Abstract: P754

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AZD2563, a new oxazolidinone: bactericidal activity and synergy studies with gentamicin and vancomycin against staphylococci and streptococci

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Background:
Emerging resistances among Gram-positive organisms has limited treatment options and stimulated development of new antimicrobial classes such as oxazolidinones. This report summarizes comparative cidal activity and synergy studies of AZD2563 and linezolid (LZD) using nonpneumococcal streptococci and staphylococci.
Methods:
Kill-curves were determined for AZD2563 at concentrations two-, four-, and eight-fold the measured MIC. Drug interactions (synergy) were evaluated also by kill-curve techniques using AZD2563 (4× MIC) combined with subinhibitory concentrations of either gentamicin (MIC/4) or vancomycin (MIC/4). Tested organisms were: *S. aureus* (one methicillin-susceptible [MS], two methicillin-resistant [MR]), CoNS (one MS, one MR), viridans gr. (three; penicillin-susceptible, -intermediate, -resistant) and *β*-hemolytic streptococci (two; gr. A and G; macrolide-susceptible and -resistant).
Results:
Consistent patterns of cidal activity was observed for both organism groups and the two oxazolidinones (LZD by earlier experiments): (1) static action; and (2) 30% of strains showing a modest concentration-dependent inhibition. AZD2563 plus vancomycin combinations were indifferent and remained static versus both genus groups. Also static action and indifferent interactions were noted for AZD2563 plus gentamicin versus the five staphylococci tested. In contrast, all streptococci were rapidly killed (>3 log 10 cfu killing; cidal action) by AZD2563 plus gentamicin. No antagonism was observed and AZD2563 findings were the same as prior experience for LZD.
Conclusions:
AZD2563, a long-acting oxazolidinone with once-daily dosing, was observed to be predominantly static in action, and generally was indifferent when combined with an aminoglycoside or glycopeptide. Cidal effects were only noted for streptococci when AZD2563 was combined with gentamicin. AZD2563 appears to possess oxazolidinone class characteristics (like LZD) and PK/PD features favorable to continued development.

Poster No. P754

AZD2563, a new oxazolidinone: bactericidal activity and synergy studies with gentamicin and vancomycin against staphylococci and streptococci

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Introduction

- Antimicrobial resistance among Gram-positive cocci has necessitated the rapid development of novel antimicrobial classes such as the oxazolidinones. This class has a specific ribosomal target and has proven to be effective (*in vitro* and *in vivo*) against isolates of Gram-positive species that possess resistances to other antimicrobial agents. The very rare occurrence of oxazolidinone resistance has been reported but only after long-term exposure to the clinically used compound linezolid (LZD), usually in at-risk patients with infected in-dwelling devices.

- AZD2563 is a new long-acting oxazolidinone, with some in-vitro potency advantages over the currently available oxazolidinone, LZD. This report summarises the results of AZD2563 tested against selected strains of staphylococci and streptococci that exhibit various resistance patterns to β-lactam, macrolide and fluoroquinolone antimicrobial agents using kill-curve methods. AZD2563 was also combined with gentamicin or vancomycin to assess possible enhanced activity or antagonism at concentrations expected to be achieved in humans.

Methods

- The organisms were chosen from nine medical centres in North America (Canada, two strains; USA, seven strains; ATCC control, one strain) as follows: oxacillin-resistant coagulase-negative staphylococci (CoNS) (two strains, one identified as *Staphylococcus warneri*); oxacillin-susceptible *Staphylococcus aureus* control strain ATCC 29213; oxacillin-resistant *S. aureus* (two strains); viridans group streptococci (VgS) (three strains, one identified as *Streptococcus mitis*) with penicillin-sensitive and penicillin-resistant patterns, and various erythromycin and clindamycin resistance levels; *Streptococcus pyogenes* (one strain); and group G β-haemolytic streptococci (one strain having resistance to levofloxacin).

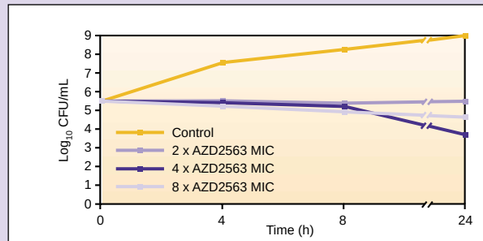
- Each strain was tested against three concentrations of AZD2563 at levels two-, four-, and eight-fold the MIC over 24 h using a kill-curve and MIC methods described by the National Committee for Clinical Laboratory Standards (NCCLS). In addition, vancomycin or gentamicin at a concentration equal to MIC/4 was combined with AZD2563 at the MIC x 4. The killing characteristics of the combination were compared to those of the individual agents tested at the same concentrations. The initial inoculum was targeted at 5.0 x 10^5 CFU/mL.

- Significant bactericidal activity was defined as a reduction of ≥3 $\log_{10}$ CFU/mL of the initial inoculum after ≤24 h incubation at 35ºC. Lesser degrees of bacterial killing were considered as bacteriostatic activity. Synergy between drugs was defined as a killing level of ≥2 $\log_{10}$ CFU/mL, greater than the rate for the best single oxazolidinone agent (AZD2563 at MIC x 4). LZD was used as a class and historic control.

Results

- In bactericidal kill-curve studies of staphylococci (Table 1), AZD2563 showed static activity with the reduction in the initial inoculum ranging from 0 to 2 $\log_{10}$ CFU/mL. Only one strain (CoNS 14-2091D) demonstrated a modest degree of concentration-dependent killing while all other strains showed no significant differences between the killing effects at two- to eight-fold the MIC (Figure 1).

Figure 1. Three concentrations (2 x, 4 x and 8 x MIC) of AZD2563 tested against an oxacillin-susceptible *S. warneri* strain (15-2662A).



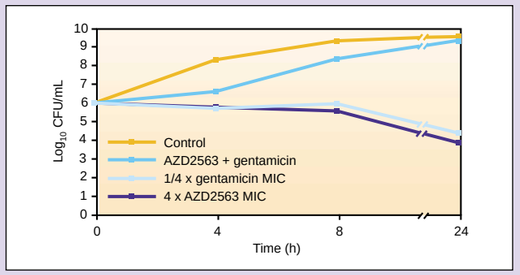
- When AZD2563 was combined with either gentamicin or vancomycin at subinhibitory concentrations (MIC/4), indifferent activity was observed for all five tested staphylococci and no enhanced bactericidal action or antagonism was demonstrated (Table 1 and Figure 2).

Table 1. Results of timed kill-curve experiments using AZD2563 alone and combined with either gentamicin or vancomycin tested against staphylococci.

	Bactericidal result[a]	Bactericidal/interaction category[b]	
Organism	**Alone**	**+ gentamicin[c]**	**+ vancomycin[c]**
CoNS (14-2091D)	Static[d]	Static/indifferent	Static/indifferent
CoNS (15-2662A)	Static	Static/indifferent	Static/indifferent
S. aureus ATCC 29213	Static	Static/indifferent	Static/indifferent
S. aureus (1-253A)	Static	Static/indifferent	Static/indifferent
S. aureus (19-487A)	Static	Static/indifferent	Static/indifferent

[a]Bactericidal (cidal) activity was defined as a ≥3 $\log_{10}$ CFU reduction in the initial inoculum at ≤24 h
[b]The interactive category was synergy if ≥2 $\log_{10}$ CFU/mL greater killing was observed when combined with co-drug (gentamicin or vancomycin at a MIC/4)
[c]Co-drugs tested at 1/4 the documented MIC and combined with three different inhibitory concentrations of AZD2563
[d]A modest concentration-dependent decrease in the initial inoculum was observed (one of five strains, only)

Figure 2. Combination effects of AZD2563 (4 x MIC) and gentamicin (MIC/4) tested against an oxacillin-resistant *S. aureus* strain (01-253A).



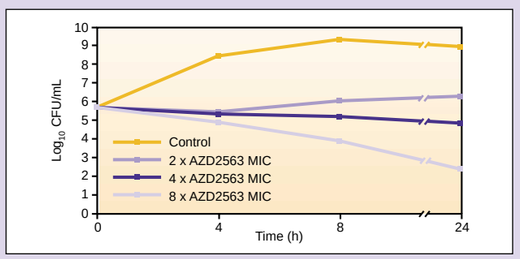
- As observed with the staphylococci, AZD2563 showed bacteriostatic action against streptococci (Table 2) but significant reductions in the initial inocula were documented (1 to 2.8 $\log_{10}$ CFU/mL). However, this degree of activity fell short of the definition of bactericidal effects (Figure 3), although a modest concentration-dependent killing was noted for two strains (Table 2).

Table 2. Results of timed kill-curve experiments using AZD2563 alone and combined with either gentamicin or vancomycin tested against streptococci.

	Bactericidal result[a]	Bactericidal/interaction category[b]	
Organism	**Alone**	**+ gentamicin[c]**	**+ vancomycin[c]**
VgS (63-11460C)	Static[d]	Cidal/synergy	Static/indifferent
VgS (11-8649A)	Static[d]	Cidal/synergy	Static/indifferent
S. mitis (38-5584A)	Static	Cidal/synergy	Static/indifferent
S. pyogenes (35-356A)	Static	Cidal/synergy	Static/indifferent
β-haemolytic streptococci, group G (15-2668D)	Static	Cidal/synergy	Static/indifferent

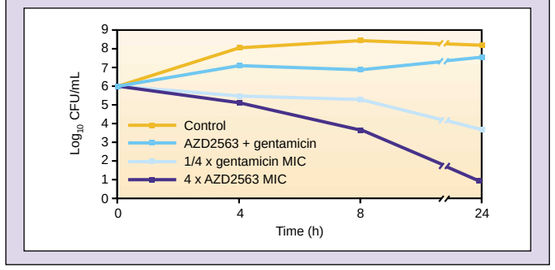
[a]Bactericidal (cidal) activity was defined as a ≥3 $\log_{10}$ CFU/ml reduction in the initial inoculum at ≤24 h
[b]The interactive category was synergy if ≥2 $\log_{10}$ CFU/mL greater killing was observed when combined with co-drug (gentamicin or vancomycin at a MIC/4)
[c]Co-drugs tested at 1/4 the documented MIC and combined with three different inhibitory concentrations of AZD2563
[d]A modest concentration-dependent decrease in the initial inoculum was observed (one of five strains, only)

Figure 3. Three concentrations (2 x, 4 x and 8 x MIC) of AZD2563 tested against a penicillin-resistant VgS strain (63-11460C)



- No enhanced antimicrobial action was noted for AZD2563 combined with vancomycin (Table 2). In contrast, subinhibitory levels of gentamicin markedly increased bactericidal activity of AZD2563 (Figure 4) for all streptococcal strains tested.

Figure 4. Combination effects of AZD2563 (4 x MIC) and gentamicin (MIC/4) tested against a penicillin-sensitive, macrolide-susceptible *S.mitis* (38-5584A).



- All kill-curve results for LZD (control and prior experience) were similar to those listed for AZD2563.
- The MIC values for AZD2563 against the staphylococci and streptococci ranged from 0.5 to 1 µg/mL, usually equal to or two-fold lower than those of LZD.

Conclusions

- The current results demonstrate antimicrobial class (oxazolidinone) characteristics of AZD2563 at least equal to those of LZD.[1] These findings warrant continued in-vivo development and expansion of AZD2563 studies for the therapy of infections in humans.
- This recommendation would also be supported by the favourable predictions of an extended serum elimination half-life[2] and pharmacokinetic/pharmacodynamic features consistent with other oxazolidinones.[3]

Acknowledgements

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