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A Cross-Sectional Study of Psychiatric Manifestations Following Oseltamivir Administration for Suspected Patients with H1N1 Swine Influenza Infection

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ABSTRACT

Introduction: Oseltamivir is an antiviral drug used to treat H1N1 influenza. FDA added a warning to the label of oseltamivir drawing attention to the risk of developing neuropsychiatric adverse events. There are some case reports reported psychiatric symptoms on oseltamivir intake. However, data is scarce on the emergence of psychiatric symptoms following oseltamivir administration.

Materials and Methods: Sixty patients, who received oseltamivir for prophylaxis or treatment for H1N1 swine influenza in the preceding six months, were enrolled in this study. The mini neuropsychiatric screener for DSM4 and a semi-structured proforma was applied that included socio-demographic information of patients, past psychiatric history, medical comorbidities, use of concomitant medication, dose and duration of use of oseltamivir. T-test and chi-square test were used to compare parametric data and categorical data respectively. P-value ≤ 0.05 was used for statistical significance.

Results: Of 60 patients, 22(36.67%) patients had developed psychiatric symptoms after receiving oseltamivir. 11(50%) patients had sleep issues, and there were 6(27%) patients with delirium, 3(9%) with depression and 3(9%) with anxiety and 1(5%) with psychosis. Among 22 patients, 4 subjects had past history of psychiatric illness (p-value = 1.00) and 15 had past medical illness (p-value = 0.003). Patients who developed psychiatric manifestations were significantly older (p-value: 0.05) and had lower years of education (p-value: 0.01).

Conclusions: 36.67% of patients developed psychiatric side effects following oseltamivir use. Predominant symptoms included sleep issues and delirium. Those who developed psychiatric symptoms had a significant background history of medical illness. Therefore, it is recommended that those who receive oseltamivir regularly be screened for psychiatric symptoms.

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Introduction

Oseltamivir is an antiviral drug that was commonly used to treat following the outbreak of H1N1. Oseltamivir is a neuraminidase inhibitor, which prevents the release of the infectious influenza virus particles from the infected respiratory tract cells of the patients. Oseltamivir has now been approved for treatment of influenza in

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adults as well as children by U.S. food and drug administration (FDA) (1, 2, 3).

Oseltamivir is a prodrug which undergoes hydrolysis by hepatic esterases to produce an active metabolite, oseltamivir carboxylate (OCB). Common adverse effects of Oseltamivir are gastrointestinal side effects such as nausea, vomiting, diarrhea, and pain abdomen (4, 5). In 2006, US Food and Drug Administration added a warning to the label of oseltamivir drawing attention to the risk of developing neuropsychiatric adverse events (NPAE) (4, 6). Oseltamivir-induced neuropsychiatric adverse effects can be either sudden or delayed onset (1).

The exact mechanism for NPAE is least understood. However, there are few postulates that explains the probable mechanism. Li et al. reported a nonsynonymous single nucleotide polymorphism (SNP), near the active site of human cytosolic sialidase which is a homolog of the virus neuraminidase. This SNP could increase the binding affinity of human sialidase to OCB, thus reducing the sialidase activity .So, administration of oseltamivir to such patients might reduce the sialidase activity and contribute to the occurrence of severe NPAE (4,7) OCB increases neuronal firing and can thus affect central nervous system (4).

Another hypothesis states that a neuraminidase inhibitor that has antiviral effects crosses the blood-brain barrier (BBB) into the central nervous system (8,9). Another study concluded that administration of oseltamivir by systemic route raised the levels of dopamine and also its metabolic products in the medial prefrontal cortices of Rats (10). One more study explains the possibilities of Limbic GABAergic dysfunction might be involved in the pathogenesis, considering the transience of the symptoms and the later persistent efficacy of benzodiazepine in their patient (11). Delayed mechanism can also been explained due to the presence of SNPs increases binding of oseltamivir carboxylate to human sialidase, further reducing its activity (7).

There are case reports which have highlighted the occurrence of psychosis and manic symptoms on administration of oseltamivir. In addition, there were cases of delirium and delirium-like events, depressed consciousness levels, parasomnia, suicidal events, accidents, and injuries (12). However there is significant paucity of original research which has studied the incidence and prevalence of psychiatric symptoms following Oseltamivir administration in suspected H1N1 patients.

In this background, the study was planned which will be useful in clinical management of the patients.

Materials and Methods

The aims and objective of the study were:

- To study the profile of psychiatric symptoms following oseltamivir administration for suspected patients with H1N1 swine influenza infection.
- To study Socio demographic profile and clinical correlates of the above patients.

The study approval was obtained from Institutional Ethics Committee with the rebefore initiating the study and confidentiality of the participants were maintained in the study.

The study was conducted in the Departments of Pulmonology and Psychiatry of a tertiary care medical college hospital. The data was collected from previous records in the preceeding 6 months and 60 patients were included in the study. The sample size of 60 was obtained using formula 4pq/d2 with the prevalence of 40 and margin of error of around 12.5. Patients who had received oseltamivir for prophylaxis or treatment for H1N1 swine influenza in our centre in the preceding 6 months were considered. The dosage of Oseltamivir was 150mg twice a day for 5 days. Based on review of past records, an average of 25-30 patients received medication per month and we expected around 100 patients in 6 months. But, we were able to contact only 60 patients in 6 months as we were not able to trace few patients. As children do not report to this centre, age group of 18 years old and above were included for the study.

Information of patients who have received oseltamivir in the preceding 6 months were collected from the registry. A phone call was made and the study details were explained

and patients were asked to report to psychiatry Outpatient Department (OPD) at a convenient time. The principal investigator or the other study investigators collected the above information. For patients who didn't report or were unwilling to come, a telephonic interview was scheduled at a convenient time and essential data was collected.

The Tools used were:

1) A Semi-structured proforma which gives us socio-demographic information of patients, past psychiatric history, medical comorbidities, use of concomitant medication, dose and duration of use of oseltamivir.

2) Mini International Neuropsychiatric Interview 5 Screener (13).

It is a clinical interview that helps in screening basic psychiatric symptoms based on DSM –IV TR. It is divided into 16 modules consisting of precise psychological questions based on which clinician will be able to assess psychiatric conditions. With the aid of this tool a semi-structured proforma was prepared.

Statistical Analysis

Frequency of various symptoms were tabulated. T-test was used to compare parametric quantitative data and chi-square test was used to compare categorical data. P value of less than or equal to 0.05 was used for statistical significance in the study. The value of Shapiro Wilk test was 0.08 indicating normal distribution of quantitative variables.

Results

We had included 60 patients who received oseltamivir 150 mg twice for five days in the study. Among 60(66.67%) patients, 40(33.33%) were male and 20 were female, 37(61.67%) belonged to nuclear family and remaining 23(38.33%) were from joint family. Around 29(48.33%) patients had received education more than ten years and 8 subjects did not have any formal education. Around 10 patients had past history of psychiatric illness where 6 were receiving psychiatric medications. 25(41.67%) patients had past medical history.

Table 1 illustrates that the patients who developed psychiatric side effects following oseltamivir administration were significantly older and had lower years of education.

Patients who developed psychiatric side effects had significant past history of medical illness which has been illustrated in Table 2.

In our study, 9 patients had more than one medical comorbidity. 41% had hypertension, 45.5% had Diabetes milletus, 13.6% had COPD, 13.6% had hypothyroidism and 4.55% had PCOD. We also found that in our study population, 22(36.67%) patients had developed psychiatric side-effects due to oseltamivir taking. 11(50%) patients had sleep issues and there were 6(27%) patients with delirium, 3(9%) with depression, 3(9%) with anxiety and 1(5%) with psychosis.

Table 1. Comparisons of Socio-demographic data of patients with and without psychiatric side-effects following Oseltamivir intake.

	A (n=22) (Mean ± SD)		B (n = 38) (Mean ± SD)		P- value
AGE (years)	46.68 ± 7.89		43.13 ± 6.19		**0.050** [a]
EDUCATION (years)	8.59 ± 1.21		10.39 ± 3.21		**0.01**[a]
GENDER	**N**	**% age**	**N**	**% age**	
MALE (N)	14	63.64	26	68.42	0.770[b]
FEMALE (N)	8	36.36	12	31.58	

*represents statistical significance.
'A' represents patients with psychiatric side effects following Oseltamivir intake.
'B' represents patients without psychiatric side effects following Oseltamivir intake.
'SD' means Standard Deviation.
[a] t-test was used for these variables.
[b] chi-square test was used for these variable.

Discussion

This study was conducted to observe the development of psychiatric manifestations following oseltamivir administration.

We found that patients who developed psychiatric side effects were significantly older than those who did not develop psychiatric side effects. This finding was concordant with another study by Nayoung Han et al which stated that psychiatric disorders were disproportionately commoner in the younger and older patients (14).

In this study, we also observed that individuals who developed psychiatric side effects had less years of education than those with individuals who did not develop side effects following oseltmivir intake. This could be explained by a possible pre-existing vulnerability to neuropsychiatric disorders wherein individuals tend to have a lower cognitive performance.

There was no significant difference in past psychiatric illness among those who developed and did not developed psychiatric side effects following oselamivir use. But another study by Lan C et al demonstrated exacerbation of psychiatric symptoms due to oseltamivir administration in chronic psychiatric patients (15). This finding was not replicated in our study probably as it was statistically underpowered.

We found that those who developed psychiatric symptoms following oseltamivir administration had significant past medical illness than those who did not develop psychiatric symptoms. This is consistent with several studies that have demonstrated the relationship between the occurrence of psychiatric manifestations due to oseltamivir intake and the presence of underlying medical illness. It is also known that higher the number of medical comorbidities, higher the chances of development of psychiatric side effects due to oseltamivir use in older population (16,17,18).

In current study, most subjects had mild symptoms which didn't require treatment. Only two required short term Benzodiazepines. The fact that around 36% of the study population developed psychiatric side effects could probably be explained by an inherent vulnerability for the development of these symptoms, stress caused by the illness and the concern for the number of physical complaints they had. As per Toovey S et al, the reported events according to International Classification of Diseases (9th edition) codes, abnormal behavior and delusions/perceptual disturbances were the largest categories of events, and delirium or delirium-like events (as defined by the American Psychiatric Association) were very common in most categories (19). This matches with our study as 27% of our patients had developed delirium. There are many case reports suggesting development of psychosis developing following use of oseltamivir. However, probably in view of low sample size and no significant past psychiatric history we did not encounter significant number of patients with psychosis. Oseltamivir may augment agonist-induced D2 receptor activity. By inhibiting neuraminidase (sialidase), oseltamivir prevents the breakdown of sialic acid linkage to glycolipids. Thereafter, these sialoglycolipids increase the effect of enhanced D2 receptor activity by agonists (4,20).

Table 2: Comparisons of past medical history and past psychiatric illness in patients with and without psychiatric side-effects following Oseltamivir intake.

	A (N=22)		B (N=38)		P - value	X^2
	PRESENT	ABSENT	PRESENT	ABSENT		
PAST PSYCHIATRIC ILLNESS	4	18	6	32	1.00	0.05
PAST MEDICAL ILLNESS	15	7	10	28	**0.003***	8.39

*represents statistical significance.
'A' represents patients with psychiatric side effects following Oseltamivir intake.
'B' represents patients without psychiatric side effects following Oseltamivir intake.

This could explain the use of anti-psychotics for the treatment of NPAEs induced by oseltamivir.

Study Limitations

The sample size was small, thus study was statistically underpowered and many patients were lost on follow up. Thus, we need larger sample size to study association between these observations.

This is one of the few studies on the prevalence of psychiatric symptoms following Oseltamivir administration in suspected H1N1 patients in Indian context.

Conclusions

Oseltamivir can develop a wide psychiatric symptoms varying from mild to severe in spectrum reported among patients who receive it. Therefore, patients receiving oseltamivir need to be assessed for psychiatric symptoms and physicians need to be aware of. There is a need for long term follow up to determine the outcome of these psychiatric symptoms.

Conflicts of interest

The authors have declared no conflict of interest.

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