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Frequency, types, severity, preventability and costs of Adverse Drug Reactions at a tertiary care hospital

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ABSTRACT

Introduction: Hospital-based adverse drug reaction (ADR) monitoring and reporting studies are conducted to identify, quantify and minimize such risks associated with the use of drugs particularly on long-term basis. Kashmir province of Indian state of Jammu and Kashmir presents a huge market for medicines that runs into millions of rupees. Yet there was no provision to monitor these drugs for their adverse effects prior to this study in any of the leading hospitals of the province. As such the present study, which was first of its kind in the valley, was undertaken to assess the frequency, preventability, category, severity, causality, extension of hospital stay and costs of drug-related adverse effects in Kashmiri patients at a Srinagar-based tertiary care hospital.

Methods: A prospective, observational, cohort study on 5482 patients was undertaken over a 270 day period. Adult patients admitted in Internal Medicine in-patient department (IPD), presenting to the Internal Medicine out-patient department (OPD) and those visiting the Accident and Emergency Department of the study hospital were included in the study. Patients belonging to both the sexes were screened and monitored on a daily basis for the occurrence of any ADRs. Definition of ADR given by the World Health Organization (WHO) was used and causality of suspected ADRs was determined using Naranjo's algorithm whereas severity was assessed using modified Hartwig's scale and preventability was determined using Hallas methodology. Costs of ADRs and extension in hospital stay were calculated as per Lagnaou and Nicholas methodology respectively.

Results: ADRs accounted for 6.23% of adult Kashmiri patients visiting the tertiary care hospital under study, either for referral or hospitalization, with the majority (81.57%) of these ADRs being preventable; 23.68% of patients had mild ADRs, 69.29% had ADRs of moderate severity, and 7.01% had severe ADRs. Four classes of drugs most frequently suspected in admissions due to ADRs were anti-infective agents (40.92%) including anti-tubercular drugs (13.15%), steroids (14.03%), anti-coagulants (8.77%), and NSAIDs (7.89%). Increasing age and female gender were identified as risk factors. The total cost to the hospital due to hospitalization of patients presenting with ADRs over the 9-month period in the internal medicine IPD was found to be USD 22469 at the time of this study.

Discussion/conclusion: The present work is the maiden pharmacovigilance study conducted on Kashmiri patients, especially at a tertiary care teaching hospital that has provided baseline information about the prevalence of ADRs and their distribution among different age groups, genders, organ systems affected, and therapeutic classes of medicines. The data collected will be useful for long term and more extensive ADR monitoring on Kashmiri patients and will also be useful in framing policies toward the rational use of drugs. This study led to the establishment of a full-fledged pharmacovigilance centre and initiation of pharmaceutical care services in the study hospital.

1. Introduction

Whilst most consumers derive far more benefit than harm, a large proportion of patients experiences Adverse Drug Reactions (ADRs) from the use of medicines at recommended doses and frequencies. For some patients, such undesirable effects are sufficiently severe to require hospital treatment and a few even die (WHO, 2002a, 2002b). There are some limitations to the drug approval process. With most drugs, approval for marketing is granted following phase III clinical trials which are conducted in relatively small number of patients (usually involving hundreds and not thousands) under conditions that are not clinically routine, and often exclude patients with co-morbidities and co-medications (Riegdman, 1981). The safety profile of a drug evolves over its lifetime on the market. Even after almost ten years experience or longer, new information that will impact the clinical use of a medicinal product can be detected. Consequently, all medicinal products need to be continually assessed for safety within the context of their perceived benefit.

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Several works of ADR monitoring in hospitalized patients have suggested that adverse drug reactions are a major public health concern (Lacoste-Roussillon, Pouyanne, Haramburu, Miremont, & Begaud, 2001). The incidence of adverse drug reactions varies with studies which show incidences ranging from as low as 0.15% to as high as 30% (Beijer & de Blaey, 2002; Jose & Rao, 2006; Lazarou, Pomeranz, & Corey, 1998). Adverse drug events can range from mild to life threatening reactions resulting in inconvenience or serious morbidity and mortality besides being a financial burden on the society. Adverse Drug Reactions are responsible for 5–7% of hospital admissions (Einarson, 1993; Jick, 1974); occur in 10–20% hospital inpatients, causing death in 0.1% of medical and 0.01% of surgical inpatients (Bates et al., 1995). Epidemiological research performed in the United States shows the occurrence of ADRs in 10–20% of all hospitalized patients (Pirmohamed, Breckenridge, Kitteringham, & Park, 1998). Bordet, Gautier, Le Louet, Dupuis, and Caron (2001) have estimated that ADRs are responsible for 3.2–6.5% of admissions to hospital.

In relation to mortality, a landmark meta-analysis of 39 prospective studies conducted by Lazarou et al. (1998) found that ADRs resulting in medical care were the fourth to sixth highest cause of death in emergency services in the United States, following only ischaemic cardiopathy, cancer and stroke. A Swedish study has also implicated ADRs as seventh most common cause of death (Wester, Jonnson, Sigset, Druid, & Hagg, 2008). In addition to their impact on human life, these reactions significantly influence health costs as well. A study developed in a hospital setting (Suh, Woodall, Shin, & Hermes-de Santis, 2000) demonstrated that the length of stay and total hospitalization costs were significantly higher for patients who presented an ADR when compared to those who did not. They inflict huge additional financial burdens to not only the patient and the hospital, but to the manufacturer and the nation, as a whole too.

Jammu and Kashmir is a state in northern part of India, often denoted by the acronym J&K having a total population of 12,548,925 souls as per the latest Indian population census conducted in the year 2011 (Census India, 2011). In spite of being a huge market for medicines, there was no provision to monitor these drugs for their adverse effects prior to this study in any of the leading hospitals of the province. Kashmir province of Jammu and Kashmir state presents a huge market for medicines. As per crude estimates, it is generally believed that drugs worth millions of rupees are sold throughout the valley every month yet there was no provision to monitor these drugs for their adverse effects vis-a-vis their therapeutic uses, in any of the leading hospitals at the time of this study. Upon literature search for ADR reports published by the authors from Kashmir valley using various database resources like PubMed, Medline, Toxline, Chemical, Biological and Pharmaceutical Abstracts between 1966 to 2013, reports not exceeding a two-digit figure in number from entire Kashmir region could be retrieved depicting a very grim scenario of ADR monitoring and reporting from the valley. As a result, there is complete dearth of information on risk–benefit ratios of drugs that are being widely used throughout the valley. Though most of the major hospitals outside the valley have centers for adverse drug reaction monitoring as well as drug information services, there are no such services or centers existing in Kashmir valley. No systematic hospital based intensive ADR monitoring study has been carried out so far in any of the hospitals of the valley.

This study aimed at estimating the incidence and prevalence of ADRs among patients at Srinagar-based tertiary care hospital, collecting the relevant data, evaluation of the data collected and its presentation with a view to prepare the ground for regular and comprehensive monitoring of ADRs in future and establishment of Drug Information Services too. This study was envisaged to evaluate the prevalence of patients presenting with ADRs to the Internal Medicine (both IPD and OPD) and Emergency Departments of a tertiary care hospital at Srinagar, J&K, India prospectively and to assess their causality, preventability and severity. The study was also aimed at determining the economic burden of ADRs from a hospital perspective. It was expected that the present study will furnish baseline data regarding the type, frequency and severity of adverse drug reactions among Kashmiri population, particularly those presenting to the study hospital.

2. Materials and Methods

2.1. Study design and patients

The study protocol was designed in accordance with ICH-GCP and WHO guidelines and cleared by the Institutional Ethics Committee prior to commencement of the study. A prospective, observational, non-interventional study was conducted at the In- and Out-patient departments of Internal Medicine and Accident & Emergency department of a tertiary care hospital at Srinagar, J&K, India over a period of 270 days.

2.2. ADR monitoring in IPD patients

All patients above the age of 18 years, admitted to the Internal Medicine ward of the study hospital during the study period were screened and intensively monitored on a daily basis for the occurrence of any Adverse Drug Reactions (ADRs), both on their first and every follow-up visit to the hospital. Data was recorded using a structured ADR reporting form designed ad hoc. The form was designed, standardized and found applicable for the participating departments. It included socio-demographic and anthropometric information, personal and family medical history, cause of admission and main clinical data. In order to validate the cases, for every adverse effect reported, efforts were made to collect the maximum amount of information on patient characteristics (sex, age, medical history, underlying diseases etc.), drug treatment (suspected drug, dosage, route of administration, indication, date of beginning and stopping therapy, concomitant drugs, etc.) and characteristics of the ADR (date of onset, clinical details, etc.). Questions regarding previous drug use were obtained by interview with parents, relatives, nurses or prescribing physicians, as and when necessary. Data was also collected from medication charts, medical records, daily ward rounds.

Once ADR reports were collected/prepared in consultation with the physicians and nurses on duty in the ward at the time of ADRs, they were scrutinized by a multi-disciplinary medical team comprising of a senior consultant in medicine, a clinical pharmacologist and a pharmacist. This mutual consultation prevented any kind of reporting bias on part of the investigator.

By visiting the ward daily and by examining medical and nursing records, details were recorded about drugs prescribed, investigations conducted and any adverse reactions experienced by the patients. All patients were followed-up until hospital discharge for arriving at the final diagnosis. WHO definition of ADR was used for the sake of assessment of ADRs (Edwards & Biriell, 1994). Where the patients were categorized as having an ADR, all relevant drug details were recorded including nature of the reaction, the outcome, total time spent in hospital, and any invasive investigations performed. Type of ADR was determined as per the classification of Rawlins and Thompson (given below) (Rawlins & Thompson, 1991) and it was ascertained whether the ADR was due to the suspected drug or due to an interaction according to the interactions listed in the summary of product characteristics or relevant literature, or both.

2.3. Inclusion criteria

All patients attending Internal Medicine OPD and those admitted to Internal Medicine ward as well as to the Accident and Emergency Department of a tertiary care hospital during the above-mentioned periods. Repeat admission of the same patient was counted as two admissions when separated by an interval of at least one month.

2.4. Exclusion criteria

1. Patients on contrast media
2. All formulations with more than three active ingredients
3. Patients treated with traditional medicines alone
4. Drug overdose (deliberate or unintentional)