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OSELTAMIVIR FOR INFLUENZA INFECTION IN CHILDREN: RISKS AND BENEFITS

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ABSTRACT

Influenza is a common disease affecting many children each year. In a number of cases, particularly in children <2 years old and in those with severe chronic underlying disease, influenza can be complicated by lower respiratory tract infections, acute otitis media, rhinosinusitis, febrile seizures, dehydration or encephalopathy. Oseltamivir is the influenza virus drug that is most commonly studied in children for both the treatment and prevention of influenza. To avoid the risk that children with mild influenza or patients suffering from different viral infections receive oseltamivir, oseltamivir treatment should be recommended only in severe influenza cases, especially if confirmed by reliable laboratory tests. However, therapy must be initiated considering the risk of complications and the presence of severe clinical manifestations at age- and weight-appropriate doses. Because the vaccine remains the best option for preventing influenza and its complications, prophylaxis using oseltamivir should only be considered in select patients.

Key-words: antiviral prophylaxis; antiviral therapy; children; influenza; neuraminidase inhibitor; oseltamivir

INTRODUCTION

Influenza is a common disease that affects a great number of children (up to 30% of the entire paediatric population) every year [1]. In most of these children, influenza is a mild disease mainly involving the upper respiratory tract and tends to resolve spontaneously within a few days.

In a number of cases, particularly in children <2 years old and in those with severe chronic underlying disease with or without immune problems, influenza can be complicated by lower respiratory tract infections, acute otitis media, rhinosinusitis, febrile seizures, dehydration or encephalopathy [2]. Complications can be due to the virus itself, secondary bacterial infections and, rarely, to the development of adverse events resulting from drugs such as antipyretics or inappropriately used antibiotics [3]. In many children with complications, hospitalization is required at a rate of up to 4.5 cases per 1,000 children under the age of 6 months [4]. Rarely, death can occur in hospitalized children with influenza [5].

Moreover, influenza in children causes relevant social and economic problems because children are the main cause of the spread of the infection in the community [6]. Administration of the influenza vaccine is the best method of preventing influenza infection and disease and reducing influenza-related medical, social and economic problems [7*]. However, influenza vaccines are not licensed for use in infants <6 months old and are not very effective in some populations including younger children and children with immune problems. Moreover, they require several weeks to be fully effective.

To treat severe cases of influenza and to prevent infection in unvaccinated children at risk or awaiting the development of protective immunity after vaccination, several drugs have been considered. The older medications amantadine and rimantadine were abandoned because they are only effective against influenza A, and their use is limited by drug resistance and poor tolerability [8]. By contrast, neuroaminidase inhibitors were considered

as possible options for the prophylaxis and treatment of influenza, mainly because they are active against all influenza virus subtypes and are, in general, apparently safe and well tolerated [8]. Among them, zanamivir and oseltamivir are worldwide on the market since several years, whereas laninamivir, licensed in Japan also for the use in children, is not available in the rest of the world [9]. Due to its inhalation administration that requires patient co-operation, zanamivir cannot be administered to younger children. Oseltamivir, however, is available as a capsule and an oral suspension and has recently become available in an intravenous preparation. This means oseltamivir can easily be administered to children of any age, including those who cannot receive zanamivir.

The World Health Organization (WHO) considers oseltamivir an essential drug [10]. Moreover, it is approved in the USA by the Food and Drug Administration (FDA) for the treatment of children ≥2 weeks old with influenza and for prophylaxis among children ≥1 year of age exposed to influenza [11]. Finally, it is licensed in the European Union by the European Medicines Agency (EMA) for treatment of all the children (including full term neonates) with influenza and for prophylaxis in exposed children ≥1 year of age during seasonal epidemics with extension to those <1 year of age in the case of pandemics [12]. Licenses for its use in children have been obtained based on the results of studies that were considered adequate to show sufficient efficacy for both the treatment and prevention of influenza in children in the absence of any relevant problems with safety and tolerability. However, in recent years, some experts have raised doubts regarding the accuracy of these conclusions and have questioned whether the use of neuraminidase inhibitors in children may be considered completely justified [13, 14**]. The main aim of this study is to detail the current knowledge regarding oseltamivir and its use in children and to discuss whether, when and how this drug may help paediatric patients facing influenza-related problems.

MECHANISM OF ACTION OF OSELTAMIVIR

In commercial preparations, oseltamivir is included as oseltamivir phosphate, i.e., a prodrug that is rapidly metabolized by hepatic carboxylesterases to the active metabolite oseltamivir carboxylate. This inhibits the neuraminidase enzyme, which is expressed on the surface of the influenza virus. The enzyme promotes the release of the virus from infected cells and facilitates viral diffusion within the respiratory tract. In the presence of this neuraminidase inhibitor, virions stay attached to the membrane of infected cells and are entrapped in respiratory secretions [15]. *In vitro* studies have demonstrated that oseltamivir is active against all the influenza subtypes with inhibitory concentrations required to inhibit the growth of 50% of isolates of ≤2.0 nM and an inhibitory constant of ≤1.2 nM [16]. Activity seems higher against influenza A than influenza B viruses [16].

DEVELOPMENT OF INFLUENZA VIRUS RESISTANCE TO OSELTAMIVIR

Variations in the genetic characteristics of influenza virus neuraminidase can reduce the efficacy of oseltamivir. H275Y mutations in influenza A/H1N1, R292K or E119V in influenza A/H3N2 and R152K or D198N in influenza B virus neuraminidase are more frequently detected, mainly after prolonged treatment [17, 18, 19*]. While in most cases these mutations lead to a reduction in influenza virulence, in other cases they may create conditions that lead to the clinical failure of oseltamivir treatment. This was evidenced in adults admitted to the hospital [17, 18, 19*] and was also reported in children. A pediatric case was evidenced by Esposito et al. in a girl suffering from cystic fibrosis who was infected by the A/H1N1 2009 pandemic virus [20]. The H275Y mutation emerged during oseltamivir treatment and was associated with a significant deterioration of the clinical condition of the patient. Only treatment with zanamivir could solve the problem. Drug

resistance can emerge during treatment with rates that differ for each of the different viral subtypes. Stephenson et al. studied 34 children infected by A/H3N2, 11 by A/H1N1 and 19 by influenza B virus and by days 4-7 after the initiation of oseltamivir treatment, antiviral-resistant viruses were recovered in 3 (27.3%) children with A/H1N1 infection and in 1 (2.9%) of those children infected by the A/H3N2 virus [21]. None of patients infected with the influenza B virus developed resistance. Emergence of resistance was also associated with the use of lower than recommended oseltamivir dosages. This seems suggested by the data collected in Japan where oseltamivir is typically administered at a dose of 2 mg/kg twice daily, and the rates of resistance in post-treatment isolates were found to be 16% and 18% [22, 23], which is significantly higher than the rates reported in countries where recommended dosages assure an approximately 20% higher plasma level of the active oseltamivir metabolite [24]. However, this conclusions is debated because emerging of resistant viruses in oseltamivir treated patients was not confirmed with conventional virus isolation using permanent canine kidney (MDCK) cells [25].

OSELTAMIVIR PHARMACOKINETIC CHARACTERISTICS

In adults, oseltamivir is well absorbed from the gastrointestinal tract following oral administration. Approximately 80% of an oral dose is absorbed and converted into oseltamivir carboxylate, with less than 5% recovered unchanged in the urine [26]. Administration with food produces no significant change in absorption, although data collected in animals indicates that concentrations after meals are slightly lower than in fasting animals [27]. Oseltamivir carboxylate is detectable in the plasma within 30 minutes of dosing, and concentrations reach near-maximal levels after 3-4 hours [26]. Liver impairment poorly influences the metabolism of oseltamivir and in patients with mild to moderate liver disease, no dose adjustment is required [28]. Oseltamivir carboxylate is widely distributed throughout the body, with minimal protein binding (3%). The volume of

distribution of oseltamivir carboxylate after intravenous administration in an adult man is 23-26 L [29]. This value is similar to the extracellular volume of body water in adult humans, suggesting that the metabolite may penetrate infection sites at concentrations similar to those in plasma. Indeed, oseltamivir and oseltamivir carboxylate are systemically distributed, with therapeutic concentrations attained in the lungs, trachea and nasal mucosa as well as the sinuses and middle ear [30, 31]. Oseltamivir carboxylate is eliminated in the urine mainly by filtration but also by means of tubular secretion with a half-life of 6–10 hours [26]. Severe renal insufficiency (creatinine clearance <30 mL/min) is associated with a marked increase in exposure to oseltamivir carboxylate. This finding has led to a significant suggested reduction of oseltamivir dosage in patients with renal failure.

In children, significant variations in pharmacokinetic characteristics of oseltamivir occur. They are strictly related to age and, the younger the patient is, the greater the effect of the drug will be. Practically, in children >12 years of age, pharmacokinetic characteristics of oseltamivir are quite similar to those found in adult subjects, and no variations in drug dosage are needed. On the contrary, younger subjects tend to require different dosages because absorption, distribution, metabolism and elimination rates of oseltamivir and oseltamivir carboxylate are different. In particular, it has been reported that the protein content of food can influence absorption. In the experimental animal model, it was evidenced that exposure to oseltamivir was reduced from 31.5% to 11.7% when oseltamivir was dissolved in milk, 5.5% when the drug was dissolved in a solution of the milk protein casein, and 5.5% when the drug was dissolved in a solution containing an inhibitor of the intestinal enzymes that favour the transport of the drug [32]. Moreover, co-administration of oseltamivir with a high-fat meal causes a significant delay and decrease in the observed maximum plasma concentration, which was 20% lower than that observed under fasting conditions [30]. These findings suggest that in neonates and younger children, the high frequency of milk-based meals can result in lower bioavailability of the

drug compared to older children and adults. Moreover, expression of the hepatic enzyme that converts oseltamivir in oseltamivir carboxylate is significantly reduced and highly variable in the first months of life and increases with increasing age. It has been reported that the formation rate of oseltamivir carboxylate is significantly slower in neonates and younger infants than in older children and adults, and the clearance rate of the drug is dictated by the rate of formation rather than the rate of elimination [30]. This factor can, *per se*, lead to a lower bioavailability of oseltamivir carboxylate in younger subjects and explains why a higher dosage of oseltamivir is required to obtain the same peak levels and total exposure to the drug in infants versus adults. At the same time, this metabolic factor could explain why, in premature infants in whom the glomerular filtration rate is extremely low, both oseltamivir carboxylate formation and elimination are equally important in determining the clearance, and the amount of drug needed to obtain therapeutic levels are similar to those used in adults.

Regarding distribution, because oseltamivir carboxylate is only marginally bound to plasma proteins, the free amount of drug remains substantially unmodified in children compared to adults, despite the lower plasma protein concentrations and the protein binding capacities in early life [34]. However, due to the higher body water content of neonates and younger infants in comparison to adults, an expanded volume of distribution has to be expected in the first periods of life. Finally, elimination rates vary with age due to the significant modifications in glomerular filtration rates and tubular excretion characteristics during the first months of life [34].

PEDIATRIC OSELTAMIVIR DOSAGE

The data derived from pharmacokinetic studies carried out in children of different ages have confirmed the differences between children and adults and the need for different doses according to age. Acosta et al. suggested the twice daily administration of 1 mg/kg

oseltamivir in neonates of gestational age ≤37 weeks and a dose of 3 mg/kg for full term infants, whereas in adults, a dose of 75 mg, approximately 1 mg/kg, was determined to be high enough to obtain the same OsC exposure [35]. Kimberlin et al. recommended the administration of 3 mg/kg twice daily in infants from birth to 8 months of age and a higher dose of 3.5 mg/kg in infants 9-11 months of age to achieve appropriate exposure [36]. Children 12-23 months of age had suboptimal exposure when they were administered the FDA-approved unit dose of 30 mg, and most children who were given 3.5 mg/kg/dose achieved target exposure levels.

However, as in adults, children of any age with severe renal insufficiency require significant reductions in oseltamivir dosage. In children ≥1 year undergoing maintenance haemodialysis (HD), Schreuder et al. suggested that oseltamivir be administered after each HD session at doses of 7.5 mg, 10 mg, 15 mg, and 30 mg in those weighing ≤15 kg, 16-23 kg, 24-40 kg, and >40 kg, respectively [37].

Utilizing the data collected in pharmacokinetic studies, health authorities have suggested oseltamivir doses for children based on weight and age. The Advisory Committee on Immunization Practices (ACIP) of the USA [38] recommends the following dosages according to age group and weight: for treatment, in infants <1 year old a 5 days course of 3 mg/kg/dose twice daily and in those ≥1 year old a 5 days course 30 mg twice daily for a weight of <15 kg, 45 mg twice daily for a weight of 15-23 kg, 60 mg twice daily for a weight of 24-40 kg, and 75 mg twice daily for a weight >40 kg; for chemoprophylaxis, in infants 3-11 months old a 7 days course of 3 mg/kg/dose once daily (oseltamivir is not recommended below 3 months of age unless situation is judged critical) and in those ≥1 year old a 7 days course 30 mg once daily for a weight of <15 kg, 45 mg once daily for a weight of 15-23 kg, 60 mg once daily for a weight of 24-40 kg, and 75 mg once daily for a weight >40 kg. However, because the pharmacokinetics of oseltamivir in children, particularly in young children with chronic illnesses, are unknown, further studies are

needed to establish whether and in which subjects the currently recommended dosages should be modified.

EFFICACY OF OSELTAMIVIR

While there are significantly fewer studies in children than in adults, a number of studies have evaluated the impact of oseltamivir administration in children both for therapy and prophylaxis. The studies can be divided into two groups: the prospective, randomized, controlled studies (RCT) and observational studies. Many of the observational studies were carried out in small groups of subjects or were not appropriately designed or powered to assess the effect of oseltamivir on influenza infection and its complications [13, 14**]. Similar limits can be evidenced in some of the RCT. Moreover, even in RCT carried out using adequate methods, the criteria for enrolment and evaluation were not uniform, therefore making it difficult to pool and compare results. In a meta-analysis of RCT carried out in children until June 2009, most of the studies initially selected were eliminated because they were not methodologically adequate [39]. Furthermore, in the few studies completed using acceptable methods, enrolment included some cases of healthy children with mild to moderate disease, and other cases of patients with asthma. The effects of treatment were evaluated differently in studies that analyzed the duration of some signs and symptoms of disease versus others that considered a more detailed clinical picture or others that also included the time needed for return to school or normal activities. Finally, only a minority of the studies enrolled children <1 year of age. However, the analysis of the available data led the authors to conclude that the treatment of influenza with oseltamivir could provide a more rapid resolution of symptoms and return to school or normal activities by reducing the duration to between 0.5 to 1.5 days [39]. These reductions were not all significant, leaving uncertainty regarding the clinical implications of these effects. Moreover, it was reported that the effects on individual symptoms and the incidence of

complications were also not consistent, although in one study there was a reduction of antibiotic prescriptions and the rates of acute otitis media (AOM) in treated children, a similar rate in those aged 5-6 and 12 years old and a significantly lower rate in children <5 years old [39]. The effect on asthma exacerbations was considered marginal to negligible, a conclusion that differed from that derived from a study that was not included in the meta-analysis in which there was evidence of a greater improvement in lung function and fewer asthma exacerbations among oseltamivir-treated children compared to those receiving placebo [40].

Similar results and similar conclusions were reported by more recent RCTs and meta-analyses [13, 14**, 41]. A RCT of oseltamivir treatment among 408 children 1-3 years of age reported that when the drug was given within 24 hours of illness onset, the median time to illness resolution was shortened by 3.5 days compared with placebo [41]. On the contrary, minimal or no benefit was reported in healthy children when antiviral treatment was initiated >2 days after the onset of uncomplicated influenza. The need for early administration of the drug to obtain positive results was confirmed when the incidence of AOM was evaluated. An 85% reduction in the development of this disease was found when oseltamivir was started within 12 hours of illness onset, while there was no reduction when treatment was initiated >24 hours later [42]. However, in this and other studies, no effect on the rate of hospital admission or the incidence of pneumonia and complications classified as serious or that led to study withdrawal was evidenced [42, 43]. Oseltamivir seemed to lead to a decrease in the amount of influenza viral shedding among treated children, but studies on whether the duration of viral shedding could be reduced by oseltamivir have been inconsistent, and the temporal and causal relationships between changes in influenza viral shedding and clinical outcomes have not been well established [44].

Few data collected in children with influenza severe enough to require hospitalization are available and included in RCT. In a study involving 63 children with influenza hospitalized for dehydration or respiratory problems, the duration of fever was 42 hours in those treated with oseltamivir and 61 hours in those receiving no treatment [44]. No data are available from controlled and randomized clinical trials measuring oseltamivir benefit in reducing negative evolution and admission to the intensive care unit. On the contrary, a great number of data have been collected in children included in observational studies. Moreover, in most of the cases, they indicate a positive impact of oseltamivir administration [45]. Observational data collected during the recent 2009 pandemic suggested that hospitalized children with influenza and children at risk of developing influenza-related complications because they suffer from a severe underlying disease could benefit from oral administration of a neuraminidase inhibitor, particularly oseltamivir. In children with chronic medical or neurologic conditions, oseltamivir administration was associated with a significant reduction in the risk of developing respiratory problems other than pneumonia but including AOM, asthma exacerbation and bronchiolitis [46]. Moreover, it was evidenced that in patients <18 years old hospitalized for the 2009 pandemic influenza, those treated with a neuraminidase inhibitor, particularly oseltamivir, within 48 hours of symptom onset were less likely to require intensive care unit admission compared with those never treated [47]. However, when the impact on mortality was evaluated, the observational studies did not always find a positive effect of oseltamivir. In March 2014, a meta-analysis by Muthuri et al. including observational individual participant data for 29,234 patients of any age admitted to the hospital with influenza due to the A/H1N1 2009 pandemic virus showed a significant reduction in mortality associated with neuraminidase inhibitor administration, in most of the cases oseltamivir [48*]. The reduction was independent from the time of drug administration, although it was higher (50% vs 20%) when treatment was started within 48 hours of symptoms onset, and the hazard rate

increased with each day's delay in the initiation of treatment up to day 5. Unfortunately, when data regarding children were evaluated alone, these associations were less pronounced and not significant. These findings are quite different from those collected by Louie et al. who, studying 784 severely ill children admitted to intensive care units with confirmed influenza, did show a significant reduction in mortality (64%) in subjects who received treatment [47]. A reduction in mortality associated with oseltamivir treatment was also reported by Farias et al., who studied 437 critically ill children admitted to the intensive care unit for a severe lower respiratory problem [49]. Among these patients, 39% died within 24 hours of hospitalization, but mortality was significantly lower among those that received oseltamivir within 24 hours of hospital admission.

Regarding the use of oseltamivir for prophylaxis, it was reported that the protective efficacy of post-exposure prophylaxis in children is 49% for influenza A and 60% for influenza B [50]. Protection was also achieved in neonates [51]. These findings were reported by both RCTs and observational studies.

Overall, all the meta-analyses composed entirely of RCTs agree that oseltamivir seems effective in reducing the duration of the signs and symptoms of disease in children with influenza when administered within 48 hours of illness onset. Late administration significantly reduces potential efficacy. However, when only RCTs were evaluated, only marginal, if any, effects of oseltamivir on the severity of influenza disease and development of lower respiratory tract complications could be demonstrated. AOM is the only complication for which there are indisputable data of an effective preventive effect of oseltamivir administration. The efficacy of oseltamivir in reducing other respiratory complications including pneumonia, hospitalization rates and mortality, remains debatable due to very limited available data. Observational studies are more optimistic and, at least in some cases, seem to demonstrate a positive effect of oseltamivir administration on reducing the risks of severe evolution of hospitalized children and mortality. Data regarding

prophylaxis with oseltamivir are scanty, although available findings seem to indicate a potential positive effect of the drug, even in younger children.

From a practical point of view, when health authorities had to decide whether and how oseltamivir had to be used in children, suggestions derived from observational studies prevailed. It was recommended that oseltamivir had to be used for the treatment and prevention of influenza in children in a significantly higher number of clinical situations than indicated by the meta-analyses that have considered only RCT. It is notable that while the ACIP of the USA also suggests oseltamivir administration in neonates <14 days of age for treatment and in children between 3 and 12 months of age for prophylaxis, oseltamivir is not FDA-approved for use in these age groups [51].

SAFETY AND TOLERABILITY OF OSELTAMIVIR

Marois et al. reported that influenza-specific CD8(+) effector T cell recruitment was reduced by up to 81% in the lungs of mice treated with oseltamivir compared to saline controls [52*]. Moreover, they showed that oseltamivir administration could significantly decrease the pools of tissue-resident and circulating effector memory (93.7%) and central memory CD8(+) T cells (45%). Finally, antiviral administration led to a significant 5.7-fold decreased production of functional anti-influenza antibodies. Practically, in the experimental animal model, antiviral treatment was found to affect the development of the adaptive immune response and protective immunity against influenza [52*]. This finding suggests that oseltamivir can impair the human immune response to the infectious agent. However, no published study has assessed whether oseltamivir impairs the immunologic response to trivalent inactivated influenza vaccine.

Vomiting is relatively common in children receiving oseltamivir. In a clinical trial carried out in children 1-2 years old, this adverse event has been found in 14% of treated patients compared to 8.5% of placebo recipients. Overall, 1% discontinued the drug secondary to

this side effect. No relevant effects on the incidence of nausea and diarrhoea was evidenced [53]. Similar data have been reported in the meta-analyses published in 2009 [38] and in 2014 [13] and in a very recent prospective observational study [54*].

However, a potential higher risk of gastrointestinal adverse events after oseltamivir administration seems suggested by the evidence that when oseltamivir was offered for prophylaxis among pupils with confirmed cases of influenza due to the A/H1N1 2009 pandemic virus, self-reported nausea and vomiting were more common than were reported in clinical controlled trials [55]. Moreover, higher than previously reported rates of vomiting and diarrhoea were also found by Rath et al. [56*]. These authors examined 65 patients <1-year-old treated with the recommended doses of oseltamivir and evidenced at least one of these adverse events in approximately 40% of the cases.

Oseltamivir has been associated with the development of transient neuropsychiatric events (i.e., self-injury or delirium). Most of the reports were among Japanese people, including many children and adolescents [57]. However, post-marketing assessment of these adverse events in influenza patients treated with oseltamivir has determined that their incidence was the same as in unexposed patients and quite similar to that usually reported as a consequence of influenza infection [58]. Evidence suggests that influenza-related encephalopathies are caused by influenza-induced inflammatory responses, and oseltamivir is not associated with an increased number of neurologic problems. However, to definitively solve the problem of a possible association between oseltamivir and the development of neuropsychiatric adverse events, FDA advises that persons receiving oseltamivir be monitored closely for abnormal behaviour [59].

Death was never associated with oseltamivir administration.

A global evaluation of oseltamivir safety and tolerability seems to suggest that the drug is safe and well tolerated. However, data regarding neonates and younger infants are few. This explains why the ACIP of the USA has highlighted that health-care providers should

be aware of the limited data on safety and dosing when considering oseltamivir use for infants, and they should carefully monitor infants for adverse events. Clinicians and pharmacists should also pay careful attention to the potential for dosing errors in young children [38].

CONCLUSIONS

Oseltamivir is the most studied drug that is active against influenza viruses in children for both the treatment and prevention of influenza infection and disease. It is generally safe and well tolerated because the incidence of adverse events, mainly limited to the gastrointestinal tract, has been found to be low, and severe cases were very rare. Its efficacy is debated because a number of meta-analyses including RCTs have raised doubts regarding the true efficacy, particularly when severe and complicated cases of influenza were considered. It was determined that early oseltamivir administration could reduce the duration of influenza illness and prevent AOM in a significant number of children. However, its effect on the risk of the development of severe respiratory infections, hospitalization rates and mortality were not definitively proven. More optimistic were the results of a number of observational studies mainly carried out during the recent A/H1N1 2009 pandemic. These studies have not only confirmed the positive impact of oseltamivir on the duration of illness but have evidenced that this drug can positively impact the incidence of complications as well as the risk of hospitalization and death. Considering that influenza in healthy children is generally a mild disease and that the advantage of oseltamivir administration is limited to a marginal reduction in disease duration, it seems irrational to suggest a widespread use of oseltamivir in the paediatric population. However, influenza can be a serious disease in children at risk of complications including those suffering from a severe chronic underlying disease, neonates and younger infants, even if they are healthy.

In healthy children, to avoid the risk that respiratory infections other than influenza are treated with oseltamivir, the best solution would be the administration of oseltamivir only to children who developed severe disease during influenza epidemic and with positive laboratory test for influenza identification. Presently, several effective rapid tests for influenza virus detection have been developed and their use, even in the community, could permit a correct identification of the cases who really need oseltamivir administration. However, this seems a little difficult from the infrastructure, cost and availability of testing point of view, especially in the developing countries. Treatment of severe respiratory cases occurring during influenza epidemic remains the simplest solution, although this leads to a not marginal number of unneeded oseltamivir prescriptions.

However, when oseltamivir administration seems reasonable, therapy has to be initiated as quickly as possible because the best results are obtained when the drug is administered within 48 hours of illness onset. Moreover, particular attention has to be paid to the dosage because it has to be decided according to the age and weight, considering that low dosages favour the emergence of resistance but high dosages can cause adverse events. Prophylaxis with oseltamivir should be considered only for a select number of clinical conditions, considering that the vaccine remains the best solution for preventing influenza and its complications and that its universal use could significantly reduce the number of patients for whom decision whether to treat or not to treat remains debatable. Unfortunately, universal use of influenza vaccine is not recommended in many industrialized areas and is quite difficult to plane in developing countries mainly for organizational and economic problems.

EXPERT COMMENTARY

The debate regarding the role of oseltamivir in the prevention and treatment of influenza stems from the dissimilarities between the results of the RCTs and the observational

studies specifically planned to evaluate the impact of oseltamivir on the total burden of influenza. Observational studies have a number of limitations and weaknesses compared to RCTs that cannot be forgotten. However, they can help in clinical practice, especially when no or few data from suitably powered placebo-controlled randomized studies are available. This is the case of influenza in children for whom there have been very few RCTs, and data collected with placebo-controlled evaluations in neonates and younger infants, patients with very severe disease and patients with severe chronic underlying disease are lacking. Unfortunately, it is difficult to carry out similar studies, and it is practically impossible for some chronic diseases, due to the relatively low frequency of the diseases and the difficulty of performing multicentre studies. This probably indicates that in children, observational studies will remain the only source of information and the only basis on which the use of oseltamivir can be established. The consistency with which benefits of oseltamivir treatment have been reported in some observational studies is difficult to ignore. Consequently, the recommendation to treat with oseltamivir all the children with severe influenza admitted to the hospital seems reasonable and should be followed. However, it should be noted that the widespread use of oseltamivir should be avoided and treatment should be limited to a very small number of patients because in most of the children infected by influenza viruses, the disease is mild, does not require hospitalization and resolves spontaneously within a few days. Moreover, particular attention has to be paid to the importance of early treatment. Because rapid identification of influenza aetiology of a respiratory disease is not always possible, this means that in epidemic or pandemic periods, all the cases of severe respiratory problems in children have to be treated before the results of laboratory tests become available. However, to reduce the risk of oseltamivir abuse, any effort to improve the diagnosis of influenza in the hospital should be made.

FIVE YEAR VIEW

In the coming years, further studies on the pharmacokinetics and pharmacodynamics of oseltamivir should be performed in the groups of subjects for whom presently no complete information is available. This would permit providers to draw firm conclusions regarding the best dosage to use in children of different ages, overcoming the doubts that some researchers have raised on the dosages officially recommended. Moreover, the role of underlying diseases in conditioning dosages will be established, and more effective doses of drugs will be used to treat severe influenza in each group of at-risk patients. Furthermore, rapid tests for influenza virus identification will be more largely diffused, and this will permit the reservation of effective treatment only for children with influenza infection, avoiding the risk of oseltamivir widespread use [60]. Finally, as soon as universal influenza vaccines become available, their use will likely solve most of the doubts regarding oseltamivir prescribing. When available, these vaccines would be effective against influenza, independent of the strain involved in the epidemic or pandemic and the potential mismatch between the viruses included in the currently prepared vaccines and the circulating virus. Their large universal use in the paediatric population, together with a systematic vaccination of pregnant women could significantly reduce the need for neuraminidase inhibitor administration and the problems related to the incomplete knowledge of their true clinical importance [61].

KEY ISSUES

- In a number of pediatric cases, particularly in children <2 years old and in those with severe chronic underlying disease, influenza can be complicated by lower respiratory tract infections, acute otitis media, rhinosinusitis, febrile seizures, dehydration or encephalopathy.

- Oseltamivir is the influenza virus drug that is most commonly studied in children for both the treatment and prevention of influenza.
- Oseltamivir is generally safe and well tolerated because the incidence of adverse events related to its administration, mainly limited to the gastrointestinal tract, has been found to be low, and severe adverse events were very rare.
- Particular attention has to be paid to the dosage because it has to be decided according to the age and weight, considering that low dosages favour the emergence of resistance but high dosages can cause adverse events.
- Early oseltamivir administration could reduce the duration of influenza illness and prevent AOM in a significant number of children, but its effects on the risk of the development of severe respiratory infections, hospitalization rates and mortality were not definitively proven.
- In children with chronic medical or neurologic conditions, oseltamivir administration was associated with a significant reduction in the risk of developing respiratory problems other than pneumonia but including AOM, asthma exacerbation and bronchiolitis.
- Data regarding prophylaxis with oseltamivir are scanty, although available findings seem to indicate a potential positive effect of the drug, even in younger children.
- Prophylaxis with oseltamivir should be considered only for a select number of clinical conditions, considering that the vaccine remains the best solution for preventing influenza and its complications.
- Presently, several effective rapid tests for influenza virus detection have been developed and their use, even in the community, could permit a correct identification of the cases who really need oseltamivir administration.

- To avoid the risk that children with mild influenza or patients suffering from different viral infections receive oseltamivir, oseltamivir treatment should be recommended only in severe influenza cases, especially if confirmed by reliable laboratory tests.

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** Of interest*
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