Int J Pharm Bio Sci 2015 Jan; 6(1): (P) 672 - 678

Research Article **Pharmacology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

RETROSPECTIVE ANALYSIS OF OSELTAMIVIR AND ZANAMIVIR IN PATIENTS OF H_1N_1 INFLUENZA IN A TERTIARY CARE HOSPITAL IN WESTERN INDIA.

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ABSTRACT

Retrospective analysis of Oseltamivir and Zanamivir in 150 randomly-selected confirmed H_1N_1 patients admitted into Medicine Department of Sassoon General Hospitals, Pune between 1st July 2009 and 31st December 2009 was undertaken.Patients predominantly in age group of 18-65 years received Oseltamivir alone or along with Zanamivir (57% males, 43% females). Mean hospital stay duration (days) was 5.2±1.97 in the combination group (n=81) as compared to 8.7+2.34 with Oseltamivir alone (n=69). Outcome was significantly better with the combination (85.18%) than Oseltamivir alone (62 %); in patients with high risk having associated comorbidities like Asthma, COPD, diabetes, CHD; in terms of treatment duration, survival and cure. The most common adverse effect with Oseltamivir therapy was gastrointestinal intolerance (48%) while bronchospasm was seen in 15 (18.51%) patients treated with Zanamivir.Oseltamivir-Zanamivir combination was superior to Oseltamivir monotherapy in patients of H_1N_1 in the High-Risk Group. However, these findings need systematic prospective study for confirmation.

KEYWORDS: **H_1N_1, Neuraminidase inhibitors, Oseltamivir, Zanamivir, Drug toxicities**

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INTRODUCTION

The Swine-Flu pandemic in 2009-10 was a global killer, and led to significant losses, both in human life, and economically as well. It was caused by a novel H_1N_1 strain, born out of a triple re-assortment of bird, pig and human viruses, further combined with the Eurasian pig flu virus [1,2]. The outbreak began in the state of Veracruz, Mexico, and soon spread globally, despite efforts to control it [2,3,4]. The Centre for Disease Control and Prevention (CDC), USA eventually declared it as a pandemic in June, 2009. In India, though the first case was reported in Hyderabad, the state of Maharashtra reported the maximum number of confirmed cases, with Pune bearing the maximum brunt of the pandemic [5].Transmission was through droplet inhalation. The clinical features comprised of an uncomplicated influenza-like illness associated with gastrointestinal symptoms in mild cases. Severe cases presented with clinical or radiological signs of lower respiratory involvement, rapidly progressing to ARDS and were more common in patients with associated comorbidities like underlying cardiorespiratory ailments, pregnancy and diabetes mellitus [6,7].The mainstays of treatment of H1N1 were the Neuraminidase inhibitors Oseltamivir (orally active prodrug, converted to active carboxylated form in the liver) and Zanamivir (for administration via parenteral route). Oseltamivir was administered in a dose of 75 mg twice a day, orally. Zanamivir was administered by the inhalational route through nebulizers in a dose of 10 mg twice a day. Supportive treatment in the form of bed rest, increased fluid intake, cough suppressants and analgesic-antipyretic agents (paracetamol and other nonsteroidal anti-inflammatory agents) were administered concurrently [6-10].However, soon after these drugs were employed, a number of reports came to the fore regarding their toxicity profiles along with doubts with regard to actual efficacy in preventing complications [11-15]. Another hurdle arose with reports of Oseltamivir resistance amongst some of the pandemic influenza strains [6,7].During the epidemic, Pune bore the maximum damage with over 1500 cases admitted, and over 300 deaths reported, mostly at Sassoon General Hospitals. Data of use of the above mentioned drugs in the Indian population is, as yet, unavailable. Considering the extensive use of these drugs during the swine-flu epidemic, and the dearth of knowledge regarding their safety and efficacy in Indian population, we undertook this study so as to lay the foundation for further research on the subject.The aims of the present study were retrospective analysis of case records of H_1N_1 influenza patients with respect to demographic variations; to compare efficacy of Oseltamivir alone, with that of Oseltamivir plus Zanamivir combination on overall prognosis and outcome; and to study adverse effects profile of these drugs.

MATERIALS AND METHODS

After obtaining the necessary approval from the institutional ethics committee, records of 150 randomly-selected patients, between 18 to 65 years of age (as on the day of admission), admitted to Sassoon General Hospitals, with confirmed H_1N_1 (by positive throat-swab analysis confirmed by real-time PCR [6,7] at National Virology Institute, Pune), between 1st July 2009 and 31st December 2009, were selected. A retrospective analysis of their data (case records, necropsy records in case of death) was conducted. Data was collected and arranged according to demographic characteristics, the toxicity-profile, associated co-morbid conditions and overall influence of the drugs on outcome and prognosis. Data was then entered in Microsoft Excel sheet and analyzed using SPSS software version 22.0.

OBSERVATIONS & RESULTS

Table I
Gender Demographics of H_1N_1 influenza patients

Groups	Males	Females	Total
Oseltamivir	31	38	69
Oseltamivir + Zanamivir	34	47	81
Total	65	85	150

Table II
Age Demographics of H_1N_1 influenza patients

Groups	<18 yrs	18 – 30 yrs	31 – 40 yrs	41 – 50 yrs	>50 yrs	Total
Oseltamivir	12	17	11	12	17	69
Oseltamivir + Zanamivir	18	18	9	10	26	81
Total	30	35	20	22	43	150

Graph I
Associated Co-morbidities and Patient Survival of H_1N_1 influenza patients

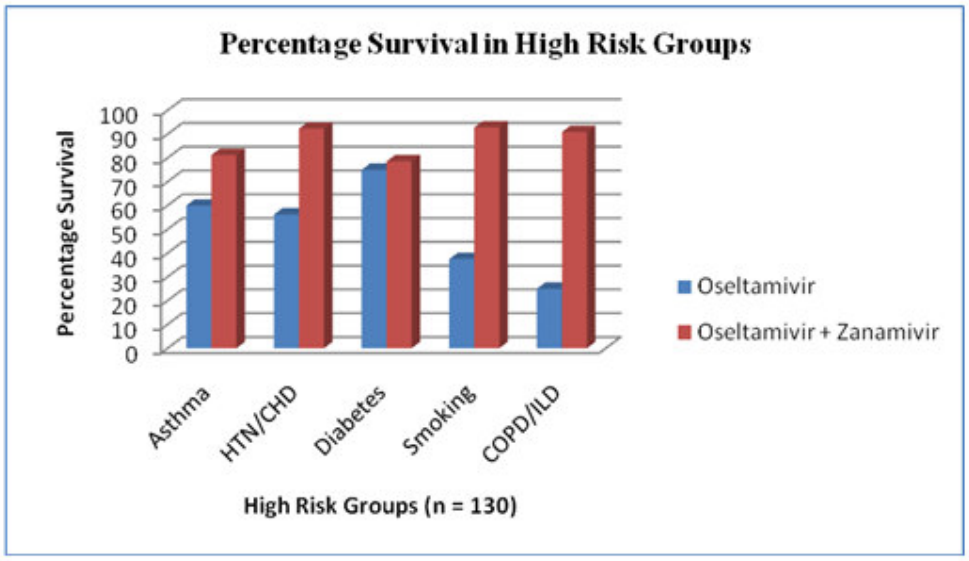


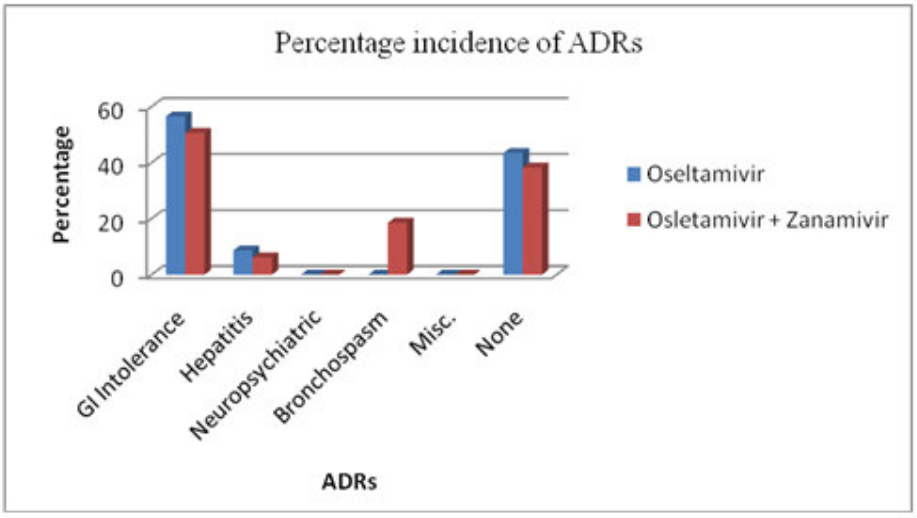
Table III
Patient Outcome in Low Risk Group of H_1N_1 influenza patients

Groups	Cured	Complications	Death	Total
Oseltamivir	16	4	0	20
Oseltamivir + Zanamivir	0	0	0	0

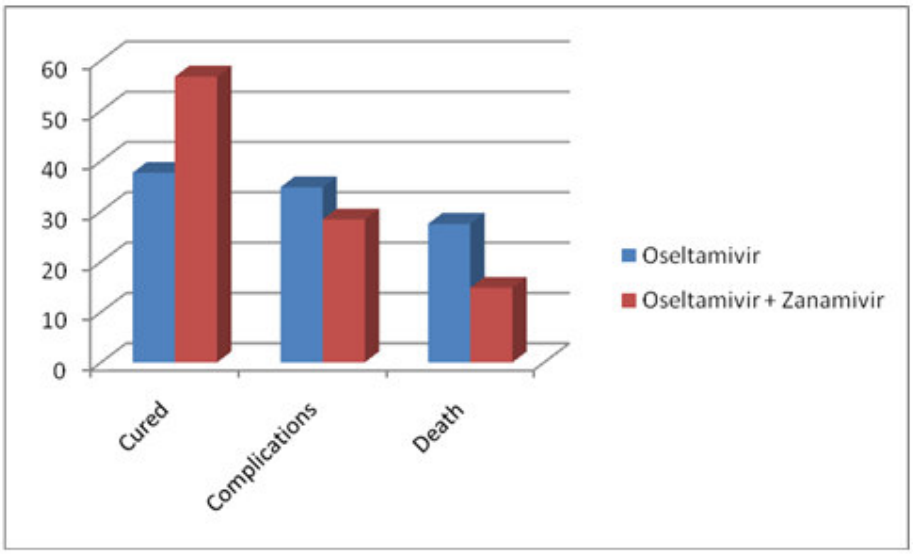
Table IV
Average Duration of Treatment of H_1N_1 influenza patients

Groups	Days
Oseltamivir	8.7 $\pm$ 2.34
Oseltamivir + Zanamivir	5.2 $\pm$ 1.97

Graph II
Incidence of adverse drug reactions (ADRs) in H_1N_1 influenza patients



Graph III
Final Outcome of H_1N_1 influenza patients



DISCUSSION

This is a retrospective study, conducted by the Department of Pharmacology in B. J. Government Medical College, Pune. 150 patients were randomly selected and a detailed analysis of their case-records was conducted and findings documented.The demographics of use of Oseltamivir monotherapy and in combination with Zanamivir are given in tables I and II. Demographics can provide valuable information regarding potential inter-subject variability in drug response due to pharmacokinetic or pharmacodynamic variations. For example, variations in age, gender, race; presence or absence of hepatic or renal diseases; diet and concomitant therapy as well as individual characteristics (body habitus, metabolic differences) can all contribute to variations in drug response. A study by Kamal et al [16] on the population pharmacokinetics of Oseltamivir revealed that body weight was the most significant covariate in Oseltamivir clearance, renal function being the next in line. The authors also postulated

that since Oseltamivir is a prodrug which requires prior carboxylation in the liver, deterioration in hepatic function may lead to decreased plasma levels of the active metabolite. However, they failed to find any significant difference in plasma levels of the active metabolite in patients with moderate hepatic impairment, as compared to normal subjects. The U.S. FDA recommended caution in use of Zanamivir in patients with renal impairment, as even mild to moderate decrease in renal function can lead to significant decrease in clearance of the drug, thereby predisposing to toxicities [17].The average duration of treatment (Table IV), in days, was significantly reduced in the combination group (5.2 $\pm$ 1.97), as compared to Oseltamivir alone (8.7 $\pm$ 2.34) suggesting that the combination of the two drugs was superior to monotherapy with Oseltamivir in reducing the viral load. Escuret et al [18] attempted to study the effect of the combination of Oseltamivir and Zanamivir as compared to monotherapy with each of the individual drugs, and noted a steady fall in viral load. However, due to inadequate sample size, the authors were unable to compare the results. A meta-analysis of data collected from over 29,000 patients revealed initiation of therapy with neuraminidase inhibitors drastically reduced mortality in patients with H_1N_1, especially in the early stages of infection [19].Analyzing the outcome in the high-risk groups (n=130, Graph I), we can conclude that a significantly favourable difference in mortality rates was found in patients in the combination group with underlying coronary heart disease and hypertension (P=0.0299), smokers (P=0.0408), and patients of COPD and Interstitial Lung disease (P=0.0478); as compared to the monotherapy group. A study performed by Borse et al revealed increased incidence of severe disease and mortality in patients with associated co-morbidities like pregnancy, hypertension, diabetes mellitus and cardiac structural defects [20]. WHO [6] and CDC [7] recommendations included the use of combination therapy in severe cases of H_1N_1 with underlying chronic cardiac and pulmonary pathologies. Patients in the low-risk group (n = 20), that is, those without underlying comorbidities, were started on monotherapy with Oseltamivir. Four patients developed complications in the form of secondary bacterial infections of the lower respiratory tract, which was successfully managed with antibiotics. The overall patient outcome was favourable in this group, with no mortality recorded.The incidence of adverse effects (Graph II) with regards to GI intolerance and hepatitis did not show any significant difference between the two groups. Neuropsychiatric adverse effects, as reported by a few studies [11-15], were however not found in our study, due to it's the retrospective nature. The incidence of bronchospasm was found only in the combination group (15 cases), but this is because Zanamivir was administered by the inhalational route. Common adverse drug reactions (ADRs) with Oseltamivir therapy are mainly gastrointestinal (nausea-vomitting, diarrhoea and abdominal pain) and headache. Rare ADRs include hepatitis and allergic reactions [11-14]. Although a few initial studies reported neuropsychiatric adverse effects with Oseltamivir use [15], recent evidence attributes this to influenza virus induced encephalopathies rather than the drug [21], with a study by Jones et al [22] going as far to propose the use of Oseltamivir prophylaxis in patients of influenza to prevent neuropsychiatric events. Zanamivir is relatively safer for use, with a low systemic toxicity profile [23], the only significant adverse effect being bronchospasm – due to its mode of delivery by the inhalational route. In mild cases, this was managed by concomitant administration of inhaled β_2 agonists like Salbutamol. Severe cases required withdrawal of the drug.The overall outcome (Graph III) was found to be significantly favourable in high-risk patients by the combination of Oseltamivir and Zanamivir, as compared to Oseltamivir alone (P=0.0195). This was evaluated on basis of development of complications (n=51, like secondary bacterial pneumonias, ARDS), need for admissions to the intensive care unit (n=57) and patient outcomes in terms of discharge or death (case records, necropsy data).Duval et al performed a similar study in patients with seasonal influenza (H_3N_2) and reported contrasting results. The authors found that the Oseltamivir-Zanamivir combination therapy was less effective than monotherapy with Oseltamivir, and called for caution in the use of the combination in clinical practice [24]. Interstrain variations in response to antiviral

drug therapy as a result of genetic reorganization during antigenic shifts and drifts might be the cause. However, further studies are needed on the subject.

CONCLUSION

The combination of Oseltamivir and Zanamivir appears to be superior to the use of Oseltamivir alone in patients with underlying chronic cardiopulmonary conditions. The combination also significantly reduced the duration of therapy in patients with H_1N_1, as compared to monotherapy alone. With regards to adverse effects, the pattern is similar in both groups, except for bronchospasm, which is specifically due to Zanamivir. One should always be alert to treat this anticipated ADR when Zanamivir is given through the inhalational route. The final outcome is also significantly favourable in patients on combination therapy, as compared to Oseltamivir alone, especially in the High-Risk groups.However, as this was a retrospective analysis, further research in the form of a systematic prospective study is needed to corroborate the findings.

CONFLICT OF INTEREST

None

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