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Serum Concentrations and Safety of Rimantadine in Paediatric Patients

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Summary. Rimantadine has been shown to be more active in vitro and less toxic than amantadine in adults with influenza A disease. Because of a lack of studies in pediatric patients, we designed a study to evaluate serum concentrations and adverse effects of rimantadine in infants receiving repeated doses. Fourteen hospitalized infants (ages 1-10 months) were given rimantadine syrup at 3 mg/kg/dose in single daily doses during influenza season. Blood samples were obtained prior to dose and at various intervals up to 8 h after doses on the fifth to ninth days of therapy. Adverse effects were assessed based on clinical status, activity level, hematologic and biochemical parameters during 10-day therapy. Steady-state rimantadine peak serum concentration ranged from 100 to 574 ng/ml and time to achieve peak concentration ranged from 2.5 to 6.0 h after the doses. No adverse effects were seen except hematuria in one infant; this patient had the highest rimantadine concentration and longest treatment duration. Hematuria resolved during a follow-up evaluation on the ninth day after stopping therapy. Our data suggest that 1. rimantadine can be given safely at repeated doses of 3 mg/kg/dose in a convenient once-daily regimen; 2. the steady-state peak serum concentrations and time to achieve peak concentration may vary substantially in infants receiving same oral doses; and 3. possible association of adverse effects and high serum concentration or long treatment duration of rimantadine needs further evaluation in small infants.

Key words: rimantadine, influenza A; adverse effects, serum concentration, infants

Rimantadine is an investigational antiviral agent for influenza A virus. In controlled studies [5, 13, 15], rimantadine has been shown to be as effective as amantadine for prophylaxis and treatment of illness due to strains of influenza A. Based on the available literature, rimantadine appears to offer three potential advantages over amantadine. First, rimantadine has been shown to be more active than amantadine against influenza A viruses in vitro [12, 3, 7] as well as in animals [11, 14]. Second, adverse effects in adults have occurred less frequently with rimantadine than amantadine. Finally, the elimination half-life of rimantadine in adults has been reported to be twice as long as amantadine [10], which may translate into a less frequent and more convenient dosing schedule for rimantadine than amantadine.

Amantadine or rimantadine therapy has been recommended for unvaccinated children in high risk groups such as those with cardiac, pulmonary and immunodeficient states [1]. It is important to note, however, that no data are available about serum concentration and safety of rimantadine therapy in infants.

This study was designed to evaluate serum concentrations and adverse effects of rimantadine following repeated doses in infants. Because the adverse effects due to amantadine have been related to both dose and duration of therapy [4, 2], we were also interested in examining the relationship between serum concentrations and potential toxicity of rimantadine during repeated therapy in these patients.

Methods

Fourteen infants (ages 1.0 to 10.5 months) hospitalized during influenza A season were enrolled into the study after obtaining an informed consent from a

Table 1. Serum concentrations and adverse effects of rimantadine in infants during repeated therapy

Patient	Age [months]	Weight [kg]	Days of therapy	Steady-state rimantadine peak conc.; [ng/ml][a]	Time to achieve peak conc.; [h]	Adverse effects
1	10.5	8.0	10	433 (8)[b]	4.0	None
2	6.5	7.3	8	298 (8)[b]	4.0	None
3	4.0	4.8	8	246 (7)[b]	4.0	None
4	8.0	5.1	7	100 (6)[b]	6.0	None
5	1.0	2.7	10	574 (8)[b]	3.0	Microscopic hematuria (10)[d]
6	6.5	8.1	7	167 (7)[b]	2.5	None
7	4.5	4.0	7	477 (5)[b]	3.0	None
8	6.5	8.7	7	438 (4)[b]	6.0	None
9-14	2 to 10	2.9 to 8.5	3-17	ND[c]	ND	None

[a] Serum concentrations were determined after once daily doses of rimantadine, 3 mg/kg/doses.
[b] Numbers in parantheses indicate the number of days of rimantadine therapy before the determination steady-state peak serum concentration.
[c] Not determined.
[d] Day of therapy when adverse effects occurred

parent or legal guardian. The reasons for hospitalization included prematurity, birth asphyxia, respiratory distress, bronchopulmonary dysplasia, failure to thrive, fever, bacteremia, lower respiratory infection, otitis media, fractured femur, and septic arthritis.

Rimantadine hydrochloride was obtained from E.I. dupont deNemours and Company, Incorporated, (Wilmington, DE) in the syrup dosage form. All patients received rimantadine in doses of 3 mg/kg/dose. Twelve infants received the drug in one daily dose, and two received in two doses daily. The rimantadine syrup was administered either orally or by a nasogastric tube. The patients were receiving other drugs including bronchodilators and antibiotics as prescribed by the physicians.

Multiple (5-8) blood samples were obtained from 8 of 14 infants. The samples were collected prior to doses and at various intervals up to 8 h after the dose following 4-8 days of rimantadine therapy. The steady-state conditions were confirmed based on two similar peak serum concentrations after a minimum of 4 days of therapy. Serum was separated by centrifugation and stored at $-70\,^{\circ}C$ until analyzed by an electron capture gas liquid chromatographic method. The coefficient of variation was less than 7% at the lowest detection limit of rimantadine, 10 ng/ml [8].

Adverse effects of rimantadine were assessed frequently during the repeated therapy over three to 17 days. Clinical status, vital signs, physical examination, activity level, feeding habits, sleeping habits, and irritability were assessed daily. These assessments were based on our interviewing the nurse and parents, complete blood count with differential, platelets, blood urea nitrogen, serum creatinine, serum glucose, serum transaminases, serum bilirubin and alkaline phosphatase. Serum electrolytes and urinalysis were determined prior to study, twice during the study and at the end of study. Follow-up studies were done in patients with abnormal laboratory values to assess if these returned to normal.

Results

The serum concentrations of rimantadine are reported in Table 1. The steady-state peak serum concentrations ranged from 100 to 574 ng/ml. The steady-state peak serum concentrations of rimantadine fell within 100 to 300 ng/ml in 4, and within 400 to 500 ng/ml in 3 infants; the peak concentration exceeded 500 ng/ml in 1 infant. The time to achieve peak serum concentration ranged from 2.5 to 6.0 h after rimantadine oral doses. A minimum of 4 days therapy was required to achieve steady-state conditions.

One of 14 patients developed adverse effects possibly due to rimantadine therapy. Patient 5 had normal urinalysis prior to study but developed microscopic hematuria at the end of 10-day therapy. Red blood cell count ranged from 11 to 20 per high power field (HPF) in the urine. A follow-up study on day nine after stopping rimantadine therapy showed an absence of red blood cells. No other adverse effects were observed in any patients.

The relationship between rimantadine serum concentrations and adverse effects was assessed in eight infants. One infant who developed hematuria had the highest steady-state serum concentrations of

rimantadine, 574 ng/ml. Three patients with rimantadine serum concentrations ranging from 433 to 477 ng/ml did not exhibit any adverse effects.

Discussion

Rimantadine hydrochloride (α-methyl-1-adamantanemethylamine hydrochloride) is an analogue of currently available amantadine for the treatment of influenza A infection. In the Soviet Union, rimantadine is widely used because it is thought to be more active and better tolerated than amantadine [16]. These agents are useful when influenza vaccine cannot provide continued protection against the disease [6]. Furthermore, these drugs are effective against all influenza A strains [7], whereas vaccine is protective only against the specific strains included in the vaccine.

This is the first study to evaluate serum concentrations and adverse effects of rimantadine in paediatric patients. We found that the steady-state serum concentrations and time to achieve peak serum concentration of rimantadine can vary markedly in infants receiving same repeated doses. A substantial intersubject variation in serum concentrations of rimantadine has also been reported in normal adults [8]. Based on this observation, it may be difficult to predict serum concentrations in all infants after same standard doses to prevent or treat influenza illness.

The steady-state rimantadine peak serum concentration was >100 ng/ml in all infants, >200 ng/ml in six of eight, and >400 ng/ml in four of eight infants. These serum concentrations may be adequate based on in vitro studies. Hemagglutinin production inhibition of influenza A/Hong Kong/68(H_3N_2) virus in rhesus monkey kidney cells has been reported at rimantadine concentration of 31 ng/ml at 3.5 h and 200 ng/ml at 12 or 24 h after infection [9].

This study was not designed to evaluate the efficacy of rimantadine in infants. Rimantadine, however, was administered during the influenza A season and none of the patients developed influenza illness during therapy.

Rimantadine therapy was found to be safe after repeated doses of 3 mg/kg/dose in infants. One infant who developed microscopic hematuria had the highest serum concentration (574 ng/ml) and the longest duration of therapy (10 days). It should be noted that hematuria developed following a surgery (plication of diaphragm for phrenic nerve palsy). Thus, other etiological factors cannot be ruled out. This infant, however, was also the youngest in this group, suggesting that small infants may require a lower rimantadine dose to minimize toxicity. It should be noted, however, that although rimantadine serum concentrations and adverse effects have been correlated in adults [8], this relationship cannot be established clearly in this study due to a small number of infants.

Based on comparative studies of amantadine and rimantadine in adult patients, rimantadine has been found to be equally effective and less toxic than amantadine [5, 13]. Our data suggest that 1. rimantadine syrup can be given safely at repeated doses of 3 mg/kg/dose in a convenient once daily regimen; 2. steady-state peak serum concentration and time to achieve peak may vary markedly in infants receiving same oral doses; and 3. possible association of adverse effects and high serum concentration or long treatment duration needs further evaluation in small infants. The rimantadine dosage regimen used in this study can be used to conduct efficacy studies for prophylaxis or treatment of influenza A disease in infants.

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