Clinical Evaluation

Post Marketing Assessment of the Efficacy and Safety of Netromax™ (Netilmicin) in the Indian Pediatric Population

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Abstract

Objective: A post-marketing study of Netilmicin (Netromax™) in Indian pediatric patients to assess the safety and efficacy of the drug in various susceptible infections. *Method:* The study was carried out by 129 pediatricians from across India in 10 states (Maharashtra, Delhi, Uttar Pradesh, Andhra Pradesh, Odisha, Chhattisgarh, Karnataka, Madhya Pradesh, West Bengal, and Bihar) from November 2011 to February 2012. A total number of 542 case report forms were collected and considered eligible for further analysis based upon the completeness of data. The disease profile of patients included bacteremia, septicemia (including neonatal sepsis), severe respiratory tract infections (RTI), intra-abdominal infections (including peritonitis), kidney and genitourinary tract infections, skin and soft tissue infections, burns, bone and joint infections, wounds and perioperative infections. *Result:* Demographic analysis showed the median age of patients to be 13 months and median duration of therapy was 5 days. Intravenous route (IV) (n= 340) was preferred over intramuscular route (IM) (n=202) by the physicians. Netilmicin was administered in the therapeutic dose range depending upon the age and severity of the condition. The results revealed a favorable clinical efficacy and safety profile of Netilmicin. Clinical Improvement was observed in 98% (n=532) of patients among whom, clinical resolution (Defined as the absence of the infection) was achieved in 63% (n=343) patients. Whereas, partial improvement (defined as partial disappearance of original symptoms and no further requirement of antibiotics) was observed in 35% (n=189) of patients. Adverse events were reported in 11% of the entire study population and were mild in nature. There was no serious adverse event reported during the study period. *Conclusion:* The present post-marketing study confirmed that at the given doses and duration of therapy, Netromax™ exhibited remarkable antibacterial efficacy with no serious incidences of toxicity. Thereby giving evidence that Netromax™ treatment is safe and effective among the Indian pediatric population.

Keywords

netilmicin, pediatric population, infection

Introduction

Serious infections caused by aerobic gram-negative bacilli, including *Escherichia coli, Klebsiella pneumoniae and Enterobacter spp.* continue to be a major cause of morbidity and mortality in hospitalized patients[1]. Clinical data recommends the use of aminoglycosides in the treatment of infections caused by these gram-negative microorganisms[2]. The principle representative drugs of this group are gentamicin, tobramycin, amikacin, netilmicin, kanamycin, streptomycin, etc[3].

An extensive use of aminoglycosides has been reported to cause bacterial resistance, ototoxicity (mainly irreversible)

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and nephrotoxicity (reversible) in previous studies[4, 5]. Amongst all aminoglycosides, netilmicin stands out because of its least toxicity and superior clinical efficacy, even in some resistant microorganisms[6, 7].

Netilmicin is a semi-synthetic aminoglycoside rapidly acting bactericidal antibiotic which probably acts by inhibiting normal protein synthesis in susceptible organisms. It is active at low concentrations against a wide variety of pathogenic bacteria including *Escherichia coli*, bacteria of the Klebsiella-Enterobacter-Serratia group, Citrobacter spp., Proteus spp. (indole-positive and indole-negative), including Proteus mirabilis, P.morganii, P.rettgeri, P.vulgaris, Pseudomonas aeruginosa and Neisseria gonorrhoeae. Netilmicin showed excellent activity against all the tested gram positive and gram negative microorganisms, with more than 90% susceptibility. Many gentamicin- and tobramycin-resistant strains were susceptible to netilmicin, although the minimum inhibitory concentration values of netilmicin were higher than those for the fully susceptible strains. In time-kill studies, netilmicin showed its bactericidal activity within 1 h against Pseudomonas aeruginosa and Staphylococcus aureus[8]. Netilmicin has been proven to be effective in treating infections of the urinary tract (UTI), skin and skin structure (SSTI), and lower respiratory tract (RTI), as well as in intra-abdominal infections and septicemia[9].

Clinical studies with netilmicin have proven it to be a highly effective agent for life threatening RTI, UTI and GI infections at doses similar to or greater than those normally used for gentamicin. It is regarded as an active agent in the treatment of infections caused by susceptible bacteria and against gentamicin or tobramycin resistant strains[10]. Netilmicin is also shown to be more efficacious in terms of eliminating pathogens than gentamicin, a difference seen most clearly with *Klebsiella and Enterobacter* infections and soft tissue sepsis[11].

Besides its use in adult patients, netilmicin is also clinically effective in the treatment of neonatal and pediatric infections. It was found to be active, alone or in combination with other agents against most of the bacteria involved in neonatal infections[12]. The comparable or superior efficacy to that of gentamicin, tobramycin, and amikacin in susceptible pathogens[13], good clinical efficacy against gentamicin-resistant strains and relative freedom from ototoxicity and reduced nephrotoxicity are the major advantages of netilmicin over other aminoglycosides[2].

Although antibacterial spectrum, clinical efficacy and reduced ototoxicity and nephrotoxicity suggests that netilmicin can be the aminoglycoside of first choice, its clinical efficacy and safety studies are not available in the Indian pediatric population. The present post marketing study has been carried out by Zuventus Healthcare Limited to identify the clinical efficacy and safety profile of Netilmicin (Netromax™) in the Indian pediatric population.

Material and Methods

Study Design

This was an open, non-comparative; multi centric study carried out among 129 pediatricians from across 10 states of India (Maharashtra, Delhi, Uttar Pradesh, Andhra Pradesh, Odisha, Chhattisgarh, Karnataka, Madhya Pradesh, West Bengal, and Bihar) and 542 patients were considered for analysis. The study was carried out from November 2011 to February 2012. All the required medications and the CRFs were provided to the investigators by Zuventus Healthcare Limited. The investigators were asked to complete CRFs pertaining to individual patients along with the therapy outcome.

The efficacy profile of Netromax™ was evaluated based upon rate of clinical resolution, partial improvement and failure of the treatment. Disappearance of originally observed symptoms or infections was considered as clinical resolution, partial improvement was defined as disappearance of original symptoms and no further requirement of antibiotics while worsening of the symptoms or treatment with other antibiotics was considered as failure.

Study Medication

Netromax™, netilmicin marketed by Zuventus Healthcare Ltd. Mumbai, was prescribed by the physician (mentioned in the acknowledgement) to study the safety and efficacy of the drug. Netromax™ is currently marketed for use in a variety of microbial infections in infants as well as adult population. It was administered intravenously (IV) or intramuscularly (IM) as per the requirement of the patients.

Data Collection

In this study case report forms (CRFs) were collected from all pediatricians participated in the study across the country. Data in the CRFs included demography of the

patient, disease condition for which netilmicin was being prescribed, dosage, frequency and route of administration, concomitant medicines being prescribed and presence of any adverse reaction in the patient. The primary endpoint of the study was clinical resolution and secondary endpoints were clinical improvement and tolerability in the pediatric population.

Data Analysis:

The demographic analysis was performed essentially descriptive using frequency tables for age, gender, and incidence of baseline infection, whereas the clinical outcome data was analyzed using percentage success rate.

Results

Demographics: Study Population

The demographic distribution of the patient population is depicted in **Table 1**.

Table 1
Demographic data of the study population

		Values
Total number of patients	N	542
Age (Yrs)	Median	13 months
	Range	0.0027(1 day) - 13
Gender (N)	Male	329 (61%)
	Female	213 (39%)
Infections (N)	A	162 (30%)
	B	111 (20%)
	C	82 (15%)
	D	43 (8%)
	E	38(7%)
	F	29 (7%)
	G	15 (5%)
	H	62 (11%)

A: Bacteremia, septicemia (including neonatal sepsis); B: Serious infections of the respiratory tract; C: Intra-abdominal infections (including peritonitis); D: Kidney and genitourinary tract infections; E: Skin, soft tissue infections; F: Burns, wounds, peri-operative infections; G: Bone and joint infections; H: Other Infections

Netilmicin: Dosage and Administration

Amongst the enrolled patients, 340 patients were treated with Intravenous (IV) route and 202 patients were treated with Intramuscular (IM) route with the therapeutic dose range, depending upon the severity of condition. The treatment characteristics in the present study are depicted in the **Table 2**.

Table 2
Treatment Characteristics of patients

	Particulars	Values
Number of patients	n	542
Dose (mg/kg/day)	Median dose	5 mg/kg/day
Route (n)	IV	340(62%)
	IM	202 (38%)
Duration (n)	<7 days	384 (71%)
	7-14 days	156 (29%)
	>14 days	3 (1%)
Frequency (n)	OD	250 (46%)
	BID	267 (49%)
	TID	25 (5%)
Treatment (n)	Netromax	488 (90%)
	Netromax + Other	54 (10%)

Out of all patients, 90% were treated with Netromax™ alone, while the rest were concomitantly given other antimicrobials like ofloxacin, ceftriaxone, tazobactam, ampicillin, amoxicillin clavulanic acid, IV fluid, IV piperacillin tazobactam, cefotaxime sodium, sulbactum, nebulization, meropenem, Inj. ceftriaxone, Inj. metronidazole, cloxacillin, antipyretics like paracetamol, linezolid, other antibiotics or other miscellaneous medications.

Netilmicin: Efficacy Profile

On evaluation of the data, 98% showed clinical improvement, 63% showed clinical resolution and 35% of patients showed partial improvement in the symptoms (**Fig. 1**). Only 2% of patients had therapeutic failure.

The disease distribution along with clinical improvement of patients in different infections is represented in **Fig. 2**.

Fig. 1
Clinical resolution with Netromax™

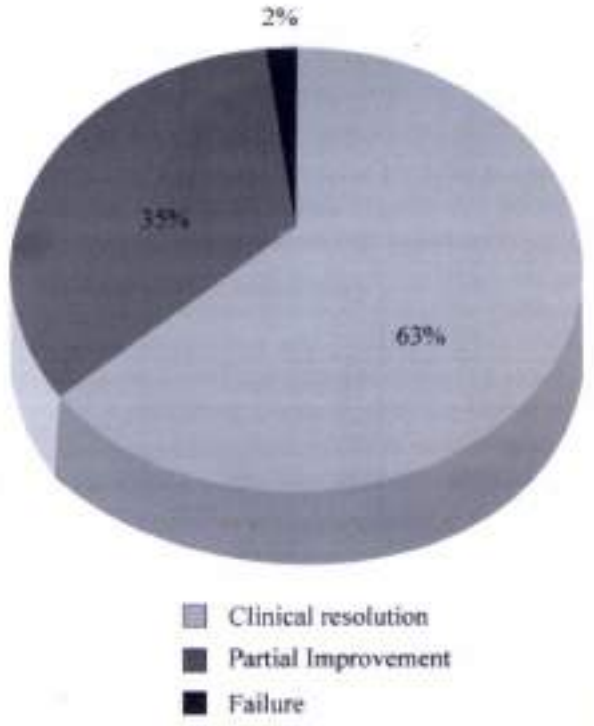
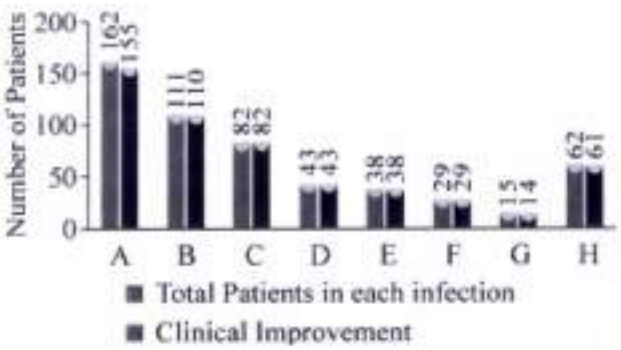


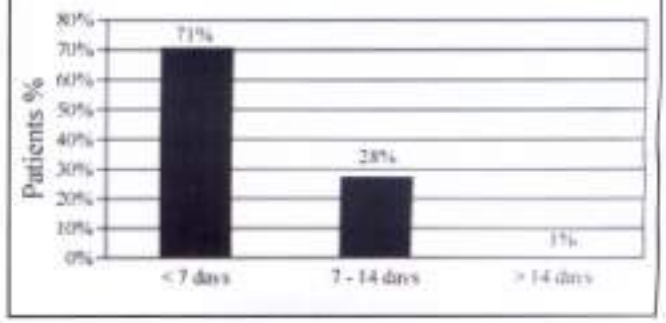
Fig. 2
Therapeutic outcome of Netromax™ in infectious conditions



A: Bacteremia, septicemia (including neonatal sepsis); B: Serious infections of the respiratory tract; C: Intra-abdominal infections (including peritonitis); D: Kidney and genitourinary tract infections; E: Skin, soft tissue infections; F: Burns, wounds, peri-operative infections; G: Bone and joint infections; H: Other Infections

The percentage of clinically improved patients with respect to the duration of therapy is depicted as follows (**Fig. 3**).

Fig. 3
Duration of Netromax™ therapy in clinically cured patients



In this study, 71% of clinically improved patients were treated with Netromax ™ for the duration of <7 days and 28% of patients had treatment duration of 7-14 days. Only 1% of the reported cases received therapy for more than two weeks.

Netilmicin: Safety Profile:

Netromax™ was well tolerated in all patients during the entire study period. Adverse events were reported in 11% patients. Among these patients, 0.1% had complained of phlebitis, 0.8% had urticaria, 10% had complained of nausea and vomiting and only 0.2% of patient showed mildly elevated hepatic transaminases. All adverse events reported resolved without sequaelae.

Discussion

The objective of this post- marketing study was to assess the safety and evaluate the efficacy of netilmicin in an Indian pediatric population in daily clinical practice. Netilmicin with its superior bactericidal activity and relative freedom from ototoxicity and lower nephrotoxicity is found to be effective in the treatment of UTI, RTI, skin and skin structure, septicaemia and in intra-abdominal infections[2-14].

Literature search shows that in the earlier studies on netilmicin, the efficacy and safety, for the treatment of gram-negative pyelonephritis in children were compared in a prospective, randomized trial. In which explicit criteria were used to define the site of infection, treatment outcome, and

adverse effects. Netilmicin was administered once and three times daily in the pediatric population. It was observed that post treatment after a week, 99% of children treated with once daily and 100% of children treated with three times daily dose of netilmicin were completely cured. In the follow up visit (after 4 weeks), no relapse was detected in the two treatment groups which shows the efficacy and safety of netilmicin in pediatric population[11]. Similar observations were seen in the current study proving the drug's safety and efficacy in Indian pediatric settings. Several studies demonstrating the efficacy and safety of netilmicin in the treatment of susceptible infections mainly concentrated on the adult population[2, 10, 14]. The present study was undertaken considering the fact that there is no direct comparison demonstrating the efficacy of netilmicin in pediatric age group.

A principal limiting factor of aminoglycoside antibiotics in the treatment of serious gram-negative bacterial infections is its narrow therapeutic and toxic serum level concentration ratio. It has been observed previously that, the peak serum concentrations of gentamicin below 4mg/ml associated with persistent bacteremia leads to a greater fatality rate; whereas higher levels of gentamicin above 8mg/ml produce an increased risk of ototoxicity and nephrotoxicity[16, 17]. However, Netilmicin demonstrate predictable serum level than those of other aminoglycosides which may be responsible for its less ototoxicity and nephrotoxicity[2]. It has been found to be active *in vitro* against MRSA strains cross resistant to gentamicin (16a) and has advantageous pharmacokinetics in cardiac valves because of the time for which the concentration of drug is more than MIC for S. aureus strains is seven times longer for netilmicin than that of gentamicin (3.5 h versus 0.5 h, respectively)[18].

Meta-analysis of over 150 clinical trials with netilmicin demonstrates its efficacy and safety in 3376 adult population. Favorable clinical responses were observed in 90% of the infections treated[19]. It showed clinical efficacy of 83.9% and bacterial clearance rates of 89.7% in respiratory infections[20], whereas in bronchopulmonary complication, 90% complete resolution and 82% pathogen eradication was observed[21]. Some studies reported a 61.9% clinical efficacy in patients having UTI[22].

The therapeutic results obtained in this study were remarkably good. We observed 100% clinical resolution in patients having RTI and UTI, and clinical resolution of 98% in other infections like skin and soft tissue, burns and wounds, peri-operative infections, bone and joint infection. In addition, there was a 78% of clinical resolution observed in patients with intra-abdominal infections after treatment with Netromax. These results are consistent with earlier reports of the trials conducted in adult patients[23], suggesting the comparable efficacy of netilmicin in both children and adult patients. The overall clinical failure rate observed in the present study was 2%, which is less than that observed in previous trials conducted on adult patients (6% failure rate)[23, 24].

Netilmicin was well tolerated and no serious adverse drug reactions (ADRs) were observed in pediatric patients. Elevated serum creatinine levels were observed in 0.2% of patients indicating a low incidence of nephrotoxicity. No significant localized action of netilmicin at the injection site was observed, except for a small incidence of phlebitis (1%). Urticaria was observed in 0.8% of patients. The most common side effect observed was nausea and vomiting (10%). The overall incidence of ADRs was 11%.

Conclusion

The present post-marketing study confirms that at the given doses and duration of therapy, Netromax™ exhibited remarkable antibacterial efficacy with no serious incidences of toxicity. Thus Netromax™ treatment is safe and effective among the Indian pediatric population.

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