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Research Article

An Observational Study Report on Adverse Drug Reactions of A Combination of Drugs in A Tertiary Care Hospital, Kolkata, West Bengal

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ABSTRACT

Background: Drugs or proper medications can be a preventive measure against several temporary or chronic human diseases and physiological conditions. But sometimes, drugs can turn out to be a bane to human life rather than becoming a boon. Administration of certain drugs may lead to several undesirable detrimental effects to human health that may even be fatal if gone unnoticed. These reactions are more commonly referred to as the Adverse drug Reactionsâ™.

Aim: In the current study, our major aim is to probe the adverse drug reactions of two particular drugs Paracetamol and Cephalosporin, when administered in combination or separately in a tertiary care hospital, Kolkata, West Bengal.

Material and methods: Our study involves a hospital-based observational study where the adverse drug reactions reported by medical practitioners over a period of six months were assessed in patients administered with paracetamol and cephalosporin group of drugs in combination or separately.

Results: In this study, 100 patients were administered paracetamol and cephalosporin drug groups both separately or in combination. Out of them, 36 patients developed ADR like hepatotoxicity, hypotension, anemia, vomiting, skin rashes as well as Steven Johnson Syndrome. Adverse drug reaction is found to be more common in women than in men. Also, middle-aged adults (15-65 years) are more prone to adverse drug reactions on the administration of a combination of paracetamol and cephalosporin drugs. Further, when the patients were subjected to a dose of a combination of paracetamol and cephalosporin drug groups, they experienced mainly vomiting along with some minor cases of hypertension, hepatotoxicity, and skin rashes.

Conclusion: Our study clearly indicates that when a patient is co-administered a combination of both paracetamol and cephalosporin drug groups, the majority of the observed adverse drug reaction symptom is vomiting which is a signature adverse drug reaction symptom of cephalosporin drug group alone, indicating a clear predominance in symptoms of adverse drug reaction exhibited by cephalosporin drug group over paracetamol.

Keywords: Drugs; Adverse drug reactions; Paracetamol; Cephalosporins

INTRODUCTION

In present-day to day life, human beings are completely dependent on drugs and medicines for better overall health. Drugs can give relief to several temporary as well as chronic long-standing health issues in human life. But in reality, the same drugs which can save millions of lives can lead to severe side effects or adverse reactions in several patients which can sometimes even lead to death [1,2]. According to a recent report, adverse drug reactions turned out to be the 4th major cause of morbidity leading to deaths of about 2.5 lakhs of people every year [3]. One of the most well-known cases of 'Adverse drug reaction' was the adverse effects of Thalidomide [4,5]. Thalidomide captured the drug market as an attractive sedative and anti-emetic drug used for the treatment of morning sickness experienced by pregnant ladies. But soon, the drug was found to be the causative agent of peripheral neuropathy in patients as well as certain birth defects in newborn babies like Phocomelia [6]. Another notable example of adverse drug reaction

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includes the withdrawal of a non-steroidal anti-inflammatory drug (NSAID) named Bromfenac due to reports of severe liver failure on its administration [7]. These incidents clearly throw light on the importance of the detection of adverse drug reactions among current circulating drugs. But still, not many past research studies are available on the topic.

A well-known highly consumable non-steroidal anti-inflammatory non-prescription drug in the present-day market is paracetamol [8,9], which is readily available to the general public. Although paracetamol is a potent antipyretic drug within the therapeutic dose, there were several reports linked to adverse effects of paracetamol in several patients [10,11]. The first reported case of adverse drug reaction of paracetamol dates back to 1966 when an overdose of the drug caused centrilobular hepatic necrosis that finally leads to renal necrosis [12,13]. There were also some reports, where an overdose of paracetamol lead to anaphylaxis reaction like hypotension [14,15] and hemodynamic/anemia [16].

Further, the number of research studies focused on the adverse drug reaction on antibiotics is very less. One of the most commonly used antibiotics is Cephalosporin [17-20]. Cephalosporin is known to show adverse drug reactions to certain patients [21]. According to recent reports, patients allergic to penicillin are more prone to adverse drug reaction to cephalosporin [22,23]. The most common adverse drug reactions to the cephalosporin group of drugs like Cefadroxil and Cefuroxime include urticaria, angioedema, anaphylaxis as well as bronchospasm [24]. In rare cases, Cefadroxil may lead to Steven Johnson Syndrome and exfoliative dermatitis [25].

In the current study, we have performed an observational-based study on the adverse drug reactions in patients administered with paracetamol and cephalosporin drugs separately as well as in combination. Adverse drug reactions are observed in 36 percent of the patients. Females are found to be more affected by adverse drug reactions as compared to males. Adult people (15-65) are found to be the high-risk group for adverse reactions to the combination of drugs. The major aim of the study was to identify the frequency and symptoms of adverse drug reactions related to common drugs like paracetamol and cephalosporin groups when prescribed alone or in combination. The effect of adverse drug reaction displayed by the cephalosporin drug group alone i.e. vomiting was found to be predominant over the symptoms of adverse drug reaction of paracetamol drug in majority of patients when both the drugs were administered simultaneously.

MATERIALS AND METHODS

Study Design

The following study was an observational study conducted at R G Kar Medical College and Hospital, a tertiary care hospital in Kolkata, West Bengal, and India over a period of six months. A total of 100 patients of all age groups and genders were considered for the study. Consent letter was collected from all the patients. Data collection was done using a predesigned case record form which included patient characteristics such as age, gender, diagnosis, as well as prescription characteristic such as the name of the drug, strength and dosage form, number of units dispensed upon (based on their prescription or prescriber record). All biological tests, physical examinations, and other analytical test reports were recorded in detail. The patients were first explained all the adverse drug reactions and was advised to fill up the Central Drug Standard Control Organisation (CDSCO) adverse drug monitoring form as a record. The study was approved by the hospital's Ethical Committee.

Drugs Administered

The patients were administered with paracetamol drug and drugs belonging to cephalosporin groups such as cefadroxil/cefuroxime were administered either separately or in combination.

Probability Algorithms

The probability of adverse drug reaction due to drug administration was evaluated by the Naranjo scale or Naranjo algorithm [26, 27] while assessment of the severity of reported adverse drug reaction was determined by the Hartwig severity assessment scale [28].

Definitions

Naranjo scale or Naranjo algorithm may be defined as a questionnaire that measures the probability of adverse drug reaction on the administration of drugs introduced first by Naranjo *et al* [26]. The algorithm was introduced to optimize casualty assessment for all adverse drug reactions Table 1. Based on the scores obtained from the assessment, the results are interpreted as doubtful adverse drug reaction (0), possible adverse drug reaction (1 – 4), probable adverse drug reaction (5 – 8), and definite adverse drug reaction (≥ 9) respectively.

Hartwig severity assessment scale is defined as an adverse drug reaction (ADR) severity assessment scale that categorizes ADR into three distinct classes: mild (1-2 points), moderate (3-4 points), and severe (5-7 points). The detailed description of the Hartwig scale is tabulated in Table 2.

Data Analysis

Several standard statistical procedures were used to analyse the data. The majority of the data are presented as a percentage and represented by corresponding bar diagrams.

RESULTS

Demographic characteristics

The whole study was conducted with 100 patients. Out of 100 patients, 61patients were male and 39 patients were female (Figure 1). A total of 36 patients developed mild to severe several adverse drug reactions (ADR) out of 100. The patients, who developed adverse drug reactions were classified according to age groups such as pediatric (1-14 age group), adult (14-65 age group), and geriatric (65-95 age group) groups. Adults (83%) are found to be more prone to developing ADRs as compared to pediatric (7%) and geriatric (10%) age groups (Figure 2). The incidence of adverse drug reaction was higher in the case of females (34.42%) than males (38.46%) (Figure 3) The summary of the demographical characteristics of patients studied is tabulated in Table 3.

Casualty and severity data

A detailed casualty assessment based on the Naranjo scale points out that almost 88.89% of adverse drug reactions (ADRs) were found to be possible while 8.33% ADRs were probable and the rest 2.78% ADRs were found definite (Figure 4). Hartwig's severity assessment scale revealed that 86.11% of the reported ADRs were mild, 11.11% were moderate and 2.78% were severe (Figure 5).

Drug related adverse drug reaction (ADR) frequency and symptoms

As previously mentioned, a total of 36 patients out of 100 developed adverse drug reactions (ADRs) The majority of

Table 1: Table 1A shows the Naranjo assessment scale is a set of questions that determine the probability of adverse drug reactions in patients. Table 1B shows the probability of ADR based on scores from Table 1A.

Table 1A.

Question	Yes	No	DoNot know	score
1. Are there previous conclusive reports on this reaction?	+1	0	0	
2. Did the adverse event appear after the suspected drug was administered?	+2	-1	0	
3. Did the adverse reaction improve when the drug was dis-continued or a specific antagonist was administered?	+1	0	0	
4. Did the adverse reaction reappear when the drug was re administered?	+2	-1	0	
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	
6. Did the reaction reappear when a placebo was given?	-1	+1	0	
7. Was the drug detected in the blood or other fluids in concentrations known to be toxic?	+1	0	0	
8. Was the reaction more severe when the dose was increased, or less severed when the dose was decreased	+1	0	0	
9. Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	
			Total score:	

Table 1B.

Total Score	Probability of ADR
≥ 9	Definite
5 to 8	Probable
1 to 4	Possible
≤ 0	Doubtful

Table 2: Table depicts the Hartwig severity assessment scale.

Severity	Descriptions
Mild	Self-limiting ADR reactions that can resolve over time without treatment and does not stay for long time
Moderate	ADR reactions that require therapeutic intervention and hospitalization prolong by 1 day but resolved in < 24 h or require a change in drug therapy or treatment procedure to check further worsening of the outcome.
Severe	ADR reactions that requires prolonged hospital stay and can pose serious threat to life sometimes may even be fatal.

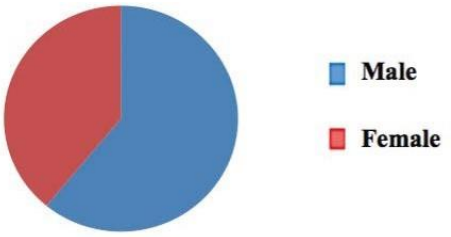

Figure 1: Pie graph representing the gender ratio of selected study group.

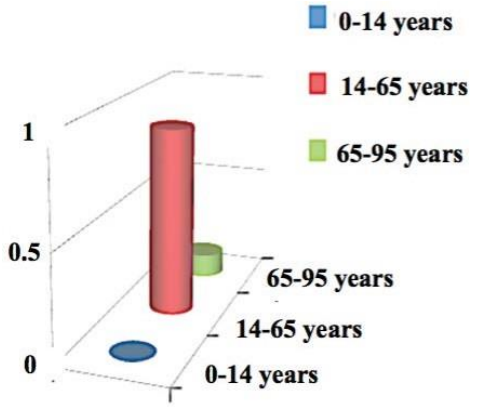

Figure 2: Bar graph representing the frequency of ADR incidents based on age: The bar diagram shows that adults (14-65 years) are most susceptible to adverse drug reactions (83%).

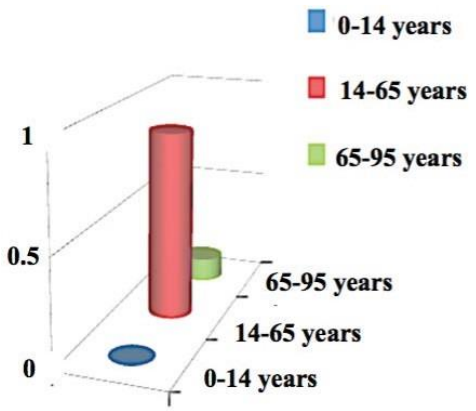

Figure 3: Bar graph representing the frequency of ADR incidents based on gender: The bar diagram clearly indicates that females (34.42%) are more prone to adverse drug reactions as compared to males (38.46%).

Table 3: Table showing the characteristics of patients used in study (total patients studied (n)=100 patients).

Demography		Percentage of patients developed ADR (%)
Sex	1) Male	34.42
	2) Female	38.46
Age	1) 0-14 years	7
	2) 14-65 years	83
	3) above 65 years	10

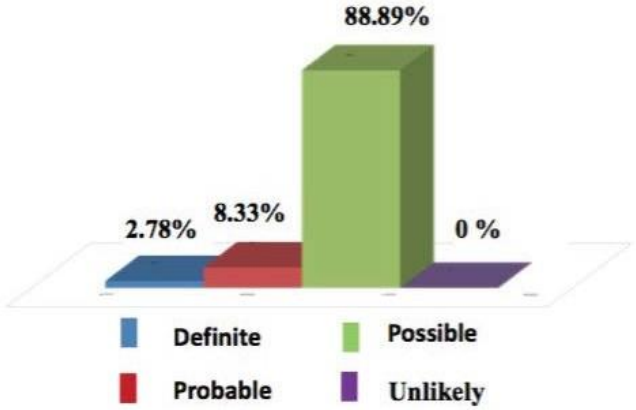

Figure 4: Bar graph representing the Naranjo casualty assessment scale: Bar graph depicting frequency of casualty of adverse drug reactions based on Naranjo algorithm. Majority of adverse drug reactions were found to be possible (88.89%) while 8.33% ADRs were probable and the rest 2.78% ADRs were definite.

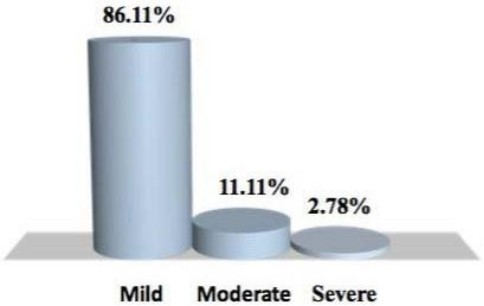

Figure 5: Bar graph representing the Hartwig's severity assessment scale: Bar diagram assessing the severity of adverse drug reactions in patients based on Hartwig's severity assessment scale. Majority of the adverse drug reactions turned out to be mild (86.11%) while 11.11% were moderate and 2.78% were severe

reported adverse drug reactions were hepatotoxicity (36.11%) and hypotension (36.11%). Some of the other adverse drug reaction symptoms include vomiting (19.44%), anemia (2.78%), skin rash (2.78%) as well as Steven Johnson Syndrome (2.78%) (Figure 6) Administration of paracetamol alone leads to ADRs like hepatotoxicity, anemia, and hypotension. The major adverse drug reaction due to the administration of cephalosporin group drugs like cefuroxime and cefadroxil was vomiting.

Administration of a combination of paracetamol and cephalosporin drug groups like cefuroxime and cefadroxil mainly leads to vomiting along with minor reports of hepatotoxicity, hypotension, anemia, skin rash, and Steven Johnson Syndrome. The detailed frequency of drug related ADRs are given in Table 4.

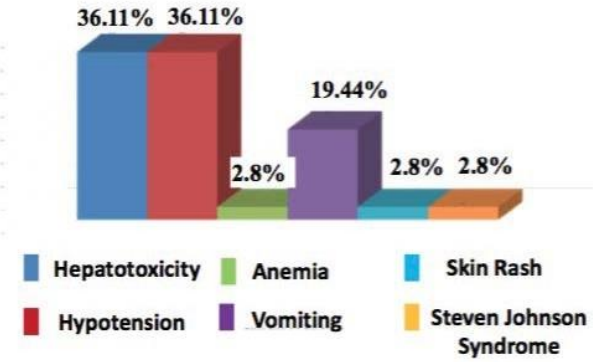

Figure 6: Bar graph representing the frequency of drug related ADR symptoms: Bar diagram depicting the frequency of different symptoms of adverse drug reactions in patients. Majority of symptoms of adverse drug reactions include hepatotoxicity, hypotension and vomiting with other minor symptoms like skin rashes, anemia and Steven Johnson Syndrome.

Table 4: ADR symptoms and frequency when patients were administered with paracetamol and cephalosporin drug groups both separately and in combination.

Drugs Administered	ADR symptoms	Number of patients developing ADR based on symptoms
Paracetamol	1. Hypotension	12
	2. Hepatotoxicity	10
	3. Anemia	1
Cephalosporin drug group	1. Vomiting	2
Paracetamol and cephalosporin both simultaneously	1. Vomiting	6
	2. Skin rashes	1
	3. Hypotension	1
	4. Hepatotoxicity	2
	5. Steven Johnson's syndrome	1

DISCUSSION

The whole study reveals in detail the frequency of casualty and severity of several adverse drug reactions (ADR) as well as their symptoms in hospitalized patients caused by commonly used life-saving medications like paracetamol and cephalosporin drug groups when prescribed separately or in combination. Our study shows that 36 % of the patients developed adverse drug reactions. The relatively higher incidence of adverse drug reaction closely matches with the previous meta-analysis study by Lazarou *et al*, where they reported a 15.1 % ADR incidents among patients [29]. Similar results were shown by *Miguel et al* with ADR incidence reports of nearly 17% in hospitalized patients [30]. Although several other recent ADR studies revealed a lower incidence rate [31-33], the main reason behind that may be the spontaneous reporting systems used in those studies which lead to underreporting [34]. Our study further indicates the fact that the incidence of ADR is relatively higher in the case of females as compared to males which correlate well with previous reports [35]. Although the exact reason for this discrepancy remains unclear, this may be attributed to the basic physiological differences between males and females such as a difference in body mass index and fat composition as well as effects of hormones on the drug metabolism. Our study also shows that adults and older people were more susceptible to drug-related ADRs as compared to paediatric groups. One of the reasons behind that may be that aging leads to physiological changes that may alter drug pharmacokinetics (absorption, distribution, metabolism, and excretion) as well as pharmacodynamics (the study of effects of a drug on the body). Previous research also indicates a two-fold increase in ADR frequency in elderly people as compared to younger people [36-38]. Results from our study demonstrate that adverse drug reactions related to paracetamol include primarily hypertension and hepatotoxicity while the adverse drug reaction related to cephalosporin drug group leads to vomiting. In total, 23 patients experienced adverse drug reactions on paracetamol administration while only 2 patients experienced adverse drug reactions on cephalosporin drug group administration. Surprisingly, when the hospitalized patients were administered a combination of both paracetamol and cephalosporin drug groups, a majority of the patients (6 out of total 11 patients who developed adverse drug reactions) suffered from vomiting which was a signature symptom of cephalosporin drug administration alone while only a small group of people experienced other adverse drug reactions like hypertension, hepatotoxicity, vomiting, and skin rashes. Administration of combination of drug also leads to a rare adverse drug reaction like Steven Johnson Syndrome in a patient (Table 4). This clearly lays out the fact that there is a clear predominance in adverse drug reaction effects exhibited by the cephalosporin drug group over paracetamol when both the drugs are administered simultaneously. Further, the majority (88.89%) of the reported ADRs were turned out to be possible (as per Naranjo scale) while Hartwig severity assessment indicated most of the reported ADRs (almost 86.11%) were mild. One of the major limitations of the study was the use of the Naranjo scale or the Naranjo algorithm. Recent studies have raised questions on the use of the Naranjo algorithm which lead to the development of various new casualty assessment scales and tools like that of Liverpool ADR Casualty Assessment Tool (LCAT) [39]. In the future, we will aim to crosscheck the casualty data using the modified casualty assessment scales [40].

CONCLUSIONS

Our study gives result consistent with previous reports such as females are more prone to adverse drug reaction effects than male and established the fact that adults (between 14-65) are more susceptible to adverse drug reactions. Our study clearly provides detail symptoms of adverse drug reactions in patients administered with paracetamol and cephalosporin drug groups separately or in combination. Our study further confirms that when a patient is administered both paracetamol and cephalosporin drug groups simultaneously, majority of the observed adverse drug reaction case is vomiting which is a signature adverse drug reaction symptom of cephalosporin group alone.

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