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Review

Oxazolidinones: a novel class of antibiotics

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Abstract. Oxazolidinones are a novel class of synthetic antimicrobial agents which have now entered phase III clinical trials. The most promising feature of these compounds is their oral activity against multidrug-resistant Gram-positive bacteria which have created tremendous therapeutic problems in recent years. In addition, development of resistance in vitro has so far remained below detectable levels. Different from many antibacterial agents used in the treatment of human infections, oxazolidinones do not block bacterial protein synthesis at the level of polypeptide chain elongation but rather seem to interfere with initiation of translation. Both binding of formylmethionine-transfer RNA to initiation complexes as well as release of formylmethionine-puromycin from initiation complexes have been reported to be targets for oxazolidinones. The major binding sites of oxazolidinones are the large (50S) ribosomal subunits.

Key words. Oxazolidinone; antibiotic; eperezolid; linezolid; translation initiation; Gram-positive bacteria; 50S ribosomal subunits; multidrug resistance.

Structure of oxazolidinones

Aryl-oxazolidinones were first described by E. I. du Pont de Nemours and Co. in 1987 as a novel class of synthetic antimicrobial agents [1]. The first representative, DuP 721 (fig. 1), showed promising pharmacological properties such as its oral activity against multidrug-resistant Gram-positive bacteria and a low occurrence of resistance development (summarised in [2]). Susceptible strains encompassed penicillin- and methicillin-resistant staphylococci as well as streptococci and enterococci, whereas little antibacterial activity against Gram-negative bacteria was found. The 50% effective dose of the orally administered DuP 721 was almost identical to that of the orally inactive, and therefore subcutaneously injected, vancomycin. DuP 721 and derivatives, however, did not advance to phase II human clinical trials. Instead, the new analogs eperezolid (PNU-100592) and linezolid (PNU-100766) were developed by Pharmacia and Upjohn (fig. 1). Linezolid has now entered phase III clinical testing and is used for the treatment of infections caused by both susceptible and antibiotic-resistant Gram-positive bacteria. (Azolylphenyl)oxazolidinones, in which the morpholine ring of linezolid is replaced with five-membered-ring heterocyclics containing nitrogen and sulfur atoms, are new developments with promisingly low minimal inhibitory concentrations towards susceptible bacteria [3–5]. Derivatives such as prodrugs of eperezolid with improved water solubility for intravenous administration and other analogs characterized by a potent antimycobacterial activity have also been developed and are being tested [6, 7].

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Oxazolidinones inhibit translation initiation

Initial studies designed to elucidate the mode of action of oxazolidinones were performed with DuP 721 [8, 9]. This compound was shown to inhibit protein synthesis in whole cells of Gram-positive (*Bacillus subtilis*) bacteria with an IC_{50} (concentration at which 50% inhibition was achieved) of 0.9 μM [8]. Protein synthesis in Gram-negative bacteria (*Escherichia coli*), however, was affected only at higher doses ($IC_{50} = 13.8$ μM) and only when their outer membrane was rendered permeable to the drug [9]. An inhibitory effect of DuP 721 was also demonstrated in cell-free protein synthesis systems prepared both from *E. coli* and the Gram-positive *Staphylococcus carnosus* [9, 10]. Inhibition was observed only in conditions in which protein synthesis was dependent on chain initiation, i.e. only if natural messenger RNAs (mRNAs) were used as templates. This finding ruled out that polypeptide chain termination and elongation were possible targets of oxazolidinones [8, 9]. The new oxazolidinones, linezolid and eperezolid, were found to inhibit cell-free transcription/translation in an *E. coli* in vitro system at an IC_{50} of approximately 2 μM, depending on the nature and amount of mRNA used [11]. When tested against the same template, linezolid and eperezolid turned out to be considerably more active than DuP 721. Thus, with a given amount of MS2 phage RNA, translation was inhibited by 20% with 250 μM of DuP 721, whereas a 50% inhibition was observed at 20 μM eperezolid [11]. Also, with linezolid and eperezolid no blockage of poly(U)-directed translation was obtained [11], indicating that initiation of polypeptide chain synthesis was the likely target for oxazolidinones.

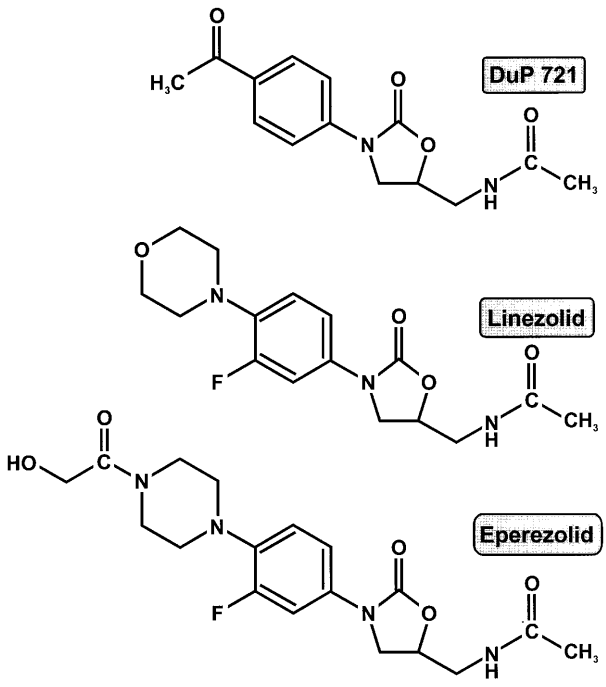

Figure 1. Chemical structures of the oxazolidinones Dup 721, linezolid and eperezolid.

Do oxazolidinones block formation of a (pre)initiation complex?

Interference of oxazolidinones with initiation of translation was investigated in considerable detail in two recent studies [10, 12]. According to a current model of translation initiation in eubacteria [13], mRNA and fMet-tRNA (formylmethionine-transfer RNA) bind in random order to 30S ribosomal subunits in the presence of initiation factors 1 and 3, giving rise to a 30S preinitiation complex. This is joined by a 50S ribosomal subunit yielding a 70S initiation complex, in which finally initiation factor 2 promotes the positioning of fMet-tRNA in the ribosomal P site. Only after having reached this stage can peptidyl transferase catalyze peptide bond formation between fMet and an acceptor substrate bound in the A site of the 70S ribosome. The latter can either be another amino acid-tRNA or puromycin.

In one set of experiments, filter binding assays were performed in which the formation of initiation complexes was dependent on fMet-tRNA, mRNA, ribosomes and initiation factors, thus faithfully reproducing the early stages of initiation of translation [10]. Moreover, when these initiation complexes were incubated with puromycin, a time-dependent release of fMet-puromycin peptide was found to occur [10], suggesting that a correct P site, accommodating fMet-tRNA in a functional manner, had in fact been formed in vitro. As expected, 100 μM aurin tricarboxylic acid, which is known to interfere with the intitiation process by inhibiting binding of mRNA to 30S ribosomal subunits [14], largely abolished binding of fMet-tRNA to ribosomes in this assay system [10]. In contrast, DuP 721 at 230 μM did not inhibit binding of fMet-tRNA to salt-extracted *Staphylococcus carnosus* ribosomes in the presence of a natural mRNA from *S. hyicus* and *E. coli* initiation factors but exhibited a 50% inhibition of the release of fMet-puromycin [10]. These findings were recently challenged by Swaney et al., reporting that linezolid inhibits binding of fMet-tRNA to *E. coli* 30S ribosomal subunits and 70S ribosomes at IC_{50}'s of 110 and 130 μM, respectively [12]. These authors used kasugamycin as a reference inhibitor to inhibit binding of fMet-tRNA to the 30S preinitiation complexes [14]. They also found interference of linezolid with the formation of 70S initiation complexes when 70S ribosomes from *S. aureus* were used. Inhibition was observed with

both AUG and synthetic mRNAs as templates. It was, however, not dependent on the presence of initiation factors. The different influences of oxazolidinones on the formation of initiation complexes described in these two studies is currently not clear. Based on the much higher effective inhibitory concentrations of DuP 721, it was concluded that millimolar concentrations of DuP 721 might have been required to see a similar inhibition of initiation complex formation as with linezolid [12]. This argument, however, ignores the fact that DuP 721 did exhibit a 50% inhibition of the release of fMet-puromycin at a concentration which showed no influence on binding of fMet-tRNA to ribosomes [10].

Do oxazolidinones directly or indirectly affect the peptidyl transferase reaction?

DuP 721 was found to inhibit the puromycin-mediated release of fMet from initiation complexes with an IC_{50} of about 215 μM [10]. No inhibitory effect, however, was observed for linezolid and eperezolid in a concentration range of 0.3–1 mM [15]. In the latter studies, AUG was used as a template as well as ribosomes prepared from *E. coli*. It is therefore possible that more natural templates than AUG are required to detect a similar inhibition of fMet-puromycin liberation by linezolid and eperezolid, as found with DuP 721. Most important, however, this inhibitory effect of oxazolidinones appears to be obscured when ribosomes prepared from *E. coli* are used. Burghardt et al. [10] describe that DuP 721 has a much more pronounced inhibitory action on 50S ribosomal subunits from Gram-positive bacteria than on those from *E. coli* (see below).

The release of ribosome-associated fMet by puromycin has two prerequisites: (i) fMet-tRNA must be correctly positioned in the P site of the 70S initiation complex and (ii) the covalent linkage formed between fMet and puromycin depends on an active peptidyl transferase. Theoretically, the observed interference of DuP 721 with the release of fMet-puromycin could therefore be due to a blockage of the peptidyl transferase activity associated with 50S ribosomal subunits. However, the reported elongation of in vivo assembled polysomes despite the presence of DuP 721 [9] and linezolid and eperezolid [11] is not consistent with the peptidyl transferase being a likely target for oxazolidinones.

Oxazolidinones interact with 50S ribosomal subunits

While the aforementioned investigations aimed at identifying functional targets of oxazolidinones, a body of evidence has now accumulated showing that the 50S ribosomal subunits represent a binding site for oxazolidinones. First, an eperezolid-resistant mutant of *S. aureus* was isolated by a spiral plating technique [16], and the mutant phenotype could be conferred to a transcription/translation assay solely by the ribosomal subfraction of the mutant strain [16]. In accordance, mutant ribosomes bind less eperezolid than those of a wild-type strain [16]. Lin et al. directly demonstrated binding of radioactively labeled eperezolid to 50S subunits of *E. coli* ribosomes with a K_d of 20 μM, and this association was competitively inhibited by chloramphenicol and lincomycin [15]. Consistent with this finding, the eperezolid-resistant mutant strain showed a decreased sensitivity also towards chloramphenicol and lincomycin [16]. Interaction of DuP 721 with 50S ribosomal subunits can also be concluded from the finding that the moderate inhibition by DuP 721 of the puromycin-induced release of fMet from *E. coli* initiation complexes was markedly enhanced upon replacement of the 50S ribosomal subunits from *E. coli* with those of the Gram-positive origin [10]. Furthermore, the inhibitory effect of oxazolidinones on the release of fMet-puromycin was maintained after isolating by centrifugation 50S ribosomal subunits that had been preincubated with DuP 721 [10]. Recently, new mutant strains of *S. aureus* and *Enterococcus faecalis* were isolated which exhibited resistance towards DuP 721, linezolid and eperezolid. The majority of the mutant strains revealed discrete nucleotide exchanges in the 23S RNA of their 50S ribosomal subunits. The mutations discovered cluster in the peptidyl transferase domain of the 23S RNA [17]. In contrast, the reported interference of linezolid with the association between fMet-tRNA and 30S preinitiation complexes [12] would actually invoke a binding of the drug to 30S subparticles. This, however, has not been verified experimentally [15]. Thus, oxazolidinones exert their inhibitory action on translation by docking to the 50S ribosomal subunits.

Do oxazolidinones discriminate between Gram-positive and Gram-negative initiation?

An open question remains whether oxazolidinones harbour different affinities for translation initiation complexes of Gram-positive and Gram-negative bacteria. The observed inhibition by DuP 721 of the puromycin-caused release of fMet was much more pronounced with *S. carnosus* ribosomes and initiation factors than with those of *E. coli* [10]. The low sensitivity of 70S *E. coli* ribosomes towards oxazolidinones could almost completely be raised to the level seen with *S. carnosus* 70S ribosomes by mixing 30S *E. coli* subparticles with 50S ribosomal subunits of *S. carnosus*, indicating a higher affinity of DuP 721 for the large ribosomal subunits of Gram-positive bacteria. In contrast, similar inhibitory concentrations of linezolid and eperezolid were reported

for *E. coli* and *S. aureus* ribosomes and mRNAs from both origins for the fMet-tRNA binding assay [12].

The true target of oxazolidinones, an evaluation of the data available

Although several detailed studies dealing with the mechanism of the action of oxazolidinones have now been published, a unique action common to all tested members of this group of antibacterial drugs is still elusive. Several steps of initiation have definitely been excluded as targets. Thus, the action of oxazolidinones does not depend on an intact Shine-Dalgarno sequence [10]. Oxazolidinones do not affect synthesis of fMet-tRNA [11] and formation of the complex between initiation factor 2 and fMet-tRNA [12], and they do not interfere with the binding of synthetic mRNA to *E. coli* 70S ribosomes [12]. Whereas a number of different experimental approaches have consistently shown interaction of all tested oxazolidinones with 50S ribosomal subunits, a discrepancy exists as to which of the single initiation events is directly inhibited. Both binding of fMet-tRNA to 30S and 70S initiation complexes as well as release of bound fMet by puromycin have been found to be affected by the presence of oxazolidinones. In principle, there is no a priori argument against a dual mode of action of these drugs. However, both sets of investigations [10–12] while demonstrating one mode of inhibition, i.e. fMet-tRNA binding versus fMet-puromycin formation, each disprove the other. It is unlikely that the discrepancy is due to concentration effects (see above). Not to be excluded is the theoretical possibility that the individual compounds used in these investigations, DuP 721 versus linezolid/eperezolid, have different effects due to their different chemical structures. DuP 721 could thus be a representative of oxazolidinones with an inherent inhibition of the fMet-puromycin release. In linezolid/eperezolid, this activity might be overwhelmed by the inhibition of fMet-tRNA binding promoted by substituents of the chemical backbone unique to linezolid/eperezolid. On the other hand, contradictory findings could also be the result of different assay conditions. Initiation is a rather dynamic complex of events only part of which might be reproduced by a given in vitro assay. Thus, in one set of conditions, binding of fMet-tRNA to initiation complexes was independent of the physiologically necessary intiation factors, and this activity could be inhibited by oxazolidinones [12], whereas in initiation assays validated by their dependence on initiation factors and their leading to functional P-sites [10] oxazolidinones had no such inhibitory effect. To finally settle this issue, however, all three compounds, DuP 721, linezolid and eperezolid, have to be tested under the same experimental conditions.

In contrast to these open questions, involvement of the 50S ribosomal subunits in the mediation of the inhibitory effects of oxazolidinones on translation initiation has unanimously been reported. One of the obvious interpretations would be that oxazolidinones interfere with the assembly of the P site as one of the final steps in initiation, which among other events involves a functional association of 50S subunits with 30S preinitiation complexes. Binding of the drug to the 50S subunit near the interface with the 30S subparticle might distort the P site and thereby interrupt translation before the first elongation step can occur.

Activity spectrum of oxazolidinones

Oxazolidinones exert a predominantly bacteriostatic effect on a variety of clinically important human pathogens when tested both in vitro against bacterial clinical isolates as well as in experimental infections in mice. A recent summary of the results obtained with linezolid and eperezolid together with the relevant literature is given in [7]. Linezolid and eperezolid are active against sensitive and multidrug-resistant Gram-positive organisms, such as *Staphylococcus* spp., including *S. aureus* und *S. epidermidis*, *Streptococcus* spp., including *S. pneumoniae* and *S. pyogenes*, *Enterococcus* spp., including *E. faecalis* and *E. faecium*, *Corynebacterium* spp., *Mycobacterium* spp., including *M. tuberculosis*, *Actinomyces* spp., *Clostridium* spp., *Lactobacillus* spp., *Peptostreptococcus* spp., *Propionibacterium* spp., *Haemophilus influenzae*, *Listeria monocytogenes*, *Moraxella catarrhalis* [18, 19]. In addition, they show activity against a variety of anaerobic, Gram-negative bacteria such as *Bacteroides* spp., *Bilophila wadworthia*, *Fusobacterium* spp., *Mobiluncus* spp., *Prevotella* spp., *Porphyromonas asaccharolyticus*, *Veillonella alcalescens* [19]. The minimal inhibitory concentrations of eperezolid and linezolid at which 90% of the bacterial isolates were killed (MIC_{90}) were generally in the range of 2–4 μg/ml. The effective doses required to cure 50% of infected animals (ED_{50}) were in the range of 2–8 mg/kg body weight. Both values compare favorably with vancomycin, where applicable. The required MICs and EDs of eperezolid and linezolid were usually in the same range, with eperezolid being often twice as active.

Linezolid also proved to be active in in vitro assays, with 148 clinical isolates of *Pasteurella* spp. obtained from animal bite-wound infections [20]. Furthermore, activity of linezolid was recently described against the *Mycobacterium avium* complex which is associated with disseminated infection in AIDS patients where it causes therapeutic problems due to the rapid development of resistance [21].

Initial results of linezolid given to patients were reported [22]. A preliminary evaluation indicates that linezolid is a viable option for patients with infections caused by multidrug-resistant Gram-positive organisms or for those with intolerance or nonresponsiveness to other potentially effective treatments.

Metabolism of oxazolidinones

Linezolid is subject to renal tubular reabsorption and is excreted primarily in urine as the parent drug or as carboxylic acid metabolites that have low antibacterial potency [23]. Thus there is only little loss of bioavailable drug due to an inactivating metabolism. High levels of linezolid are reported to be achieved in sweat and other, such as nasal, secretions [24].

Adverse drug reactions

Several reports on phase I and II clinical studies state that linezolid in general is well tolerated, with gastrointestinal disturbances (diarrhea, nausea and tongue discoloration) being the most common adverse events observed in 8–33% of the treated subjects [7, 22, 24]. As a chemical class, oxazolidinones inhibit monoamine oxidase (MAO) and thereby increase the level of biogenic amines in the central nervous system. As such they are used in the treatment of mental depression. Linezolid, however, is only a weak, reversible inhibitor of human monoamine oxidase A in vitro, and no indication for MAO A inhibition has been obtained in phase I and II clinical trials [25].

Resistance

Oxazolidinones have been successfully used to inhibit bacterial strains which were resistant amongst others to methicillin, vancomycin, penicillin, rifampin and other antitubercular agents [7, 18]. The lack of cross-resistance with other, contemporary antibiotics is explained by the unique mechanism of action of the oxazolidinones. The incidence of the development of spontaneous resistance to twice the MIC (3–13 μg/ml) of linezolid and eperezolid in 12 strains of staphylococci was below detectable limits [26]. In an eperezolid-resistant mutant isolated by a spiral plating technique, the MIC increased from 2 to 32 μg/ml.

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