Drug Interactions as a cause of Adverse Drug Reactions in a Tertiary Care Hospital

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Drug-drug interactions (DDIs) are an important issue in clinical practice as management of co-morbidities necessitates polypharmacy and some of these interactions can transmute into or accentuate adverse drug reactions (ADRs). The objective was to estimate the proportion of ADRs due to DDIs and to describe the pattern of drug-drug interactions that resulted in ADRs. Cross-sectional study was done in the Department of Pharmacology of a Government Medical College in Kerala for a period of 1 year after getting clearance from the Institutional Ethics Committee. ADR reports submitted to the ADR Monitoring Centre from June 2015 to May 2017 formed the study material and details were entered in a structured proforma. Each suspected drug and concomitant drugs were entered in MICROMEDEX®, MEDSCAPE, and LEXICOMP drug interaction softwares to identify all potential DDIs (pDDIs). The interactions which matched with ADR description were considered to be the probable cause of that ADR. SPSS software version 16 was used for data analysis. Descriptive data were expressed as frequencies and percentages. Of the 345 ADR patients reported during the study period, 249 had concomitant drugs (mean 2.84±1.85 drugs/patient) from whom we identified 295 pDDIs (mean 1.18 ± 1.59 pDDIs/patient). Of the 295 pDDI, 30 matched the description of ADR, thus the proportion of ADRs due to DDIs was 12.05% (30 out of the 249 ADRs). Aspirin with Clopidogrel (n=5) and Heparin with Clopidogrel (n=5) topped the list of interactions contributing to ADR. Amongst the 30 suspected drug interactions causing ADR, 23 (76.67%) were pharmacodynamic, 21(70%) were of major severity and in 27(90%) the time of onset were not specified. Drug-drug interactions attributed to 12.05% of the ADRs in which data on concomitant drugs were available. Pharmacodynamic interactions (76.7%) contributed to sADRs more than pharmacokinetic interactions.

Keywords: Adverse Drug Reactions; Drug Interaction; Pharmacokinetic interaction; Pharmacodynamic interaction.

Drug-drug interactions (DDIs) are an important issue in clinical practice as management of co-morbidities necessitates polypharmacy and some of these interactions can transmute into or accentuate adverse drug reactions (ADRs). The objective was to estimate the proportion of ADRs due to DDIs and to describe the pattern of drug-drug interactions that resulted in ADRs. Cross-sectional study was done in the Department of Pharmacology of a Government Medical College in Kerala for a period of 1 year after getting clearance from the Institutional Ethics Committee. ADR reports submitted to the ADR Monitoring Centre from June 2015 to May 2017 formed the study material and details were entered in a structured proforma. Each suspected drug and concomitant drugs were entered in MICROMEDEX®, MEDSCAPE, and LEXICOMP drug interaction softwares to identify all potential DDIs (pDDIs). The interactions which matched with ADR description were considered to be the probable cause of that ADR. SPSS software version 16 was used for data analysis. Descriptive data were expressed as frequencies and percentages. Of the 345 ADR patients reported during the study period, 249 had concomitant drugs (mean 2.84±1.85 drugs/patient) from whom we identified 295 pDDIs (mean 1.18 ± 1.59 pDDIs/patient). Of the 295 pDDI, 30 matched the description of ADR, thus the proportion of ADRs due to DDIs was 12.05% (30 out of the 249 ADRs). Aspirin with Clopidogrel (n=5) and Heparin with Clopidogrel (n=5) topped the list of interactions contributing to ADR. Amongst the 30 suspected drug interactions causing ADR, 23 (76.67%) were pharmacodynamic, 21(70%) were of major severity and in 27(90%) the time of onset were not specified. Drug-drug interactions attributed to 12.05% of the ADRs in which data on concomitant drugs were available. Pharmacodynamic interactions (76.7%) contributed to sADRs more than pharmacokinetic interactions.

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More than one drug is prescribed to a patient either to achieve a synergistic effect or because more than one drug is required to treat multiple conditions.\(^1\) This can lead to drug-drug interactions (DDIs). Potential drug-drug interactions (pDDIs) are common and they can be apparent or become clinically significant. When there are marked alterations in the effects of some drugs it may be therapeutically beneficial or cause adverse drug reactions(ADRs), toxicity, or therapeutic failure which complicate drug co-administration.\(^1,2\) DDIs pose a crucial concern in clinical practice and drug utilization because we cannot stop the drug from causing the interaction as the specific drug might be essential for the patient and the benefits of its use outweigh the risk posed
by the drug interaction (DI). Recognition of every potential DDI when prescribing or dispensing is a challenge. While the incidence of pDDI is near 40% when a patient is on five concomitant drugs, it doubles to 80% with the use of seven or more drugs. In patients with multiple co-morbidities, it is yet another challenge to identify adverse effects due to DDI and classify them as pharmacokinetic, pharmacodynamic, or combinations. However, with the use of computerized screening softwares, DDIs are now predictable and we can identify potential drug therapy problems and prevent ADRs due to DDIs.

ADRs are unintended, noxious reactions that occur in the therapeutic dose of the drug and add to the pharmacoeconomic burden of society by causing increased hospitalization. Depending on various study designs, populations, and periods, the proportion of patients developing ADR due to drug interactions has varied from 0.63 to 56%. Of the ADRs that necessitate hospitalization, 26% are due to DDIS. Due to controlled settings in clinical trials the ADRs due to DDI which we encounter in real-life settings are seldom discovered or systematically investigated during the development of drugs. ADRs due to co-administration of drugs can be an enhancement of the already known ADR of a drug or it may be a new unanticipated effect that cannot be associated with either of the drugs when used alone. Based on the similarity of drug molecular structure, drug targets, drug-side effects, and drug target protein sequence several computational methods that predict DDIs have been published. There are also published models that predict the therapeutic potential of drugs and adverse drug reactions based on genome-wide drug-protein interactions. More than 60 free and paid software such as Medscape Drug Interaction checker, Lexi-Interact by Lexicomp online, Micromedex drug interaction checker, Epocrates, Harmavista, Stockley’s Drug interactions, British National Formulary are available which can detect potential DDIs. The data regarding the proportion of ADRs caused by drug interactions are sparse in the Indian population. This study aimed to estimate the proportion of ADRs that occurred due to drug-drug interactions during the study period and to describe the pattern of drug-drug interactions that resulted in ADRs.

**MATERIALS AND METHODS**

This cross-sectional study was done in the Department of Pharmacology, Government TD Medical College, Alappuzha for a period of one year from July 2016 to June 2017 after getting Institutional Research Committee and Ethics Committee clearance number EC 04/2016 dated 26.05.2016. All suspected ADR (sADR) reports submitted to the ADR Monitoring Centre, Department of Pharmacology from June 2015 to May 2017 formed the study material. Any reports of poisonings due to insecticides/pesticides/ acids/alkalis/kerosene/plant products as well as sADR reports without concomitant drugs were excluded from the study. A sample size of 284 was calculated considering a prevalence of 26% of hospitalized ADRs due to drug interactions. Data from the sADR reports collected in the common standardized format IPC-ADR form were entered in a structured proforma regarding the gender, description, and type of ADR, the suspected drug and its class, the number and names of concomitant drugs, the causality using Naranjo Scale, severity using Hartwig and Siegel Scale and preventability assessment using Schumock and Thornton Scale. ADRs with no concomitant drugs were excluded from further study. Each suspected drug and concomitant drugs were entered in the MICROMEDEX Drug Interaction Checker Software, MEDSCAPE drug interactions checker, and LEXICOMP Online software Lexi-Interact. Drug interaction identified in any of the software was considered as a potential drug-drug interaction. The description of the interaction was matched with that of the ADR and reported by the investigators independently. Criteria for selection of ‘ADR due to drug interaction’ were an involvement of the suspected drug in the drug interaction and a match in the description of the ADR reported and drug interaction detected through software. The suspected drugs were entered along with the concomitant drugs in the software and any drug interactions which matched with the adverse drug reactions were selected manually. If in a patient more than one interaction with the suspected drug could result in an adverse drug reaction, all the interactions were included for analysis. The type of interaction, the severity of interaction, and the
onset of interaction were entered in the proforma. SPSS software version 16 (SPSS Inc., Chicago, USA) was used for data analysis. Descriptive data were expressed as frequencies and percentages.

RESULTS

A total of 345 patients were reported to develop ADR from June 2015 to May 2017 of which 93 were eliminated from the study because of a lack of details or absence of concomitant drugs. Of the remaining 249 patients with ADRs, 90 were reported from June to December 2015, 127 were reported in the year 2016, and 32 from January to May 2017. The mean age was 44.84±19.60 years with females being 135(54.2%) and males 114(45.8%). Cefotaxime (n=18), followed by Amoxicillin (n=17) and Azithromycin as well as Ciprofloxacin (each n=13) topped the list of drugs that resulted in sADRs. Antibiotics (n=106) followed by NSAIDs (n=27) topped the list of drug classes contributing to sADRs. Pruritus (n=78) followed by rash (n=60) topped the list of sADRs. Of the 249 patients, 38.5% (n=96) received the drug intravenously, 30.52% (n=76) received it through oral route, 32(12.9%) intradermally, 8(3.2%) intramuscularly, 4(1.6%) subcutaneously and 1(0.4%) each as inhalation and suppository. Type B-Bizarre ADRs occurred in 79.11% (n=197) and the rest were Type A-Augmented (n=52). The ADRs were not serious in 185 patients and were serious in 64 patients, 34 resulting in prolonged hospitalization, and 30 were life-threatening. All sADRs were managed symptomatically and at the time of the report of sADR, 227 patients had recovered from it and 22 were recovering. The severity of ADRs were mild in 130 patients (Level 2), moderate in 88 [Level 3 (n=50), Level 4(n=38)], and severe in 31 (Level 5). The ADR was definitely preventable in 242 patients, probably preventable in 2, and not preventable in 5.

In the 249 ADR patients, we identified 295 potential drug interactions as shown in table 1, the maximum number in a patient being 8 and the least 1. The average number of potential interactions per patient was 1.18±1.59. The number of concomitant drugs ranged from 1(n=62, 24.9%) to 9(n=1, 0.4%), with a mean of 2.84±1.85. There was a positive correlation between the number of concomitant drugs and the number of pDDIs (correlation coefficient r=0.313) as shown in Fig 1. Of the 295 pDDI, 117 pDDI were due to the suspected drug with the concomitant drugs and 178 pDDI were between the concomitant drugs. The potential interactions of the suspected drug were pharmacodynamic (n=77), pharmacokinetic (n=32), pharmaceutical (n=2) and unknown (n=6). There were 59 major, 49 moderate, and 9 minor

![Fig. 1. Correlation of potential drug-drug interactions with concomitant drugs](image-url)
interactions. The interactions were delayed (n=16), rapid (n=11) and non-specified (n=90).

Of the 117 potential interactions of the suspected drug, we identified 30 drug interactions whose description matched with that of the ADR. Thus the proportion of ADRs due to DDIs was 12.05% (30 out of the 249 ADRs). The mean age of patients who developed ADR following DDI was 54.73±17.36 years and 18(60%) were females and the rest males. Table 2 shows the distribution of drug interactions concerning age group and gender. As shown in table 2 majority of drug interactions that resulted in ADR occurred in the 19-60 years age group (46.7%) of which 9 occurred in females and 8 in males. Type A-Augmented reactions occurred in 24(80%) and Type B-Bizarre in 6 (20%). Skin and appendages (5,16.7%) followed by Central Nervous System (4, 13.3%) topped the list of organ systems affected. In 16(53.3%) patients ADR due to DDI resulted in prolonged hospitalization, in 5(16.7%) it was life-threatening, and in 9(30%) it was not serious. Of the 30 ADRs due to DDI, 6(20%) were severe (Level 5), 21(70%) had moderate [Level 3=8(26.7%), Level 4=13(43.3%)] severity, and 3(10%) were mild (Level 2) in severity. Twenty-seven (90%) were definitely preventable and 3(10%) were probably preventable ADRs. Causality assessment revealed that 28(93.4%) were probable, 1(3.3%) was possible and 1(3.3%) was certain. At the time of reporting, in 24 patients the suspected drug was stopped, in 3 the dose was reduced and 29 (96.7%) had recovered and 1(3.3%) was recovering from it.

As summarized in Table 3, Aspirin with Clopidogrel (n=5) and Heparin with Clopidogrel (n=5), topped the list of drug interactions contributing to ADR. Twenty-two (73.3%) patients who developed ADR as a result of DDI received more than 1 concomitant drug. Amongst the 30 DDIs, 23(76.67%) were pharmacodynamic, 2(6.66%) were pharmacokinetic, 4(13.33%) were both pharmacodynamic and pharmacokinetic and 1(3.33%) had unknown interaction type. The severity was major in 21(70%) interactions and moderate in 9(30%). The onset of interaction was delayed in 2(6.7%), immediate in 1(3.3%), and not specified in 27(90%). All the interactions occurred at the normal therapeutic dose of the suspected and concomitant drugs. In 5 out of the 30 interactions the suspected drug was Fixed-Dose Combination of Aspirin+ Clopidogrel interacting among themselves as shown in Table 3.

DISCUSSION

"An adverse drug reaction is any response to a drug which is noxious and unintended, and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function”. While adverse drug reactions can occur in appropriately prescribed, dispensed, or administered drugs they can also occur when the pharmacological effect of one drug is modified by another. A total of 345 patients developed ADR during the study period, the commonest ADR was pruritus, the commonest

<table>
<thead>
<tr>
<th>Number of DDIs/ADR patient</th>
<th>Number of ADR patients (%)</th>
<th>Frequency of DDIs (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>119 (79.8%)</td>
<td>0</td>
</tr>
<tr>
<td>1</td>
<td>60 (24.09%)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>22 (8.83%)</td>
<td>14 (55.05%)</td>
</tr>
<tr>
<td>3</td>
<td>20 (8.03%)</td>
<td>6 (23.07%)</td>
</tr>
<tr>
<td>(20.3%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>18 (7.22%)</td>
<td>72 (24.40%)</td>
</tr>
<tr>
<td>5</td>
<td>4 (1.60%)</td>
<td>20 (6.77%)</td>
</tr>
<tr>
<td>6</td>
<td>4 (1.60%)</td>
<td>24 (8.13%)</td>
</tr>
<tr>
<td>7</td>
<td>1 (0.40%)</td>
<td>7 (2.37%)</td>
</tr>
<tr>
<td>8</td>
<td>1 (0.40%)</td>
<td>8 (2.71%)</td>
</tr>
<tr>
<td>Total</td>
<td>249</td>
<td>295</td>
</tr>
</tbody>
</table>

Table 2. Demographic profile of patients with drug interactions that resulted in adverse drug Reactions

<table>
<thead>
<tr>
<th>Age Group</th>
<th>Gender</th>
<th>Number of Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-18 years</td>
<td>Female n=18</td>
<td>3 (16.7%)</td>
</tr>
<tr>
<td>19-60 years</td>
<td>Male n=12</td>
<td>8 (66.7%)</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>4 (33.3%)</td>
<td>17 (56.7%)</td>
</tr>
</tbody>
</table>

Table 1. Number of potential Drug-Drug Interactions
<table>
<thead>
<tr>
<th>Suspected Drug causing ADR</th>
<th>Concomitant Drug suspected to cause Drug Interaction</th>
<th>Number of concomitant drugs</th>
<th>Serial Number and Suspected ADR</th>
<th>Suspected Interaction</th>
<th>Interaction type of Drug Interaction</th>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>1</td>
<td>1. Hematuria</td>
<td>PD</td>
<td>Additive effect-antiplatelet action</td>
<td>Major</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>5</td>
<td>2. Hemoptysis</td>
<td>PD</td>
<td>Additive effect-antiplatelet action</td>
<td>Major</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>4</td>
<td>3. Hematemesis</td>
<td>PD</td>
<td>Additive effect-antiplatelet action</td>
<td>Major</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Clopidogrel</td>
<td>1</td>
<td>4. Hematemesis</td>
<td>PD</td>
<td>Additive effect-antiplatelet action</td>
<td>Major</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Tirofiban</td>
<td>5</td>
<td>5. Black tarry stools, giddiness</td>
<td>PD</td>
<td>Additive effect-antiplatelet action</td>
<td>Major</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Levetiracetam</td>
<td>1</td>
<td>6. Gum bleeding</td>
<td>PD</td>
<td>May enhance the toxic effect of Carbamazepine</td>
<td>Major</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>Cyclosporine</td>
<td>1</td>
<td>7. Stevens Johnsons Syndrome</td>
<td>PD</td>
<td>Decreased clearance of Levetiracetam by Carbamazepine</td>
<td>Major</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>Furosemide</td>
<td>1</td>
<td>8. Hyperglycemia</td>
<td>PD</td>
<td>Increases serum Dexamethasone concentration by affecting CYP3A4 metabolism and by P–glycoprotein (MDR1) efflux transporter</td>
<td>Major</td>
</tr>
<tr>
<td>Digoxin</td>
<td>Furosemide</td>
<td>4</td>
<td>9. Edema</td>
<td>PD</td>
<td>Reduce the natriuretic effect of loop diuretics by</td>
<td>Major</td>
</tr>
<tr>
<td>Heparin</td>
<td>Clopidogrel</td>
<td>6</td>
<td>10. Ventricular tachycardia</td>
<td>PD</td>
<td>Co-administration of Digoxin and Loop diuretic may result in increased risk of digoxin toxicity-Hypokalemia can trigger calcium release causing arrhythmias</td>
<td>Moderate</td>
</tr>
<tr>
<td>Heparin</td>
<td>Aspirin</td>
<td>4</td>
<td>11. Ecchymotic patches</td>
<td>PD</td>
<td>Additive effect-Heparin can cause autoimmune thrombocytopenia and Clopidogrel is an antiplatelet drug</td>
<td>Major</td>
</tr>
<tr>
<td>Heparin</td>
<td>Aspirin</td>
<td>5</td>
<td>12. Thrombocytopenia</td>
<td>PD</td>
<td>Synergism-Synergism-cause autoimmun thrombocytopenia and Clopidogrel is an antiplatelet drug</td>
<td>Major</td>
</tr>
<tr>
<td>Heparin</td>
<td>Furosemide</td>
<td>1</td>
<td>13. Bleeding, Ecchymosis</td>
<td>PD</td>
<td>Decreased clearance of furosemide by pantoprazole</td>
<td>Major</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Pantoprazole</td>
<td>1</td>
<td>14. Gastritis-abdominal pain and vomiting</td>
<td>PD</td>
<td>Increased concentration of methotrexate and metabolite, decreased renal elimination of 7-hydroxymethotrexate by pantoprazole</td>
<td>Major</td>
</tr>
<tr>
<td>Metoprolol</td>
<td>Isosorbide dinitrate</td>
<td>5</td>
<td>15. Giddiness, Bradycardia</td>
<td>PD</td>
<td>Synergism-cause hypotension</td>
<td>Major</td>
</tr>
<tr>
<td>Ondansetron</td>
<td>Tramadol</td>
<td>1</td>
<td>16. Renal Failure</td>
<td>Unknown</td>
<td>Lower the threshold of contrast reactions with increased risk of more severe reactions</td>
<td>Major</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Clopidogrel</td>
<td>4</td>
<td>17. Hyperesthesia (Serotonin syndrome)</td>
<td>PD</td>
<td>Additive serotonergic effect (excessive stimulation of 5HT₁a and 5HT₂a)</td>
<td>Major</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>Lithium</td>
<td>3</td>
<td>18. Decrease speech and difficulty in walking</td>
<td>PD</td>
<td>Inhibition of CYP2C9 mediated Phenytoin metabolism by Clopidogrel</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Clozapine</td>
<td>3</td>
<td>19. Tremor, Rigidity</td>
<td>PD</td>
<td>Lithium enhances the neurotoxic effect of Quetiapine</td>
<td>Moderate</td>
</tr>
<tr>
<td>Risperidone</td>
<td>Lithium</td>
<td>3</td>
<td>20. Dyskinesia</td>
<td>PD</td>
<td>Depression of CNS</td>
<td>Moderate</td>
</tr>
<tr>
<td>Streptokinase</td>
<td>Furosemide</td>
<td>2</td>
<td>22. Intracranial bleeding</td>
<td>PD</td>
<td>Prolongation of bleeding time</td>
<td>Major</td>
</tr>
<tr>
<td>Tirofiban</td>
<td>Aspirin</td>
<td>5</td>
<td>23. Hematuria, Blood from gums</td>
<td>PD</td>
<td>Increase the anticoagulant effect of heparin</td>
<td>Major</td>
</tr>
<tr>
<td>Tizanidol</td>
<td>Mesenchymide</td>
<td>3</td>
<td>24. Dizziness, Dryness of mouth</td>
<td>PD</td>
<td>Additive pharmacological effect-increased CNS depression</td>
<td>Moderate</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Aspirin</td>
<td>4</td>
<td>25. Hematuria, Bleeding from gums</td>
<td>PD</td>
<td>Synergistic hypotrombinemia, Displace warfarin from plasma protein binding site</td>
<td>Major</td>
</tr>
</tbody>
</table>
suspected drug class was antibiotic and the drug
was a Beta-lactam, Cefotaxime. In a study done
earlier from the same institution the commonest
ADR was maculopapular rash, the drug class
was antibiotics and the drug was a Beta-lactam,
Amoxicillin.19

Drug-drug interactions are seldom
recognized in clinical practice. With the advent
of electronic decision support tools, the physician
can be alerted about potential DDIs and careful
selection and monitoring can help in preventing
adverse outcomes.20 The role of DDI is an important
predisposing factor for ADR. The theoretical
probability of occurrence of potential interactions is
higher than clinically relevant adverse reactions.21
In a study by Palappallil et al., 12.73% of ADRs
were due to DI, of which the majority were
significant pharmacodynamic interactions and were
delayed in onset and DDIs had more probability
of causing severe ADRs with an Odds ratio of
1.75.19 A study by Fotker et al, found that of the
potential DDIs identified in 51% of patients on
admission, only in 1.2 % it was the reason for the
admission.22 Faspie et al, identified 1851 pDDIs
among 118 patients receiving drugs for Chronic
kidney disease.11

Pichala et al, identified that drug
interactions resulted in the majority of the problems
identified by drug therapy assessment, however
only 20% were clinically significant, and most
required monitoring of the patients.7 Lucca et al.,
found that the incidence of pDPI in psychiatric
patients was 55.2% and 12% of patients with DDI
developed ADRs.23 In this study, we identified
295 pDDIs of which 117 pDDI were due to the
suspected drug of which 30(10.17% ) resulted in
ADR cases. Of the 30 adverse drug reactions due
to drug interactions 18 occurred in females and 12
in males and the majority occurred in the 19-60
years age group. Lucca et al., found that amongst
the 97 patients who developed ADRs in which DDI
was suspected majority were males (57%).23 This is
in contrast to our study. Lucca et al., found that
87(89.6%) developed ADR due to drug interaction
in the adult age group as compared to the pediatric
and geriatric group.23 This is in line with this study
in which 17(56.7%) developed ADR in the adult
age group, 10% developed in the pediatric age
group, and 33.3% developed in the geriatric age
group.

Co-administration of drugs in the same
infusion can lead to pharmaceutical interaction
among drugs or with the intravenous fluid.24 Of the
117 potential interactions of the suspected drugs,
two were pharmaceutical. We did not encounter
any pharmaceutical interaction which resulted in
ADR in this study.

When the action of one drug is modified
by another without change in the serum levels it
results in pharmacodynamic interactions. These
interactions are difficult to classify as some drugs
instead of directly affecting the object drug may
interfere with the physiological mechanisms.24
Amongst the potential DDIs with the suspected
drug, 65.81% were pharmacodynamic and of the
30 DDIs which resulted in ADR, 76.7% were
pharmacodynamic. Aspirin and Clopidogrel are
two antiplatelet drugs and the combined use
of these drugs helps in preventing ischaemic
episodes due to synergism. The Clopidogrel in
Unstable angina to prevent Recurrent Ischemic
Events (CURE) trial has shown a 20% reduction
in myocardial infarction (MI), stroke, and
cardiovascular deaths.25 This dual antiplatelet
therapy also helps in checking the restenosis of
stented coronaries. However, the Management of
Atherothrombosis with Clopidogrel in High-risk
patients with a recent transient ischaemic attack
or ischaemic stroke (MATCH) trial has shown
that serious bleeding in high-risk stroke patients
doubles with dual antiplatelet therapy.26 In this
study, five patients developed bleeding causing
hemoptysis, hematuria, hematemesis, and black
tarry stools because of the additive effect. Two
patients received concomitant aspirin and tirofiban
and one developed gum bleeding and the other
thrombocytopenia. Another patient received aspirin
as a concomitant drug in a patient who developed
bleeding per rectum after receiving heparin. Five
patients who received heparin and clopidogrel
developed bleeding, ecchymotic patches, and
thrombocytopenia. Bleeding is the most serious
complication of heparin therapy. Heparin-induced
thrombocytopenia due to platelet aggregation
is mild and of brief duration. Clopidogrel also
causes thrombocytopenia and has an additive
effect with heparin.24 Warfarin an oral anticoagulant
had synergistic interactions with aspirin causing
hypoprothrombinemia (pharmacodynamic
interaction) as well as displaced warfarin from the plasma protein binding site (pharmacokinetic) resulting in hematuria and bleeding gums in a patient and ecchymosis in another. Administration of Streptokinase with aspirin and heparin resulted in bleeding in two patients. Clinical use of Streptokinase has reduced to a large extent as it exhausts the circulating fibrinogen thereby causing bleeding. Diclofenac is a non-steroidal anti-inflammatory drug that decreases prostaglandin synthesis and this can affect the diuretic effect of Furosemide as renal vasodilatation mediated through prostaglandin is blunted and this can lead to edema as seen in one of the ADRs. The increase in systemic venous capacitance is mediated through prostaglandin and accounts for the rapid respite it offers in left ventricular failure and pulmonary edema. There is also competition between furosemide and diclofenac for tubular secretion which delays the action of furosemide. Ondansetron and tramadol caused hyperesthesia in a patient because of the additive serotonergic effect (excessive stimulation of \(5\mathrm{HT}_{1A}\) and \(5\mathrm{HT}_{2A}\)). Risperidone when administered with lithium, an antimanic drug resulted in dyskinesia as extrapyramidal symptoms are aggravated in the presence of lithium. Some moderate severity pharmacodynamic interactions were also noted as shown in Table 3.

Pharmacokinetic interactions result in variation of serum levels of the drug due to interference at the level of absorption, distribution, metabolism, or excretion. This can alter the effectiveness of the drug which may be identified by scientific knowledge or detected by therapeutic drug monitoring. There were six ADRs due to pharmacokinetic interactions of which three had pharmacodynamic interactions also. Levetiracetam enhanced the toxic effect of Carbamazepine and resulted in Stevens Johnson’s syndrome. Sisodiya et al., described a series where four patients who developed adverse reactions due to carbamazepine with concurrent use of Levetiracetam, and this was presumed to be due to additive central nervous system depressant effects as there was no change in the carbamazepine levels. Increased concentration of methotrexate, as well as decreased renal elimination of 7-hydroxymethotrexate by pantoprazole, resulted in gastritis viz abdominal pain and vomiting. Several case reports have been published establishing that the abnormality in methotrexate concentration and elimination were not evident with prior or subsequent administration of methotrexate without concurrent proton pump inhibitor and concurrent use was significantly associated with delayed methotrexate elimination. The possible mechanism proposed is the inhibition of renal elimination of hydrogen ions by proton pump inhibitors, which interferes with the secretion of methotrexate which is actively secreted in the distal renal tubules with hydrogen ions produced via the hydrogen-potassium ATPase pump. Clopidogrel can inhibit the metabolism of Phenytoin and this resulted in hypersensitivity reactions due to Phenytoin. Clopidogrel and Phenytoin utilize Cytochrome Pigment (CYP) 2C19 enzyme and Clopidogrel is also an inhibitor of CYP2C19 causing raised Phenytoin levels. Two patients developed bleeding in the form of hematuria and ecchymosis with concomitant use of Warfarin and Heparin. Apart from having synergistic pharmacodynamic interaction Heparin can displace Warfarin from the plasma protein binding site and result in an increased concentration of free warfarin resulting in bleeding. Similarly, Cyclosporine and Dexamethasone in addition to the synergistic interaction increase serum Dexamethasone concentration by affecting CYP3A4 metabolism and P-glycoprotein efflux transporter resulting in drug-induced hyperglycemia. This study was conducted based on the ADRs reported to the Department of Pharmacology and may not be representative of all the ADRs that occurred in the institution during the study period. Of the 345 ADRs reported to the department 93 were eliminated from the study because of lack of details or absence of concomitant drugs.

**CONCLUSIONS**

A total of 345 ADRs were reported during the study period, of which 249 were included in the study. Pruritus was the most frequent sADR, antibiotics topped the list of drug classes causing sADR and the most frequent suspected drug was Cefotaxime. The majority of the ADRs were bizarre, not serious, and mild in severity. In the 249 ADR reports, 295 potential Drug-Drug Interactions were found out of which 117 were due to the suspected drug which caused ADR. In 30(10.17%)
ADRs drug-drug interaction was suspected as the cause. The majority of the ADRs due to DDI were augmented, affected Skin and appendages, were serious, severe, definitely preventable, and probable in causality. The most common drug interaction resulting in ADR was that of Aspirin with Clopidogrel and Heparin with Clopidogrel. The majority were pharmacodynamic and of major severity. Intense monitoring for pDDI and constant vigilance may improve the therapeutic outcome and reduce the burden of extremely harmful and preventable ADRs.

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