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COMPARATIVE STUDY ON ASSESSMENT OF DRUG-DRUG INTERACTIONS IN HOSPITALIZED PEDIATRIC PATIENTS IN A TERTIARY CARE HOSPITAL

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ABSTRACT

There are numerous compendia for assessment of drug-drug interaction, like BNF, the Vidal, the Micromedex program, the Drug Interaction Fact, the Lexicomp program, the US Pharmacopeia Drug Information etc. In the study population majority of patients fall under the age group of 2-11 years. Mean value of overall population is 4.52±2.52; Mean value of DDIs present is 7.58±1.Majority of DDIs have moderate severity when assessed by Lexicomp individually. More than 80% of DDIs assessed by BNF are belongs to NSC.

KEYWORDS: Drug-Drug Interactions, NSC, ADEs, BNF.

INTRODUCTION

Drug interactions[1] refer to the interference of a drug in the action of another drug or the interference of food or nutrient in the action of drugs. The outcome can be harmful if the interaction cause an increase in the toxicity of the drug. A drug – drug interaction occurs when the effect of one drug is altered by the presence of another drug in the body.

With the high number of reports on new drug interactions, it has been difficult for health professionals to keep constantly updated. Today, some standard textbooks and computer systems are used to verify the risk of potential drug interactions, thus preventing the utilization of drugs that cause important and harmful interactions and reducing the patient's exposure to them. For this reason, it become important to verify the rate and profile of drug interactions in medical prescriptions to hospitalized paediatric patients.

Children[2] are more vulnerable to various ADEs to drug and poor understanding of instructions on prescription by the patient or care taker where likely to cause medication error and less effective treatment.

Clinical trial of drugs is a major component of Evidence Based Medicine, which provides good evidence about drug safety and efficacy. Unfortunately there is a lack of paediatric[3] randomised clinical trial (RTC), which has contributed to the scarcity of knowledge about the drug safety and efficacy in children.

Paediatric patients require special attention from health professionals in terms of drug interactions, as they react to drugs differently from adults. The body parts that are responsible for the excretion and elimination processes are not fully developed until 1 year of age, resulting in extended half-life of metabolized drugs and reduced excretion, which may result in toxicity problems.[3,4,5]

There are numerous compendia for assessment of drug-drug interaction, like BNF, the Vidal, the Micromedex program, the Drug Interaction Fact, the American Hospital Formulary Service Drug Information, the Lexicomp program, the US Pharmacopeia Drug Information, Stockley's Drug Interactions, Hansten;s Drug Interactions Analysis And Management etc. However, compendia often do not document methodology for listing as well as ranking the potential clinical severity of drug – drug interaction .This may be reason for inconsistent informing. Inconsistent drug-drug interaction information can cause variation and confusion in prescribing, possibly may increasing the incidence of morbidity and mortality.[6] As an example, according to British National Formulary co-administration of corticosteroids and macrolide antibiotic had no serious consequence but had moderate severity according to other authoritative sources. Stockley's Drug Interaction even reports that Co-administration may be therapeutically beneficial. Additionally, previous studies have shown that there is inconsistency in Drug-drug interaction information.

Paediatric Health professionals often do not have specialized interaction textbooks to hand or support

drug- drug interaction screening programs. Therefore, it is becomes necessary to study is to identify whether there is consistency in listing as well as ranking clinical significance of drug-drug interaction in three authorative freely accessible drug information sources.[7]

Drug Interaction

Drug interactions refer to the interference of a drug in the action of another drug or the interference of food or nutrient in the action of drugs. The outcome can be harmful if the interaction cause an increase in the toxicity of the drug. It is an important to know the difference between a drug interaction and a side-effect. A side effect, also known as an adverse effect, is caused by a single drug.

1. Drug-Drug Interactions

A drug – drug interaction occurs when the effect of one drug is altered by the presence of another drug in the body. For example:

- One drug might reduce or increase the effect of another drug
- Two medications taken together may produce a new and dangerous interaction.
- Two medications that work the same way may produce an effect that would be expected from taking just one drug if they are taken at the same time.

1.1. Mechanisms of drug interaction

Some drugs interact together in totally unique ways but many drugs interact together not by a single mechanisms but often by two or more mechanisms. The mechanisms of interactions can be subdivided into those that involve the pharmacokinetics of a drug, and those that are pharmacodynamics.

1.1.1. Pharmacokinetic interactions

Pharmacokinetic interactions are those that can affect the processes by which drugs are absorbed, distributed, metabolised, and excreted so called ADME interactions.

1.1.1.1. Drug absorption interactions

Most of drugs are given orally for absorption[8,9,10] through the mucous membranes of the GIT, and the majority of interactions that go on within the gut result in reduced rather than increased absorption. A clear distinction must be made between those that decrease the rate of absorption and those that alter the total amount absorbed. For drugs that are given long-term, in multiple doses (e.g. the oral anticoagulants) the rate of absorption is usually unimportant, provided the total amount of drugs absorbed is not markedly altered. On the other hand for drugs that are given as single doses, intended to be absorbed rapidly (e.g. hypnotics or analgesics), where a rapidly achieved high concentration is needed, a reduction in the rate of absorption may result in failure to achieve an adequate effect.

1.1.1.1.1 Effect of changes in gastrointestinal pH

The passage of drugs through mucous membranes by simple passive diffusion depends upon the extent to which they exist in the no-ionised lipid soluble form. Absorption therefore governed by the pKa of the drug, its lipid solubility, the pH of the content of the gut and various other parameters relating to the pharmaceutical formulation of the drug. Thus the absorption of salicylic acid by the stomach is much greater at low pH than at high. On theoretical grounds it might be expected that alteration in gastric pH caused by drugs such as the H_2receptor antagonists would have a marked effect on absorption, but in practice the outcome is often uncertain because a number of other mechanisms may also come in to play, such as chelation, adsorption and change in gut motility, which can considerably affect what actually happens. However, in some cases the effect can be significant. Rises in pH is due to 'proton pump inhibitors' 'H_2receptor antagonist', can markedly reduce the absorption of ketoconazole.

1.1.1.1.2 Changes in gastrointestinal motility

Since most drugs are largely absorbed in the upper part of the small intestine, drugs that alter the rate at which the stomach empties can affect absorption. Propanthaline, for example, delays gastric emptying and reduce the circulation. Some drugs are totally dissolved in the plasma water, but many others are transported with some proportion of their molecules in the solution and the rest bound to plasma proteins, particularly the albumins. The extend of binding varies enormously but some drugs are extremely highly bound. Drugs can also become bound to albumin in the interstitial fluid, and some, such as digoxin, can bind to the heart muscle tissue. The binding of drugs to the plasma protein is reversible, an equilibrium being established between those molecules that are bound and those that are not. Only the unbound molecules remains free and pharmacologically active, while those that are unbound form are circulating but pharmacologically inactive reservoir which, in the case of drugs with a low extraction ratio, is temporarily protected from metabolism and excretion. As the free molecule become metabolised, some of the bound molecules become unbound and pass into solution to exert their normal pharmacological action, before they, in their turn are metabolised and excreted.

1.1.1.2. Drug distribution interactions

1.1.1.2.1. Protein binding interactions

Following absorption, drugs are around the body by the circulation. The binding of drugs to the plasma proteins is reversible, an equilibrium being established between those molecules that are bound and those that are not. Only the unbound molecules remain free and pharmacologically active. Depending on the concentration and relative affinities for the binding sites, one drug may successfully compete with another and displace it from the site it is already occupying.

1.1.1.2.2. Induction or inhibition of drug transport proteins

It is increasingly being recognised that distribution of drugs into the brain, and other organs such the testes, is limited by the action of drug transporter proteins such as p-glycoprotein. These proteins actively transport drugs out of cells when they have passively diffused in. Drug that are inhibitors of these transporters could therefore increase the uptake of drug substrates in to the brain, which could either increase adverse CNS effects, or beneficial.

1.1.1.3. Drug metabolism (biotransformation) interactions

Drug metabolisms goes on in the serum, the kidneys, the skin and the intestines, but the greatest proportion is carried out by enzymes that are found in the membranes, but the greatest proportion is carried out by enzymes that are found in the membranes of the endoplasmic reticulum of the liver cells. If liver is homogenised and then centrifuged, the reticulum breaks up in to small sacs called microsomes which carry the enzyme of the liver are frequently referred to as the 'liver microsomal enzymes'. Drug interaction may occur.[11,12]

1.1.1.3.1. Changes in first-pass metabolism

i. Changes in blood flow through the liver

After absorption in the intestine, the portal circulation takes drugs directly to the liver before they are distributed by the blood flow around the rest of the body. A number of highly lipid soluble drugs undergo substantial biotransformation during this first pass through the gut wall and liver and there is some evidence that some drugs can have a marked effect on the extent of first pass metabolism by altering the blood flow through the liver. However, there are few clinically relevant examples of this, and may can be explained by other mechanisms, usually altered hepatic metabolism.

ii. Inhibition or induction of first-pass metabolism

The gut wall contains metabolising enzymes, principally the cytochrome P450 isoenzymes. In addition to the altered metabolism caused by changes in the hepatic blood flow there is evidence that some drugs can have a marked effect on the extent of first pass metabolism by inhibiting or including the cytochrome p450 isoenzymes in the gut wall or in the liver. An example is the effect of grapefruit juice, which seems to inhibit the cytochrome P450 isoenzyme CYP3A4, mainly in the gut, and therefore reduces the metabolism of oral calcium channel blockers. Although altering the amount of drug absorbed these interactions are usually considered drug metabolism interactions.[13,14]

1.1.1.3.2. Enzyme induction

When barbiturate were widely used as hypnotics it was found necessary to keep increasing the dosage as time went by to achieve the same hypnotic effect, the reason being that the barbiturates increase the activity of the microsomal enzymes so that extent of metabolism and excretion increase. This phenomenon of enzyme stimulation or induction not only not only accounts for the need for an increased barbiturate dose but if another drug that is metabolised by the same range of enzymes is also present, its enzymatic metabolism is similarly increased and larger doses are needed to maintain the same therapeutic effect. However, note that not all enzyme inducing drugs induce their own metabolism. The metabolic pathway that is most commonly induced is Phase I oxidation mediated by the cytochrome P450.

Enzyme induction is a common mechanism of interaction. If one drug reduce the effect of another by raising the dosage of the drug affected, but this requires good monitoring, and there are obvious hazards if the inducing drugs are eventually stoped without remembering to reduce the dosage again. The raised drug is may be an overdose when the drug metabolism has to normal.[15,16]

1.1.1.3.3. Enzyme inhibition

More common than enzyme induction is the inhibition of enzymes. This results in the reduced metabolism of an affected drug, so that it may begin to accumulate within the body, the effect usually being essentially the same as when the dosage is increased. Unlike enzyme induction, which may take several days or even weeks to develop fully, enzyme inhibition can occur within 2-3 days, resulting in the rapid development of toxicity. The metabolic pathway that is most commonly inhibited is Phase I oxidation mediated by the cytochrome P450. The clinical significance of many enzyme inhibition interactions depends on the extent to which the serum level of the drug rises. If the serum levels remain within the therapeutic range the interaction may not be clinically important

1.1.1.3.4. Genetic factor in drug metabolism

An increased understanding of genetics has shown that some of the cytochrome P450 isoenzymes are subject to 'genetic polymorphism', which simply means that some of the population have a variant of isoenzymes with activity.[16]

1.1.1.4. Drug excretion interactions[17,18]

With exception of inhalation anaesthetics, most drugs are excreted either in the bile or in the urine. Blood entering the kidney along the renal arteries is, first of all, delivered to glomeruli of the tubules where molecule small enough to pass through the pores of the glomerular membrane (e.g. water, salt, some drugs) are filtered through in to the lumen of the tubules. Larger molecules, such as plasma proteins, and blood cells are retained within the blood. The blood flows then passes to the remaining parts of the kidney tubules where active energy using transport systems are able remove the drugs and their metabolites from the blood and secrete them in to the tubular filtrate. The renal tubular cells additionally possess active and passive transport systems for the reabsorption of drugs. Interference by drugs with renal

tubular fluid pH, with active transport systems and with blood flow to the kidney can alter the excretion of other drugs

1.1.1.4.1. Changes in urinary pH

The pH changes that increase the amount in the ionised form (alkaline urine for acidic drugs, acid urine for basic drugs) increase the loss of the drug, whereas moving the pH in the opposite direction will increase their retention. The clinical significance of this interaction mechanism is small, because although a very large number of drugs are either weak acids or bases, almost all are largely metabolised by the liver to inactive compounds and few are excreted in the urine unchanged.

1.1.1.4.2. Changes in active renal tubular excretion

Drugs that use the same active transport systems in the renal tubules can compete with one another excretion for excretion. For example, Probencid reduces the excretion of penicillin and other drugs

1.1.1.4.3. Changes in renal blood flow

The flow of blood through the kidney is partially controlled by the production of renal vasodilatory prostaglandins. If the synthesis of these prostaglandins is inhibited the renal excretion of some drugs may be reduced. An interaction where this is the suggested mechanism is the rise serum lithium seen with some NSAIDs.

1.1.1.4.4. Biliary excretion and the enterohepatic shunt

A number of drugs are excreted in the bile, either unchanged or conjugated (e.g. as the glucuronide) to make them more water soluble. Some of the conjugate are metabolised to the parent compound by the gut flora and are then reabsorbed. This recycling process prolongs the stay of the drug in the body, but if the gut flora is diminished by the presence of an antibacterial, the drug is not recycled and is lost more quickly.

Increasing research shows that numerous drug transporters are involved in the hepatic extraction and secretion of drugs into the bile. The relevance of many of these to drug interactions is still unclear, but the bile salt export pump is known to be inhibited by a variety of drugs.[19,20]

1.1.2. Pharmacodynamic interactions

Pharmacodynamic interactions are those where the effects of one drug are changed by the presence of another drug at its site of action. Sometimes the drug directly competes for particular receptors (e.g.beta2 agonist) but often reaction is more indirect and involves interference with physiological mechanisms. These interactions are much less easy to classify neatly than those of pharmacokinetic type. This may result in an enhanced response (synergism), an attenuated response (antagonism) or an abnormal response.[21,22]

1.1.2.1. Synergistic interaction

If two drugs with similar pharmacological effects are given together, the effects can be additive. Although not strictly drug interactions, the mechanism frequently contributes to adverse drug reactions. For example, the concurrent use of drugs with CNS depressant effect, such as antidepressants, hypnotics, antiepileptic and antihistaminic, may lead excessive drowsiness; yet such combinations are frequent encountered. E.g. .aspirin with paracetamol.[23,24]

1.1.2.2. Antagonistic interaction

It is to be expected that a drug with an antagonistic action at a particular receptor type will interact with antagonists at that receptor E.g. atropine with acetylcholine.

1.2. Type of drug-drug interaction[25,26]

Depending on the type of effect produced, drug-drug interaction may be classified as.

1.2.1. Inhibitory drug-drug interaction

An inhibitory drug -drug interaction partially or completely prevents a drug from exerting its action, thus diminishing its effect in the patient. Antagonism, a type of inhibiting interaction occurs when a drug with a given activity is blocked by a drug with a nullifying action e.g.

- Amphetamine and barbiturates
- Morphine and naloxone
- Adrenaline and propranolol

1.2.2. Potentiating/modifying drug-drug interaction

A potentiating interaction enhances the toxic or therapeutic effects of a drug in patients. Synergism, supra addition, modification, absorption, distribution, metabolism and excretion of drug or modification of the drug action at receptor or site may be involved Synergism, a type of potentiation, occurs when the combined effect of two or more drugs, acting simultaneously is greater than the sum of the individual effects produced when each drug is administered alone e.g.

- Levodopa and Carbidopa
- Sulphonamide and Trimethoprim
- Isoniazid and Rifampicin

1. 3. Causes of Drug-drug Interaction[27,28]

1.3.1. Drug explosion, administration of more drugs simultaneously

It is common practice to prescribe more drugs at a time which is referred as "therapeutic jungle "or poly pharmacy

1.3.2. Patients may refer many doctors

Sometimes a patient is not satisfied by one doctor and may consult other doctors without informing about the consultation of the first doctor.

1.3.3. Irrational poly pharmacy concurrent use of prescribed and non-prescribed drugs

A patient may take drugs like aspirin; antacid which are which are available without physician's prescription. If such patients are on other drugs prescribed by physician for example digoxin or tetracycline, drug-drug interaction may occur.

1.3.4. Patient's non compliance

Sometimes the patients does not compile with the instructions given by the physician and pharmacist about the drug administration.

1.4. Factors Responsible For Drug-Drug Interaction[29]

1.4.1. Insufficient knowledge

Inadequate understanding of the pharmacokinetic and pharmacodynamics of the drug may lead to drug – drug interaction.

1.4.2. Poly pharmacy

Taking more number of drugs which are differ in pharmacology, may leads antagonism or synergism of drug action.

1.4.3. Physiology of individual

Factors such as age, sex, weight, genetic and genetic abnormalities influence the occurrence of drug-drug interaction.

1.4.4. Presence of disease state

Pathological conditions like liver disease, kidney damage or altered enzyme systems may affect the handling of drugs by the body and lead to adverse drug-drug interaction.

2. Assessment of Drug-Drug Interaction

Drug-drug interactions are the important cause of therapeutic problems and increased number of hospital admission[30]. A large number of drugs are introduced every year and new interactions between the medications are increasingly being reported. Multiple drug regimens, is on the rise because of which the risk of adverse interactions has increased.[31]

Among medical errors, DDIs have recently received increased attention. Currently available estimates of DDIs incidences vary widely depending on the method of defining and finding DDIs and the method of defining the population assessed.[32,33,34] The clinical result of a DDIs may manifested as antagonism, synergism or idiosyncratic.[35]

The consequence of mistakes and drug errors such as DDIs affect millions of patients every year and contribute to 5% of patient admission in to hospitals.[36,37,38] These medication errors also increase the patient's expenses which ultimately affect the whole society[40].There is little knowledge in terms of DDIs on the clinical level and most evidences and documentations on this came from.[41]

There are numerous compendia for assessment of drug-drug interaction, like BNF, the Vidal, the Micromedex program, the Drug Interaction Fact, the American Hospital Formulary Service Drug Information, the Lexicomp program, the US Pharmacopeia Drug Information, Stockley's Drug Interactions, Hansten;s Drug Interactions Analysis And Management etc. However, compendia often do not document methodology for listing as well as ranking the potential clinical severity of drug – drug interaction. This may be reason for inconsistent informing. Inconsistent drug-drug interaction information can cause variation and confusion in prescribing, possibly may increasing the incidence of morbidity and mortality. As an example, according to British National Formulary co-administration of corticosteroids and macrolide antibiotic had no serious consequence but had moderate severity according to other authoritative sources. Stockley's Drug Interaction even reports that Co-administration may be therapeutically beneficial. Additionally, previous studies have shown that there is inconsistency in Drug-drug interaction information.[42,43,44]

2.1 British National Formulary

The BNF is joint publication of the British Medical association and the royal Pharmaceutical society. It is published biannually under the authority of Joint Formulary Committee which comprises representatives of the two professional bodies, the UK Health Departments, The Medicines and healthcare products Regulatory agency, and the national guideline producer. The BNF aims to provide prescribers, pharmacist, and other healthcare professionals with sound up-to-date information about use of the medicines.

The BNF includes key information on selection, prescribing, dispensing and administration of medicines. Medicines generally prescribed in the UK are covered and those considered less suitable for prescribing are clearly identified.

Information on drugs is drawn from the manufacturer's product literature, medical and pharmaceutical literature, UK Health departments, regulatory authorities, and professional bodies

BNF for children should be consulted for detailed information on the use of medicines in children. The BNF should be interpreted in the light of professional knowledge and supplemented as necessary by specialized publication and by reference to the product literature. Information is also available from medicines information services. The print edition of the BNF is updated in March and September each year.[45,46]

2.2 Stockley's Drug Interactions

This comprehensive, peer-reviewed, fully referenced text book is comprised of thirty chapters; the first of which discussed general consideration and explanation of concepts, regarding the mechanisms of drug interactions. Over 3,100 monographs are contained within individual chapters that discussed specific drugs and drug classes, and a final chapter that deals with miscellaneous drugs. Monographs are grouped individually, pharmacologically, or therapeutically, and cover potential drug-drug, drug-food, drug-juice, and drug-herbal product interactions. Each clearly written monograph is detailed, yet concise, and consists of information in the following subsection, based upon a large body of published literature.

- Introductory summary
- Clinical evidence
- Mechanism
- Important and management
- Reference

Some monographs contain fewer subsections where there is information available, or the need to be comprehensive is less necessary. This reference textbook is a very practical resource for several reasons. The introductory summary subsection provides a quick assessment of the potential drug interaction, which is extremely useful for the busy health care clinician. Besides providing information on the clinical significance of potential interactions, the important and management subsection presents a practical method to avoid possible clinical problems. By relying on evidence based information, discussion of concerns regarding theoretical potential drug interactions is reduced, thereby minimizing consideration of theoretical concerns.

Stockley's Drug interactions are invaluable reference, when evaluated, evidence based and clinically relevant information concerning drug interactions is required.[47,48]

2.3 Lexicomp

Lexicomp develops superior medication safety. Our comprehensive content provides clear, concise, and accurate information which is updated daily by clinical staff. The data base includes:

- Dosing by
  - Rout
  - Population
  - Indication
  - Renal/ hepatic impairment adjustments
- Special FDA Alerts/ Black Box Warnings
- Drug interaction Analysis

Clinical pearls addressing anesthesia, cardiology, critical care, oncology etc.[49]

3. Importance of Paediatric Patients

Paediatric population has distinct physiology, and cannot be treated as miniature of the adult population. In international level, this population this population is grouped in to preterm newborn infants, term newborn infants (0-11 days), infants and toddlers (23days–23 months), children (2-11 years), and adolescents (12-18 years).[50]

Paediatric population are more vulnerable to various ADEs to drug and poor understanding of instructions on prescription by the patient or care taker where likely to cause medication error and less effective treatment.

Clinical trial of drugs is a major component of Evidence Based Medicine, which provides good evidence about drug safety and efficacy. Unfortunately there is a lack of paediatric randomised clinical trial (RTC), which has contributed to the scarcity of knowledge about the drug safety and efficacy in children.[51,52]

Paediatric patients require special attention from health professionals in terms of drug interactions, as they react to drugs differently from adults. The body parts that are responsible for the excretion and elimination processes are not fully developed until 1 year of age, resulting in extended half-life of metabolized drugs and reduced excretion, which may result in toxicity problems.[53,54]

OBJECTIVES AND METHODOLOGY

Aim

A comparative study on assessment drug-drug interactions in hospitalized paediatric patient in a tertiary care hospital

Objectives

The study entitled 'A comparative study on assessment major drug-drug interactions in hospitalized paediatric patient in a tertiary care hospital' was aimed to the following objectives:

- To estimate the prevalence and assessment of Drug-Drug interaction in hospitalized paediatric patients
- Comparison of Drug-Drug Interactions [DI] using Lexicomp, BNF and Stockley's Drug Interactions.

Study Location

- The study is to be carried out in the paediatric department of a tertiary care hospital in kerala

Study Plan

Submission of protocol and obtaining consent from hospital Authorities.

- Literature survey.
- Designing of Data entry format.
- Patient information & consent form.
- Data collection.
- Data compiling, processing and submission.

Study design

Prospective-Observational study

Study criteria
Inclusion criteria
The study included hospitalized patients between 2 month and 15 years old, containing 2 or more drugs in their medical prescriptions.

Exclusion criteria
The study excluded patients hospitalized in emergency areas and oncology unit

Sample size: 130
The sample size is calculated by using the following equation
$n = Z^2_{1-\alpha/2} p(1-p)/d^2$

Expected prevalence of event in the study group= p

Expected absolute error in the P = d (eg as 10% of relative absolute error as 10% of P)

Value of the normal deviate at considered level of confidence = $Z_{1-\alpha/2}$

Study procedure
The study is a Prospective Observational study. The institutional ethics committee approval was obtained prior to initiation of this study. Patient in the ward and ICU of paediatric department during the study period is monitored actively for the occurrence of any one of drug-drug interaction till their discharge from the hospital. The entire patients of the paediatric age group less than 15 years of age are included for the study. Monitoring of drug – drug interactions has based on regular questioning of care takers and healthcare professionals for occurrence of drug interaction as well as laboratory investigation, if indicated clinically. The assessments of drug interaction among the prescribed drugs have been performed using Stockley's drug interaction, BNF and Lexicomp database, and estimate the prevalence of drug interaction. Then list out drug interactions based on BNF, Stockley's drug interactions and Lexicomp and compare the effect and severity of drug interactions.

Data collection: Tools and techniques
The data were collected by gathering medical record of paediatric in-patient at tertiary care hospital in kerala. The data were collected are documented in the data collection form. The drugs written in the medical record were checked for Drug-Drug interaction using three compendia- Lexicomp, BNF and Stockley's Drug interaction.

Ethical consideration
- Informed consent was obtained from all care taker of patients meeting inclusion criteria
- The study started only after getting the approval from Human Ethics Committee.

Plan of analysis
Analysis of data was done using SPSS VERSION 21.0 statistical software.

RESULT AND DISCUSSION
The project entitled "comparative study on assessment of drug - drug interaction in paediatric patients in a tertiary care hospital" was carried out for a period of 6 months from March to August. During this period 130 people enrolled in this study based on inclusion and exclusion criteria mentioned earlier. Overall 141 patient's prescription were collected and analysed. The analysis based on inclusion and exclusion criteria revealed that only 130 patients prescription were included in the study. Further analysis revealed that only 45 prescriptions contain drug-drug interactions

In this study 130 patent's prescription were analysed. An attempt to categorise the study population based on their gender were tabulated in table no: 1. The overall study population contains 79 male patients and 51 female patients. That is the overall study population showed male patients are more in number (60.76%) and 39.76% patients belongs to female category. There are a total of 45 prescriptions contain DDIs, and in which 34 male's prescriptions and 11 are female's prescriptions. That is in case of prescription containing DDIs male population is also predominant (75.56%) and only 24.44% female patient's prescription contains DDIs. This similar study observed *Umi Chairani Manik et al (2013).* In which 50.9% of male population had DDIs and 49.1% female had DDIs.

Table 1: Distribution of patients based on gender.

Gender	DDIs Present		DDIs Absent		Overall	
	Count	Percentage (%)	Count	Percentage (%)	Count	Percentage (%)
Male	34	75.56	45	52.94	79	60.76
Female	11	24.44	40	47.06	51	39.24

Paediatric population has distinct physiology, and can't be treated as miniature of adult population. In international level this population are grouped in to preterm new born infants, new born infants (0-28 days), infants and toddlers (23 days-23months), children (2-11years) and adolescents(12-18years). In the study population majority of patients fall under the age group of 2-11 years (54.61%). No one belongs to the age group of 0-28 days.34.62% of patients belongs to age group >28days-23 months and 10.77% of patients belongs to the age group of 12-17 years. In the case of DDIs majority of patients fall under same age group i.e.2-11 years (64.45%), 24.44% patients belongs to >28days-23 months and 11.11% of patients belongs to the age group

of 12-17 years(table 2) Mean value of overall study population is 4.95±3.95, mean value of DDIs present is 5.32±3.84 and DDIs absent is 4.84±3.86. Similar study conducted by *Umi Chairani Manik et al (2013).* In their study the percentage of patients at the age between 2-11 years was 55.6% and in case of DDIs 40.5%.

Table 2: Distribution of patients based on age.

Age	Overall		DDIs present		DDIs absent	
	count	Percentage (%)	count	Percentage (%)	count	Percentage (%)
0-28 days	0	0	0	0	0	0
>28days-23months	45	34.62	11	24.44	30	35.29
2-11 years	71	54.61	29	64.45	48	56.47
12-17 years	14	10.77	5	11.11	7	8.24
Mean ±SD	4.95±3.95		5.32±3.84		4.84±3.86	

$X^2 = 1.878$, P = 0.5982

In the study population majority of patient's prescription contains 2-3 drugs (44.62%), 24.62% of patient's prescription contains 4-5 drugs, 10.00% of patient's prescription contains 6-7 drugs and 20% of patient's prescription contains ≥ 8drugs. In case of DDIs majority of patient's prescription contains ≥ 8drugs (60.00%), 2.22% of patient's prescription contains 2-4 drugs, 11.11% of patient's prescription contains 5-6 drugs and 26.67% of patient's prescription contains 6-7 drugs(table 3). Mean value of overall population is 4.52±2.52; Mean value of DDIs present is 7.58±1.64 and Mean value of DDIs absent is 2.92±0.93.The p value is calculated as <0.0001 revealed that there is a statistical significant difference. When number of drugs increases number of DDIs also increased, i.e. poly pharmacy is a factor of causing DDIs. *Lio Hl et al* conduct similar study also showed that a strong relationship between number of drugs and DDIs. Another study conducted by *Umi Chairani Manik et al.* revealed that the amount of drug has strong co relation with the DDIs(r=0.645).

Table 3: Distribution of patients based on number of drugs.

Number of drugs prescribed	DDIs present		DDIs absent		Overall	
	Count	Percentage (%)	Count	Percentage (%)	count	Percentage (%)
2-3	1	2.22	57	67.06	58	44.62
4-5	5	11.11	27	31.77	32	24.62
6-7	12	26.67	1	1.17	13	10.00
≥8	27	60.00	0.00	0.00	27	20.77
Mean ±SD	7.58±1.64		2.92±0.93		4.52±2.52	

P = **<0.0001

Major class of drug involved in DDIs are antiepileptic, antacid, corticosteroid and antibacterial drugs. The details are given in the table:4. In which antiepileptic class of drugs involved most of DDIs. Out of 79 prescribed antiepileptic 86.08% of drugs involved DDIs, 54.55% of prescribed antacids involved in DDIs, 40.00% of prescribed corticosteroids involved in DDIs and only 20.41 % of prescribed antibacterial in DDIs.

Table 4: Major classes of drugs involved.

	DDIs present		DDIs absent		Overall	
Class of Drugs	Count	Percentage (%)	count	Percentage (%)	Count	Percentage (%)
Antiepileptic	68	86.08	11	13.92	79	47.59
Antacid	12	54.55	11	45.45	23	13.86
Corticosteroid	6	40.00	9	60.00	15	36.14
Antibacterial	10	20.41	39	79.59	49	29.52

Assessment of severity of DDIs using all three compendia companied together are given in the table: 5.According to Lexicomp there was a five range of severity by BNF two range of severity, and there is no severity range were mentioned by Stockley. Out of 90 numbers of DDIs 15.56% major severity range, 73.33% of DDIs had moderate severity, 11.11% had minor severity, 25.55% of DDIs had No Serious Consequence (NSC) and only 3.33% of DDIs are potentially Hazardous (PH).

Table 5: Severity of Drug-drug interaction.

Severity	Count	Percentage (%)	Database
Contraindicated	0	0	Lexicomp
Major	11	15.56	Lexicomp
Moderate	61	73.33	Lexicomp
Minor	3	11.11	Lexicomp
Unknown	0	0.00	Lexicomp
PH	3	11.54	BNF
NSC	23	88.46	BNF

There was a comparison of DDIs in prescription assessed using three different compendia. The details are given in the table:6 and .A total of 130 prescriptions analysed using three different compendia - Lexicomp, BNF and Stockley's. Lexicomp assessment revels that 45 prescriptions contain DDIs i.e. 34.61% and 65.39 prescription not contain DDIs. BNF assessment reveals that 21.54 % of prescription had DDIs and 78.46% of prescription not contains any DDIs. Stockley's assessment reveals that only 18.46 % had DDIs and more than 80% of prescriptions not contain any DDIs. There no significant association (p = >0.999). . The similar study was observed by *Bozana S et al* revealed that most of the DDIs (60.63) were identified in only one compendium.

Table 6: comparison of DDIs

Category of prescription screened (n=130)	Lexicomp		BNF		Stockley's	
	Count	%	Count	%	Count	%
Prescription with DDIs	45	34.61	28	21.54	24	18.46
Prescription without DDIs	85	65.39	102	78.46	106	81.54
Prevalence	34.61 %		21.54%		18.46%	

An attempt to compare assessment of major DDIs revealed that there is a mild agreement between three compendia. The details are given in the table: 7. Most of prescription contains single DDIs when compendia assessed individually. The prescription contains 4 or more number of DDIs was not identified by both BNF and Stockley. But Lexicomp assessment reveals that 8.80% and 4.45% prescription contains 4 and 5 number of DDIs respectively. There is significant agreement between the three compendia.

Table 7: Comparison of number of DDIs per prescription.

Number of DDIs	Number of prescription					
	Lexicomp		BNF		Stocker's	
	Count	Percentage (%)	count	Percentage (%)	Count	Percentage (%)
1	20	44.44	19	67.85	11	45.83
2	13	28.88	6	21.43	9	37.50
3	6	13.33	3	10.72	4	16.67
4	4	8.89	0	0.00	0	0.00
5	2	4.45	0	0.00	0	0.00
Mean ±SD	0.69±1.17		0.31±0.67		0.32±0.74	

X^2=43.073 p=**<.0.0001

There is an attempt to compare the DDIs as listed in three compendia. The details are given in the table no: 8 Only 13(17%) DDIs were listed in all three compendia. More than 20(25%) of DDIs were listed in 2 compendia. More than 50% of DDIs were identified only by one compendium.

Table 8: comparison of DDIs as listed in three compendia.

DDIs listed in	No: of DDIs listed	No: of DDIs listed in various combination of compendia					
		Lexicomp		BNF		Stockley	
		count	%	Count	%	count	%
All 3 compendia	13	13	17.33	13	17.33	13	17.33
2 compendia	7	7	9.33	0	0	7	9.33
	13	13	17.33	13	0	0	0
One compendia	42	67	56.00	0	0	0	0
Total	75	75		26		20	

When compare the severity rating in three compendia reveals that there no severity rating in Stockley, and Lexicomp severity classes are contraindicated, major, moderate, minor and unknown, and BNF severity classifications are NSC and PH. The details are given in the table: 9.63.64% of major DDIs are not included in BNF and 65.57% of moderate DDIs are not listed in BNF. 36.36% of major DDIs are reported as NSC in BNF. Three PH DDIs are reported as moderate severity class in Lexicomp(table 9). There is no significant level

of association. The similar study was observed by *Michael J et al.* In their study severity score for all DDIs by proprietary databases (Micromedex and Lexicomp) were compared.

Table 9: Comparison of severity of DDIs.

Lexicomp	BNF			
	PH	NSC	NI	Total
Contraindicated	0 (0.00%)	0(0.00%)	0(0.00%)	0(0.00%)
Major	0(0.00%)	4(36.36%	7(63.64%)	11(14.57%)
Moderate	3(4.92%)	18(29.52%)	40(65.57%)	61(81.33%)
Minor	0(0.00%)	0(0.00)	3(100%)	3(4.00%)
Unknown	0(0.00%)	0(0.00)	0(0.00)	0(0.00%)
Total	3(4.00%)	22(29.33%)	50(66.67%)	75(100%)

r =0.3714 p=0.2759

CONCLUSION

A total of 130 prescriptions were analysed. Out of 130 prescriptions only 45 prescriptions contains DDIs. The prevalence of DDIs found to be 34.61%. Out of 90 DDIs 25 DDIs were found to be repeated.76 DDIs analysed using Lexicomp. Out of 76 DDIs 20 are not present in Stockley's Drug interaction, 37 DDIs are not present in BNF as compared to Lexicomp. Only two had potentially hazardous DDI. More than 60% of DDIs were found to be moderate. Paediatric health professionals often do not have specialized interactions textbook to hand or support Drug-drug interaction screening program. Therefore it become necessary a comparative study to identify whether there is consistency in assessment of drug-drug interactions in at least three authoritative drug information sources

REFERENCE

1. Stockly IH. Drug interactions. In: A source book of adverse interactions, their mechanisms, clinical importance and management. 5th edition. London: pharmaceutical press, 1999.
2. Chan D, Chen J, Kuo H, Jung C, Chiu S et al. Drug related problems (DRPs) identified from paediatric medication safety review clinics. Archives of paediatrics, 2011; 1-7.
3. Sehn R, Camargo AL, Heineck I, Ferreira MBC. Interações medicamentosas potenciais em prescrições de pacientes hospitalizados. Infarma, 2003; 15(9/10): 77-81.
4. Castro CGS, Teixeira CC. In "Interações Medicamentosas". Fuchs FD, Wannmacher L, Ferreira MB. Farmacologia Clínica – Fundamentos da Terapêutica Racional. 3ªed. Rio de Janeiro: Guanabara Koogan, 2006; 67-72.
5. Lisboa SML. In "Interações e Incompatibilidades Medicamentosas". Gomes MJVM, Reis AMM. Ciências Farmacêuticas – Uma Abordagem em Farmácia Hospitalar. 1 ed. São Paulo: Atheneu, 2000; 147-62.
6. Bozana S. Nikolic et al, Assessment of the consistency among three drug compendia in listing and ranking of drug-drug interactions; Bosn J Basic Med Sci, 2013; 13(4): 253-258.
7. MackKichan JJ. Protein binding drug displacement interactions. Fact or fiction? Clin Pharma- cokinet, 1989; 16: 65-73.
8. Dahlstorm M. Paediatric Zuckermann, Dos Santos et al, Profile of drug interaction in Hospitalized children, Journal of pharmacy practice, 2007; 5(4): 157-16. 1rugprescribing. Eur J clin pharmacol, 1989; 37: 65-8.
9. Sanson LN, Evans IS What is the true clinical significance of plasma protein binding displacement interactions. Drug safety, 1995; 12: 227-33.
10. Benet LZ, Hoener B-a. changes in plasma protein binding have little clinical relevance. Clin Pharmacol Ther, 2002; 71: 115-121.
11. Philips Ka, Veenstra DL, Oren e, Lee JK, Sadee w. Potential role of Pharmacogenomics in reducing adverse drug reaction: a systemic review. JAMA, 2001; 286: 2270-79.
12. Bjornsson TD, Callaghan JT, Einolf HJ, Fischer V, Gan L, Grimm S, Kao J, King SP, Miwa G, Ni L, Kumar G, McLeod j, Obach RS, Roberts S, Roe A, Snikeris F, Sullivan JT, tweedie D, Vega JM, Walsh J, Wrighton SA. The conduct of in vitro and in vivo drug-drug interaction studies: a PhRMA perspective. J Clin pharmacol, 2003; 43: 443-69.
13. Bachmann KA, Ghosh r. The use of in vitro methods to predict in vivo pharmacokinetics and drug interactions. Curr drug Metab, 2001; 2: 299-314.
14. Yao C, Levy RH. Inhibition- based metabolic drug-drug interaction: prediction from in vitro data. J Pharm Sci, 2002; 91: 1923-35.
15. Worboys PD, Carlie DJ. Implications and consequence of enzyme induction on preclinical and clinical drug development. Xenobiotica, 2001; 31: 539- 56.
16. Venkatakrishnan K, Von Moltke LL, Obach RS, Greenblatt DJ. Drug metabolism and drug interaction: apllication and clinical value of invitro models. Curr Drug Metab, 2003; 4: 423-59.
17. Lee W, Kim RB. Transporters and renal drug elimination. Annu Rev Pharmacol Toxicol), 2004; 44: 137-66.

18. Faber KN, Muller M, Jansen PLM Drug transport protiens in the liver. Adv Drug Deliv Rev, 2003; 55: 107-24.
19. Sternbach H. The serotonin syndrome. Am J psychiatry, 1991; 148: 705-13.
20. Miller Lg. Herbal medicinals. Selected clinical considerations focusing on known or potential drug herb interactions. Arch Intern Med, 1998; 158: 2200-11.
21. Wang Z, Gorski JC, Hammam MA, Huang S_M, lesko LJ, Hall SD. The effects of St John's wort (hyperium perforatum) on human cytochrom P450 activity. Clin pharmacol. Ther, 2001; 70: 317-26.
22. Henderson L, Yue QY, Berguist C, Gerden B, arlett p. St John's Wort (hyperium perforatum): drug interaction and clinical outcomes. Br J Clin Pharmacol, 2002; 54: 349-56.
23. Gurley BJ, Gardner SF, Hubbard MA, Williams DK, Gentry WB, Cui Y, Ang CYW. Cytochrome P450phenotypic ratios for predicting herb-drug interactions. Clin Pharma- col Ther, 2002; 72: 276-86.
24. Dresser GK, Schwarz UI, Wilkinson GR, Kim RB. Coordinate induction of both Cytochrome P4503 A and MDRI BY st John's wort healthy subjects. Clin Pharmacol. Ther, 2003; 73: 41-50.
25. Tripathi KD, Essential of Medical pharmacology, 6th edition, Jaypee Brothers, Medical Publisher (P) Ltd, 889-896.
26. Patidar Dindayal; Pharmacology –IV (Clinical and Drug interaction), Sree Sai Prakashan Meerut.
27. Scott R Penzak, Pharm D. Director, Clinical pharmacokinetics Research Laboratory Clinical centre pharmacy department National Institute of Health December 9, 2010.
28. Guideline on the Investigation of Drug interactions, Draft, 2010. [Internet]. London: European Medicines Agency, Committee for Human Medical Products. Available from:http://www.aaps.org. [accessed: 10 March 2010].
29. Paul W. Ament, Pharm D,John G Bertolino, MD, M.S.P.H and James L. Liszewski, M. D , Clinically significant Drug interaction, 2000; 61(6): 1745-1754.
30. Kohn LT, Corrigan JM, Donaldson MS, eds. To err Is human: Building a safer health system. Washington DC, National Academy Press, 1999.
31. Expert Group on Learning from Adverse Events in the NHS. An organisation with a memory. London, Stationery Office, 2000. http://www.doh.gov.uk/orgmemreport/index.htm.
32. Australian Council for Safety and Quality in Healthcare. Second national report on patient safety: improving medication safety. Canberra, Australian Council for Safety and Quality in Healthcare, 2002.
33. Rosholm JU, Bjerrum Hallas J, Worm J, Gram LF. Polypharmacy and the risk of drug–drug interactions among Danish elderly. Danish Med Bull, 1998; 42: 210–3.
34. Pirmohamed M, James S, Meakin S, Green C, Scott A, Walley T, Farrar K, Park B, Breckenridge A. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. BMJ, 2004; 329: 15–9.
35. Shojania KG, Duncan BW, McDonald KM, Wachter RM, eds. Critical analysis of patient safety practices. Evidence Report/Technology Assessment No. 43. AHRQ Publication No. 01-E058. Rockville, MD, Agency for Healthcare Research and Quality, 2001.
36. Hazlet TK, Lee TA, Hansten P, Horn J. Performance of community pharmacy drug interaction software. J Am Pharm Assoc, 2001; 41: 200–4.
37. Mukasa D, Hughes, J. Drug interactions in the elderly: frequency, significance and differences among standard reference resources. Australian Pharmacist, 2002; 21: 603–8.
38. Chen YF, Neil KE, Avery AJ, Dewey ME. Prescriptions with potentially hazardous/ contraindicated drug combinations presented to community pharmacies. Int J Pharm Pract, 2002; 10(Suppl): R29.
39. Bergk V, Haefeli WE, Gasse C, Brenner H, Martin-Facklam M. In- formation defi cits in the summary of products characteristics preclude an optimal management of drug interactions: a comparasion with evidence from the literature. Eur J Clin Pharmacol, 2006; 61(5- 6): 327-335.
40. Vitry AI. Comparative assessment of four drug interaction com- pendia. Br J Clin Pharmacol, 2007; 63(6): 704-713.
41. Fulda TR, Valuck RJ, Vander Zanden J, Parker S, Byrns PJ, Th e US Pharmacopeia Drug Utilization Review Advisory Panel. Disagree- ment among drug compendia on inclusion and ratings of drug- drug interactions. Curr Th er Res Clin Exp, 2000; 61(8): 540-548.
42. Abarca J, Malone DC, Armstrong EP, Grizzle AJ, Hansten PD, Van Bergen RC, et al. Concordance of severity ratings provided in four drug interaction compendia. J Am Pharm Assoc (2003), 2004; 44(2): 136-141.
43. http://www.bnf.org British National Formulary website.
44. Aronson, J. K. "Drug interactions-information, education, and the British National Formulary". *British Journal of Clinical Pharmacology*, 2004; **57**(4): 371–372. doi:10.1111/j.1365-2125.2004. 02125.x. PMC 1884473. PMID 15025733. edit.
45. Wade, O. L. "British National Formulary: Its birth, death, and rebirth". *BMJ (Clinical research ed.)*, 1993; 306 (6884): 1051–1054. doi:10.1136/bmj. 306.6884.1051.PMC 1676980. PMID 8490505. edit.
46. Anon "British National Formulary 1976-8". *British medical journal*, 1978; 2(6136): 580–581. doi:10.1136/bmj.2.6136.580-b. PMC 1606955. PMID 20792725. edit
47. http://www.wolterskluwerhealth.com/News/Pages/ WoltersKluwerHealthtoAcquireLeadingGlobalDrugInformationProviderLexi-Comp.aspx.

48. Cruciol-Souza JM, Thomson JC. A pharmacoepidemiologic study of drug interactions in a Brazilian teaching hospital. Clinics, 2006; 61(6): 515-20.
49. Hohl CM, Dankoff J, Colacone A, Afilalo M.Polypharmacy, adverse drug-related events, and potential adverse drug interactions in elderly patients presenting to an emergency department. Ann Emerg Med, 2001; 38(6): 666-71.
50. Sehn R, Camargo AL, Heineck I, Ferreira MBC. Interações medicamentosas potenciais em prescrições de pacientes hospitalizados. Infarma, 2003; 15(9/10): 77-81.
51. Castro CGS, Teixeira CC. In "Interações Medicamentosas". Fuchs FD, Wannmacher L, Ferreira MB. Farmacologia Clínica – Fundamentos da Terapêutica Racional. 3ªed. Rio de Janeiro: Guanabara Koogan, 2006; 67-72.
52. Novaes MRC, Gomes KLG. Estudo de utilização de medicamentos em pacientes pediátricos. Infarma, 2006; 18(7/8): 18-20.
53. Bozana S. Nikolic, Maja S. Ilic, Bosn J. Assessment of the consistency among three drug compendia in listing and ranking of drug-drug interaction.Basic Med Sci, 2013; 13(4): 253-258.
54. Umi Chairani Manik, Urip Harahap, Gulishan Dasa Tjipta. A retrospective study on drug interaction for paediatric in patients at central public hospital Haji Adam Malik. Int.J basic Clin pharmacol, 2014; 3(3): 512-516.