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Clinical and microbiologic efficacy and safety profile of linezolid, a new oxazolidinone antibiotic

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Abstract

Gram-positive cocci are important causes of infection both in the community and in the hospital, with repercussions on mortality and increased economic costs. Treatment of these infections is made difficult by the increasing emergence of multi-resistant organisms, primarily among Gram-positive cocci, such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci, and penicillin-resistant pneumococci. Linezolid, a member of the new class of synthetic antimicrobials named oxazolidinones, has several favourable characteristics including high activity against multiresistant Gram-positive cocci. In a number of clinical trials, linezolid showed good clinical and microbiologic efficacy in the therapy of infections caused by these organisms. It can be considered a valid option for treating both community- and hospital-acquired infections due to multiresistant Gram-positive cocci.

Keywords: Gram-positive cocci; Antibiotic resistance; Enterococci; Staphylococci; Pneumococci; Linezolid

1. Introduction

The last decade has witnessed significant shifts in the aetiology of nosocomial infections from easily treated pathogens such as *Escherichia coli*, *Proteus mirabilis*, *Klebsiella pneumoniae* to more resistant pathogens (staphylococci, enterococci, *Enterobacter* spp, *Pseudomonas aeruginosa*, and *Candida* spp). In general, there is also a shift from Gram-negative bacilli (GNB) to gram-positive cocci (GPC) and fungi [1,2]. Thirty nine percent of nosocomial infections are currently caused by GPC, and this percentage increases to over 50% in surgical site infections (SSIs) and bloodstream infections (BSIs), whereas it has decreased to approximately 25% in urinary tract infections (UTIs) and lower respiratory tract infections (LRTIs) Fig. 1 [3].

A further problem associated with the current epidemiology of nosocomial infections is the emergence of resistant and multiresistant GPC such as vancomycin-resistant enterococci (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (MR–CNS), and also *S. aureus* with reduced susceptibility to glycopeptides (GISA). The problem of penicillin-resistant pneumococci (PRP) as a cause of severe community-acquired infections should not be underestimated as well.

Clinically relevant VRE first appeared in the United States (US) in the early 1990s, where a dramatic increase of VRE prevalence rates from 0.3% in 1989 to 3.2% in 1993 in non-intensive care units (non-ICU) and from 0.4% to 13.6% in ICUs was reported [4]. This

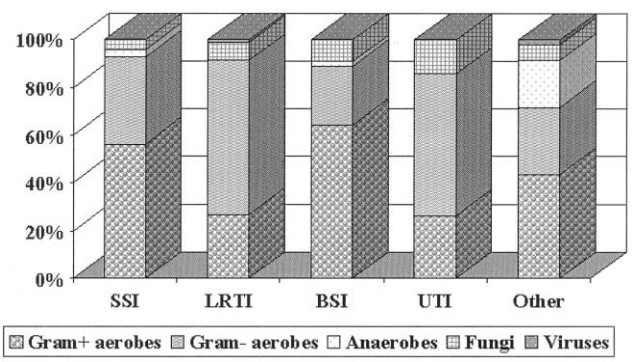

Fig. 1. Etiology of nosocomial infections: prevalence rates (%) of groups of organisms [3].

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trend continued in subsequent years, and has reached 15.4% for non-ICU units and 23.2% for ICUs in 1997 [5]. A multicentre study carried out in Europe in 1995, showed a low incidence of VRE, ranging from 0.6% in Belgium to 4.2% in Switzerland for vancomycin, and from 0.6% in Belgium and Italy to 3.5% in Spain for teicoplanin [6].

MRSA strains emerged in the early 1960s [7] but have spread worldwide only since the 1980s. A recent nationwide US study on nosocomial BSIs reported 29.3% of MRSA, with a higher incidence in the Eastern than in the Western states [8]. A European multicentre study showed an average prevalence rate of 12.8% of MRSA, but differs widely between Scandinavian ($<$ 1%) and Mediterranean ($>$ 30%) countries [9]. Higher rates were found in ICU patients; the EPIC study showed an average rate of 59.6%, with the highest (81%) reported from Italy [10].

Until recently, *S. aureus* has been fully susceptible to the glycopeptides, the first strain with reduced susceptibility to vancomycin isolated in 1996 in Japan [11]. Two other isolates were reported in 1997 from the US [12]. Strains with reduced susceptibility to teicoplanin have been isolated, such that the acronym GISA (glycopeptide-intermediate *S. aureus*) has been proposed. GISA is currently of great concern because of its potential resistance to all available antimicrobial agents. The prevalence of MR–CNS is even higher than that of MRSA. In the US, 65% of CNS isolates from blood are resistant to methicillin [13], and in Finland the incidence of methicillin-resistant *Staphylococcus epidermidis* (MRSE) increased from 28% in 1983 to 77% in 1994 [14]. Obviously, the prevalence of MRSE has increased in the ICU. The EPIC study showed an average rate of prevalence of 70.1% [10].

Streptococcus pneumoniae, initially susceptible to penicillin and other β-lactams as well as other antimicrobial agents, acquired reduced penicillin susceptibility (MIC = 0.6 mg/L) in 1967 in Australia [15]. Resistance to multiple antibiotics was reported in 1977 from South Africa [16]. Currently, the prevalence of PRP in the US, France, Spain, most of Eastern Europe, Turkey, South Africa, and the Far East is greater than 30%, whereas a lower prevalence ($<$ 10%) is found in North Africa, New Zealand, and some parts of Europe [17].

The most important consequence of bacterial resistance to antibiotics is the difficulty in treating infections caused by resistant and multi-resistant organisms. Selection is limited to a few antimicrobials that have a low therapeutic index or which exert selective pressure for the emergence of resistance. The prudent use of antibiotics and the introduction of new potent antimicrobials are very desirable.

2. Bacteriologic and pharmacokinetic properties of linezolid, a new oxazolidinones

Oxazolidinones, a new class of synthetic antimicrobials unrelated to any other currently available agents, were first presented at the 27th Interscience Conference on Antimicrobial Agents and Chemotherapy in New York in 1987 [18]. Linezolid, the most studied member, has a number of favourable characteristics such as a specific mechanism of action, lack of cross-resistance with other agents, high oral bioavailability, and a spectrum of activity that includes multi-resistant bacteria. Linezolid has been shown to have high activity against *S. aureus* and *S. epidermidis*, enterococci, and streptococci [19]. Gram-negative anaerobes and mycobacteria are generally susceptible as well, whereas Enterobacteriaceae and other Gram-negative bacteria are resistant [20]. Linezolid selectively binds to the 50S subunit near the interface with the 30S subunit. This results in distortion that inhibits the formation of the initiation complex constructed with 30S ribosomes, mRNA, initiation factors IF2 and IF3, and fMet-tRNA [19,21]. It does not inhibit the peptide elongation phase, such that this drug is generally believed to be bacteriostatic. Concentration-dependent killing has been described for some species (especially streptococci), while no concentration-dependent killing could be demonstrated for staphylococci or enterococci [22]. Because of its mechanism of action, linezolid does not exhibit cross-resistance with other groups of antibiotic. Preliminary studies suggested that spontaneous mutations for resistance among staphylococci rarely occur and that the appearance of resistant mutants during clinical application is unlikely or may occur very slowly [19,23].

Linezolid can be administered both orally and parenterally. After oral administration, the maximum peak plasma concentrations occur within 1–2 h. Linear kinetics are seen with both oral and parenteral routes. The elimination half-life is approximately 5 h and the protein binding is approximately 31% [19].

Several studies have evaluated the in vitro efficacy of linezolid against important GPC and compared it with other antibiotics, such as glycopeptides, fluoroquinolones, and streptogramins. Against *S. aureus*, linezolid has a MIC_{90} of 2 mg/L. The MICs ranged from 0.25 to 2 mg/L for both vancomycin-susceptible and -resistant enterococci. All streptococci were inhibited at MICs of 4 mg/L or less [19]. Wise et al. reported MICs of 0.5–1 mg/L for both methicillin-susceptible and -resistant *S. aureus*, *S. epidermidis*, and *S. saprophyticus*, MICs of 0.5–2 mg/L against streptococci, including penicillin- and fluoroquinolone-resistant *S. pneumoniae*, and MICs of 0.5–2 mg/L against anaerobes. *Enterococcus faecalis* and *Enterococcus faecium*, including VRE strains (with both *vanA* and *vanB*) were uniformly highly susceptible to linezolid [20]. Sim-

ilar MIC values have been reported by other workers [21–25]. Von Eiff and Peters found that the in vitro activity of linezolid was similar to that of glycopeptides against MRSA, and its antistaphylococcal activity remained almost unchanged, irrespective of the methicillin resistance phenotype [24].

The combination of the pharmacokinetic profile and post-antibiotic effect (PAE) of linezolid is important in determining the most appropriate dosing interval. Linezolid's PAE is relatively short. It is greater at four times MIC (range: 0.2–1.4 h) than at the MIC (0.1–0.8 h) against all organisms tested, and it is considerably lower against *E. faecalis* than against *E. faecium* and staphylococci. Based upon preliminary pharmacokinetic studies which reported a prolonged serum half-life (5–6 h), this agent may be given at intervals of 8–12 h [23].

3. Clinical and microbiologic efficacy and safety profile of linezolid

In a few phase II clinical trials, linezolid was used at either low (375 mg bid or 250 mg tid) or high (625 mg bid or 375 mg tid) doses intravenously. This was followed by oral administration for an overall duration ranging from 5 to 14 days (up to 28 days in bacteremias). In patients with community-acquired pneumonia, clinical success was obtained in 93% of cases (87% with low doses and 100% with high doses) and bacterial eradication in 94% of both pneumococcal and nonpneumococcal pneumonias. At short-term follow-up, *S. pneumoniae* was eradicated in 100% of patients in both low- and high-dose groups. In subjects with skin or soft-tissue infections (SSTIs), the rates were 91% for clinical efficacy (92% with low doses and 89% with high doses) and 95% for bacterial eradication, which was obtained for all relevant pathogens. At short-term follow-up, the microbiologic eradication rates were 98% for the low-dose group and 100% for the high-dose group [26].

In a clinical trial on patients with various infections (primarily bacteremias and intra-abdominal infections) caused by multi-resistant GPC such as VRE, clinical success was achieved in 17 out of 18 evaluable patients, and bacterial eradication in all evaluable subjects [27]. In a phase II study on a number of community-acquired infections, primarily SSTIs, treatment with linezolid at daily doses ranging from 375 to 625 mg bid produced clinical and microbiologic success in 90 and 92% of cases, respectively [28].

Despite the reported lack of in vitro bactericidal activity, Noskin et al. have successfully treated a 23-year-old neutropenic woman with persistent VRE bacteremia with linezolid 600 mg bid iv plus gentamicin 1 mg/kg tid iv. The *E. faecium* isolate from blood had high-level resistance to vancomycin and ampicillin and was resistant to all antimicrobial agents except chloramphenicol and gentamicin. The MIC for linezolid was 2 mg/L and especially significant was that the bacteremia cleared while the patient remained profoundly neutropenic ($< 100/mm^3$) [29].

Among adverse events (AEs) observed in clinical trials with linezolid, headache, nausea, and diarrhoea predominated (10–15% incidence), while vomiting, insomnia, dizziness, asthenia, and phlebitis in the injection site appeared less frequently (5–10%). Mild-to-moderate and reversible increases in both hepatocellular and pancreatic enzymes were the main changes in laboratory parameters, although haematological changes could be observed during therapy. They were however minimal when the doses used in the phase II protocols were administered for the typical dosing duration of 10–14 days [26].

In a clinical trial with linezolid for compassionate use, Birmingham et al. reported an overall AE rate of 36.3%; 11.4% of these possibly linezolid-related As resulted in discontinuation of therapy. The most common were thrombocytopenia, dermatological reactions, decreased haemoglobin level, leukopenia, and allergy [30]. Another phase II study on safety and tolerance of linezolid reported AEs in 75.6% of patients, but only 32.7% of patients had AEs considered drug-related. No life-threatening drug-related AEs have been reported and no clear evidence of mono-amino-oxydase inhibitor reactions or serious drug interactions have been observed [31].

Linezolid is an important option for treating both community- and hospital-acquired infections due to multi-resistant Gram-positive cocci and for reducing the increasing selective pressure exerted by glycopeptides on hospital Gram-positive cocci because of its clinical and microbiologic efficacy and its safety profile [24]. It is exciting to be able to offer patients with serious Gram-positive infection home oral therapy once they are stabilised, rather than prolonged hospitalisation or home intravenous infusions. Instituting a sequential therapy makes early discharge from hospital or home treatment possible, with obvious economic savings.

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