Clinical Pharmacist’s Interventions In Adverse Drug Reactions

Author
Sukesh Krishna Chaitanya Loka
Department of Pharm.D, Malla Reddy Institute of Pharmaceutical Sciences
Corresponding Author
Sukesh Krishna Chaitanya Loka
Plot No: 2-1/28, II floor, Opp KVR towers B block, Widia Colony, Cine town lane Miyapur, Hyderabad- 500049, Telangana, India
Email: sukeshloka@gmail.com

Abstract
Adverse drug reactions (ADRs) are broadly divided into predictable (related to pharmacologic actions of the drug in otherwise normal individuals) and unpredictable reactions (related to individual’s immunological response and, on occasion, to genetic differences in susceptible patients). Drug allergy is a type of unpredictable reaction. "Drug allergy" refers to immunologically mediated drug hypersensitivity reactions. These may be either immunoglobulin E (IgE)–mediated (immediate) or non–IgE-mediated (delayed) hypersensitivity reactions. The involvement of a critical care pharmacist has been shown to prevent ADE, and reduce the morbidity and today they are recognized as an integral member of critical care team along with the other health care professionals. The idea of a specialized intensive care pharmacist was first established in the world of pharmacy in 1982. I report a series of three case reports to display the interventions of clinical pharmacist in the management and further prevention of the drug reactions. Penicillin induced acute urticaria, Cefexime induced Steven Johnson Syndrome and Valproate induced Rise in Liver enzymes are three cases of drug reactions and the interventions of Clinical Pharmacist in the management and prevention of further recurrence has been reported in the present article.

Key Words: Adverse Drug Reactions, Cefexime, Penicillin, Valproate, Clinical Pharmacists role
INTRODUCTION

Adverse drug reactions (ADRs) are defined as any harmful or unintended reaction to a drug that occurs at doses used for prevention, diagnosis, or treatment [1]. ADRs are classified as either predictable reactions that may occur in anyone (type A) or unpredictable reactions that occur in only susceptible individuals (type B) [2]. Drug allergy is one type of unpredictable ADR that encompasses a spectrum of immunologically-mediated hypersensitivity reactions with varying mechanisms and clinical presentations [1]. The followings are the criteria for a drug reaction to be considered as an immune-mediated: reaction occurs in a small number of patients receiving the drug, reaction does not resemble the drug’s pharmacologic effects, reaction occurs even with small amount of the drug, reaction occurs with drugs with similar structures, presence of eosinophilia, and reaction resolves after discontinuation of the drug (3). Factors associated with an increased risk of developing a drug allergy include age, gender, genetic polymorphisms, certain viral infections and drug-related factors (e.g., frequency of exposure, route of administration, molecular weight) [4]. Recent examples of ADRs detected exclusively in the paediatric age group include: greenish discoloration of teeth following ciprofloxacin use in neonates [5]; gastric outlet obstruction due to prostaglandin infusion in neonates [6]; fatal hepatic dysfunction risk following valproic acid polytherapy in developmentally-delayed, mentally retarded & children with congenital anomalies of below 2 years of age [7]. It has been observed that ADRs in children not only result in hospital admissions or prolonged hospitalization but also may lead to permanent disability or even death [8]. Children are particularly at risk, with estimates suggesting that as much as 16.6% of hospitalized children experience ADRs, with nearly 30% of these being severe [9,10].

Need for intervention by clinical pharmacist (CP) in managing the policy is well established. Clinical pharmacist interventions eliminate (37.4%) of treatment problems related to efficacy and monitoring of medications [11], promote efficacy of therapy [12] and enhance desired health outcomes [13]. I report three cases of Adverse Drug Reactions which highlight the importance of clinical pharmacist’s role in the clinical decision making and prevention of further recurrence of the reactions.

CASE REPORT - 1

A five year old male patient bearing weight of 16.2 kg had been admitted in the Pediatric Intensive Care Unit (PICU) of our tertiary care hospital. The chief complaints were erythematous rashes and wheal all over the body and dry cough as shown in Fig.1. His previous medical history included common cold, cough and 2 episodes of loose stools for which he got consulted in the pediatrics Outpatient department of our hospital. He was prescribed with tablet amoxicillin twice daily at 50 mg per kg of body weight. He then developed erythematous rashes and wheal all over the body after the first dose and then got admitted in the PICU. Laboratory findings revealed an elevation in the Total WBC (18,500). The drug
amoxicillin was de-challenged and managed symptomatically with antihistamines (Levocetirizine, hydroxizine and ranitidine).

**Fig: 1. Rashes over the body**

**CASE REPORT - 2**

A 35 year old female had been admitted in the skin& VDL department our hospital with complaints of erythematous rashes and blisters all over the body, swollen lip, salivation, swollen tongue, severe itching. Patient had a previous history of fever with chills and body pains five days prior to admission and was prescribed with Tablet Cefexime 100 mg twice daily for 5 days. The patient then developed these manifestations upon the third dose. Laboratory data showed an elevation in the eosinophils (18%), Aspartate amino Transferase (93U/L), Alanine amino-transferase (123 U/L), Alkaline phosphatase (363 U /L), total bilirubin (3.3 mg/dl), direct bilirubin (1.6 mg/dl), indirect bilirubin (1.7mg/dl). Adequate fluid replenishment has been provided along with steroids and topical white soft paraffin cream.

**CASE REPORT - 3**

A 15 month old male child was admitted in the pediatrics in patient ward with the complaints of fever since three days and an episode of convulsion before the admission. The child had a history of seizures six months earlier for which he was started on syrup sodium valproate at 200 mg per day. Chest auscultations revealed tachypnea and crepitations were positive. Laboratory investigations showed an increase in ESR (70 mm/hr), Aspartate amino Transferase (50 U/L), Alkaline Phosphatase (174 U/L). The child was treated with Intra Venous antibiotics (ceftriaxone, amikacin), salbutamol nebulization.

**DISCUSSION**

According to the WHO in 1972: an adverse drug reaction (ADR) is a response to a drug which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function \[14\].

In our present study ADRs were caused by amoxicillin, cefexime and valproic acid which are the most common culprits drugs as reported by SBMS Ghazi, et al \[15\].

In the case report-1, amoxicillin produced an Ig-E mediated immediate hypersensitivity reactions (Type-I hypersensitivity reactions). The major symptoms of immediate hypersensitivity reactions are urticaria, angioedema, bronchospasm, pruritis, diarrhea and anaphylaxis. The first time a body is exposed to an immunogenic drug the T-cells, specifically T-helper-2 (TH2) cells, initiate the allergic reaction by releasing interleukine-4 and
interlukine-13 (IL-4,IL-13), which activate and induce proliferation of the B-cells, which then produce the antigen specific Ig-E. There is a cross-link between multivalent antigen and basophils or mast cells by Ig-E specific for that antigen which leads to the degranulation of basophils and mast cells and release of inflammatory mediators such as Histamine, eosinophilic chemotactic factor, leukotrienes, prostaglandins, thromboxane A2, and platelet activating factor, bradykinins, tumor necrosis factor-alpha, IL-4, IL-5, IL-6, and IL-13. As the result, these chemicals lead to bronchospasm, hypersecretion of mucus glands, increased capillary permeability and other inflammatory reactions [16].

The clinical pharmacist’s intervention in case-1 would be the identification of an irrational prescription of antibiotic (amoxicillin) for conditions for which antibiotics were not recommended by WHO [17], like common cold and diarrhea. Misuse of antibiotics is due to diagnostic uncertainty, lack of prescriber knowledge, lack of opportunity for follow-up, easy availability of antibiotics and lack of treatment guidelines [18].

The other intervention I have done as a clinical pharmacist is recommending only levocterizine as the first line therapy in managing urticaria. First-generation H1 antihistamines are highly liposoluble, they have low molecular weight and a high degree of affinity for cerebral H1 receptors, which means that sedation occurs with frequency, even at therapeutic doses. Second-generation H1 antihistamines, in contrast, have greater molecular weight, low liposolubility and low affinity for cerebral H1 receptors. Therefore, the majority of compounds in this generation, at therapeutic doses, are apparently devoid of significant side effects on the CNS. They are minimally metabolized and so are safer. The majority of first-generation H1 antihistamines exhibit pharmacological effects that are not related to their binding with H1 receptors, most commonly the anticholinergic effect, resulting from their capacity to bind to muscarinic receptors, causing dry mouth, tachycardia and urinary retention. These effects have not been reported with second-generation H1 antihistamines [19] and are recommended as initial pharmacotherapy [20].

In the case-2, Steven Johnson Syndrome (SJS) induced by cefexime has been reported which is a non Ig-E mediated hypersensitivity reaction. As reported by Lam A et al [21] fatty acid synthetase (FAS) and FAS ligand (FASL) are more responsible for keratinocyte death.

The use of an alert card which features the allergy data can help to prevent recurrence of the reaction and alert the prescribers in future medical consultations since records of drug allergy are not consistent and according to patient, there exists no drug allergy history [22]. Therefore, alert cards can be of life-or-death importance in emergency scenarios. As a clinical pharmacist, I have provided an allergy alert card as shown in the Fig.2, documenting the description of reaction and suspected drug, for the two cases of penicillin induced urticaria and cefexime induced SJS.
Fig: 2. Allergy Alert Card

In the case report-3, valproic acid (VPA) induced elevation in liver enzymes was reported. Certain risk factors for VPA-induced liver failure have been identified and include: Younger age, mental retardation, history of metabolic disorders or inborn error of metabolism, polypharmacy, stressful condition such as infection and underlying liver disease. Retrospective studies have demonstrated a transient elevation of liver aminotransferases in up to 10—15% of patients on VPA. The incidence of VPA induced fatal hepatic dysfunction is highest, 1/500, in children under 2 years of age. If follow-up reveals an increase in the values of the enzymes, investigations for coexistent liver disease are warranted and may require a switch to an alternative AED. I, as a clinical pharmacist recommended the replacement of VPA with clobazam which appears to be a useful alternative and has the advantages of a rapid onset of action, minimal side effects, well tolerated and effective than phenytoin. The easiness of oral intake, better compliance (2 doses for 2 days), and fewer adverse effects besides the equal efficacy of clobazam as compared the diazepam makes clobazam superior to diazepam.

CONCLUSION
Clinical Pharmacy services have influenced a great impact on health care system. The clinical pharmacists should be alert regarding allergy identification in the patient and documenting in medical records to alert other health care team. The clinical pharmacist should be integrated with the multi health care team for the promotion of patient safety. Pharmacists have greater responsibility in preventing and/or minimizing Drug Related Problems (DRPs) and also to reduce the unnecessary healthcare expenditures arising from DRPs occurring in patients. Active participation of a clinical pharmacist in the health care settings may greatly improve the patient outcome. The clinical pharmacist’s involvement in the drug therapy decision making may help/assist healthcare professionals in the overall management of patient.

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