SPONTANEOUS REPORTING OF ADVERSE DRUG REACTIONS IN GERIATRIC PATIENTS IN INDIA

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Abstract

Background: In India, spontaneous reporting of adverse drug reactions (ADRs) by healthcare professionals was initiated in 2010. The drug safety issues for geriatric population are critical due to age-related physiological changes, pharmacodynamics and pharmacokinetics changes.

Objective: Our objective was to assess the spontaneous reports of adverse drug reactions, observed in geriatric patients (over 65 years of age) in India during the period from 1 July 2011 to 31 June 2013.

Method: The spontaneous reports of 4357 elderly patients (≥65 years) were retrieved at national pharmacovigilance centre from the database containing all ADR reports from 90 ADR Monitoring Centres (AMCs) in India under Pharmacovigilance Programme of India (PvPI) for the period of two years. These reports were analysed for various characteristics of patients, drugs and ADRs using a search and analysis tool.

Results: Of the 4357 geriatric Individual Case Safety Reports (ICSRs), more ADRs were reported from the male (57.77%) than the female patients (41.38%). The ADRs from 1120 (25.71%) patients of the total geriatric patients were found to be serious of which 8 (0.71%) were fatal. Cisplatin, carboplatin, cyclophosphamide, acetylsalicylic acid and insulin were the common drugs prescribed to the elderly patients and the commonest ADRs reported were vomiting, diarrhoea and constipation. The ADRs in geriatric population mostly affected Gastro-intestinal system and Skin & appendages system.

Conclusion and implications of key findings: This study from spontaneous reporting indicates the common ADRs in the geriatric patients in India which will help healthcare professionals in better understanding of the drug safety issues in elderly.

Background

India is a vast country with diversity, both physical and cultural. As per Census 2001, the geriatric population accounted for 7.4% (76622) of the total population which increased to 8.2% (98470) by 2011 and is likely to be 10.7% (143244) by the year 2021 [1, 2]. Drugs play a crucial role in geriatric health care as they treat chronic diseases, alleviate pain and improve quality of life [3]. About one third of the elderly patients are hospitalized due to the adverse reactions of the drugs [4, 5], which have also reported to be among the leading causes of morbidity and
mortality [6-8]. 80% Adverse Drug Reactions (ADRs) of type A contribute to it [9, 10]. Majority of studies have shown that prevalence of ADRs is higher in the elderly as compared to adult [11]. An association between old age and increased rate of adverse drug reactions is established arising out of confounding association between age and polypharmacy contributed by age-related physiological changes, pharmacodynamics and pharmacokinetics changes which influence drug handling, drug response and sensitivity in these patients [9, 12, 13]. Moreover, preventable ADRs were found to be more common in geriatric patients [14].

In various studies, the most common classes of drugs causing ADRs in geriatric population are found to be antidiabetics, nonsteroidal anti-inflammatory drugs (NSAIDs), anticancer drugs, cardiovascular drugs, oral anticoagulants and antiplatelets drugs [15-17] and the most common ADRs being oedema, nausea or gastrointestinal disturbances, drowsiness or fatigue, headache, and nightmares [17, 18].

At present, the prevalence of ADRs in geriatric population is very limited in India [19, 20]. This study aims to identify the ADRs in geriatric patients reported under Pharmacovigilance Programme of India (PvPI) and to establish evidence based data to ensure the safe use of medicines in geriatric population.

Material & Methods

A prospective observational study was carried out at National Coordination Centre - Pharmacovigilance Programme of India (NCC-PvPI), Indian Pharmacopoeia Commission, Ghaziabad, from July 2011 to June 2013 for the Individual Case Safety Reports (ICSRs) of the patients above 65 years of age, reported from 90 ADR Monitoring Centres (AMCs) under PvPI across India.

The data of 4357 elderly patients who reported adverse reactions due to drugs taken by them to their nearest AMC were included in the study. Data of each patient was collected using structured format. For details of each patient, an ADR form was completed with regard to patient age, sex, diagnosis, prescribed medications, daily doses, treatment durations, indications for each drug, ADR occurred, laboratory investigation reports and history of the patient.

The details of each patient was then entered into a web-based WHO global ICSR database “VigiBase” and sent to NCC-PvPI via Uppsala Monitoring Centre’s ICSR management system “VigiFlow”. At NCC, these reports were reviewed, evaluated and further committed to World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC), Sweden. These 4357 committed reports were then analysed for various characteristics of patient, drugs and ADRs using search and analysis VigiBase tool “VigiLyze”.

Results

Of the total 50,490 ICSRs reported under PvPI in the two year study of ADRs, 4357 (8.63%) ICSRs were reported by the geriatric patients from the 90 AMCs across India, of which 3387 (77.74%) patients belong to the age group 65-74 year and the remaining 970 (22.26%) were 75 or more year of age. These 4357 ICSRs had a total of 5115 ADRs and 13957 prescribed drugs.
Out of the total 4357 ICSRs from geriatric patients, 2517 (57.77%) ICSRs were reported from the males patients and 1803 (41.38%) from female patients. Remaining 0.85% ICSRs were unknown. Sex Distribution of ICSRs from geriatric patients is represented in fig1.

1120 (25.71%) patients of the total geriatric patients were found to be having serious ADRs as compared to that of 2484 (57.01%) patients with non-serious ADRs (fig 2). Remaining 17.28% were unknown. Of the serious ICSRs, 8 (0.71%) ICSRs were found to be fatal; 582 (51.96%) ICSRs with prolonged hospitalization; 61 (5.45%) ICSRs with life threatening conditions; 48 (4.29%) ICSRs with disability; 398 (35.54%) ICSRs with other serious conditions and 23 (2.05%) ICSRs with unknown serious ADRs.

Gastro-intestinal system disorders were found to be associated with 1246 ADRs, followed by 770 ADRs of Skin & appendages disorders; 533 ADRs of Central & peripheral nervous system disorders. The system organ class (SOC) of reported ADRs, are represented in fig 3.

Total ADRs caused by the suspected drugs were found to be 4643, of which 287 were vomiting, followed by 230 ADRs of diarrhoea, 189 ADRs of constipation among the most common ADRs in this study. Among the 5997 suspected drugs prescribed to the patients, cisplatin was found to have caused maximum ADRs i.e 334, followed by 225 ADRs of carboplatin; 172 ADRs of cyclophosphamide. Table 1 shows the profile of top 10 drugs prescribed to the geriatric patients causing ADRs.

**Discussion**

In our two year study from 2011 to 2013, the ADRs reported under PvPI by the geriatric patient population were found to be 8.63%. Indian data contributed 1.73% of the geriatric ICSRs in the UMC global database. The ADR reporting in this study was lower as compared to a similar two year study in Italy by Cutroneo et al. [21], where 21.7% ADRs from 1307 reports were found to be from geriatric patients.

In the present study, more ADRs were reported in male patients than the female patients. In contrast, Conforti et al. [22] reported higher ADRs in females compared to men. Serious ADRs accounted for 25.71% of the total ADRs reported under PvPI of which 0.71% were fatal. The serious ADRs in this two year study were found to be about four times and fatal ADRs were about twice to that of a thirty year study from U.S hospitals to estimate the serious and fatal ADRs in hospitalized patients, by Lazarou et al. [23]

Anticancer drugs were found to be among the top ten drugs inducing ADRs in geriatric patients in this study; cisplatin was the topmost causing maximum number of ADRs i.e. 334, which was about 7.1 % of the total ADRs induced by the suspected drugs. The most common ADRs induced by cisplatin include vomiting, alopecia, anorexia, constipation and diarrhoea. The second drug was carboplatin (with 225 ADRs) followed by cyclophosphamide (with 172 ADRs) causing alopecia, constipation and vomiting, most commonly. Prasad et al. studied the similar pattern of ADRs due to cancer chemotherapy in a six month study in eastern India and found 87% patients receiving
Chemotherapy developed ADRs mainly due to Cisplatin and cyclophosphamide, thereby commonly causing nausea and vomiting [24].

The most commonly observed ADR in this study was vomiting with about 6.2% of the total ADRs due to suspected drugs, followed by diarrhoea (4.96%), constipation (4.07%) and hypoglycaemia (3.70%). In most of the cases, gastrointestinal system was affected. Gurwitz et al. [25], in a year study also reported gastrointestinal adverse events among the most common types of ADRs in elderly. Another eighteen year study of suspected ADRs reported to the Committee on Safety of Medicines (CSM) in relation to patient age by Castleden CM [26], also showed gastrointestinal system to be the commonest system from which the ADRs were reported.

Elderly people are more prone to the adverse drug reactions; possible reasons could be the changes in pharmacokinetics, pharmacodynamics and homeostasis with the advancing age [27], which can alter drug absorption, distribution, metabolism and excretion, thereby altering drug's effects [28].

**Conclusion**

Our study revealed the most commonly prescribed drugs and their ADRs in the geriatric patient population in India. This will help healthcare professionals in better understanding of the patient safety while prescribing drugs to elderly patients.

**Acknowledgement**

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<table>
<thead>
<tr>
<th>S.No.</th>
<th>Top 10 Suspected Drugs</th>
<th>No. of ADRs</th>
<th>Most Common ADRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cisplatin</td>
<td>334</td>
<td>Vomiting (68), Alopecia (39), Anorexia (29), Constipation (24), Diarrhoea (24), Fever (19), Anaemia (11)</td>
</tr>
<tr>
<td>2.</td>
<td>Carboplatin</td>
<td>225</td>
<td>Alopecia (41), Constipation (21), Vomiting (21), Anaemia (19), Anorexia (13), Leg pain (12), Myalgia (11), Diarrhoea (10)</td>
</tr>
<tr>
<td>3.</td>
<td>Cyclophosphamide</td>
<td>172</td>
<td>Alopecia (41), Nausea (17), Vomiting (13), Constipation (12), Leucopenia (10)</td>
</tr>
<tr>
<td>4.</td>
<td>Acetylsalicylic acid</td>
<td>134</td>
<td>Gastritis (8), Abdominal pain (13), GI haemorrhage (9)</td>
</tr>
<tr>
<td>5.</td>
<td>Insulin</td>
<td>128</td>
<td>Hypoglycaemia (93), Sweating increased (20),</td>
</tr>
<tr>
<td>6.</td>
<td>Amlodipine</td>
<td>113</td>
<td>Oedema peripheral (34), Oedema dependent (10), Hyponatraemia (8), Oedema(8), Constipation(6), Headache(6)</td>
</tr>
<tr>
<td>7.</td>
<td>Ceftriaxone</td>
<td>95</td>
<td>Diarrhoea (18), Vomiting (9), Rigors (7), Rash (6)</td>
</tr>
<tr>
<td>8.</td>
<td>Furosemide</td>
<td>81</td>
<td>Hyponatraemia (39), Hypokalaemia (18)</td>
</tr>
<tr>
<td>9.</td>
<td>Docetaxel</td>
<td>74</td>
<td>Anorexia (11), Diarrhoea (11), Alopecia (9), Constipation (7), Vomiting (7)</td>
</tr>
<tr>
<td>10.</td>
<td>Diclofenac</td>
<td>70</td>
<td>Gastritis (15), Rash (7), Abdominal pain (6)</td>
</tr>
</tbody>
</table>
Fig. 1: Sex distribution of ICSRs

Fig. 2: Serious vs Non-serious patients
Fig. 3: System organ class in reported ICSRs