COMPARISON OF THE EFFICACY AND SAFETY OF ISEPAMICIN AND AMIKACIN IN THE TREATMENT OF URINARY TRACT INFECTION IN CHILDREN

Arif Bahar, M.D.* / Ferhan Karademir, M.D.* / Tolga Unsur, M.D.*
Mustafa Özyurt, Ph.D. / İsmail Göçmen, M.D.***

** Department of Pediatrics, GMMA Haydarpaşa Training Hospital, Istanbul, Turkey.*
*** Department of Microbiology, GMMA Haydarpaşa Training Hospital, Istanbul, Turkey.*

ABSTRACT

Objective: In this study we aimed to compare the efficacy and safety of isepamicin versus amikacin at a dose of 7.5 mg/kg of body weight twice daily for 10-14 days in children with urinary tract infections (UTI).

Methods: One hundred and seventeen patients with urinary tract infection were enrolled in this study. Patients were randomized to treatment with isepamicin or amikacin in a 1:2 ratio. Urinary tract infections were treated with isepamicin (n=42), or amikacin (n=75).

Results: The most commonly isolated pathogens were Escherichia coli, Staphylococcus spp., Klebsiella pneumonia, Proteus mirabilis and Enterobacter spp. The overall clinical response rate at the end of treatment was excellent in all treatment groups (93.0/93.4% cured) with no significant differences between isepamicin and amikacin in patients with infections. None of the patients had a life-threatening or severe adverse event that required discontinuation of the drug.

Conclusion: Isepamicin was shown to be as effective and as well tolerated as amikacin in the treatment of urinary tract infections in pediatric patients.

Key Words: Isepamicin, Amikacin, Aminoglycoside, Pediatrics.

INTRODUCTION

Children suspected of having pyelonephritis should be treated empirically at the time of diagnosis because of the frequency of associated bacteriemia (1). Empiric therapy for newborn infants with UTI and impending sepsis should include ampicillin and gentamicin or both. Any of other aminoglycoside can be used instead of gentamicin. Older children with suspected pyelonephritis can be treated empirically with gentamicin, possibly with the addition of ampicillin (1,2).

In recent years, the increasing resistance problem has been limiting antibiotic options for the treatment of all sorts of infections as well as UTI of children (1-4).

At present, amikacin-resistant pathogens account for some 40% to 60% of the aminoglycoside-resistant Gram-negative aerobic isolates in some South American and European countries, and their incidence is increasing predominantly in countries where amikacin use is prevalent (5).

Marmara Medical Journal 2003;16(2):107-112

Correspondence to: Arif Bahar, M.D, - Department of Pediatrics, GMMA Haydarpaşa Training Hospital, Haydarpaşa, 34668 Istanbul, Turkey.
e.mail address: arbahar@hotmail.com

Isepamicin is a new aminoglycoside antibiotic, which, presented with superior stability to aminoglycoside-inactivating enzymes compared with the currently available antibiotics of this class. In invitro studies of isolates susceptible to amikacin, isepamicin was generally equipotent to two-fold more potent against Escherichia coli, Citrobacter, Klebsiella, Enterobacter, Salmonella, Shigella and Serratia (6). Although, isepamicin was shown to be effective in intraabdominal infections, surgical infections, respiratory and urinary tract infections (UTI) (6-9) by open label trials, there are limited numbers of studies assessing the efficiency of isepamicin on the pediatric population (3,6,10-12). The present study was conducted in GMMA Haydarpasa Training Hospital to evaluate the efficacy and safety of twice-daily administration of isepamicin in comparison with that of amikacin in pediatric patients with urinary tract infections. Although the first choice of treatment is the third generation of cephalosporins for the empirical treatment of children with urinary tract infection, we considered appropriate to compare isepamicin whose efficacy and tolerability were originally thought to be investigated in the present study, with amikacin which was of the same class and has been introduced to the clinical practice earlier, thus being well known in terms of its side-effect profile and spectrum of action.

METHODS

During the period of February to December 2001, a total of 200 patients with urinary tract infections were enrolled into a prospective, randomized trial at the GMMA Haydarpasa Training Hospital. The study group consisted of patients who admitted to our outpatient clinic with complaints of fever, pain during micturition, urinary incontinence, flank or abdominal pain, foul smelling urine and those with abnormal urine sample, leukocytosis, high erythrocyte sedimentation rate and high C-reactive protein (CRP) levels suggesting an UTI.

Urine samples were taken by using the suprapubic aspiration technique for infants and if the culture showed any colonization it was considered a UTI. A midstream urine samples were taken in toilet-training children after proper skin preparation. If the culture showed greater than 100000 colonies/mm^3 of a single pathogen, or if there was 10 000 colonies and the child was symptomatic it was considered a UTI.

For the cases having bacterial growth on the urine culture, upper urinary tract infection was concluded in case of side pain, high sedimentation rate and CRP positivity.

Written informed consent was obtained from parents and treatment was begun with isepamicin or amikacin after obtaining the urine culture and hemoculture from each patient. In case of isepamicin or amikacine resistance, patients were excluded from the study and their treatment was continued with a proper antibiotic. Treatment was started either before the initial culture results were obtained or within 24 hours after the diagnosis was confirmed by culture. In culture negative patients antibiotherapy was discontinued.

The aminoglycosides have been recommended for the empiric treatment of UTI in newborns (1). Thus we prefer to use amikacin or isepamicin to treat UTI of our study patients in whom the predominant causative agent was E. coli.

Eligible patients were randomly assigned to receive intravenously or intramuscularly either isepamicin 7.5 mg/kg twice daily or amikacin 7.5 mg/kg twice daily for a period of three or 14 days. Patients were followed up in daily visits during the study period for the occurrence of side effects. Urine cultures were repeated 72-90 h after the end of treatment in each patient. Adverse events were graded as mild, moderate, severe or life threatening. Safety evaluations, including physical examination, audiometric tests and laboratory assessments were performed prior to and at the end of treatment. Patients were monitored closely for evidence of 8th cranial nerve toxicity. Audiometric testing was performed to all of the patients over 3 years old. Because of technical inadequacy, the audiometric test could not be applied to children below 3 years of age.

Peak and through serum aminoglycoside levels were monitored at the beginning, during and at the end of treatment by using Abbot Axym

System. Peak serum levels were measured 15-30 minutes after the end of intravenous infusion or 30 minutes after an intramuscular injection. Through serum levels were measured immediately before administration of the next dose. Nephrotoxicity was defined as an increase in serum creatinine of 0.5 mg/dL.

Proportions of noncontinuous variables were compared by chi-square analysis. $P<0.05$ was considered statistically significant.

RESULTS

A total of 200 patients was enrolled and received treatment. One hundred and seventeen patients satisfied all criteria for evaluation. Eighty-three patients were excluded for protocol violation. The main reasons for exclusion from the study were unacceptable baseline data such as negative cultures and infections with pathogens resistant to one or both of the study drugs (n:76), and insufficient efficacy data (n:5), unacceptable concurrent therapy (n:2). Of the cases who were excluded from the study due to the antibiotic resistance, 35 were resistant to isepamicin, and 41 to amikacin. The difference between the study groups was not statistically significant for the rate of antibiotic resistance (p=0.49).

During the study period, while 14 patients were hospitalized, the remaining 103 patients were followed from the outpatient clinic. The study subjects were 52 boys and 65 girls, with a mean age of 2.5±2.4 (range 13 days-10 years). There were 42 patients in the isepamicin group (17 male, 25 female with a mean age of 3.1±2.6 years). Among these patients 5 had an upper and 37 had lower urinary tract infection. The audiograms and renal functions remained within normal limits however, only flushing was observed in one patient with isepamicin therapy. Amikacin group consisted of 75 subjects (35 male, 40 female, mean age of 2.2±2.2) 8 with upper and 67 with lower UTI. While there were no deterioration in audiograms of 22 patients, one renal and one hepatic dysfunction was observed in amikacin therapy group (Table I).

Table I: Demographic characteristics of study subjects.

Characteristic	Isepamicin (n=42)	Amikacin (n=75)
Sex (F;M)	25;17	40;35
Age (y)		
Mean (range)	3.1 (0-10)	2.2 (0-9)
Age group		
< 6 months	6	23
6 months-2 years	4	11
> 2 years	32	41

Escherichia coli was the most commonly isolated pathogen, accounting for 76/200 of the positive cultures followed by Staphylococcus spp., Klebsiella pneumonia, Proteus mirabilis, Enterobacter spp. and Pseudomonas aeruginosa respectively. Resistance against amikacin and isepamicin was detected in 27.5% and 24% of the subjects respectively (p=0.42) (Table II)

Positive hemoculture was defined in 8 patients in the isepamicin group and 6 patients of amikacin group. In the hemoculture of the cases in the isepamycin group, S.epidermidis grew in one

Table II: The resistance rate to amikacin and isepamicin.

Organism	Number of cases	Number resistance to Amikacin	Number resistance to Isepamicin	P
Escherichia coli	76	5 (6.5%)	3 (3.9%)	0.15
Proteus mirabilis	22	4 (18.1%)	2 (9%)	0.15
Staphylococcus spp.	46	21 (45.6%)	18 (39.1%)	0.08
Enterobacter spp.	17	13 (76.4%)	13 (76.4%)	1.00
Klebsiella pneumonia	26	3 (11.5%)	3 (11.5%)	1.00
Pseudomonas aeruginosa	12	8 (66%)	9 (75%)	0.31
Acinetobacter	1	1 (100%)	0 (0%)	-
TOTAL	200	55 (27.5%)	48 (24%)	0.42

case, E. coli in five cases, Klebsiella in two cases, and Enterobacter spp. in one case. The incidence of microorganism growing on hemoculture in the amikacin group was as follows: Staphylococcus spp. in 2 cases, Enterobacter spp. in 2 cases, Klebsiella pneumonia in one case and Escherichia coli in one case.

In the isepamicin group, one case who had S.epidermidis growing on hemoculture had E. coli growing on urine culture, 4 out of 5 cases who had E.coli growing on hemoculture had E.coli and the remaining case had S.epidermidis on urine culture, two cases who had Klebsiella growing on hemoculture had also Klebsiella growing on urine culture, and one case who had enterobacter growing on hemoculture had E. coli growing on urine culture.

In the amikacin group, the cases who had S.epidermidis growing on hemoculture had also E.coli growing on urine culture, one out of two cases who had enterobacter growing on hemoculture had E.coli and the remaining case had Klebsiella growing on urine culture, and one case who had E.coli growing on hemoculture had also E.coli growing urine culture.

Due to positive urine cultures obtained at the 4th day of treatment, 5 patients (6.6%) of the amikacin group and 3 patients (7.0%) of the isepamicin group were defined as treatment resistant and their antibiotics were changed. The bacteriological elimination rate was 93.0% for the isepamicin group and 93.4% for the amikacin group ($p>0.05$). There was no statistically significant difference between two groups in regard to the relief of dysuria and urinary frequency, and clearance of bacteriuria and pyuria ($p>0.05$). Clinical response rates are presented in Table III.

Table III: Clinical response rates.

Clinical response	Isepamicin	Amikacin
Cure	40 (93.0%)	70 (93.4%)
Failure	3 (7.0%)	5 (6.6%)

Peak serum levels ranged from 8.16 to 33.30 mg/L (median: 14.51) and from 11.82 to 23.65 mg/L (median: 21.40) for isepamicin and amikacin, respectively. Through serum levels ranged from 0.14 to 4.10 mg/L (median: 0.80) and from 0.12 to 1.90 (median: 0.52), respectively.

Adverse events were seen in 1/42 (2.3%) of patients in the isepamicin group and 2/75 (2.6%) in the amikacin group. These adverse events were considered as probably or possibly related to the study drug: flushed face (1 isepamicin), liver function impairment (1 amikacin), and nephrotoxicity (1 amikacin).

The mean treatment duration was 7.5±3.9 days in the isepamicin and 7.1±3.3 days in the amikacin group ($p>0.05$). Twenty-nine patients in the isepamicin group (69%) and fifty-five (73%) in the amikacin group were treated for five days or more ($p>0.05$). All urine cultures obtained at the 15th day after the end of the treatment were negative.

The extent of exposure to the study drugs in terms of cumulative dose was similar for both treatment groups (1548.2 mg for isepamicin, 1345.2 mg for amikacin).

Analysis of the audiograms did not show any ototoxicity at the > 20 dB in air conduction threshold in the isepamicin and amikacin groups; hearing loss, tinnitus or vertigo were not evident in any of the cases.

DISCUSSION

The microorganisms isolated as causative agents of UTI show some similarities and generally they may be accounted as for Esherichia coli, Pseudomonas aeruginosa, Proteus mirabilis, Staphylococcus aureus, and Klebsiella pneumonia as regards prevalence, respectively (5,13). The rate of resistant bacteria serotypes defined by antibiograms is increasing day by day. In our study, the frequency of culture positive bacteria was Escherichia coli, Staphylococcus spp., Klebsiella pneumonia, Proteus mirabilis, Enterobacter spp. and Pseudomonas aeruginosa, respectively. Among these organisms, resistance to isepamicin was observed in 24% and to amikacin in 27.5% ($p>0.05$). The rate of amikacin resistance has been observed in 49.7% whereas isepamicin resistance in 29.7% of aminoglycoside-resistant bacteria (9). The results of our study, conducted

on randomly selected patients, demonstrated that the rate of aminoglycoside resistance of our community was equal that of other studies carried out on specifically aminoglycoside resistant subjects. Thus the results of our study point out a clear indication that antibiotic regiments in the pediatric population shold be reviewed.

The results of a double-blind trial in patients with urinary tract infections in Japan showed that bacteriological elimination rates and clinical efficacy were significantly higher with isepamicin than with amikacin (4). In our study, although a lower rate of resistance to isepamicin than amikacin was observed among the microorganisms isolated from urine cultures, it was inappropriately high rate for a given new antibiotic. This finding also supports the previous observations elucidating a very rapid cross-resistance against antibiotics through the mechanism of plazmid transfer between bacteria (3). Although, the rate of invitro resistance was high, invivo efficacy of isepamicin was 93.0%. The difference in the clinical efficacy of amikacin and isepamicin between the adult and pediatric population may indicate an increasing rate of resistant serotypes in the community.

Side effect rates of aminoglycosides have been reported as 6-25% for amikacin and 9-15% for isepamicin by several previous studies. According to frequency of occurrence these side effects were phlebitis, nephrotoxicity, audio toxicity, rashes, gastrointestinal irritation, headache and central nervous system complaints, respectively (5,14-16). A lower rate of side effects was observed in our study in comparison to previous works which nearly all included adult patients. Aminoglycosides have been reported to be less toxic in children than in adults or the elderly (10). Nephrotoxicity in particular has not been reported to be a significant problem in pediatric patients, perhaps because the elimination of aminoglycosides is more rapid (16). In this study isepamicin was found to be extremely well-tolerated. There was no evidence of any local irritation.

The results of this study indicate that treatment with isepamicin once daily is effective and well tolerated in children with urinary tract infections, but might not prove an advantageous alternative in areas with high incidence of resistance to other aminoglycosides.

REFERENCES

1. *Krasinski KM. Urinary tract infections. In: Katz SL, Gershon AA, Hotez PJ.(eds) Krugman's Infectious Diseases of Children. 10th edition. St Louis, Missouri. Mosby Year Book, 1998: 606-619.*
2. *Wald ER. Cystitis and pyelonephritis. In: Feigin RD, Cherry JD, Demmler GJ, Kaplan SL, eds. Textbook of Pediatric Infectious Disease. 5th edition. Phyladelphia; Saunder, 2004: 541-553.*
3. *Johnson JG, Hardin TC. Aminoglycosides, imipenem, and aztreonam. Clin Pediatr Med Surg 1992; 9: 443-464.*
4. *Shimizu K, Kumada T, Hsieh W, et al. Comparison of aminoglycoside resistance patterns in Japan, Formosa and Korea, Chile and the United States. Antimicrob Agents Chemother 1985; 28: 282-288.*
5. *Sturm W. Isepamicin versus amikacin in the treatment of urinary tract infection. J Chemother 1995; 7: 149-154.*
6. *Vigano A, Principi N. A randomised comparison of isepamicin and amikacin in the treatment of bacterial infections in paediatric patients. J Chemother 1995; 7: 95-101.*
7. *Miller GH, Sabatelli FJ, Naples L, et al. The most frequently occuring aminoglycoside resistance mechanism-combined results of surveys in eight regions of the world. J Chemother 1995; 7: 17-30.*
8. *Gur D, Tutar I, Unlu GV, et al. Isepamisinin hastane izolatı gram-negatif bakterilere karşı invitro etkisi. Hastane Inf Derg 2001; 5: 19-24.*
9. *Over U, Gur D, Unal S, et al. The changing nature of aminoglycoside resistance mechanism and prevalence of newly recognised resistance mechanism in Turkey. Clin Microbiol Infect 2001; 7: 470-478.*
10. *McCracken GH. Aminoglycoside toxicity in infants and children. Am J Med 1986; 80: 172-178.*
11. *Scaglione F, Vigano A, Colucci R, et al. Pharmacokinetics of isepamicin in paediatric patients. J Chemother 1995; 7: 63-69.*
12. *Skaer TL. Dosing considerations in the pediatric patients. Clin Ther 1991; 13:526-544.*

13. Rodrigez-Noriega E, Esparza-Ahumada S, Morfin-Otero R. Comparison of the efficacy and safety of isepamicin and amikacin in the treatment of skin and skin structure infections. J Chemother 1995; 7: 155-160.

14. Tulkens PM. Nephrotoxicity of aminoglycosides. Toxicol Lett 1989; 46: 107-123.

15. Tulkens PM. Pharmacokinetic and toxicological evaluation of the once-a-day regimen versus conventional schedules of netilmicin and amikacin. Chemother 1991; 27: 49-61.

16. Tulkens PM, et al. Efficacy and safety of aminoglycosides once-a-day; Experimental and clinical data. Scand J Infect Dis 1990; 74: 249-257.