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Evaluation of potential drug-drug interactions in hospitalized patients at a tertiary care hospital: A pilot study

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Abstract

Drug-drug interactions (DDIs) are termed as alteration of drug response with concurrent use of another drug. DDIs which are responsible from 20-30% of all adverse drug reactions lead to preventable morbidity and mortality, prolonged hospital stay and higher financial burden. The aim of this retrospective study was evaluation of prevalence and severity of potential DDIs in inpatient settings. We conducted this study between February-April 2019 in inpatient services of Farabi Hospital of Karadeniz Technical University. Data which consist of patient demographic features and drugs used by patients were obtained from patient files and case sheets. In this study, 25 patients (68% female; 32% male) were included; the mean age of the subjects was 63.32 ± 15.72 years. The drugs were analyzed for the potential DDIs using Lexi-Interact™ Online which is available on the www.uptodate.com. According to our results the prevalence of potential DDIs which involve alimentary tract and metabolism drugs (n=69, 27.4%) followed by cardiovascular system drugs (n =43; 17.06 %) were common among the drugs. The average number of drugs received in the units were similar. The total number of pDDIs determined as 204, and the mean number of pDDIs per patient was 8.16±6.4 in the units. It is identified that among the total drug interactions 76.5% in the risk category C (monitor therapy), 15.2% in the risk category B (no action needed), and 4.4% in the risk category D (consider therapy modification). The highest total number of pDDIs were identified in the patients of chest diseases unit. Furosemide (n=24, 11.8%) followed by salbutamol (n=21, 10.3%) and the furosemide-budesonide (n=5, 2.5%) combination were the most prevalent drugs which involved in pDDIs. These results indicate the importance of critical evaluation of the patient's medication order in the hospital and the urgency of developing strategies to improve drug safety.

Keywords: Adverse drug reaction, drug interaction, inpatient

Introduction

Drug-drug interactions (DDIs) are termed as the altered response of one drug by a concurrent use of another drug. DDIs present growing concern in polypharmacotherapy since it has been associated with adverse drug reactions (ADR) and decreased efficacy of drugs leading to prolonged hospital stay, morbidity, mortality and higher healthcare costs [1-3]. Therefore, identification of potential DDIs (pDDIs) will help to prevent ADRs, improve quality and effectiveness of medical care while increasing the clinical knowledge and awareness on this issue. The incidence of DDIs can vary widely among reports- estimates range from 3 to 30%- due to study design, patient characteristics and the DDI screening tool [4]. It is common that patients in an inpatient unit receive a number of medications and they are more susceptible to pDDIs. However, reports on DDIs mostly involve outpatient settings and only limited number of studies evaluate the hospitalized patients. The aim of this pilot study was to identify pDDIs in medications of hospitalized patients and analyse its severity and prevalence in a teaching hospital in our region.

Materials and Methods

Study design and settings

This retrospective descriptive study was conducted for 3 months (February-April 2019) in the inpatient services of cardiology, endocrinology, general surgery, infectious diseases, and chest diseases units of Farabi Hospital of Karadeniz Technical University, Trabzon. Access to patient files for the study was approved by an internal committee of the institution. Patients' demographic and medical data were collected from patient files and case sheets.

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Drugs were classified according to the Anatomical Therapeutic Chemical Classification (ATC Code) as recommended by World Health Organization (WHO) [5].

Identification and analysis of pDDIs

The drugs were analyzed for the pDDIs using Lexi-Interact™ Online, an online software available on the website www.uptodate.com [URL-1]. The pDDIs were categorized as A-No known interaction, B-No action needed, C-Monitor therapy, D-Consider therapy modification, or X-Avoid combination according to the software. The progression from A to X is accompanied by increased urgency in the action to be taken. In general, A and B are of academic, but not of clinical concern whereas C, D, or X always require attention. The relationship among the number of drugs, the age of the patients and the number of pDDIs were also evaluated [URL-1].

Statistical analysis

All data were recorded in Microsoft Excel v.2010 spread sheet® and analyzed using GraphPad Prism 5.0 (GraphPad Software, Inc., San Diego, CA). Data were presented as mean/median ± standart deviation (SD) or percentage of cases. The Spearman correlation coefficient was used to determine the relationship between two variables. $p<0.05$ was considered significant.

Results

A total of 25 cases (n=5/unit) were included in the study. Of the cases investigated, mean age was 63.32±15.72 years, and the number of male vs female patients was 8 to 17 (32 % and 68%, respectively). Total number of drugs (n=252) for the female patients was 179 (71.0%), and for the male patients was 73 (29.0%). Alimentary tract and metabolism drugs (n=69, 27.4%) were the most prevalent group (n = 43; 17.1%), followed by cardiovascular system drugs (Table 1).

Table 1. The frequencies and ATC 1st level classification of drugs used by patients

Anatomical group	Frequency n (%)
A:Alimentary tract and metabolism	69 (27.4)
C: Cardiovascular system	43 (17.2)
R: Respiratory system	32 (12.7)
B: Blood and blood forming organs	30 (11.9)
N: Nervous system	27 (10.7)
J: Antiinfectives for systemic use	20 (7.9)
H:Systemic hormonal preparations, excl. sex hormones and insulins	14 (5.6)
D: Dermatologicals	9 (3.6)
G: Genito urinary system and sex hormones	4 (1.6)
M: Musculo-skeletal system	4 (1.69)

Evaluation of 25 patients' drug record showed that minimum number of drugs received by a patient was 5 (cardiology and endocrinology units) and maximum number was 18 (chest diseases unit) (Figure 1). Average number of drugs received in the units were similar ($p>0.05$, Figure 1).

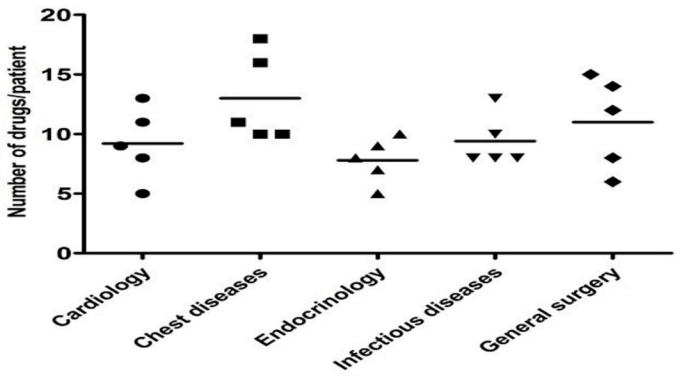

Figure 1. Number of drugs received per patient in the inpatient units (n=5 patient/unit)

The total number of pDDIs identified was 204. The mean number of pDDIs per patient was 8.16±6.41. Among the total drug interactions, 76.47% were in the risk category C, 15.20% in the risk category B, and 4.41% in the risk category D (Table 2). The highest total number of pDDIs were identified in the patients of chest diseases unit (Table 3). Number of pDDIs was positively correlated with the number of drugs (Spearmen correlation coefficient $r=0.48$, $p<0.05$).

Table 2. Risk category distribution of pDDIs

Risk category	All patients	Females	Males
B, n (%)	31 (15.2)	29 (19.2)	2 (3.8)
C, n (%)	156 (76.6)	109 (72.2)	47 (86.7)
D, n (%)	9 (4.4)	7 (4.6)	2 (3.8)
X, n (%)	8 (3.9)	6 (4.0)	2 (3.8)

Table 3. Inpatient unit distribution of risk category of pDDIs

	Risk category (frequency, n)				
Unit	B	C	D	X	Total number
Chest diseases	17	53	4	4	78
Cardiology	5	41	2	1	49
Infectious diseases	3	26	0	3	32
Endocrinology	0	24	0	0	24
General surgery	6	12	3	0	21

The most common drugs involved in pDDIs was given in the Table 4; furosemide (n=25, 12.25%) was the most prevalent drug involved in pDDIs.

Table 4. The most common drugs involved in pDDIs

Anatomical group	Frequency n (%)
Furosemide	25 (12.25)
Acetylsalicylic acid	18 (8.82)
Enoxaparine	17 (8.33)
Methylprednisolone	16 (7.84)
Salbutamol	15 (7.35)
Budesonide	15 (7.35)
Salbutamol	15 (7.35)
Amlodipine	12 (5.88)
Insulin aspart	12 (5.88)
Insulin glulisine	10 (4.90)
Clopidogrel	9 (4.41)
Ondansetron	9 (4.41)
Insulin detemir	9 (4.41)
Ipratropium	9 (4.41)

We determined the most prevalent drug pairs which lead to pDDIs; the clinical consequences and recommended interventions of these pDDIs were also indicated (Table 5).

Table 5. The most frequent combinations involved in pDDIs

Drugs	Number of pDDIs (%)	Risk category	Clinical consequence	Recommended intervention
Budesonide-salbutamol	6 (2.94)	B	Hypokalemia	No action needed
Furosemide-budesonide	5 (2.45)	C	Hypokalemia	Serum potassium monitoring
Ondansetron-paracetamol	5 (2.45)	B	Decreased the analgesic effect of acetaminophen	No action needed
Furosemide-salbutamol	5 (2.45)	C	Hypokalemia	Serum potassium monitoring
Furosemide-methylprednisolone	3 (1.47)	C	Hypokalemia	Serum potassium monitoring
Pethidine-tramadol	3 (1.47)	D	Enhancement the CNS depressant effect Serotonin syndrome	Consider therapy modification

Budesonide-salbutamol (6;2.9%), furosemide-budesonide (5;2.5%) and ondansetron-paracetamol 5 (2.4%) were the most frequent drug combinations implicated in pDDIs. Furosemide-budesonide, furosemide-salbutamol and furosemide-methylprednisolone interactions which were in risk category C, also have the potential which can lead to hypokalemia. Pethidine-tramadol interaction which was in risk category D, can cause to CNS depression and serotonin syndrome.

Discussion

There is an unmet need to critical evaluation of patient medication order in the hospital and developing strategies to improve drug safety. To our knowledge, this is the first study which aimed to identify the nature, prevalence and severity of potential DDIs in inpatient services in a training hospital in our region. This retrospective study was conducted with 25 patient from cardiology, endocrinology, general surgery, infectious diseases, and chest diseases services in a training hospital and the mean age of the subjects was determined as 63.32 ± 15.72 years. The number of medication per patient was established as 10.08 and it was positively correlated with the number of pDDIs in this study. The results obtained from previous studies [7, 8] which determines average (9.99±2.55) or median [8] of medication number per patient was consistent with our results and indicates that polypharmacy increases the frequency of DDIs [9]. However the number of drugs per patient in different inpatient services were found similar to each other which demonstrates that polypharmacy is a common clinical issue. Total number of pDDIs and the number pDDIs per patient were determined as respectively 204 and 8.16±6.41 in this study. In previous studies average pDDIs numbers per patient was identified as 7.63 ± 3.53 [8], 7.6±8.8 [10] and 3.4 [11]. In different studies the prevalence of pDDIs was determined as 86.2% [10], 59,1% [12], or 49.2% [13]. A meta-analysis study ascertained the prevalence of pDDIs and the number of pDDIs per patient as 16.3-71.1% and 0.3-4.5 respectively from the previous reports [14]. Incidences of pDDIs varies according to study design, DDI screening tool, number of patients with multiple comorbidities, study population [4, 15]. Regarding this issue the pDDI prevalence which were ascertained in this study is comparable with previous studies in the literature. Our study showed that risk category C (76.5%) of pDDIs is more common in inpatient settings. However, pDDIs of a risk category X that is classified as a combination to be avoided, were also identified in these cases. Similarly Mousawi et. al. determined the frequency of pDDI in category C as 78.6% in a cross-sectional study [10]. Identified pDDIs in category C were considered the conditions which requires clinical consideration and therapy monitoring. We ascertained the highest number of pDDIs in the patients from chest diseases unit. Alimentary tract and metabolism drugs followed by cardiovascular system drugs were the most prevalent group which were involved in the pDDIs. Furthermore the drug which were involved in pDDIs in the highest ratio were furosemide, the combinations most frequently involved in pDDIs was budesonide-salbutamol followed by furosemide-budesonide. Barot et. al. suggested that anti-infective agents, steroids, antiplatelets, diuretics anticoagulants are the most common drug groups that cause pDDIs. [8]. It is also proposed that non-steroidal anti-inflammatory drugs (NSAIDs) were frequently associated with pDDIs in the clinic [16,17]. Contrary to previous reports, gastrointestinal system drugs were determined as the drug group which were the most often involved in pDDIs; these results provides a new insight to drug groups associated with DDIs. The possible clinical consequence of the interactions between furosemide and budesonide, salbutamol and methylprednisolone was hypokalemia; it is recommended to monitor the serum potassium levels in the patients which are used this drug combinations. Also the interaction between pethidine-tramadol which could lead to clinical outcomes like enhanced CNS depression and serotonin syndrome require to consider therapy modification. It needs to be monitored the laboratory tests like renal function, serum electrolyte levels and coagulation for the assessment of the clinical relevance of pDDIs. Determination of pDDIs, evaluation the clinical relevance and appropriate interventions need to prevent ADR related to DDIs [18]. Several studies have shown that the collaborative relationship between clinical pharmacists and physicians in prescribing and monitoring the drug therapy could effectively decrease the prevalence of ADR associated with DDIs. [19-23]. Clinical pharmacist plays an essential role in the analysis and prevention of prescribing errors by providing appropriate information and monitoring the drug therapy regimen of inpatients [22,23]. It is shown that direct communication between clinical pharmacist and physicians provide the acceptance of recommended interventions associated with prescribing modification [20,24]. Further studies are necessary to investigate the important role of clinical pharmacist in inpatient settings to monitor the drug therapy and prevent pDDIs.

Conflict of interest
We declare that we have no conflict of interest.

Financial Disclosure
This study received no financial support.

Ethical approval
Access to patient data for the study was approved by responsible committee of the institution.

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