A Study to Monitor Adverse Drug Reactions in Patients of Chronic Obstructive Pulmonary Disease: Focus on Theophylline

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ABSTRACT

Background. Multiple drugs used in the treatment of chronic obstructive pulmonary disease (COPD) may result in a variety of adverse drug reactions (ADR) during therapy. This, in turn, could contribute significantly to morbidity and mortality and thus it is important to monitor such ADRs, with an aim to rationalise drug therapy in these patients.

Objective. To monitor adverse drug reactions in patients with COPD in an outpatient setting.

Methods. A prospective, hospital based, study was carried out by the Departments of Pharmacology and Respiratory Medicine, Vallabhbhai Patel Chest Institute, Delhi. Out patients diagnosed as COPD were enrolled after taking written informed consent. On the first visit, the general physical examination was done and the prescription was noted and the patient was interrogated for any ADRs. Dechallenge and rechallenge were done wherever feasible and laboratory investigations were performed when desirable. Patients were followed weekly for a month, and evaluated for any new ADRs on each visit. Causality assessment of ADRs was done by the Naranjo’s scale.

Results. The drugs prescribed included, inhaled corticosteroids, β₂ agonists and anticholinergics, oral corticosteroids and theophylline, and in some cases N-acetylcysteine. In general, most of the ADRs were non-serious in nature, except for oral N-acetylcysteine induced serious adverse drug reactions which had to be discontinued. Oral theophylline showed a wide profile of adverse effects viz. anxiety and related manifestations, gastrointestinal symptoms, muscle cramps, etc. In most cases causality assessment showed that there was a temporal relationship between the drug administration and occurrence of adverse event.

Conclusions. Theophylline needs careful therapeutic dose monitoring and dose individualisation and more safety studies are needed to evaluate all the possible adverse drug reactions and their mechanisms. [Indian J Chest Dis Allied Sci 2008; 50: 199-202]

Key words: ADR monitoring, COPD, Theophylline, Causality assessment.

INTRODUCTION

According to WHO, an adverse drug reaction (ADR) is defined as “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 for a disease and for the modification of function excluding failure to accomplish the intended purpose”.¹ Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects, or any other medicine related problem.² Adverse drug reactions are one of the major causes of morbidity and account for nearly 5% of all hospital admissions all over the world. At times these are not much different from non-drug related disease states and on rare occasions may cause a fatal outcome. Over two million ADRs occur yearly that result in 5% fatality annually. Adverse drug reaction is the fourth leading cause of death ahead of pulmonary disease, diabetes mellitus, AIDS, pneumonia and automobile deaths.³

Chronic obstructive pulmonary disease (COPD) is an obstructive airways disease characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lungs to noxious particles or gases (GOLD, 2005).⁴ Chronic obstructive pulmonary disease is usually treated with inhaled steroids, oral theophylline, oral steroids, antibiotics, etc. and polypharmacy is common. Theophylline, a methylxanthine, was introduced by H.H. Salter as a bronchodilator in asthma therapy, more than 100 years ago.⁵ In view of the narrow therapeutic index and interactions with other drugs, the drug is
known to cause adverse effects ranging from dyspepsia and anxiety at low doses, to agitation, convulsions, coma and even death at higher doses. Untoward effects of theophylline are usually linked to plasma concentrations and tend to occur when plasma levels exceed 25 mg/L, and thus careful therapeutic drug monitoring is required to make dose individualisation. Adverse drug reaction monitoring is absolutely essential for such drugs with narrow therapeutic index. As the number of ADRs usually increase with the number of medications prescribed/taken, and since no systematic study has been done to monitor ADRs in COPD, the present study was designed to monitor ADRs occurring during treatment of COPD. Further, causality assessment of ADRs, that reflects the association of the drug with the adverse effects, was done for confirmatory purposes.

**MATERIAL AND METHODS**

The study was open, prospective and carried out over a period of one year, jointly by the Departments of Pharmacology and Respiratory Medicine, Vallabhbhai Patel Chest Institute, Delhi. The study protocol had the approval by the Institutional Ethical Committee.

Patients were diagnosed as COPD by the physician at the OPD on the following clinical and pulmonary features: history of smoking, exertional dyspnoea, cough and expectoration, FEV$_1$ < 80%, FEV$_1$/FVC less than 70% predicted, negative bronchodilation test (FEV$_1$ ≤ 200 ml or 12% with respect to basal value). Patients relatively stable and ambulatory were included for the study.

The exclusion criteria were as follows: Pulmonary TB (past/present), any other respiratory disorder, pregnant/lactating females, presence of IHD/Overt LVF, liver/kidney disease, patients on treatment for COPD for less than four weeks.

The patients were enrolled after a written informed consent as per prescribed proforma and the study was conducted in accordance with the International Conference on Harmonization-Good Clinical Practice (ICH-GCP) guidelines.

At first visit, for each patient, current medical history, diagnosis, demographic profile and prescription were noted. The general physical examination was done on each patient, any ADR was noted. The ADRs were recorded in the specify proforma designed by the National Pharmacovigilance Programme for this purpose. Laboratory investigations were done in appropriate cases. Dechallenge and rechallenge were done if possible. The patient was followed up weekly for a month and any new change in prescription and status of each ADR was noted down. Causality assessment was done using the Naranjo’s Scale. This scale evaluates the degree of association of an adverse effect with the suspected drug and involves a set of questionnaires, which are ascribed a certain score (ranging from -1 to +2). Total score for a particular drug-ADR combination is calculated and the association is termed - highly probable, probable, possible or doubtful-depending on the score (see Appendix).

**RESULTS**

A total of 60 outpatients were enrolled in the study after an informed consent, out of which 56 were males and four females. Dechallenge was attempted in seven cases which led to amelioration or disappearance of the ADR. Rechallenge was not attempted in any case. The general profile of drug treatment and ADRs in COPD are summarised in table 1.

Common ADRs observed with inhaled steroids were sore throat, dysguesia, hoarseness of voice, hyperpigmentation of face, glossitis, etc. Anticholinergics were associated with ADRs including dry mouth, thirst, urinary difficulty, etc.

The ADR profile of oral theophylline included: spasm of muscles - calves (commonly), sternocleidomastoid and intercostals, anxiety, dyspepsia, insomnia, dizziness, paresthesia, colicky pain in the abdomen, diuresis and theophylline withdrawal-induced constipation. Dyspepsia, anxiety and muscle spasms were most common (Table 2). As per the Naranjo’s Scale, the total score for these ADRs with oral theophylline ranged from 5 to 8, which fell in the ‘probable’ category.

All the ADRs recorded were of non-serious nature except those in two patients on N-acetylcystiene, who reported serious ADRs viz. severe epigastric distress, dizziness and increased cold perceptions thus requiring immediate stoppage of the drug.

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**Table 1. General profile of drug treatment and adverse drug reactions (ADRs) in COPD**

<table>
<thead>
<tr>
<th>Drug Given</th>
<th>No. of Patient Receiving the Drug</th>
<th>No. of Patient Complaining of ADR</th>
<th>% Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled steroids</td>
<td>53</td>
<td>30</td>
<td>56</td>
</tr>
<tr>
<td>Inhaled anticholinergics</td>
<td>44</td>
<td>10</td>
<td>22.7</td>
</tr>
<tr>
<td>Oral theophylline</td>
<td>43</td>
<td>20</td>
<td>46.5</td>
</tr>
<tr>
<td>Oral steroids</td>
<td>14</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Antibiotics (Oral)</td>
<td>14</td>
<td>3</td>
<td>21.4</td>
</tr>
<tr>
<td>Short acting $\beta_2$-agonist</td>
<td>55</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>N-acetylcysteine (oral)</td>
<td>2</td>
<td>2</td>
<td>100</td>
</tr>
</tbody>
</table>

Total number of outpatients = 60 (with multi-drug prescriptions containing more than one of the above listed drugs).
The association of this ADR with theophylline was observed in this study and has not been reported earlier. Oral theophylline (100-400 mg) showed a tendency to produce severe spasms of calves, sternocleidomastoid, and intercoastal muscles. Six such patients were encountered, out of which three patients were dechallenged by dose reduction to half, and this ameliorated the spasms. The cause of spasms could be due to hypokalemia caused by theophylline and causality assessment by the Naranjo’s Scale labelled these as “probable” ADRs. However, muscle spasm could also have resulted due to beta-2 agonists, but the fact that theophylline dechallenge abolished the muscle spasm strongly suggests involvement of this drug. One case of theophylline withdrawal induced constipation was also reported. That was relieved when the oral theophylline was restarted. The theophylline withdrawal induced constipation was a novel ADR observed in this study and has not been reported earlier. The association of this ADR with theophylline was proved when rechallenge attenuated this effect, and causality assessment put the ADR in the probable category. This finding can be termed as a signal and more such reports would strengthen it. Further, pharmacokinetic studies i.e. therapeutic drug monitoring of theophylline in COPD patients are required to confirm this finding. As the therapeutic use of theophylline is of importance in obstructive airway disease, strategies to facilitate its safe use are worth exploring. In an attempt to study the possible mechanisms in the anxiogenic and convulsogenic effects of the drug, experiments in rats and mice have shown that treatment with antioxidants attenuate theophylline-induced anxiety and seizures. These results suggest that oxidative stress may contribute to the theophylline-induced adverse effects, and follow up clinical pharmacodynamic and pharmacokinetic studies would be helpful to confirm this.

CONCLUSIONS

Chronic obstructive pulmonary disease is a chronic inflammatory disease that is treated life-long as permanent cure is not possible. A number of drugs in combination are used and ADRs are often multiple. Use of oral theophylline needs careful therapeutic monitoring, and dose individualisation. More safety studies are necessary. Clinical studies to elicit the toxicodynamics of these ADRs and safety vs risk issues could be beneficial in devising strategies for its rational use in obstructive airway disease.
APPENDIX

Naranjo ADR probability scale to assess the adverse drug reaction, please answer the following questionnaire and give the pertinent score:

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Are there previous conclusive reports on this reaction?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>2. Did the adverse event appear after the suspected drug was administered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>4. Did the adverse reactions appear when the drug was readministered?</td>
<td>+2</td>
<td>-1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?</td>
<td>-1</td>
<td>+2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>6. Did the reaction reappear when a placebo was given?</td>
<td>-1</td>
<td>+1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>7. Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>10. Was the adverse event confirmed by any objective evidence?</td>
<td>+1</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Total Score

9  Highly Probable
5-8  Probable
1-4  Possible
0   Doubtful

REFERENCES