ISSN:0971-7684

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Volume 17 I Number 8 I

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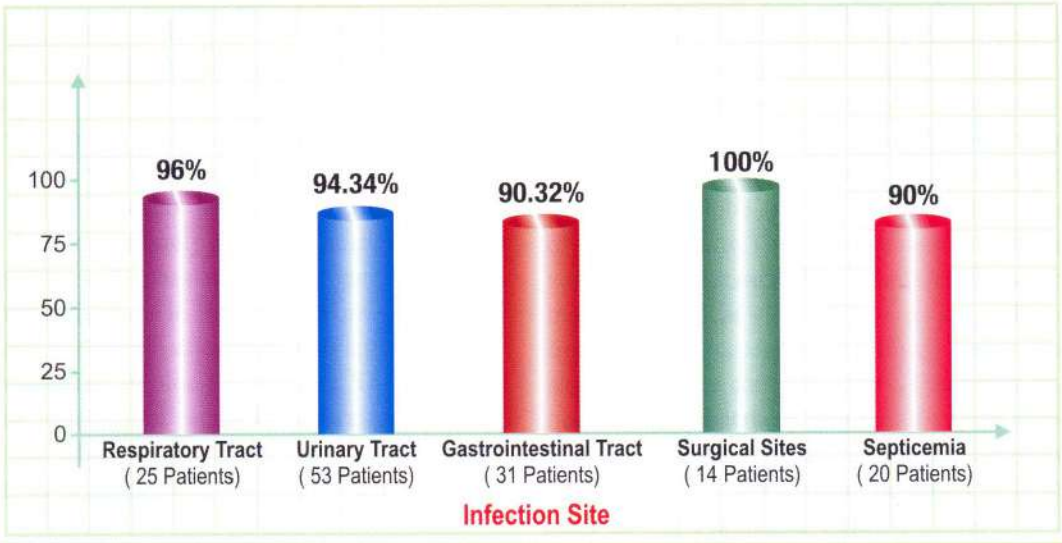
Clinical Efficacy & Safety of Netilmicin in Indian Population: Practitioner's Perspective

Multicentric Trial at 23 Centers
Involving 105 Medical Practitioners & 202 Patients

• Efficacy Evaluation In 161 Patients Confirms

Netilmicin **(Netromax)** showed favorable clinical response in 94.4% patients



• Safety Evaluation In 187 Patients confirms

Netilmicin **(Netromax)** was well tolerated with only two patients (1%) complaining of adverse events.

Abridged Prescribing Information

Therapeutic segment: Injectable Aminoglycoside Antibiotic **Composition:** Netilmicin sulfate equivalent to Netilmicin 10 mg/mL, 25 mg/ml, 150 mg/ 2ml, 300 mg/ 3ml. **Indications:** bacteremia, septicemia (including neonatal sepsis), serious infections of the respiratory tract, kidney and genitourinary tract infections, skin, soft tissue infections, bone, joint infections, burns, wounds, peri-operative infections, intra-abdominal infections (including peritonitis), infections of the gastrointestinal tract. **Adverse events:** Ototoxicity, nephrotoxicity, neuromuscular blockade, respiratory depression and muscular paralysis. **Contraindications:** Hypersensitivity to aminoglycosides or any other component of the drug. **Precautions:** Care should be taken in patients of Parkinsonism and other muscular diseases like myasthenia gravis. Caution should be taken in patients with impaired renal function. **Dosage and administration: Adults:** The dose varies from 4-7.5 mg/kg/day given in equally divided doses or once daily depending upon the severity of infection. Doses should be adjusted with degree of renal impairment. **Children:** dose varies from 3-7 mg/kg/day in divided doses or once daily. (for detailed information please refer to full prescribing information or contact medical@zuventus.com).

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Clinical efficacy and safety of Netilmicin in the Indian population: Practitioner's perspective

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ABSTRACT:

Aim: To determine the Indian Practitioner's Perspective on the clinical efficacy and safety of Netilmicin **(NETROMAX)**

Materials & Methods: 105 practitioners, including surgeons, chest specialists, pediatricians and internal medicine specialists, throughout India collaborated in the recruitment of 202 patients over a period of 6 months. Patients with bacterial infections were administered Netilmicin **(NETROMAX)** as determined by the practitioner, and the practitioner's opinion on the clinical efficacy and safety were observed at the end of treatment duration.

Results: 161 patients were evaluable for efficacy of Netilmicin **(NETROMAX)**. The most commonly employed regimen by the practitioners was administrating 300 mg Netilmicin **(NETROMAX)** I.V. once daily for up to 14 days. Favorable clinical response, as correlated with the practitioner's opinion, was observed in 94.4% of the patients. The opinion that Netilmicin **(NETROMAX)** provided excellent therapeutic, rather than only prophylactic, benefits to the infected patients was given by 57.55% of the practitioners. Netilmicin **(NETROMAX)** was well tolerated in the evaluable patients with only two patients (1%) complaining of adverse events.

Conclusion: Netilmicin **(NETROMAX)** was found to be a safe, well tolerated and useful aminoglycoside to treat a number of bacterial infections in current Indian scenario.

Key words: Netilmicin, efficacy, safety.

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BACKGROUND

Serious infections involving aerobic gram negative bacilli like hospital acquired pneumonia (33%),[1] surgical wound infections (55%),[2] burns (53%)[3] and complicated UTI (62%)[4] continue to be a major cause of morbidity and mortality of hospital patients. Their treatment is one of the principal indications for the use of aminoglycoside antibiotics.

Since the discovery of streptomycin, aminoglycosides have been considered as potent antibiotics displaying bactericidal, concentration-dependent killing action against a wide range of aerobic gram-negative bacilli. They are also active against staphylococci and certain mycobacteria. Aminoglycosides are effective even when the bacterial inoculum is large.[5] These potent antimicrobials, including gentamycin, amikacin, and tobramycin, are used in the prophylaxis and/or treatment of a variety of clinical situations although their potential for nephrotoxicity and ototoxicity has also been apparent.

However, the rampant use of aminoglycosides, especially amikacin, has led to significantly increased bacterial resistance over the past few years.[6] The need for an agent active against these resistant organisms and with an enhanced safety profile prompted extensive research which resulted in the discovery of Netilmicin.

Netilmicin, a third generation aminoglycoside derived from sisomicin, is reported to have good clinical efficacy in most bacterial infections when administered pre or post-operatively.[7,8]

Most bacteria are susceptible to Netilmicin because of its structure that minimizes the actions of major aminoglycoside-modifying enzymes.[9] Further, clinical trials have shown that gentamicin, tobramycin and amikacin resistant strains are susceptible to Netilmicin.[10] In addition, Netilmicin is less nephrotoxic and ototoxic compared to the other aminoglycosides.[11,12]

The present study is a postmarketing surveillance carried out to determine the Indian practitioner's perspective on the clinical efficacy seen after administering Netilmicin (NETROMAX) to their patients as well as to reaffirm its safety in the Indian population.

MATERIAL AND METHODS

This is an open, non-comparative, multicentric, epidemiological survey carried out among practitioners from 23 different centers across 7 Indian states (Maharashtra, Delhi, Uttar Pradesh, Assam, Tripura, West Bengal, and Haryana). The study was carried out from September 2008 to February 2009. All the required medications and the CRFs were provided to the investigators by Zuventus Healthcare Limited. All therapeutic decisions were determined solely by the attending practitioner. Each practitioner had to complete a questionnaire that included details of the patient, disease condition for which Netilmicin (NETROMAX) was being prescribed, the dosage, frequency and route of administration, the concomitant medications being prescribed, the practitioner's opinion on Netilmicin (NETROMAX) and presence of any adverse reaction in the patient. The practitioner's opinion of Netilmicin (NETROMAX) use in each patient was considered as the outcome of therapy in that patient. The data from the questionnaire was then entered into an electronic database for further descriptive analysis.

RESULTS

Study population

Demographic profile

Data corresponding to a total of 202 patients was obtained from 105 different practitioners. Of these, 161 patients were included in the evaluation of efficacy while 187 patients were included for evaluation of safety. Only the completed case report forms with valid entries were included in the efficacy assessment. To be included in the analysis for treatment safety, the patients should have received Netilmicin for more than 72 hrs.[13] The demographic data of the included patients are shown in table 1.

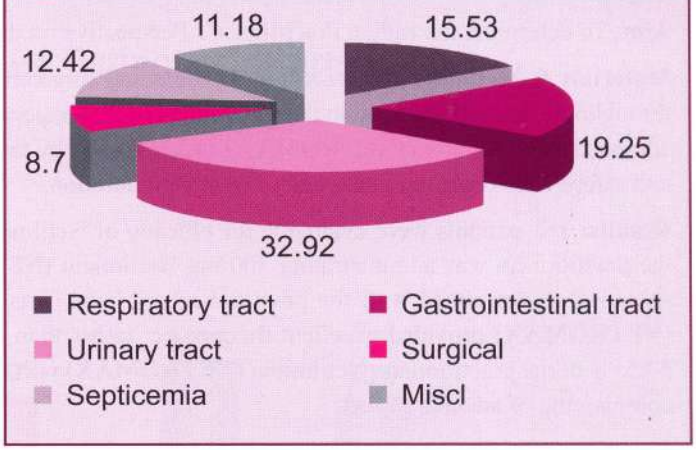
Infection sites

For the 161 patients included in the efficacy assessment, the most common site of infection (Fig. 1) was the urinary tract, accounting for 32.9%. The next most frequently treated infections were gastrointestinal infections (19.25%), respiratory tract infections (15.53%) and septicemias (12.42%).

Table 1. Demographic profile of study population

		Evaluation of	
		Efficacy	Safety
Total number of patients		161	187
Sex	Males	105	121
	Females	56	66
Mean Age (yrs)	Pediatrics (less than 12 yrs)	3.98 ± 1.26	3.36 ± 1.71
	Adolescents & adults	40.21 ± 5.94	38.42 ± 6.69
	Geriatrics (more than 65 yrs)	71.38 ± 2.16	70.91 ± 2.33

Figure 1. Commonly encountered infection sites



Efficacy

Clinical response

The practitioner's opinion on the therapy outcome of the patient was correlated to the clinical efficacy of Netilmicin (NETROMAX). Practitioner's opinions were categorized as excellent, good, satisfactory or poor depending on the improvement their patients showed. Accordingly, a favorable clinical response was considered to be either excellent or good, whereas, an unfavorable clinical response was satisfactory or poor.

Of the 161 patients evaluable for the clinical efficacy, 52.79% of the practitioners (85/161) found that Netilmicin (NETROMAX) was excellent. An opinion that Netilmicin (NETROMAX) showed good clinical response was stated by 67 or 41.61% of the practitioners. Therefore, a favourable clinical response occurred in 94.4% of the patients. The practitioner's opinion on Netilmicin (NETROMAX) in the various infection sites is seen in table 2.

Clinical response and purpose of therapy

Of the 161 patients, 22 received Netilmicin (NETROMAX) for prophylaxis while the remaining 139 received it for treatment purpose. The practitioners found that Netilmicin (NETROMAX) demonstrated favorable clinical response in both prophylaxis

Table 2. **Practitioner's opinion on Netilmicin in various infection sites**

Infection site	Practitioner's opinion			Total	Favorable response (%)
	Excellent	Good	Satisfactory		
Respiratory tract	12	12	1	25	96
Urinary tract	29	21	3	53	94.34
Gastrointestinal tract	13	15	3	31	90.32
Surgical Sites	9	5	0	14	100
Septicemia	12	6	2	20	90
Miscellaneous	10	8	0	18	100
Overall	**85**	**67**	**9**	**161**	**94.4**

Table 3. Trends in practitioners' prescribing pattern

Diagnosis		RTI	UTI	GI	Surgical	Septicemia	Misc.	Total
No. of patients		**25**	**53**	**31**	**14**	**20**	**18**	**161**
Dose (mg)	150	10	24	12	3	8	9	66
	300	13	27	17	11	10	7	85
	Misc	2	2	2	0	2	2	10
Route	I.V	22	46	26	14	19	16	143
	I.M.	3	7	5	0	1	2	18
Frequency	OD	15	27	16	9	11	8	86
	BID	9	25	15	4	9	10	72
	TID	1	1	0	1	0	0	3
Duration (days)	<7	9	29	22	8	9	7	84
	7-14	16	24	9	6	11	9	75
	>14	0	0	0	0	0	2	2

(19/22) and therapy (133/139) of infections. However, 57.55% (80/139) of the practitioners were of the opinion that Netilmicin (NETROMAX) provided excellent therapeutic, rather than only prophylactic, benefits to the infected patients.

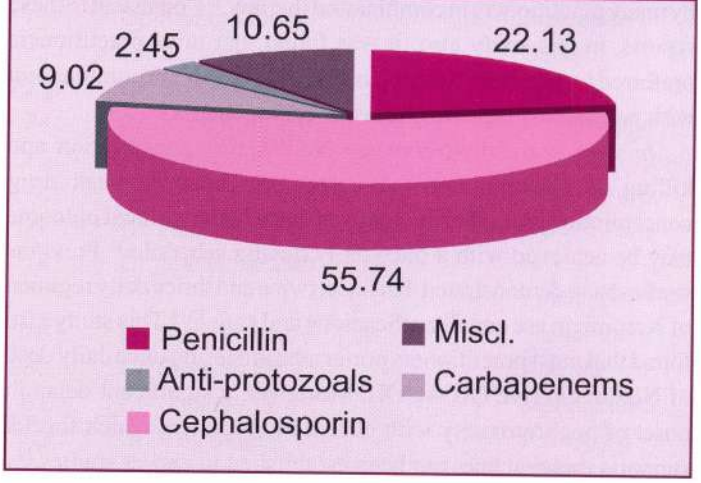
Trends in netilmicin dosage and administration

The most commonly employed regimen by the practitioners was administering 300 mg Netilmicin (NETROMAX) I.V. once daily for up to 14 days. There was no statistically significant difference in the clinical efficacy of Netilmicin (NETROMAX) when given once daily or twice daily (favorable responses, of 96.5% and 92% respectively). The trends in the practitioners prescribing pattern can be seen in table 3.

Concomitant medications

Of the 161 patients evaluable for efficacy, only 24.22% of the patients (39/161) were administered Netilmicin (NETROMAX) monotherapy. The remaining 75.77% of the patients (122/161) received other concomitant medicines (Fig. 2). Cephalosporins like cefoperazone-sulbactam, ceftriaxone and cefixime were the most commonly co-administered drugs accounting for 55.74%.

Figure 2. Concomitant medicines with Netilmicin



Safety

Of the 187 patients included for safety assessment, only 2 patients (1%) complained of adverse effects after administration of Netilmicin (NETROMAX). The first patient who complained of nausea & vomiting was also on therapy with mannitol and

aspirin while the second patient complaining of maculopapular rash and weakness was being co-administered doxycycline and ranitidine. Thus, these reactions can only be "possibly" related to Netilmicin (NETROMAX).

DISCUSSION

An aminoglycoside is usually required for the initial therapy of nosocomial suspected or known gram negative bacterial infection. Factors that dictate the choice of an aminoglycoside antibiotic include favorable clinical and experimental therapeutic experience, the spectrum of antibacterial activity, prevalence of resistant strains, and the toxicity of the drug.[14] In view of its effectiveness, more predictable serum levels after standard dosage and apparent lack of toxicity, Netilmicin should be considered as the first choice aminoglycoside antibiotic.[15] The results obtained for the clinical efficacy of Netilmicin (NETROMAX) in this study, as correlated with the practitioner's opinions, are favorable.

Nearly all of the practitioners have indicated that Netilmicin (NETROMAX) provided favorable benefit to patients presenting with varied underlying diseases. Previous clinical trials have reported the clinical success of Netilmicin to be 80-96% in different medical conditions including complicated urinary tract infection, septicemia, skin and skin structure infections, intra-abdominal infections and respiratory tract infections.[7,16] In this study also, the clinical efficacy of Netilmicin (NETROMAX), correlated to the practitioner's opinion on the drug, was found to be 94.4%.

It has also been clinically proven that aminoglycosides provide a better opportunity to treat bacteria when they are used in combination with Cephalosporins and Penicillins.[5] Netilmicin, in particular, has shown increased effectiveness when administered in combination with other antibiotics; it has been prescribed globally by many practitioners in combination therapy.[15] Consistent to these reports, in this study also, it was found that most practitioners preferred to prescribe Netilmicin (NETROMAX) in combination with penicillins, cephalosporins or carbapenems.

In vitro correlation between Netilmicin concentration and killing of bacteria, and the correlation between peak drug concentration and efficacy suggests that a better clinical outcome may be achieved with a once daily dosing schedule.[17] Previous studies have demonstrated that once, twice and thrice daily regimen of Netilmicin are equally efficacious and safe.[17,18] This study also found that most practitioners prefer administering once daily dose of Netilmicin (NETROMAX). Moreover, a significant delay in onset of nephrotoxicity with once daily regimen, which further supports this practice, has been established in earlier studies.[19]

Consistent to a few earlier reports,[8,18] this study found Netilmicin (NETROMAX) to be safe and well tolerated by all the patients. There were only 2 patients who reported adverse events, which could not be directly linked to the drug. Previous studies that report higher incidences of adverse events with the use of Netilmicin, have however found that the rates of nephrotoxicity and ototoxicity are less than those reported with the other aminoglycosides like gentamycin and amikacin.[11,16,19]

From the data presented above, it becomes clear that Netilmicin (NETROMAX) continues to remain a very promising agent to treat patients, even those suffering from infections due to resistant bacteria. Its ability to synergise with other antibiotics, its excellent tolerance and once daily dosage which increases patient compliance are added benefits that help in providing better efficacy and further reducing toxicity. Thus, this post-marketing surveillance has helped establish the fact that Netilmicin (NETROMAX) is a well tolerated and useful aminoglycoside to treat a number of bacterial infections.

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ACKNOWLEDGEMENT

We would like to acknowledge the active participation of the following practitioners in this study.
(Names in Alphabetical order)

No.	NAME	PLACE
1	Dr. A.D.Pukdle	Barshi
2	Dr. A.K.Kalita	Dibrugarh
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4	Dr. Amit Agarwal	Mirzapur
5	Dr. Amit Kalwar	Silchar
6	Dr. Anand Gupta	Faizabad
7	Dr. Anil Sabharwal	Delhi
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