CODEN [USA]: IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.1405117

Available online at: http://www.iajps.com Research Article

ADVERSE DRUG REACTION MONITORING AND OCCURRENCE IN DRUGS USED IN PULMONARY DISORDERS

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Abstract:

Drug-related problems, including adverse drug reactions (ADRs), contribute to a significant health- and quality issues. Based on prevalence studies in different settings, approximately 5 to 35% of hospital admissions are due to adverse drug reactions (ADR). An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy. ADRs are considered as the fourth to sixth leading cause of death among hospitalized patients. About 2.9-5.6% of all admissions are caused by adverse related events, and approximately 35% hospitalized patients experience an ADR. . ADRs not only increase the mortality and morbidity but also multiply the health care cost. ADR monitoring is primarily essential for drugs with narrow therapeutic index. Theophylline has been used for many years for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The incidence of ADRs due to theophylline has been found to be 4.71%, of which nausea, loss of appetite (anorexia) and palpitation were common. The study of ADRs is essential in order to determine the incidence of ADRs in medical inpatients, estimate the contribution of ADRs to hospital admissions, characterize the types of ADRs observed, determines predisposing risk factors and to estimate the costs of ADRs in terms of ADR-related excess hospital stay.

Keywords: *adverse drug reactions, Pharmacovigilance, pulmonary medicine*

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Please cite this article in press Mudasir Maqbool et al., ***Adverse Drug Reaction Monitoring and Occurrence in Drugs Used In Pulmonary Disorders.,*** *Indo Am. J. P. Sci, 2018; 05(08).*

INTRODUCTION:

Drug-related problems, including adverse drug reactions (ADRs), contribute to a significant health- and quality issues. Based on prevalence studies in different settings, approximately 5 to 35% of hospital admissions are due to adverse drug reactions (ADR) [1]. An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended, or undesired effect of a drug that occurs at doses used in humans for prophylaxis, diagnosis, or therapy [2]. ADRs are a major cause of morbidity and place a substantial burden on limited healthcare resources [3]. Multiple factors influence ADR susceptibility, including multiple drug therapy, disease severity, age, and the type and number of drugs prescribed [4-9]. ADRs are considered as the fourth to sixth leading cause of death among hospitalized patients. About 2.9-5.6% of all admissions are caused by adverse related events, and approximately 35% hospitalized patients experience an ADR. ADRs are associated with significant morbidity, permanent disability and are a huge economic burden on patients due to prolonged hospitalization. Drugs, no matter how safe and efficacious, are always coupled with the inescapable risk of adverse reactions. Though modern medicines have changed the way in which diseases are managed and controlled, despite all their benefits, evidence continues to mount that adverse reactions to medicines are common, yet often preventable, cause of illness, disability and even death [10]. In some countries, ADRs rank among the top ten leading causes of mortality [11]. ADRs increase morbidity, mortality and add to the overall healthcare cost [12-16]. Early detection, evaluation and monitoring of ADRs are essential to reduce harm to patients and thus improve public health. Pharmacovigilance is therefore an important post-marketing tool in ensuring safety and efficacy of pharmaceuticals and health related products.

PHARMACOVIGILANCE: Pharmakon (Greek): means drug and
Vigilare (Latin): to keep alert or awake.
World Health Organization (WHO) defines pharmacovigilance as "The science and activities relating to the detection, assessment, understanding and prevention of adverse effects or of any other drug-related problems [2, 17-19]."

EPIDEMIOLOGY of ADRs

- Account for 5% of all hospital admissions.
- Occur in 10-20% of hospital inpatients.
- Cause deaths in 0.1% of medical and 0.01% of surgical inpatients.
- Adversely affect patients' quality of life.
- Cause patients to lose confidence in their doctors.
- Increase costs of patient care.
- Preclude use of drugs in most of the patients, although they may
- Occur in only a few patients.
- May mimic disease, resulting in unnecessary investigations and delay in treatment [19].

Reports of ADRs have become an important component of monitoring and evaluation activities performed in hospitals [20]. This information may be useful for identifying and minimising preventable ADRs while generally enhancing the ability of prescribers to manage ADRs more effectively [21,22]. Adverse drug reaction is considered to be the sixth leading cause of death. The incidence rate estimates approximately 2% of hospital admissions are due to ADRs. Drug-attributed deaths are estimated to be 0.17% in all medical inpatients. About 0.40% of ADRs identified were directly linked to high costs. ADRs not only increase the mortality and morbidity but also multiply the health care cost.[23] ADR monitoring is primarily essential for drugs with narrow therapeutic index.[24-26] Theophylline has been used for many years for the treatment of asthma and chronic obstructive pulmonary disease (COPD). The incidence of ADRs due to theophylline has been found to be 4.71%, of which nausea, loss of appetite (anorexia) and palpitation were common [27]. The study of ADRs is essential in order to determine the incidence of ADRs in medical inpatients, estimate the contribution of ADRs to hospital admissions, characterize the types of ADRs observed, determines predisposing risk factors and to estimate the costs of ADRs in terms of ADR-related excess hospital stay[28].

Although the concept of ADR monitoring and evaluation of data is four decades old in western and developed countries, the subject is still in the stage of infancy in our country. This is due to ignorance of the subject and also lack of training. WHO started the programme of ADR monitoring in 1968 and India became a member of it in 1997 [29]. With India becoming an attractive center for clinical trials and being one of the largest pharmaceutical producers in the world it has become very necessary to set up a very strict pharmacovigilance system to prevent the population of potential harm that may be caused by the marketed drugs [30].Clearly aware of the enormity of task and determined to set up a vibrant and well- functioning ADR monitoring programme in the country, the central drugs regulatory authority - The Central Drugs Standard Control Organization(CDSCO) has started the National

Pharmacovigilance Programme (NPP)[31].

Benefits of ADR monitoring

An ADR monitoring and reporting programme can furnish following benefits:

a) It caters information about quality and safety of pharmaceutical products.
b) It initiates risk-management plans.
c) It prevents the predictable adverse effects and helps in measuring ADR incidence.
d) It instructs health care team, patients, pharmacists and nurses about adverse drug effects and creates awareness regarding ADRs.

The main objective of ADR monitoring is to disclose the quality and frequency of ADRs and to identify the risk factors that can cause the adverse reactions [32-33]

ADRs IN PULMONARY MEDICINE SETTINGS:

Adverse drug reactions (ADRs) related to drugs used in treating pulmonary related disorders are posing a serious threat to the patient's health. Serious or potentially fatal ADRs are often detected with drugs that are widely in practice. Premarketing clinical trials are designed primarily to identify benefits and common side effects of new drugs. However, the size of these studies generally does not exceed 3,000 patients, limiting the likelihood of detecting rare ADRs before approval. When previously unidentified but serious ADRs are reported after the drug has been approved by the US Food and Drug Administration (FDA), information dissemination occurs through revised package inserts (PIS), so-called Dear Doctor letters, and/or publications in medical journals. Despite medical professionals' and patients' dependence on this information to ensure safe pharmaceutical usage, ADR reporting is often delayed and inconsistent in format [34].

The incidence of drug-induced adverse effects is likely to increase as a result of advanced age and exposure of elderly patients to poly-pharmacy. Therefore, pharmacological therapy of asthma and chronic obstructive pulmonary disease (COPD) in the elderly patient can be potentially hazardous. beta(2)-agonists, administered as therapy for asthma and COPD, have recognized systemic sequelae, such as hypokalemia and chronotropic effects, which may be life-threatening in susceptible patients. Adverse effects such as hypokalemia can be aggravated by concomitant treatment with other drugs promoting potassium loss including diuretics, corticosteroids and theophylline. In addition, relatively minor adverse events associated with the administration of beta(2)-agonists, such as tremor and blood pressure changes, may be of significance to the elderly patient leading to impairment in the quality of life. However, long-term treatment with beta (2)-agonists may reduce the incidence of drug-induced adverse effects as a result of beta-receptor sub-sensitivity. Oral and inhaled corticosteroids have been used for the treatment of acute asthma and COPD in the elderly patient. Long-term treatment with oral corticosteroids can result in serious systemic adverse effects such as suppressed adrenal function, bone loss, skin thinning and cataract formation. In contrast to beta(2)-agonists, oral corticosteroids can up-regulate beta(2)-adrenoceptors and thereby potentiate the systemic sequelae of beta(2)-agonists. Hence, oral corticosteroids should be administered with caution for as short a duration as possible. Inhaled corticosteroids appear to be relatively well tolerated when administered at doses below approximately 1000 micrograms. However, larger doses of inhaled corticosteroids may affect hypothalamic-pituitary-adrenal function and bone turnover. In the case of inhaled corticosteroids, spacer devices, often used in older patients who cannot operate metered dose inhalers, can potentiate the systemic sequelae of both corticosteroids and beta(2)-agonists. The use of theophylline in the treatment of COPD or chronic asthma is controversial. Theophylline have a wide adverse effect profile and are prone to drug-drug interactions. The adverse effects may be mild or life threatening and include nausea and vomiting or sinus and supraventricular tachycardia. Therefore, theophylline should be prescribed with extreme caution to elderly patients with asthma or COPD. In contrast, inhaled anticholinergic drugs such as ipratropium bromide and oxitropium bromide are generally safe in elderly patients and have useful bronchodilator function. Commonly reported adverse effects are an unpleasant taste and dryness of the mouth. When used as first-line therapy, anticholinergic drugs may optimize the bronchodilator effects of low-dose inhaled beta(2)-agonists in patients with chronic airflow obstruction, and hence obviate the need for higher doses[35,36]. The CHM has recently advised that the balance of risks and benefits associated with the use of cough and cold medicines for children younger than 2 years of age is no longer favorable. The advice was based on a safety assessment carried out following recent safety advice from the US Food and Drug Administration. Cough and cold medicines containing antihistamines (e.g. chorphenamine and diphenhydramine), antitussives (e.g. dextromethorphan and pholcodine), expectorants

(e.g. guaifenesin and ipecacuanha) and decongestants (e.g. ephedrine, phenylephrine and xylometazoline) should no longer be used in children younger than 2 years of age. For children older than 2 years, cough and cold medicines are considered safe at the recommended doses [37].

Many studies have been done separately in the different diseases related to respiratory system like COPD, Tuberculosis, Asthma, Respiratory tract infections (upper/lower), etc. For instance "A Study to Monitor Adverse Drug Reactions in Patients of Chronic Obstructive Pulmonary Disease: Focus on Theophylline" by N.Tyagi et.al reported some common ADRs observed with inhaled steroids like sore throat, hoarseness of voice, hyperpigmentation of face, glossitis, etc. and also by the anticholinergics like dry mouth, thirst, urinary difficulty etc [28,38-41]. In a paper entitled "Adverse Drug Reactions in Patients with Bronchial Asthma" by Vesna Cukic et.al. reported that β- blockers are relatively contra-indicated in asthma –including topical β- blockers such as timolol used in glaucoma. Aspirin is contra-indicated in Samter`s triad and where asthma is aggravated by aspirin. Aspirin sensitivity is present in 4-6 % of asthmatics on history, but if aspirin challenges are conducted, 20 to 30% of asthma patients are shown to be aspirin sensitive. Paradoxically, aspirin has been reported to improve asthma symptoms in some patients. Whether aspirin should have a blanket prohibition in asthma is debatable. Non-steroidal anti–inflammatory agents fall into the same group as aspirin. The alternative, paracetamol (acetaminophen) has recently been reported to increase the risk of development of asthma when given to young children. Anaphylaxis has been reported to paracetamol. Phase III of the International Study of Asthma and Allergies in Childhood (ISAAC) programme investigated the association between paracetamol consumption and asthma. Authors have shown that use of paracetamol in the first year of life and in later childhood, is associated with the risk of asthma, rhino-conjunctivitis and eczema at age 6 to 7 years .They suggest that exposure to paracetamol might be a risk factor for the development of asthma in childhood. Attributable risks are between 22% and 38% [42-46].

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