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**Linezolid treatment of nosocomial bacterial infection with
multiresistant Gram-positive pathogens in preterm infants – a
systematic review**

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Abstract

Linezolid is an antibiotic of the oxazolidinone class that has bacteriostatic and bactericidal activity against a broad range of Gram-positive bacteria, including multiresistant pathogens. Due to increasing resistance of Gram-positive pathogens to traditional antibiotics like vancomycin the oxazolidinones were introduced into therapy. Aim of this review was to summarize actual data on pharmacokinetics, safety and clinical use of linezolid in preterm infants. MEDLINE and EMBASE were searched using the term “linezolid” combined with “newborn”, “neonate”, “preterm” and “premature” between 1988 and 2008. Studies reporting on a population including preterm infants and other age-groups and case reports on preterm infants only were acceptable for analysis. Five studies and eight case reports were identified evaluating linezolid in preterm infants. A dosage regimen of 10 mg/kg body weight given either orally or intravenously every 8 hours in infants aged one week or more and the same dose given every 12 hours in infants younger than one week was shown to be safe and effective with mean treatment duration of 10 to 28 days. In summary linezolid has shown to be a safe and effective alternative to vancomycin in the treatment of infections with multiresistant Gram-positive pathogens in preterm infants.

Key words: linezolid, preterm infant, gram-positive bacteria, nosocomial infection

1. Introduction

Gram-positive pathogens are the most common and troublesome causes of nosocomial infections in neonatal intensive care units particularly coagulase-negative staphylococci (CONS) and enterococci^{1,2}. Those pathogens accumulate with indwelling catheters and focal complications associated with prematurity and can be the cause for early- and more over late-onset sepsis^{3,4}. Due to increasing resistance of these pathogens to traditional antibiotic therapy like ampicillin, aminoglycosides and cefotaxime, glycopeptides like vancomycin are often required for adequate therapy. Unfortunately it is assumed that the potential overuse of vancomycin might be dangerous (i.e., need for parenteral therapy with the risk of phlebitis or other injection reactions, unnecessary use of a nephrotoxic drug, increased risk of antibiotic resistance and possible colonization with multiply resistant organisms, fungi, or both)⁴. Therefore linezolid, a member of the oxazolidinones, a new class of antibiotics with a completely novel mechanism of action⁵, has become an alternative treatment option. Especially in glycopeptide-resistant Gram-positive bacterial infections and in cases of glycopeptide treatment failures linezolid has shown to be a potent second-line drug. Linezolid possesses excellent microbial activity against a wide variety of Gram-positive pathogens, with bactericidal effects against most strains of *Streptococcus* spp. and bacteriostatic action on *Enterococcus* spp. and *Staphylococcus* spp., including vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and Methicillin Resistant Coagulase-Negative *Staphylococcus* (MRCNS)^{6, 7, 8, 9}. Linezolid is also active against anaerobes, atypical microbes such as

Chlamydia and Mycoplasma spp., some rapidly growing mycobacteria and selected Gram-negative bacilli^{10,11, 12}. Linezolid or N-([S]-[3-fluoro-4-morpholinophenyl]-2-oxo-5-oxazolidinyl) methyl) acetamide is a totally synthetic antimicrobial agent structurally unrelated to other agents with an unique mechanism of action^{6,7}. Thus, cross-resistance with other protein synthesis inhibitors such as aminoglycosides and macrolides is generally avoided¹³. Moreover the development of resistance to linezolid seems difficult to achieve, requiring specific 23S recombinant RNA mutations¹⁴.

In the U.S. linezolid is approved for paediatric patients since December 2002. In Austria as in many other European countries its use in paediatric patients is off-label. Aim of this systematic review was to summarize actual data on pharmacokinetics and safety, as well as to outline experiences in clinical use of linezolid in preterm infants.

2. Methods

2.1 Literature sources and search terms

MEDLINE and EMBASE were searched systematically to identify all papers published in the English and German literature regarding the use of linezolid in preterm infants, including the period from January 1988 to June 2009. This time window was chosen due to the fact that all identified papers about the class of oxazolidinones and linezolid were published after 1987. For the search the following keywords were utilized both individually and in different combinations: linezolid, newborn, neonate, preterm and premature. Cross-referencing of important articles was also applied.

2.2 Study selection

Original observational or interventional population or hospital-based studies involving preterm infants < 37 weeks of gestational age with severe infections with multiresistant Gram-positive infections being treated with linezolid were included. In addition, only studies with well-defined participants' characteristics and number of subjects treated with linezolid were included in the analysis.

2.3 Data abstraction

One author extracted and screened potentially relevant articles to determine whether they met the inclusion criteria. Then data was abstracted from each included article and reviewed cross-referencing with the co-authors for additional potentially relevant articles. Abstract discrepancies were resolved by repeated review and discussion.

- 1 We extracted the following types of data from each study identified as specified
- 2 by our protocol: indications, pharmacokinetics and recommended dosage,
- 3 duration of treatment, efficacy and side effects.

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3. Results

A total of five pharmacological and/or clinical studies and eight case reports were identified. Data of pharmacological and clinical studies are summarized in table 1.

3.1 Pharmacologic properties in preterm infants

In the manufacturer's prescribing information¹⁵ the pharmacokinetic properties of single dose intravenous linezolid in paediatric patients are reported. Results are based on studies of linezolid 10 mg/kg in paediatric patients aged <7 days (gestational age <34 weeks [n=9], gestational age ≥34 weeks [n=10]), 7-28 days (n=10), >28 days to 3 <3months (n=59), and 3 month to 11 years (n=59), and linezolid 600 mg or 10 mg/kg to a maximum to 600 mg in adolescent volunteers and patients aged 12-17 years (n=36)¹⁵. The pharmacokinetics in these age groups are compared with those in 29 adult subjects receiving a single intravenous infusion of linezolid (dose normalized to 600 mg)¹⁵. The studies showed that values including pharmacokinetic parameters (area under the plasma concentration-time curve [AUC], systemic clearance [CL] and elimination half-life [$t_{1/2}$]) of linezolid change with increasing age (figure 1)¹⁵. Preterm neonatal patients aged <1 week demonstrated a higher mean AUC than the other age groups; however, there was no difference at the age of 7 days.

In a similar manner, mean clearance for infants <7 days postnatal age is substantially less than in older infants and the CL of linezolid increases rapidly during the first week after birth in both preterm and full-term neonates¹⁶. Among preterm infants <7 days old the clearance of linezolid is lowest; clearance rates

are similar to those observed in adult patients. However, the clearance of linezolid increases markedly in the first week of life, regardless of gestational age, such that infants >7 days old have clearance values that are ≈ 3 -fold greater than those of adults ([figure 1](#)). The age-dependent differences in the CL of linezolid may be partially the result of differences with age in activity of non-CYP isoforms (e.g. amidases, peptidases and peroxidases), although these enzymes have not specifically been identified as playing a role in linezolid metabolism^{17,18}. In contrast to AUC, CL and $t_{1/2}$ the age of paediatric patients does not affect the $C_{\max}$ or steady-state volume of distribution (V_{ss}) of linezolid¹⁵.

Kearns et al¹⁹ reported the results from a multicenter study of linezolid disposition in preterm and term neonates and young infants. The population of 42 infants was stratified into 4 subgroups: group 1 (n=9), gestational age <34 weeks and postnatal age <8 days; group 2 (n=7), gestational age <34 weeks and postnatal age 8 days to 12 weeks; group 3 (n=11), gestational age >34 weeks and postnatal age <8 days; and group 4 (n=15), gestational age >34 weeks and postnatal age 8 days to 12 weeks. The study was conducted as an open label, single-dose evaluation of linezolid pharmacokinetics and tolerance at a single dose level (10 mg/kg). Single-dose linezolid was well tolerated in neonates and young infants in this study. There were no clinically significant adverse events or clinically significant changes in vital signs or physical findings associated with the study drug or experimental procedures. The pharmacokinetic parameters of the study are comparable with data reported above^{15,17}.

3.2 Recommended dosages and duration of treatment in preterm infants

The recommended dosage of linezolid in most indications is 10 mg/kg every 8 hours in children aged 0-11 years and 600 mg every 12 hours in adolescents aged ≥ 12 years¹⁵. Because CL is slower in preterm neonates (gestational age < 34 weeks) aged < 7 days as well as in term neonates aged < 7 days, a longer interval between doses (every 12 hours) is initially recommended in these patients; however, the clinical response should be assessed considering the site and severity of infection and the underlying medical condition. An 8-hour dosing interval may be used in preterm and term neonates under 7 days of life, if the response to linezolid is suboptimal and should be used in all neonates by 7 days of age. This recommendation is supported by the results gained by Kearns' et al. in their multicenter study of linezolid disposition in preterm and term neonates and young infants¹⁹. Biedenbach and Jones have suggested the following breakpoints for linezolid: minimum inhibitory concentration (MIC) ≤ 4 mg/L for susceptibility and ≥ 16 mg/L for resistance²⁰.

No dosage changes are required when switching from intravenous to oral formula of linezolid. The recommended durations of treatment are 10-14 days in patients with skin and skin-structure infections or pneumonia and 14-28 days in those with vancomycin-resistant E. faecium infections¹⁵.

3.3 Side effects – tolerability in preterm infants

Kaplan et al²¹ assessed the clinical efficacy and safety of linezolid vs. vancomycin in 316 hospitalized children including 34 preterm infants infected with nosocomial multiresistant Gram-positive bacteria. They were randomized 2:1 to receive either linezolid iv 10mg/kg every 8 h or vancomycin iv 10 to 15

1 mg/kg every 6 to 24 h at least for 3 days followed by oral linezolid or
 2 vancomycin and then by an appropriate oral agent. Treatment duration was 10
 3 to 28 days. The overall clinical cure rate was 89% compared to 85% ($p=0.31$).
 4 Pathogen eradication rates were high for both linezolid and vancomycin
 5 regarding methicillin susceptible *S. aureus* (95% vs. 83%, $p=0.87$). Linezolid
 6 treated patients required significantly fewer days of iv therapy compared with
 7 vancomycin treated patients (8.0 ± 4.8 vs. 10.9 ± 5.8 , $p<0.001$). In addition
 8 significantly fewer linezolid-treated patients had drug-related adverse events
 9 compared to vancomycin-treated patients (19% vs. 34%, $p=0.003$) including
 10 rash, moniliasis, red man syndrome, pruritus and fever (see [Table 2](#))²¹.
 11 Hematologic effects were uncommon and similar between treatment groups.
 12 Details of the 34 preterm infants of the above mentioned study were reported by
 13 [Deville et al](#)²² focussing on the results of a total of 63 newborns. Twenty-six preterm
 14 infants <34 weeks were in the linezolid group and compared to eight in the
 15 vancomycin group. The clinical cure rate was 84% compared to 77% ($p=0.553$).
 16 Pathogen eradication rates comparing both groups were 67% vs. 60% ($p=0.850$) for
 17 *S.aureus* and 88% vs. 100% ($p=0.397$) for coagulase-negative staphylococci. Study-
 18 emergent adverse events were similar in both groups (76.7% compared with 73.7%,
 19 $p=0.795$). Drug-related adverse events were reported in 11.6% of linezolid-treated
 20 compared with 31.6% of vancomycin-treated infants ($p=0.058$). Oral candidiasis was
 21 only observed in two of 19 (10.5%) vancomycin treated compared to none of the
 22 linezolid treated infants ($p=0.031$). The percentage of patients with abnormal
 23 hematology or serum chemistry values was not statistically different between groups.
 24 However, more linezolid-treated patients had decreases in hemoglobin (linezolid
 25 23.3% vs. vancomycin 5.3%; $p=0.087$) and hematocrit (linezolid 23.3 vs. vancomycin

5, $p=0.172$) and increases in total bilirubin (linezolid 19.0% vs. vancomycin 10.5%, $p=0.405$).

Meissner et al²³ evaluated the occurrence of hematologic effects of linezolid compared to vancomycin in the same study group²². Overall, no significant differences were noted in drug-related hematologic events, such as thrombocytopenia (linezolid, 1.9% vs. vancomycin, 0%; $P = 0.170$), anaemia (linezolid, 1.4% vs. vancomycin, 1.0%; $P = 0.771$) or neutropenia (linezolid, 0% vs. vancomycin, 0%). No clinically relevant changes in reticulocyte index or iron studies were noted between treatment groups.

3.4 Case reports

In our literature review we found eight case reports on a total of 14 preterm infants successfully treated with linezolid. In all cases linezolid was applied after glycopeptide treatment failures with known or suspected glycopeptide-resistant Gram-positive bacteria. Seven patients suffered from ventriculitis or an infection of the cerebral spinal fluid (CSF). As linezolid has previously been shown to have excellent penetration into the CSF in adults²⁴, it also achieved good concentrations in CSF in those preterm infants^{25,26,27}. Another two patients suffered from endocarditis^{28,29}, three patients suffered from peritonitis³⁰ or necrotizing enterocolitis³¹, one patient had nosocomial pneumonia (?)³⁰ and one child suffered from a persistent septicaemia³². In most cases glycopeptide-resistant Enterococcus faecium could be isolated. Other isolated pathogens were Methicillin-resistant Staphylococcus aureus (MRSA), Staphylococcus epidermidis, Staphylococcus haemolyticus or Staphylococcus capitis. In two cases there was a co-infection with Klebsiella oxytoca.

1 Dosage and duration of linezolid was according to the manufacturer's
2 recommendations in 12 of 14 patients. Except for temporary thrombocytopenia
3 in one patient no haematological or other laboratory or clinical side effects of
4 linezolid were observed. In one patient dosage had been increased to 12 mg/kg
5 every 8 without evidence of bone marrow suppression²⁶, and even treatment
6 over 9 weeks in one patient was well tolerated²⁸.

4. Conclusion

In clinical studies comparing the efficacy and safety of linezolid versus vancomycin linezolid proved to be well tolerated and as effective as vancomycin in a total of 51 preterm infants. Adding the information out of eight case studies including 14 preterm infants linezolid demonstrated to be a safe and potent second-line drug in the treatment of nosocomial bacterial infection with multiresistant Gram-positive pathogens in preterm infants. Benefits of linezolid compared to vancomycin include its availability in equivalent intravenous and oral formula and its safer use in combination with aminoglycosides. Linezolid should be used as second-line treatment, but due to overwhelming nosocomial infections in very low birth weight infants its use might be considered earlier in case of unassertive clinical improvement of the baby or knowledge of multiresistant Gram-positive pathogens at the NICU. Study results are limited by the low number of preterm infants included. Further prospective studies are needed to confirm the efficacy and safety of linezolid in the treatment of multiresistant Gram-positive infections in this particular vulnerable group of preterm infants. Additionally information on linezolid levels in plasma and cerebrospinal fluid is warranted.

5. Recommendations

Considering the available data on linezolid in preterm infants we recommend its use as second line antibiotic in preterm infants infected with glycopeptide-resistant bacteria and/or in case of glycopeptide treatment failures. However, in cases of known or suspected glycopeptide resistant pathogens we advise to consider linezolid at an earlier stage of treatment. A dosage regimen of 10 mg/kg body weight given either orally or intravenously every 8 hours in infants aged one week or more and the same dose given every 12 hours in infants younger than one week was shown to be safe and effective with mean treatment duration of 10 to 28 days. Due to the risk of myelosuppression weekly evaluation of complete blood counts is recommended.

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None.

Competing interest

No competing interests are identified by any of the authors.

Ethical approval

This review needed no Ethical Approval.

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Tables:

Table 1: Summary of pharmacological studies, studies on tolerability and case studies on linezolid use in preterm children^{15,19,21-23,25-32}

Year	Age of patients	Number Total/preterm	Dosage (mg/kg)	interval	Duration	Adverse events (%)	Reference
2002	PT, T, ≤ 17 y	136/9	10	1 dose	1 d	n. sp.	15
2003	PT, T, ≤ 12 w	42/16	10	1 dose	1 d	n. sp.	19
2003	PT, T, ≤ 12 y	215/26	10	8 h	10-28 d	18.8	21
2003	PT, T, ≤ 11 y	215/26	10	8 h	10-28 d	13.1	22
2003	PT, T, ≤ 90 d	43/26	10	8 h	10-28 d	7.0	23
2002	29 w	1/1	10	8 h	21 d	0	25
2007	35 w	1/1	10	8 h	21 d	0	26
			12	8 h	14 d		
2008	mean 26.4 w	5/5	10	8 h	mean 20.8 d	0	27
2003	26 w	1/1	15	8 h	9 w	0	28
2008	28 w	1/1	10	8 h	10 d	0	29
2006	24 and 30 w	2/2	10	8 h	16/14 d	0	30
2004	26 and 28 w	2/2	10	12 h	20 d	50	31

PT preterm, T term infant, w weeks, d days, y years,

n.sp. not specified

Table 2: Treatment-related adverse events reported in >1% of 316 hospitalized children including 34 preterm infants <34 weeks of gestational age (randomized 2:1 to linezolid vs. vancomycin) infected with nosocomial multiresistant Gram-positive pathogens ²¹

Adverse Event	Linezolid (n=213)	Vancomycin (n=99)	p-value
Diarrhea	8 (3.8)*	6 (6.1)	0.3601
Vomiting	4 (1.9)	1 (1.0)	0.5699
Thrombocytopenia	4 (1.9)	0 (0)	0.1700
Loose stools	4 (1.9)	0 (0)	0.1700
Rash	3 (1.4)	7 (7.1)	0.0082
Nausea	3 (1.4)	0 (0)	0.2354
Anemia	3 (1.4)	1 (1.0)	0.7710
Eosinophilia	3 (1.4)	0 (0)	0.2354
Oral moniliasis	2 (0.9)	4 (4.0)	0.0634
Fever	1 (0.5)	3 (3.0)	0.0613
Red man syndrome	0 (0)	10 (10.1)	<0.0001
Pruritus	0 (0)	2 (2.0)	0.0374

*numbers in parentheses, percent

Figures

Figure 1: Comparison of linezolid pharmacokinetics in pediatric patients, adolescents and adults¹⁵.

Fig.1: Pharmacokinetics of linezolid in pediatric patients, adolescents and adults. (a) Mean area under the plasma concentration-time curve (AUC), (b) systemic clearance, and (c) elimination half-life of single dose intravenous linezolid 10 mg/kg (maximum 600 mg) in (columns from left to right) pre-term [gestational age <34 weeks], full-term neonates aged below 1 week and between 1 and 4 weeks, infants, children, adolescent and adult volunteers.