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Oxazolidinones – a new class of broad-spectrum chemotherapeutics

Oxazolidinones are potent inhibitors of bacterial protein biosynthesis. These new chemotherapeutics block the translation process by inhibiting initiation complex formation, while postinitiation translation by polysomes and poly (U)-dependent translation is not a target for these compounds. Oxazolidinones inhibit translation of natural mRNA templates but have no significant effect on poly (A)-dependent translation. These drugs inhibit ribosomal peptidyltransferase activity in the simple reaction of 70 S ribosome's using initiator-t-RNA or N-protected CCA-Phe as a P-site substrate and puromycin as an A-site substrate. Oxazolidinones display a competitive inhibition pattern with respect to both the P-site and A-site substrates. This is consistent with a rapid equilibrium, ordered mechanism of the peptidyltransferase reaction, wherein binding of the A-site substrate can occur only after complex formation between peptidyltransferase and P-site substrate. In conclusion, oxazolidinones inhibit bacterial protein biosynthesis by interfering with binding of translation initiator fMet-tRNA(i)(Met) to the ribosomal peptidyltransferase P-site, which is vacant only prior to the formation of the first peptide bond (12, 15, 22, 29).

The first significant member of oxazolidinones, the newest class of broad spectrum chemotherapeutics of antimicrobial properties is linezolid ((S)-N-[[3-[3-fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5--oxazolidinyl]methyl]-acetamide, Zyvox, Zyvoxid, PNU-100766). This drug is applied for the treatment of Gram-positive bacterial infections, including those caused by resistant microorganisms (8, 15, 30).

Linezolid is excreted primarily intact, and as two inactive, morpholine ring-oxidized metabolites: PNU-142586 and PNU-142300. In human liver microsomes, linezolid is oxidized to a single metabolite – hydroxylinezolid (M1). The formation of hydroxylinezolid is determined to be dependent upon microsomal protein and NADPH. Over concentration range 2 to 700 μM, the rate of M1 formation conforms to first-order (nonsaturable) kinetics. Inhibitor/substrates for various cytochrome P-450 (CYP) enzymes are unable to inhibit hydroxylinezolid formation. The formation of M1 does not correlate with any of the measured catalytic activities across a population of human livers and is not detectable in incubations using microsomes prepared from a baculovirus insect cell line expressing CYPs 1A1, 1A2, 2A6, 2B6, 2C8, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 3A5, 4A11. The results obtained from an *in vitro* P-450 inhibition screen revealed that linezolid was devoid of any inhibitory activity toward the following cytochrome P-450 enzymes: CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4. Conducted *in vitro* studies excluded the possibility of flavin-containing monooxygenase and monoamine oxidase as potential enzymes responsible for hydroxylinezolid formation. This metabolite formation was found to be optimal under basic pH conditions, which suggests the potential involvement of either an uncharacterised P-450 enzyme or an alternative microsomal mediated oxidative pathway (36).

After a single radioactive dose, linezolid was the major circulating drug-related material accounting

for about 78% (male) and 93% (female) of the radioactivity under the curve (AUC). PNU-142586 (T_{max} of 3–5 h) accounted for about 26% (male) and 9% (female) of radioactivity AUC. The second inactive linezolid metabolite – PNU-142300 (T_{max} of 2–3 h) accounted for about 7% (male) and 4% (female) of the radioactivity AUC. Linezolid circulates in the plasma mainly as the parent drug. Linezolid and two major inactive metabolites (PNU-142586, PNU-142300) account for the major portion of linezolid disposition, with urinary excretion representing the major elimination route. The formation of PNU-142586 is the rate-limiting step in the clearance of linezolid (30).

Linezolid is dosed intravenously or orally at 400 or 600 mg b.i.d. Because its bioavailability is approximately 100 per cent and the area under the plasma concentration curve (AUC) is identical after an oral and intravenous administration, no dosage adjustment is needed when changing from intravenous to oral therapy. After an oral 600-mg dose, steady-state peak plasma concentrations of 21.2 ± 5.78 μg ml^{-1} are obtained at a T_{max} of 1.03 ± 0.62 h. The plasma elimination half-life is 5.40 ± 2.06 h. Clearance, which occurs by both renal and nonrenal (65%) mechanisms is 80 ± 29 ml min^{-1}. Linezolid is neutral in the physiological pH range and undergoes renal tubular reabsorption. Plasma protein binding is low at 31% and the volume of distribution approximates total body water (40–50 litres) (12, 19). Linezolid is a weak and reversible monoamine oxidase (MAO) inhibitor and although no increased frequency of adrenergic and serotonergic adverse events has been reported it is recommended that this drug is used in caution in patients treated with other medicines from the group of MAO inhibitors. Linezolid pharmacokinetic is not affected by concomitant administration with vitamins C and E and therefore no dose adjustment is necessary in patients taking vitamin C and E (18, 30, 32).

Linezolid has a wide spectrum of *in vitro* activity against Gram-positive microorganisms, including methicillin-resistant staphylococci, penicillin-resistant pneumococci and vancomycin-resistant enterococci. Some anaerobes, such as *Clostridium spp.*, *Peptostreptococcus spp.*, *Prevotella spp.* are also susceptible to linezolid. Linezolid has exhibited good efficacy in experimental animal models of acute endocarditis, meningitis, and otitis due to many common aerobic Gram-positive bacteria. In clinical trials involving hospitalised patients with skin and soft tissue infections, community-acquired pneumonia and serious Gram-positive bacterial infections, linezolid appeared to be an effective treatment option, comparable in efficacy to vancomycin (1, 10, 17, 35, 37).

It has been shown that linezolid had *in vitro* activity against Gram-positive uropathogens of hospitalised patients with complicated urinary tract infections. The minimal inhibitory concentrations (MIC) of linezolid determined by an agar dilution method ranged for methicillin-susceptible *Staphylococcus aureus* (MSSA) between 2 and 4 μg ml^{-1}, for methicillin-resistant *Staphylococcus aureus* (MRSA) between 1 and 2 μg ml^{-1}, for methicillin-susceptible coagulase-negative staphylococci (MSSE) between 0.5 and 4 μg ml^{-1}, for methicillin-resistant coagulase-negative staphylococci (MRSE) between 0.25 and 2 μg ml^{-1}, for *Enterococcus faecalis* between 0.5 and 4 μg ml^{-1}, for *Enterococcus faecium* and for *Streptococcus spp.* between 0.25 and 1 μg ml^{-1} were determined, indicating that all strains were susceptible. According to conducted examination, linezolid may be considered a promising antibacterial agent for the treatment of complicated urinary tract infections caused by Gram-positive uropathogens (19, 20).

There has been confirmed *in vitro* activity of linezolid against Gram-positive cocci isolated in Poland. A total of 417 Gram-positive cocci selected from isolates collected in 2000 year in 61 medical centres were included in the examination. Linezolid inhibited all isolates between 0.12 and 2 μg ml^{-1}. This drug showed equally good activity against methicillin-susceptible and methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci (CNS) with an MIC_{90} of 2 μg ml^{-1}. Also the $MICs_{90}$ of linezolid, vancomycin and teicoplanin for methicillin-resistant *Staphylococcus aureus* were the same (2 μg ml^{-1}). Linezolid was also very active against methicillin-resistant coagulase-

negative staphylococci (MRCNS) including strains with MIC of teicoplanin of 4 μg ml^{-1}. Besides multiresistant enterococci: *Enterococcus faecalis* and *Enterococcus faecium* with VanA, VanB, and high-level aminoglycoside resistance (HLAR) phenotypes were all inhibited by linezolid at concentrations of 0.5 to 2 μg ml^{-1}. Linezolid exhibited excellent activity against all pneumococci, including those with lowered susceptibility to penicillin. For intermediate-susceptible and penicillin-resistant *Streptococcus pneumoniae* linezolid had good activity with MIC_{90} value equal 1 μg ml^{-1} (28).

There has been confirmed *in vitro* activity of linezolid against clinical Gram-positive isolates from Taiwan. Minimal inhibitory concentrations (MICs) of linezolid were established for 371 clinical isolates of staphylococci, pneumococci, enterococci and a group A streptococci from Taiwan. All isolates tested, including those resistant to beta-lactams, erythromycin, vancomycin were uniformly susceptible to linezolid, with MICs ranging from 0.125 to 2 μg ml^{-1}. These data support the observation that there is no cross-resistance between linezolid and other classes antimicrobial drugs (11).

Linezolid was also tested against 1585 Gram-positive cocci, 1260 staphylococci and enterococci isolates from patients hospitalised in Brazilian hospitals and 325 *Streptococcus pneumoniae* isolates for patients with community acquired infections. Based on susceptibility tests performed using broth microdilution according to National Committee for Clinical Laboratory Standards (NCCLS) procedures, it has been shown that linezolid was the most active compound and only linezolid inhibited 100 per cent isolates at the susceptible breakpoint (< or = 4 μg ml^{-1}). The excellent *in vitro* Gram-positive activity by linezolid indicates that this medicine may represent an important therapeutic option for the treatment of infections caused by these pathogens (25, 26).

The activity of linezolid was also determined against 225 recently isolated methicillin-resistant *Staphylococcus aureus* (MRSA) and 20 methicillin-resistant coagulase-negative staphylococci (CoNS) with decreased levels of susceptibility to teicoplanin. The *in vitro* activity of linezolid was similar to that of vancomycin. Linezolid inhibited all MRSA strains at between 0.1 and 2 μg ml^{-1} and all CoNS strains tested at between 0.2 and 0.5 μg ml^{-1}. The results suggest that this drug would be useful for the treatment of infections involving these microorganisms (4, 9, 23).

The activities of linezolid (25 mg kg^{-1} of body weight, administered intraperitonally every 8 h) and of vancomycin of the same dosage were compared in a rat model VanA, vancomycin-resistant *Enterococcus faecium* experimental endocarditis. Results were expressed as median log (10) colony-forming unit (CFU) per gram of vegetation after 3 days of treatment. The median log (10) CFU per gram of vegetation was 10.1 among 7 untreated control animals, 10.2 among 9 vancomycin-treated animals and 7.9 among 10 linezolid-treated animals. It has been proved linezolid treatment was more effective than vancomycin treatment (21).

It has been proved that linezolid was active against clinically significant rapidly growing mycobacteria. In this trial 249 clinical isolates and 10 reference strains of rapidly growing mycobacteria were tested for susceptibility to linezolid by broth microdilution method. Clinical species included the *Mycobacterium fortuitum* (74 strains), *Mycobacterium abscessus* (98 strains), *Mycobacterium chelonae* (50 strains), *Mycobacterium mucogenicum* (10 strains) and *Mycobacterium fortuitum* third biovariant complex (10 strains). The modal MIC for *Mycobacterium mucogenicum* was 1 μg ml^{-1} and the MIC at which 90 % of the isolates tested are inhibited (MIC_{90} was 4 μg ml^{-1} and these species were susceptible to linezolid. The modal MIC for the *Mycobacterium* fortuitum group was 4 μg ml^{-1} and MIC_{90} was 16 μg ml^{-1} and these species were moderately susceptible. The modal MIC for the Mycobacterium fortuitum third biovariant complex was 4 μg ml^{-1} and the MIC_{90} was 8 μg ml^{-1} and these both species were respectively moderately susceptible and susceptible to linezolid. 90 per cent of 50 isolates of *Mycobacterium chelonae* were inhibited by linezolid at MICs < or = 16 μg ml^{-1} with a modal MIC 8 μg ml^{-1}. This included strains that are resistant to clarithromycin (5, 34).

Linezolid therapy was also successful in a case of vancomycin-resistant *Enterococcus meningitis*. This therapy was applied in the case of a patient who suffered a cerebrovascular haemorrhage after embolization of a cerebellar arteriovenous malformation. Although the patient was on a broad spectrum of antibiotics including vancomycin, he remained febrile and grew vancomycin-resistant *Enterococcus faecium* from the cerebrospinal fluid. The patient was also treated with intravenous chloramphenicol without success. The patient received four weeks of intravenous linezolid with complete eradication of the meningitis. Therefore intravenous linezolid appears to be a safe and an effective therapy for vancomycin-resistant *Enterococcus meningitis* (31).

Linezolid was also applied for the treatment of vancomycin-resistant enterococcal peritonitis. The concentration of linezolid above the minimum inhibitory concentration for the most Gram-positive pathogens, including vancomycin-resistant *Enterococcus faecium* was achieved in the dialysate fluid after an oral loading dose of 1200 mg (2).

There has been proved the susceptibility of 53 erythromycin-resistant *Staphylococcus pneumoniae* isolates, 117 *Staphylococcus pyogenes* strains (64 erythromycin-susceptible and 53 resistant) and 101 *Streptococcus agalactiae* (53 erythromycin-susceptible and 48 resistant) isolates to linezolid. All these strains were susceptible to < or = 2 $\mu g\ ml^{-1}$ (3).

Linezolid is the first antimicrobial drug demonstrated to be active against all *Nocardia species*. This drug was tested by broth microdilution method against 140 clinical *Nocardia isolates* belonging to seven species and against 25 strains of *Nocardia brasiliensis*. The MIC_{50} and MIC_{90} for all species other than *Nocardia farcinica* were 2 and 4 $\mu g\ ml^{-1}$. Also all *Nocardia brasiliensis* strains tested were sensitive to linezolid. The MIC_{90} and MIC_{50} values were respectively 2 $\mu g\ ml^{-1}$ and 1 $\mu g\ ml^{-1}$ and this antimicrobial drug might constitute a good alternative for the treatment of actinomycetoma (6, 33).

It has been proved that systemic and intracerebral infections of mice with *Listeria monocytogenes* may be successfully treated with linezolid. Linezolid activity against the facultatively intracellular bacterium *Listeria monocytogenes* was examined *in vitro*, in tissue culture and in animal models of systemic and intracerebral infection and compared with ampicillin, antibiotic of choice for the treatment of listeriosis. All strains of *Listeria monocytogenes* were susceptible to linezolid, with MICs ranging from 0.38 to 1.5 $\mu g\ ml^{-1}$ which is below the preliminary breakpoint of this drug. Linezolid was bacteriostatic against *Listeria monocytogenes* since up to 64 times the MIC did not kill the bacteria in 24 hours. Linezolid was also bacteriostatic to *Listeria monocytogenes* in infected tissue culture cells. In animal models of systemic and intracerebral infection, linezolid was able to inhibit bacterial growth but was less effective than ampicillin and, therefore, linezolid might be useful for the treatment of infections with *Listeria monocytogenes* in humans when ampicillin may not be used (7).

Linezolid was tested against 70 strains of *Helicobacter pylori* by the agar dilution method. The MIC range and MICs at which 50% and 90% of strains were inhibited were 8 to 64, 16 and 32 $\mu g\ ml^{-1}$ respectively. With minimum and maximum fractional inhibitory concentration summation values of 0.31 and 2.50, respectively, the combination of linezolid with amoxicillin, clarithromycin or metronidazole showed either partial synergy or indifference for the majority of strains (14).

There has been found the ecological effect of linezolid versus amoxicillin/clavulanic acid on the normal intestinal microflora. During the administration of linezolid, enterococci in the intestinal aerobic microflora were markedly suppressed while *Klebsiella* organisms increased in number. In the anaerobic microflora, the numbers of bifidobacteria, clostridia, lactobacilli and *Bacteroides* decreased markedly while no impact on the other anaerobic bacteria was observed. The microflora was normalized after 35 days. Amoxicillin/clavulanic acid administration caused increased numbers of enterococci and *Escherichia coli* in the aerobic intestinal microflora while numbers of bifidobacteria, lactobacilli and clostridia decreased significantly. In comparison the administration of linezolid mainly had an impact on Gram-positive bacteria and this drug thus had an ecological profile different from that of amoxicillin/clavulanic acid (16).

The *in vitro* susceptibility of *Coxiella burnetii* belonging to parasites and derived from patients with acute Q fever was determined in comparison with its susceptibilities to quinolones, doxycycline and clarithromycin. MIC of linezolid and clarithromycin ranged from 2 to 4 μg ml^{-1}; those of doxycycline, trovafloxacin and ofloxacin ranged from 1 to 2 μg ml^{-1}; those of pefloxacin ranged from 1 to 4 μg ml^{-1} and those of ciprofloxacin ranged from 4 to 8 μg ml^{-1}. Linezolid was effective in controlling intracellular parasites in culture cells infected by *Coxiella burnetii* and no bactericidal activity by linezolid was obtained against these parasites at 8 μg ml^{-1} (13).

Recently some enterococcal and staphylococcal strains resistant to linezolid were isolated. This resistance to linezolid was also found in the case of strains of *Mycobacterium smegmatis, Enterococcus faecalis* and in some *Clostridium difficale*. DNA sequencing of the 23 S rRNA genes revealed that linezolid resistance in *Enterococcus faecalis* isolates was associated with a guanine to uracil transversion at bp 2576 (24, 27).

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SUMMARY

The oxazolidinones are a new class of broad spectrum chemotherapeutics of antibiotic properties. These drugs have good activity against Gram-positive pathogenic bacteria. Oxazolidinones possess an unique mechanism of inhibitory bacterial protein biosynthesis. These compounds inhibit the formation of N-formylmethionyl-tRNA, which is a requisite of beginning translation process. Linezolid, the first oxazolidinone to be approved for the clinical treatment of Gram-positive bacterial infections, displays a wide spectrum of *in vitro* activity against many important pathogens, including for instance methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci and penicillin-resistant pneumococci. Linezolid is a pararental drug that also possesses near-complete oral bioavailability and a favourable pharmacokinetic profile. In clinical trials involving hospitalised patients with skin and soft tissue infections oxazolidinones appeared to be effective treatment option, comparable in efficacy to vancomycin.

Oksazolidynony – nowa klasa chemioterapeutyków o szerokim spektrum aktywności

Oksazolidynony są nową klasą chemioterapeutyków o szerokim spektrum działania antybiotycznego. Leki te odznaczają się wysoką aktywnością przeciw patogennym bakteriom Gram-dodatnim. Posiadają one unikalny mechanizm hamowania biosyntezy białka bakteryjnego poprzez zapobieganie tworzeniu się kompleksu N-formylometionylo-tRNA, koniecznego do rozpoczęcia procesu translacji. Linezolid zalecany do leczenia zakażeń bakteriami Gram-dodatnimi wykazuje *in vitro* szerokie spektrum aktywności przeciwko opornym patogenom, włączając w to metycylinooporne gronkowce, wankomycynooporne ziarniaki i penicylinooporne pneumokoki. Linezolid jest stosowany parenteralnie, a także po podaniu doustnym posiada niemal całkowitą biodostępność i wykazuje korzystne parametry farmakokinetyczne. Badania kliniczne wykazały, że oksazolidynony są porównywalnie skuteczne jak wankomycyna, np. w leczeniu zakażeń skóry i tkanek miękkich.