Original Article

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Health outcome and safety assessment of a fixed dose combination of Amantadine, Paracetamol, Chlorpheniramine maleate, and Phenylephrine introduction in India: A prescription event monitoring study

Abstract

To assess the likely impact of a fixed dose combination (FDC) of Amantadine, Paracetamol, Chlorpheniramine maleate, and Phenylephrine on the health outcome and safety profile arising from the complementary action of amantadine and other ingredients, we conducted a Prescription Event Monitoring study for patients with suspected Influenza symptoms who were prescribed this FDC in 'real life clinical settings' or clinical practice. Between August 2010 and March 2011, Questionnaires were sent to doctors who provided data on the health outcome or safety profile. Sedation and allergy, including rash, were noted in few of the patients. None of the patients reported any major events. Most of the patients (60%) were initiated on FDC therapy within the first 24 hours of symptom onset. Even as a significant proportion of the patients (24.9%) had a concurrent history of allergy / rhinitis including asthma, few of them (4.1%) reported lack of improvement and had to be complemented with antibiotics. The FDC of Amantadine, Chlorpheniramine, Paracetamol, and Phenylephrine was found to be safe and well-tolerated when administered to patients within the first 24 to 48 hours of symptom onset.

Key words: Fixed dose combination, health outcome, prescription-event monitoring, safety

INTRODUCTION

Influenza remains an enigma, having a long history that has had a significant impact on society due to the high rates of morbidity or mortality that it causes, especially in children.

There are 16 and nine types of H and N proteins that are used in combination to designate influenza virus strains, which are, H1N1, H3N2, H2N2, H5N1, and so forth. Among these, H1N1 and H3N2 are currently in circulation in several parts of the globe, including India,[1] where they tend to circulate throughout the year, but usually peak during monsoon and winters.

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Early treatment with antivirals or virostatic agents in such cases, as advocated by Infectious Diseases Society of America (IDSA) (2009), not only reduces the hospitalization rate, but also a further spread of the disease, by reducing the extent or quantity of viral shedding.

Amantadine, belonging to a class of adamantanes, was the first antiviral agent that was found to be suitable for general use in the management of seasonal influenza A. Despite the regulated availability of newer advanced antiviral agents, the World Health Organization (WHO)[2] continues to recommend Amantadine use for Seasonal Influenza A (H1N1), even in suspected cases. However, in line with the IDSA[3] guidelines on the management of Influenza, use of antiviral therapy is usually recommended, based on the local patterns of viral strains in circulation and their sensitivity to the drugs.

In this regard, in an *in vitro* study conducted at the Haffkine Institute of Virology (Mumbai), the current prevalent strains, namely, Seasonal Influenza A H1N1 / Pune / 2009 and Seasonal Influenza A H3N2 / Pune / 2010, were tested for sensitivity to Amantadine, using cell culture lines.[4]

The results showed that at varying concentrations of 1 to 5 mcg / ml there was a dramatic decrease to complete inhibition of virus growth. This confirmed the virostatic action, as documented for Amantadine.[5] Amantadine therapy decreased the viral load and related inflammatory symptoms of pyrexia and peripheral airway dysfunction, while preventing the spread of the disease. Similarly the virostatic action of Amantadine improved the immunological response of the body, further decreasing the chances of recurrence or severe infection.[6]

However, due to the concurrent presence of respiratory symptoms and diagnostic limitations involving RT-PCR, ancillary administration of acetaminophen,[7] antihistaminic, and a decongestant, is done, to provide early symptomatic relief, while preventing future recurrences.[8]

An antiviral FDC containing Amantadine, chlorpheniramine (CPM), Paracetamol (PCM), and Phenylephrine that has been introduced in India to manage this high-risk population. It has quick action in controlling respiratory symptoms especially in children who are extremely susceptible in developing complications that may require hospitalization.

Amantadine administration results in side effects that are short-lived or transient, when given as a short-course therapy.[9] With regard to this, we intended to carry out a Prescription Event Monitoring study, to determine the safety and health outcome in patients when Amantadine is prescribed in combination as FDC.

Prescription event monitoring (PEM) is a well-established, non-interventional, observational tool of postmarketing surveillance when giving or prescribing drugs in 'real life' clinical practice, on a national level.[10] Importantly, in a PEM study, there is no need for the prescribing doctor to give an opinion about whether an 'event' might have been caused by the drug. At the end of the observation period, this data would be submitted for subsequent analyses.

Prescription event monitoring is therefore a useful tool in proactively observing the 'events' related to the safety or adverse health outcome parameters, especially for drugs that are recently introduced in the market.[11]

This PEM study with FDC was therefore conducted, to better understand the behavior or safety profile of the combination when administered in 'real life clinical settings,' including patients irrespective of their comorbidities or concurrent medications, without influencing the prescription pattern of the doctors.

MATERIALS AND METHODS

To assess the impact of FDC on the health outcome and safety profile when prescribed in 'real life clinical settings' a Prescription Event Monitoring study was conducted between August, 2010 and March 2011 with doctors across India especially during monsoon and winter seasons

A prescription event monitoring study booklet, containing a letter of introduction to the doctor, a PEM report form, and a study flow chart with a patient log sheet, was sent to these prescribing doctors, requesting information on any 'events' that occurred during the observation period of the prescription. From each doctor, observations from ten patients were requested for whom FDC syrup or tablet was prescribed for at least five days. The dosage schedule was 2.5 ml four times a day, for child weighing 10 kg, with an Amantadine dose of 5 mg / kg / day being the recommendation. Similarly for adults, one tablet was given four times a day for at least five days.

The term 'event,' in PEM, is defined as, suspected reaction to formulation, unexpected deterioration or improvement in the medical condition, any reason for referral or hospitalization or any complaint of sufficient clinical importance.

The PEM report form also included additional questions regarding the concurrent conditions (whether the patient had a history of asthma, allergic disorders; heart disease; diabetes mellitus; kidney disease; liver disease; glaucoma; epilepsy; past history of nasal influenza vaccination) and the previous use of other medications or drugs including antibiotics or inactivated flu vaccine.

During the observation period of five days, each patient was observed for any 'events' that may arise thereof. In case of any 'event' the doctors were requested to note it down on the PEM Report Form. In case of any major events, such as, death, disability, hospitalization or congenital anomaly, the doctor was advised to notify immediately the Sponsor Pharmacovigilance Center, for subsequent Regulatory submission.

At the end of the observation period, the PEM booklets were collected. On the basis of the safety profile or observations with the drug, additional follow-up was done with the prescribing doctors for confirmation and causality assessment, based on the pharmacological properties, concurrent disease, and drug use.

Descriptive statistics are used to present the data.

RESULTS

Baseline demographics

Data from 337 patients was available at the end of the observation period. Among the patients who were prescribed FDC, 56% patients were in the age group of 2 to 10 years with 3.6% being > 50 years of age.

When the mean distribution by weight for these children was analyzed, 36% of the patients were between 10 and 20 kg.

Patients were initiated on FDC therapy, based on a clinical suspicion of seasonal influenza, especially in terms of the presenting symptoms including fever, rhinitis, nasal block, cough and bodyache.

Most of the patients (60%) had symptoms in the preceding 24 hours. However, 35% patients had a symptom onset of ≥ 48 hours before visiting the doctor for treatment.

Concurrent Medical history

Several patients who were initiated with FDC therapy had a concurrent history of allergic disorders (18%), while others had a history of asthma (7%).

Event analyses

Even as several adverse events including insomnia, nervousness, and dizziness have been observed with short-term therapy of amantadine, none of these major observations have been noted in this PEM study. Only four patients (1.2%) developed symptoms of sedation, while other events such as mouth dryness, drug allergy or rash were rarely observed, as shown in Figure 1.

Similarly, in few of these patients (3.2%), FDC was discontinued [Figure 2] due to lack of improvement in the symptom profile, and was supplemented with antibiotics, to prevent the complications that could arise.

In the remaining cases, FDC therapy was successfully completed, with no reports of any undue deterioration in the health or symptoms.

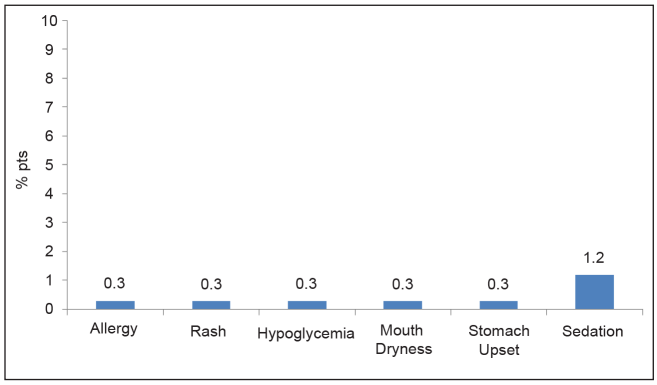

Figure 1: Percentage of patients showing 'events' at the end of the study

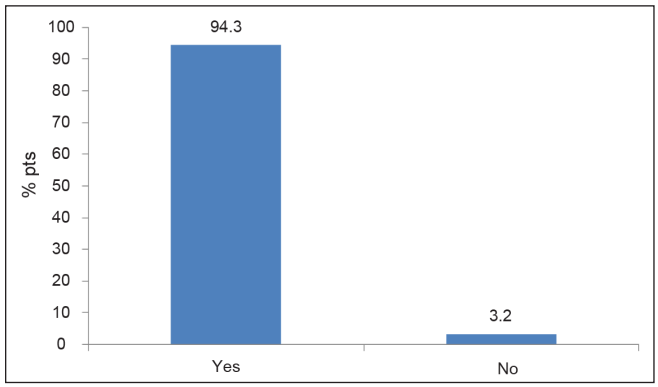

Figure 2: Percentage of patients showing physician assessment as 'effective'

DISCUSSION

Influenza virus infection has a significant societal impact, as it causes significant morbidity and mortality, especially in young children, who may be immunocompromised or suffering from allergic disorders, including asthma. Even otherwise, children generally have a higher viral load than adults, and shed virus for at least 10 days,[12] leading to concurrent affliction of family members or spread in schools where they are in close contact with other children. On account of this, early treatment with antiviral therapy is helpful in preventing the complications and the spread of the disease, even in suspected cases, as recommended by the international guidelines.

Local sensitivity and the WHO / IDSA guidelines continue to recommend Amantadine for the management of Seasonal influenza A. However, taking into consideration the concurrent presence of respiratory symptoms at the time of diagnosis, ancillary administration of an analgesic (paracetamol) and an antihistaminic (chlorpheniramine maleate) along with Amantadine has been highlighted by clinical studies, taking into account the side effect profile.

PEM studies are being conducted worldwide to provide more information on the drug. Likewise, this provides proactive post-marketing surveillance data when prescribed on a national level, taking into consideration the racial or ethnic diversity observed in countries, including India.

As PEM represents 'real world' usage of the drug in general practice, including children, elderly or in patients with comorbidities and on concurrent medications, it

is helpful in identifying these risk factors, for a better assessment of the hazard associated with the new drug or combination.

In this line, although antibiotics are usually prescribed or used in patients with respiratory tract infections, the problems arising due to the long duration of therapy and the consequent development of bacterial resistance in case of patient noncompliance is quite obvious. The same antiviral compounds or a combination of the same, including FDC, offer early symptomatic control of the viral symptoms when used in initial line settings, to prevent development of complications.

In the current study, 337 patients with suspected seasonal influenza symptoms were initiated on FDC for five days, with further evaluation of adverse events related to safety or other health outcome parameters, assessed during the course of the therapy.

Most of the patients (60%) were initiated on FDC therapy within the first 24 hours of symptom onset. However, a significant proportion of the patients (24.9%) had a concurrent history of allergy / rhinitis, including asthma.

In case of persistence of symptoms or undue deterioration, subsequent use of antibiotics is usually recommended, to prevent or treat the complications that may arise. In the current study 3.2% of the patients discontinued use of the drug due to lack of improvement and had to be complemented with antibiotics. This is in line with the available international literature including that of Lao,[8] who has shown a low rate of poor response (3.3%) when administered to patients within the first 24 to 48 hours of symptom onset, without confirmatory evidence through RT-PCR for seasonal influenza viral strains (H1N1).

Sedation and allergy, including rash, were the most frequent adverse events in four (1.2%) and one (0.3%) of the patients. The symptoms of hypoglycemia and stomach upset could not be possibly related to the use of the drug. However, none of the patients developed symptoms of nervousness, insomnia or dizziness, as observed in the published literature on Amantadine. None of the patients reported any major events that necessitated drug discontinuation.

This PEM study for the first time evaluated the impact of FDC on the health outcome and safety profile in Indian patients suspected to be diagnosed with clinical symptoms of seasonal influenza.

FDC containing a combination of Amantadine, Chlorpheniramine, Paracetamol, and Phenylephrine was found to be safe and well-tolerated when administered to patients within the first 24 to 48 hours of symptom onset.

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