

Adverse drug reaction profile of oseltamivir in children

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ABSTRACT

Aim: To monitor and evaluate the pattern of ADRs to oseltamivir in pediatric population suffering from H1N1 influenza at a tertiary care hospital. **Materials and Methods:** Children offered oseltamivir for treatment and chemoprophylaxis were monitored for adverse events by direct questioning for symptoms and clinical examination on day 5 and day 10. Assessment of neurological events was done by asking the parents or guardians regarding development of specific symptoms. Adverse events obtained were analyzed for severity, causality and age-group wise. **Results:** Out of 191 children (median age, 3 years), 69 (36.1%) developed ADRs. Most common symptoms were vomiting (16.2%) followed by diarrhea (12.0%), ear disorders (8.9%), and insomnia (6.8%). The incidence of neuropsychiatric symptoms was 12.6% which were mild-to-moderate on severity scale. There was no significant difference in the incidence of adverse events between children less than 1 year and other age groups. **Conclusion:** Oseltamivir is well tolerated in Indian children with suspected or confirmed H1N1 influenza. Our study also indicates safety of oseltamivir in infants.

Key words: Adverse drug reactions, antiviral agent, child, infant, oseltamivir

INTRODUCTION

Monitoring and documentation of adverse drug reactions (ADR) encourage safe use of drugs by ensuring benefits outweighs the risks that may be associated with use of drugs. For newer drugs, available safety data is mainly from clinical trials, conditions of which differ from actual clinical use.^[1,2] In pediatric population, ADRs are responsible for significant morbidity and deaths. Since, clinical trials involving neonates, infants, children, and adolescents are limited, the safety and tolerability of newer drugs are not established until they are used in large number of patients in postmarketing phase.^[3-5]

Oseltamivir is an ethyl ester prodrug indicated for treatment and prevention of infections due to influenza A and B virus.

It inhibits viral neuraminidase, blocking its ability to cleave sialic acid residues on the surface of infected cells and to release progeny virions.^[6] Recent pandemic of swine flu (H1N1) in India resulted in significant morbidity in children and adolescents. Oseltamivir is the mainstay in treatment and chemoprophylaxis of swine-origin influenza A. Oseltamivir is generally well tolerated, adverse effects in adults being gastrointestinal disturbances, headache, insomnia, vertigo, bronchitis and hypersensitivity reactions.^[7] Information regarding the safety profile of oseltamivir in pediatric population is limited, especially in Indian population. Acute onset of neuropsychiatric manifestations and sudden deaths have been reported mainly in children and adolescents in Japan.^[8,9] Concerns were also raised regarding safety of oseltamivir in infants under 1 year of age.^[10] The use of oseltamivir in infants is based on the emergency use authorization granted by United States - Food and drug administration (US-FDA). Our study was designed to investigate the ADR profile of oseltamivir in pediatric population in a tertiary care hospital.

MATERIALS AND METHODS

This was a prospective study carried out among patients of

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pediatric age group visiting the swine flu Outpatient Department of a tertiary care hospital. The study was carried out over 3 months from January to March 2010. Ethical Clearance was obtained from the Institutional Ethics Committee prior to initiation of study.

The study included children of age less than 12 years of either gender who were offered oseltamivir as treatment and chemoprophylaxis. Patients with significant gastrointestinal and/or neurological disorders and critically ill patients receiving oseltamivir were excluded from the study. Informed consent was obtained from parents/legally acceptable representatives of the children for participating in the study. Data regarding age, sex, presenting complaints, indication for oseltamivir, and concomitant drug therapy were obtained from the patients. No changes in treatment decision, dose or duration were made as a part of study. The recommended dose of oseltamivir (on basis of weight and age) is to be taken twice a day for 5 days as treatment and once a day for 10 days as prophylaxis. The children were followed up for adverse events for a period of 10 days after receiving first dose of oseltamivir. The parents or guardians of children were asked to note development of new symptoms or worsening of existing symptoms in children and to report it to the hospital if necessary during the study period. Monitoring for adverse events to oseltamivir was done by direct questioning for symptoms and clinical examination on day 5 and day 10. Assessment of neurological adverse events included questions to parents or guardians and children (>5 years) regarding development of symptoms of unconsciousness, dizziness, seizures, involuntary movements, headache, irritability, hyperactivity, aggressive behavior, hallucinations (>5 years), vision or hearing problems, and sleeping disturbances during the study period. Parents were also encouraged to report such symptoms developed after the study period and within 30 days of receiving first dose of oseltamivir. Causality of ADRs was assessed using Naranjo's algorithm and the severity of ADRs was assessed using modified Hartwig and Seigel scale.

RESULTS

One-hundred ninety one children were included in the study group with age range from 2 months to 11 years [Table 1]. One-hundred seventy two children completed full course of 10 doses of oseltamivir. One-hundred forty six adverse events were documented in 69 children (36.1%). Most frequently reported symptoms were vomiting followed by diarrhea, ear disorders, and insomnia [Table 2]. Incidence of adverse outcomes did not differ significantly in age groups less than 1 year, 1 year, 1 - 4 years and 5 - 12 years [Table 3]. Severity was assessed using modified Hartwig and Seigel criteria with 113 ADRs categorized as mild and 33 categorized as moderate grade. All the ADRs belonged to possible and probable category according to Naranjo's Algorithm.

DISCUSSION

Oseltamivir is indicated in treatment and prophylaxis of influenza A and B in adults and children. Previously healthy

Table 1: Preliminary data of children receiving oseltamivir (n = 191)

Age, years	
Median (interquartile range)	3 (1-6)
0-1	36 (18.9)
1-4	81 (42.4)
5-12	74 (38.7)
Male/female	124/67
Indication for oseltamivir use	
Treatment	160 (83.8)
Prophylaxis	31 (16.2)
Concomitant drugs	163 (85.3)
Antimicrobials	123 (64.4)
Antihistaminics	163 (85.3)
Others	161 (84.3)

Table 2: Suspected ADRs in children receiving oseltamivir

	Treatment (n = 160)	Prophylaxis (n = 31)	Total (n = 191)
Vomiting	25 (15.6)	6 (19.4)	31 (16.2)
Diarrhea	18 (11.3)	5 (16.1)	23 (12.0)
Ear disorders ^a	17 (10.6)	0 (0.0)	17 (8.9)
Insomnia	12 (7.5)	1 (3.2)	13 (6.8)
Abdominal pain	8 (5.0)	3 (9.7)	11 (5.8)
Dizziness/ vertigo	8 (5.0)	2 (6.5)	10 (5.2)
Sinusitis	7 (4.4)	1 (3.2)	8 (4.2)
Headache	7 (4.4)	0 (0.0)	7 (3.7)
Fever	5 (3.1)	2 (6.5)	7 (3.7)
Nausea	3 (1.9)	3 (9.7)	6 (3.1)
Epistaxis	3 (1.9)	1 (3.2)	4 (2.1)
Cough	2 (1.3)	1 (3.2)	3 (1.6)
Conjunctivitis	2 (1.3)	0 (0.0)	2 (1.0)
Mood changes	1 (0.6)	0 (0.0)	1 (0.5)
Rash	0 (0.0)	1 (3.2)	1 (0.5)
Pneumonia	1 (0.6)	0 (0.0)	1 (0.5)
Seizures	1 (0.6)	0 (0.0)	1 (0.5)
Any suspected ADR	56 (35.0)	13 (41.9)	69 (36.1)

Figures in parentheses indicate percentages; ^aEar disorders include otitis media, otitis externa, and ear pain

Table 3: Age-group wise distribution of ADRs

	<1 (n = 36)	1-5 (n = 81)	5-12 (n = 74)	P value*
Number of children having neuropsychiatric symptom	3	8	13	0.24
Number of children having gastrointestinal symptom	9	17	19	0.7
Number of children having any ADRs	11	27	31	0.40

*By Chi-square test; P value<0.05 significant

children between the ages of 1 and 12 years with laboratory diagnosis of influenza showed a reduction of 36 h in the median duration of illness after treatment with oseltamivir.^[11,12] Prophylaxis with oseltamivir provided protective efficacy of 80% in pediatric population.^[11] In our study, oseltamivir was administered according to the guidelines issued by the Directorate General of Health Services (DGHS), Ministry of Health and Family Welfare (MOHFW), India which did not require laboratory diagnosis of influenza for administration of oseltamivir for treatment.^[13] In phase III trials of oseltamivir involving patients aged 1-12 years, the most frequently reported adverse event was vomiting (15%) followed by diarrhea (9.5%), otitis media (8.7%), and abdominal pain (4.7%). Others included nausea, epistaxis, pneumonia, sinusitis, bronchitis, conjunctivitis, dermatitis, and lymphadenopathy.^[7] Rare adverse events reported from postmarketing surveillance include serious skin hypersensitivity reactions, cardiac arrhythmias, and neuropsychiatric episodes. The most common ADRs to oseltamivir in our study were gastrointestinal ADRs like vomiting and diarrhea, the incidences of which were comparable to that of published literature.^[11,14] Though none of the gastrointestinal adverse event required discontinuation of oseltamivir, few required treatment in form of antiemetics and rehydration therapy.

Neuropsychiatric manifestations including deaths have been reported in children and adolescents less than 17 years of age mainly from Japan. These included delirium with prominent behavioral disturbances, suicidal events, panic attacks, delusions and disturbances in consciousness.^[8,9] Most of the symptoms had temporal relationship to that of oseltamivir intake and had onset within one day. The neuropsychiatric events were probably related to central depressant effect of oseltamivir.^[15] A review of available information on safety of oseltamivir in pediatric patients by United States- Food and Drug Administration (US-FDA) suggested that increased reports of these events were due to increased awareness of influenza associated encephalopathy, increased access to oseltamivir and coincident period of intensive monitoring.^[16] An internet based cross-sectional study of oseltamivir side effects among children taking oseltamivir as prophylaxis reported neuropsychiatric side effects in one out of five children with sleeping problems as most common.^[14] The overall incidence of neuropsychiatric symptoms in our study was less than 13% and was mostly sleeping difficulties, dizziness/vertigo and headache. All adverse events resolved spontaneously and none required discontinuation of oseltamivir. There is also possibility that the neuropsychiatric manifestations might be due to influenza infection. Disorders reported in children with influenza include ataxia, changes in mental state, confusion, delirium, encephalitis, encephalopathy, hallucinations, inappropriate behavior, psychosis, and seizures.^[17]

Oseltamivir is currently not recommended for use in infants

younger than 1 year of age because of lack of data on safety and effectiveness in this age group. Concerns were raised about use of oseltamivir in infants due to poorly developed blood-brain barrier. An animal study showed that mortality occurred in oseltamivir-treated infant rats in which the concentration in brain was 1500 times higher than adult rats.^[10] However, US-FDA has granted Emergency Use Authorization for oseltamivir in infants of age in anticipation that this group would require prophylaxis and treatment.^[18] Guidelines issued by DGHS, MOHFW, India for pandemic Influenza A (H1N1) recommend oseltamivir in dose of 12, 20, and 25mg in infants younger than 3 months, 3--5 months and 6--11 months, respectively. The oseltamivir use in our study in infants less than one year of age ($n = 36$) was not associated with increase in adverse events including neurological symptoms when compared to other age groups. These results were consistent with other studies which concluded no association of increased adverse events including neurological disorders and oseltamivir use in infants.^[19,20]

Limitations of our study include small sample size for rare adverse events and no definitive laboratory diagnosis for influenza (H1N1) for all patients who received oseltamivir for treatment.

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