, etc. In tuberculosis three or four different drugs are combined to prevent occurrence of resistance to mycobacteria [9]. However, drug-drug interaction is one of the undesirable consequences of polypharmacy. The competence of physician to prescribe suitable medicine in a safe manner is a critical factor in polypharmacy [10]. There have been serious concerns regarding prescription practices in Pakistani hospitals, and more specifically in public hospitals [11,12]. Many studies have highlighted the issue of potential drug-drug interactions in different hospitals in Pakistan [13-15]. For instance, in a cross-sectional study of 400 patients' from the internal medicine ward of two different tertiary hospitals was performed. The prevalence and nature of potential drug-drug interactions (pDDIs) showed that 63.6 % and 23% of the identified 675 pDDIs were of moderate and major severity [16].

Likewise, in tuberculosis, drug-drug interactions is more important because the conditions can be potentially fatal due to therapeutic failure [17]. This study deals with the prevalence of pDDIs in medication profiles of patients with Tuberculosis. In order to point out frequently occurring pDDIs of different levels such as contraindicated, major, moderate and minor severity.

MATERIAL AND METHODS

Settings, data collection and approval

This study was carried out in pulmonology and medical wards of a tertiary care hospital Khyber Teaching Hospital, Peshawar, Khyber Pakhtunkhwa, Pakistan, which is a 1200-bed teaching hospital. Khyber Teaching Hospital provides health care facilities and referral services to a population of about 350,000 inhabitants of Jamrud Road, Peshawar and adjacent areas of the city. A study was conducted which analyzed of 409 TB patients admitted during the month of January 2011 to January 2014 in medical wards and from January 2012 to December 2013 in pulmonology ward. Both genders (194 males and 215 females) were included in this study.

Permission was obtained from hospital authorities to use medical records of patient for collection of data, which included patient's age, gender, date of admission, date of discharge, diagnosis and detail of medication therapy provided in the hospital.

Screening of potential drug-drug interactions

Micromedex Database (Thomson Reuters Healthcare Inc., Greenwood Village, Colorado, United States) was used to analyze patients' medication profiles for pDDIs [18]. The software displays all drug-interactions present in the patient's profile. The identified pDDIs were categorized on the basis of their levels of severity, onset, and scientific evidence as per classification of Micromedex.

Severity

Contraindicated: the drug-combination is contraindicated for Co-administration. *Major:* there is high chances of death and supervision is required to prevent or minimize serious side effects. *Moderate:* this may cause worsen patient's condition and may require alteration of drugs. *Minor:* minor effects are produced that don't impair therapeutic outcome and there is no need of any major change in therapy

Documentation

Excellent: the interaction has been clearly demonstrated in well-controlled studies. *Good:* studies strongly suggest that the interaction exists except proof of well controlled studies. *Fair:* available evidences are poor, but the interaction is suspected on the basis of pharmacologic considerations; or, evidences are good for an interaction of pharmacologically similar drug. *Poor:* theoretically, the interaction may occur but reports are very limited, such as few case reports. *Unlikely:* data are very poor and lack a proper pharmacologic basis.

Data analysis

Prevalence of pDDIs, of any of the severity-levels (overall-prevalence), was identified. Likewise, number of patients exposed to different types of pDDIs such as contraindications, major, moderate and minor pDDIs were determined. All identified pDDIs were categorized on the basis of their levels of severity, onset and scientific evidence. SPSS for Windows version 22 (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

RESULTS AND DISCUSSION

In our study 409 tuberculosis patients (47.4% males and 52.% females, respectivley) were analyzed for the nature and prevalence of pDDIs (Table 1).

Unexpectedly, 74.1% (304 in number) of the drug combinations exhibited around 1437 drug-drug interaction. Among the identified pDDIs 65.6% were of moderate severity while those of major severity constituted 44.3% of the pDDIs. Moreover, 6.3% of the pDDIs were of contraindication nature (Table 2).

With regards to the documentation of pDDIs most of the pDDIs were good reported (*i.e.,* 49.4%) while documentation of fair and excellent nature was 34.7% and excellent 15.9%, respectively (Table 3).

This study shows that the prevalence of pDDIs in tuberculosis patients (*i.e.* 74.1%) is higher than that reported in other patients from different hospitals. For instance, 45% and 64.8% prevalence of pDDIs were observed in pulmonology and psychiatry ward of Khyber Teaching Hospital, Pakistan [13,14]. Moreover, a Brazilian teaching hospital showed prevalence of 52% [19]. Similarly, 28% prevalence was observed in Dutch University Hospital [20]. Nevertheless, most of the pDDIs reported in this paper are of moderate nature (*i.e.* 60.6%), while 26.9% are major pDDIs. These results are consistent with other studies performed on different type of patients and hospitals [13,19,20].

As for as the interacting drug combination are concerned, most of the major pDDIs are observed with Rifampin when co-administered with other drugs (Fig. 1). For instance, 8% and 9% of the major pDDIs were observed when Rifampin co-administred with Isoniazid and Pyrazinamide, respectively. Similarly, Dexamethasone-Rifampin combination were observed in around 4% of the intermediate pDDIs. The frequent interaction Rifampin with other drugs is quite well reported, which might be due to the effect of Rifampin on the clearance of many drugs [21] and liver enzyme inducing property of rifampicin. Hence, the metabolism of many drugs by the liver is increased, thereby decreasing their levels and reducing their effects.

Moreover, the contraindications which constituted 6.% of the total pDDIs happened to be primarily due to co-administration of drugs like Artemether with Rifampicin, Isoniazid and Pyrazinamide etc. Combining these medications may significantly reduce the blood levels of artemether and reduce its effectiveness in treating malaria. If doctor does prescribe these medications together, pharmacist need to adjust the dose using special tests to safely administer both medications.

Characteristic		**Number, n (%)**
Gender	Female	215 (52.6)
	Male	194 (47.4)
Age (years)	≤ 20	48 (11.7)
	21 - 39	96 (23.5)
	40 - 59	121 (29.6)
	60 - 70	101 (24.7)
	≥ 70	43 (10.5)
Hospital stay (days)	≤ 3	100 (24.5)
	4 - 6	166 (40.6)
	≥ 7	143 (35.0)
Prescribed medications per patient	≤ 4	78 (19.1)
	5 - 8	229 (56.1)
	> 9	102 (25.0)

Table 1. General Characteristics of samples (TB patients).

Type of prevalence		**Frequency (%)**
Overall		304 (74.1)
Severity-wise prevalence	Contraindicated	26 (6.3)
	Major	181 (44.3)
	Moderate	268 (65.6)
	Minor	83 (20.3)
Number of pDDIs per patient	1 - 2	117 (28.6)
	3 - 5	94 (23.03)
	≥ 6	93 (22.7)

Table 2. Prevalence of the potential drug-drug interactions (pDDIs).

		Frequency (%)
Severity	Contraindicated	38 (2.6)
	Major	387 (26.9)
	Moderate	871 (60.6)
	Minor	141 (9.8)
Documentation	Excellent	228 (15.9)
	Fair	499 (34.7)
	Good	710 (49.4)

Table 3. Distribution of pDDIs with respect to severity and documentation.

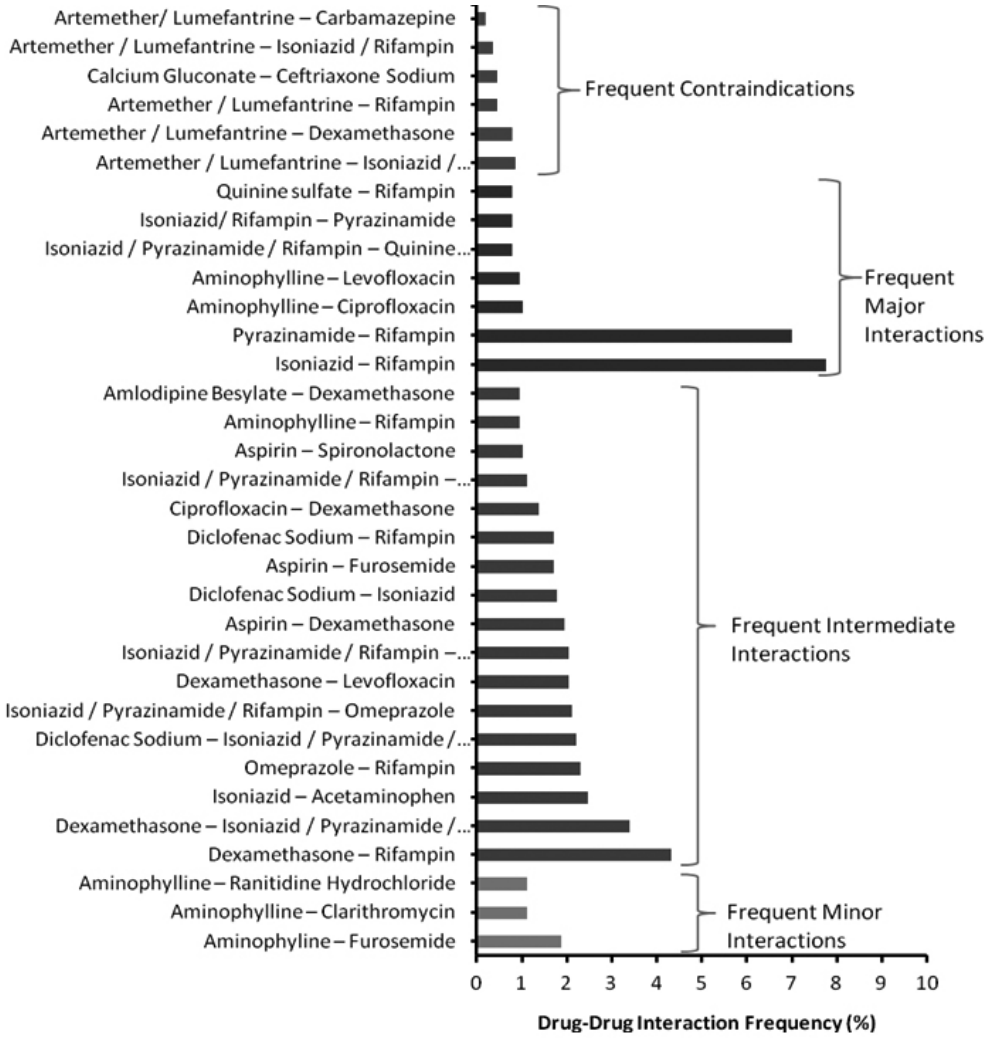

Figure 1. Diagrammatic Representation of Common interacting drug-combinations.

Limitations of the study

This study only presents potential drug-drug interactions observed in a tertiary care hospital of Khyber Pakhtunkhwa province of Pakistan. Therefore, it cannot be generalized to other hospitals. However, similar pattern of pDDIs is expected in other hospitals in Pakistan. Nevertheless, a thorough work needs to be done to ascertain the actual clinical consequences of these interactions.

CONCLUSIONS

We have recorded a high prevalence of pDDIs in tuberculosis patients. Most of the interactions were of moderate severity, however, major pDDIs were also recorded in substantial number. The list of most frequently identified major or moderate pDDIs will be helpful in screening medication therapies for pDDIs. Strict patient monitoring is recommended to manage and prevent therapeutic flaws, and in turn avoid negative clinical consequences of these interactions in the tuberculosis therapeutic strategy.

Acknowledgment. The authors are thankful to the technical staff of the Department of Pharmacy University of Peshawar and Khyber Teching Hospital, for their technical support.

REFERENCES

1. Baxter, K. & C.L. Preston (2010) *Stockley's drug interactions,* Pharmaceutical Press, London.
2. Ansari, J. (2010) *J. Young Pharm*. **2**: 326-31.
3. Ayub, M.N., D. da Silva, J.K. Martinbiancho& T.S. Dal-Pizzol (2010) *Lat. Am. J. Pharm*. **29**: 688-93.

4. Venkatesan, K. (1992) *Clin. Pharmacokin.* **22**: 47-65.
5. Shah, S.N., M. Ilyas, S. Azhar & G. Murtaza (2013) *Lat. Am. J. Pharm.* **32**: 191-6.
6. Pan, X., L. Wang, D. Gründemann & D.H. Sweet (2013) *Antimicrob. Agents Chemother.* **57**: 5053-9.
7. Peloduin, C.A. (2008) *Clinical pharmacology of the antituberculosis drugs,* in *Clinical Tuberculosis* 4th Ed. (P.D.O. Davies, P.F. Barnes & S.B. Gordon, eds.) Hodder Arnold, pp. 205-24.
8. Pittinger, C. & J. Long (1959) *AMA Arch. Surg.* **79**: 207-12.
9. Kothari, N. & B. Ganguly (2014) *J. Clin. Diagn. Res.* **8**: HC01.
10. Sinclair, L.I., S.J. Davies, G. Parton & J.P. Potokar (2010) *Int. J. Psychiatr. Clin. Pract.* **14**: 212-9.
11. Hafeez, A., A. G.Kiani, S. ud Din & W. Muhammad (2004) *J. Pak. Med. Assoc.* **54**: 187-91.
12. Najmi, M.H., R.A. Hafiz, I. Khan & F.R.Y. Fazli (1998) *J. Pak. Med. Assoc.* **48**: 73-6.
13. Ismail, M., Z. Iqbal, M.B. Khattak, A. Javaid & T.M. Khan (2011) *Afr. J. Pharm. Pharmacol.* **5**: 1303-9.
14. Ismail, M., Z. Iqbal, M.B. Khattak, A. Javaid, M.I. Khan, T.M. Khan, *et al.* (2012) *Trop. J. Pharm. Res.* **11**: 289-96.
15. Ismail, M., Z. Iqbal, M.B. Khattak, A. Javaid, M.I. Khan & T.M. Khan (2012) *Healthmed* **6**: 1618-24.
16. Ismail, M., Z. Iqbal, M.B Khattak, M.I. Khan, H. Arsalan, A. Javaid, *et al.* (2013) *Int. J. Clin. Pharm.* **35**: 455-62.
17. Yew, W. (2002) *Drug Safety* **25**: 111-3.
18. Micromedex Solutions. Available at <http://www.micromedexsolutions.com/home/dispatch> (Accessed on 12 May 2014).
19. Cruciol-Souza, J.M. & J.C. Thomson (2006) *Clinics* **61**: 515-20.
20. Zwart-van Rijkom, J.E., E.V. Uijtendaal, M.J. ten Berg, W.W, van Solinge & A.C.G. Egbertsmation (2009) *Br. J.Clin. Pharmacol.* **68**: 187-93.
21. Wanwimolruk, S., W. Kang, P.F. Coville, S. Viriyayudhakorn & S. Thitiarchakul (1995) *Br. J. Clin. Pharmacol.* **40**: 87-91.