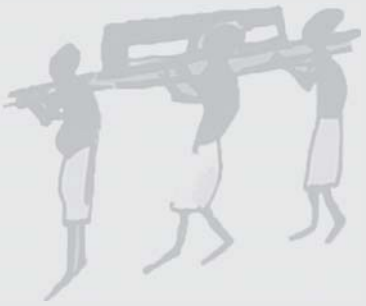
Linezolid in multidrug-resistant tuberculosis

Bolhuis, Mathieu



Chapter 2

Pharmacokinetic drug interactions of antimicrobial drugs: a systematic review on oxazolidinones

M.S. Bolhuis, P.N. Panday, A.D. Pranger,
J.G.W. Kosterink, and J.W.C. Alffenaar

Adapted from: Bolhuis MS, Panday PN, Pranger AD, Kosterink JGW, Alffenaar J-W. Pharmacokinetic Drug Interactions of Antimicrobial Drugs: A Systematic Review on Oxazolidinones, Rifamycines, Macrolides, Fluoroquinolones, and Beta-Lactams. *Pharmaceutics*. **2011**; 3(4):865-913.

ABSTRACT

Like any other drug, antimicrobial drugs are prone to pharmacokinetic drug interactions. These drug interactions are a major concern in clinical practice as they may have an effect on efficacy and toxicity. The original article provides an overview of all published pharmacokinetic studies on drug interactions of the commonly prescribed antimicrobial drugs oxazolidinones, rifamycines, macrolides, fluoroquinolones, and beta-lactams, focusing on systematic research. However, in this chapter we present the data of the oxazolidinones. We describe drug-food and drug-drug interaction studies in humans, affecting antimicrobial drugs as well as concomitantly administered drugs. Since knowledge on mechanisms is of paramount importance for adequate management of drug interactions, the most plausible underlying mechanism of the drug interaction is provided when available. This overview can be used in daily practice to support management of pharmacokinetic drug interactions of antimicrobial drugs.

INTRODUCTION

Antimicrobial drugs manifest a wide variety of drug interactions, which can differ greatly in extent of severity and clinical relevance. Not only co-medication, but also food and herbal medicine can interact with antimicrobial drugs and vice versa. The nature of these interactions can be of pharmacodynamic (PD) and/or pharmacokinetic (PK) origin.

A PD interaction consists of an alteration of a pharmacological response, through either agonism or antagonism, without affecting the kinetics of the drug. In cases of PD interactions physicians are advised to re-evaluate the benefit-risk ratio of the co-prescribed drug for each individual patient (1). PK interactions result in an altered disposition of a drug within a patient and can take place at the level of each of four processes influencing drug exposure, i.e. absorption, distribution, metabolism, and excretion, commonly described by the acronym ADME. Historically the relevance of drug distribution, particularly of protein binding, has been over-emphasized in the assessment of drug interactions, and nowadays the main cause of drug-drug interactions has been recognized to be modulation of the activity, i.e. inhibition or induction, of cytochrome P450 (CYP) enzymes and transporters.

Clinicians, prescribing the drug and pharmacists — often involved in medication review, therapeutic drug monitoring (TDM), or consultation on drug choice or dose — should be aware of clinically relevant interactions between antimicrobial drugs and co-medication, herbal medicine, and/or food in order to avoid toxicity, side effects, or inadequate treatment. PK interactions are in most cases manageable by adjusting the dose and by monitoring of drug levels (TDM) or vital signs. This review article will address PK interactions of antimicrobial drugs. The scope of the original article is to present an overview of PK studies on drug-drug and drug-food interactions of commonly prescribed antimicrobial drugs in daily clinical practice, i.e. oxazolidinones, rifamycines, macrolides, fluoroquinolones, and β-lactam antimicrobial drugs. In this chapter we present the data of the oxazolidinones.

EXPERIMENTAL SECTION

The Pubmed database was searched for PK interaction studies on drug-drug and drug-food interactions of antimicrobial drugs (Figure 1). The search was limited through the following selections: "Humans", "Clinical Trial", "Randomized Controlled Trial", "Comparative Study", and "Controlled Clinical Trial". Only articles written in English were included. Per group of antimicrobial drugs, a separate search was conducted consisting of the name of the group,

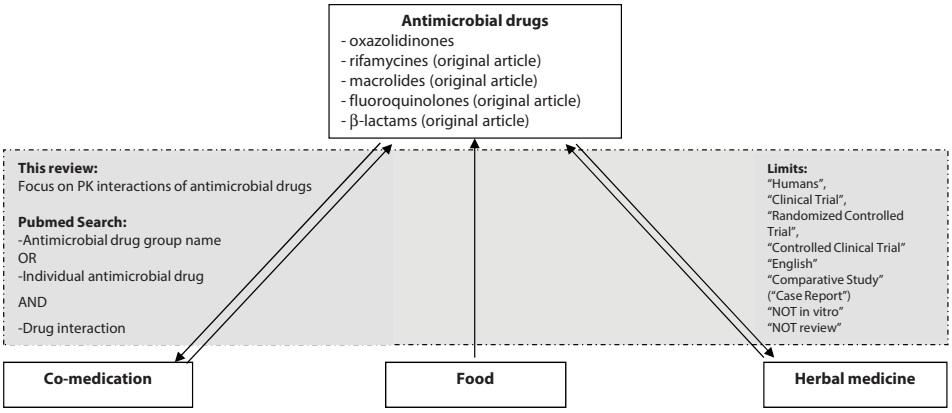


Figure 1 Scope of the original review and summary of the experimental section.
The adapted version of the review, presented in Chapter 2, focuses on interactions with drugs of the oxazolidinone group. The gray area symbolizes the focus of this review, i.e. PK drug interactions of antimicrobial drugs.

the name of the individual drugs, and the term "drug interaction". When the Medical Subject Heading (MeSH) term "drug interaction" was used, indented terms such as "Herb-Drug Interaction" and "Food-Drug Interaction" were also searched. The search terms "NOT *in vitro*" and "NOT review" were added since this review focuses on original articles of studies with human subjects. Summaries of product characteristics or package leaflets were not consulted since these sources will only present a snapshot of the available information and will therefore not give a good overall impression of their use in clinical practice.

When a search resulted in only a few results, the query was expanded with the criterion "Case Report" and explicitly marked as such in this review since its contents have to be interpreted carefully because of the limited level of evidence.

All searches were conducted in March and April 2011. The relevant results were described per group of antimicrobial drugs. For each group, the drug interactions are divided into interactions affecting the antimicrobial drugs and interactions effecting the co-medication. The drug that is affected is identified by the term '*victim*' and the drug that causes the effect by '*perpetrator*'. A table summarizing the most important drug interactions is provided for each group of antimicrobial drugs.

Since the scope of the original article is broader than the scope of this thesis, an adapted version is included. In this chapter, we only presented the drug interactions with drugs of

the oxazolidinone group. Both interactions where the drug is the *victim* or the *perpetrator* are included in this chapter.

RESULTS AND DISCUSSION

Oxazolidinones

At this moment linezolid (LZD) is the only oxazolidinone authorized by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA). The number of properly designed drug-interaction studies with oxazolidinones is limited and the underlying mechanisms of some drug interactions are not yet fully elucidated. Furthermore, there is a lack of reviewed publications on drug interactions of newer compounds such as PNU-100480, posizolid (AZD2563), radezolid (RX-1741), torezolid and others, several of which are still being studied in phase I, II or III clinical research. A summary of LZD PK interactions is provided in Table 1.

Oxazolidinones as victims

Antimicrobial drugs: In an open-label comparative study of 8 healthy volunteers receiving 600 mg of both LZD and rifampicin (RIF) intravenously, a reduction of LZD plasma concentration was observed (2). An *in vitro* study demonstrated that LZD is not detectably metabolized by human CYP and did not inhibit the activities of human CYP isoforms 1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 (3). Based on these observations along with the fact that RIF is a well-known P-gp inducer, the authors suggest LZD to be a P-gp substrate (2). This hypothesis was further supported by a case report of a patient with MDR-TB. This patient

Table 1 Summary of interactions of the oxazolidinone LZD with enzyme systems and/or food

	Absorption		Metabolism:	Excretion:	
	Fat meal	Antacids	CYP	P-gp	Reactive Oxygen Species
LZD	↓	=	-	S*	=

Downwards arrow (↓) indicates inhibition resulting in <50% decrease of AUC. "S" indicates the drug being a substrate, and "=" interaction is not relevant.
* Mostly based on case reports: in need of further research.
Note: Systematic research on newer compounds such as PNU-100480, posilozid (AZD2563), radezolid (RX-1741), torezolid, and others is not available.
Since there were no interactions affecting displacement / distribution this process was not included in the table.

received LZD and clarithromycin (CLR), a potent inhibitor of P-gp and a well-known CYP3A4 inhibitor. It was shown that co-administration of CLR with LZD resulted in a markedly increased LZD AUC (4).

The combination of aztreonam and LZD in an open-label cross-over study that included 13 healthy volunteers resulted in a statistically significant, although probably not clinically relevant increase of LZD AUC of approximately 18% (5). The authors suggest that the mechanism for this interaction is partly explained by a common elimination pathway, i.e. renal excretion. However, the definite mechanism remains unknown.

Food and antacids: In a two-phase single-dose open-label cross-over study of 12 healthy volunteers, a fatty meal caused a small but statistically significant reduction of mean LZD plasma concentration (6). The C_{max} decreased by 23% and t_{max} increased from 1.5 hours to 2.2 hours, probably due to prolonged gastric residence time. An open-label cross-over study in 28 healthy volunteers tested the hypothesis that a disturbed balanced of reactive oxygen species might lower the *in vivo* clearance of LZD by supplementing dietary antioxidants, i.e. vitamin C and E, but concluded there was no significant effect on LZD C_{max} and AUC (7). This is in line with current literature indicating that supplemented antioxidant vitamins have subtle effects on *in vivo* reactive oxygen species balance (7). A randomized open-label cross-over study of 17 healthy volunteers showed that the antacid Maalox® has no effect on the PK of LZD (8).

Oxazolidinones as perpetrators

Serotonin reuptake inhibitors: A single randomized controlled trial (RCT) (9) and several case reports (10-23) describe LZD's potential for drug interactions due to its reversible monoamine oxidase-A inhibitor activity. In case reports, serotonic toxicity was observed after co-administration of LZD with drugs that influence serotonin levels like selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, monoamine oxidase inhibitors, and other serotonergic agents such as citalopram, diphenhydramine, duloxetine, fluoxetine, paroxetine, sertraline, trazodone, and venlafaxine. However, one case report presented a depressed patient receiving co-administered mirtazepine and LZD being treated successfully without toxic signs (24). The RCT focused on the PK interaction of LZD with the over the counter (OTC) sympathomimetic drugs pseudoephedrine and phenylpropanolamine. A slight increase in blood pressure and a minimal effect on the PK of both co-administered drugs was found in 42 healthy individuals (9). The serotonin reuptake

inhibitor dextromethorphan was co-administered with LZD with no clinical effect: only a slight decrease of dextrorphan, the primary metabolite of dextromorphan, was observed (9).

CONCLUSIONS

The original article, presenting an overview of PK studies on drug-drug and drug-food interactions of macrolides, fluoroquinolones, rifamycines, oxazolidinones, and β-lactam antimicrobial drugs, can be used by physicians and pharmacists in daily practice to assist in preventing and managing PK drug interactions of antimicrobial drugs. This chapter, adapted from the original article, provides an overview of drug-interactions of oxazolidinones. The interactions presented vary in extent of severity and clinical relevance. Potential clinical problems can range from therapeutic failure due to low drug exposure to adverse events due to toxic drug concentrations. PK interaction studies in both patients and healthy volunteers are included. It has been demonstrated that PK characteristics of drugs can differ between healthy volunteers and patients (25). As a result of an underlying disease, physiological changes can influence drug PK, although the mechanism remains to be elucidated. In many critically ill patients extracellular fluids have increased, possibly resulting in a higher volume of distribution that might affect PK (26). One should bear in mind that findings in PK interaction studies performed in healthy volunteers might not be observed in clinical practice in specific patient populations.

Furthermore, PK interaction studies administering both single doses and multiple doses to study subjects were used in this overview. It need hardly be mentioned that multiple-dose studies will reflect best clinical practice. This is particularly true for PK interaction studies with biotransformation as possible underlying mechanism since induction of enzyme systems might require days to 2 – 3 weeks to develop fully (27). The interaction may also persist at a similar length of time when the inducing agent is stopped. Unlike induction, inhibition of enzyme systems can occur within 2 – 3 days (27).

Physicians and pharmacists should also be aware of the fact that some of the included studies used doses that are higher or lower than those used in daily clinical practice. Especially in non-linear PK, this makes PK interactions difficult to interpret.

Finally, drug interactions not only occur when two or more interacting drugs are administered, but can also surface when one of the interacting drugs is halted. Most electronic health record systems include a program that can routinely check for drug-drug interactions and

could assist in preventing drug interaction-related adverse events. However, these programs rarely check for interactions that can occur when one of the interacting drugs is halted. Multidisciplinary vigilance of physicians, pharmacists, and other health care professionals remains necessary for adequate management of drug-interactions of antimicrobial drugs.

REFERENCES

1. **Bruggemann, R. J. M., J. W. Alffenaar, N. M. A. Blijlevens, E. M. Billaud, J. G. Kosterink, P. E. Verweij, and Burger.** 2008. Pharmacokinetic drug interactions of azoles. Curr Fungal Infect Rep. **2:**20-27.
2. **Egle, H., R. Trittler, K. Kummerer, and S. W. Lemmen.** 2005. Linezolid and rifampin: Drug interaction contrary to expectations? Clin. Pharmacol. Ther. **77:**451-453.
3. **Wynalda, M. A., M. J. Hauer, and L. C. Wienkers.** 2000. Oxidation of the novel oxazolidinone antibiotic linezolid in human liver microsomes. Drug Metab. Dispos. **28:**1014-1017.
4. **Bolhuis, M. S., R. van Altena, D. R. Uges, T. S. van der Werf, J. G. Kosterink, and J. W. Alffenaar.** 2010. Clarithromycin significantly increases linezolid serum concentrations. Antimicrob. Agents Chemother. **54:**5418-5419.
5. **Sisson, T. L., G. L. Jungbluth, and N. K. Hopkins.** 1999. A pharmacokinetic evaluation of concomitant administration of linezolid and aztreonam. J. Clin. Pharmacol. **39:**1277-1282.
6. **Welshman, I. R., T. A. Sisson, G. L. Jungbluth, D. J. Stalker, and N. K. Hopkins.** 2001. Linezolid absolute bioavailability and the effect of food on oral bioavailability. Biopharm. Drug Dispos. **22:**91-97.
7. **Gordi, T., L. H. Tan, C. Hong, N. J. Hopkins, S. F. Francom, J. G. Slatter, and E. J. Antal.** 2003. The pharmacokinetics of linezolid are not affected by concomitant intake of the antioxidant vitamins C and E. J. Clin. Pharmacol. **43:**1161-1167.
8. **Grunder, G., Y. Zysset-Aschmann, F. Vollenweider, T. Maier, S. Krahenbuhl, and J. Drewe.** 2006. Lack of pharmacokinetic interaction between linezolid and antacid in healthy volunteers. Antimicrob. Agents Chemother. **50:**68-72.
9. **Hendershot, P. E., E. J. Antal, I. R. Welshman, D. H. Batts, and N. K. Hopkins.** 2001. Linezolid: pharmacokinetic and pharmacodynamic evaluation of coadministration with pseudoephedrine HCl, phenylpropanolamine HCl, and dextromethorpan HBr. J. Clin. Pharmacol. **41:**563-572.
10. **Mason, L. W., K. S. Randhawa, and E. C. Carpenter.** 2008. Serotonin toxicity as a consequence of linezolid use in revision hip arthroplasty. Orthopedics. **31:**1140.
11. **Das, P. K., D. I. Warkentin, R. Hewko, and D. L. Forrest.** 2008. Serotonin syndrome after concomitant treatment with linezolid and meperidine. Clin. Infect. Dis. **46:**264-265.
12. **Packer, S., and S. A. Berman.** 2007. Serotonin syndrome precipitated by the monoamine oxidase inhibitor linezolid. Am. J. Psychiatry. **164:**346-347.

13. **Steinberg, M., and A. K. Morin.** 2007. Mild serotonin syndrome associated with concurrent linezolid and fluoxetine. Am. J. Health. Syst. Pharm. **64:**59-62.

14. **Strouse, T. B., T. N. Kerrihard, C. A. Forscher, and P. Zakowski.** 2006. Serotonin syndrome precipitated by linezolid in a medically ill patient on duloxetine. J. Clin. Psychopharmacol. **26:**681-683.

15. **DeBellis, R. J., O. P. Schaefer, M. Liquori, and G. A. Volturo.** 2005. Linezolid-associated serotonin syndrome after concomitant treatment with citalopram and mirtazepine in a critically ill bone marrow transplant recipient. J. Intensive Care Med. **20:**351-353.

16. **Morales, N., and H. Vermette.** 2005. Serotonin syndrome associated with linezolid treatment after discontinuation of fluoxetine. Psychosomatics. **46:**274-275.

17. **Thomas, C. R., M. Rosenberg, V. Blythe, and W. J. Meyer 3rd.** 2004. Serotonin syndrome and linezolid. J. Am. Acad. Child Adolesc. Psychiatry. **43:**790.

18. **Jones, S. L., E. Athan, and D. O'Brien.** 2004. Serotonin syndrome due to co-administration of linezolid and venlafaxine. J. Antimicrob. Chemother. **54:**289-290.

19. **Tahir, N.** 2004. Serotonin syndrome as a consequence of drug-resistant infections: an interaction between linezolid and citalopram. J. Am. Med. Dir. Assoc. **5:**111-113.

20. **Serio, R. N.** 2004. Acute delirium associated with combined diphenhydramine and linezolid use. Ann. Pharmacother. **38:**62-65.

21. **Hammerness, P., H. Parada, and A. Abrams.** 2002. Linezolid: MAOI activity and potential drug interactions. Psychosomatics. **43:**248-249.

22. **Wigen, C. L., and M. B. Goetz.** 2002. Serotonin syndrome and linezolid. Clin. Infect. Dis. **34:**1651-1652.

23. **Lavery, S., H. Ravi, W. W. McDaniel, and Y. R. Pushkin.** 2001. Linezolid and serotonin syndrome. Psychosomatics. **42:**432-434.

24. **Aga, V. M., N. E. Barklage, and J. W. Jefferson.** 2003. Linezolid, a monoamine oxidase inhibiting antibiotic, and antidepressants. J. Clin. Psychiatry. **64:**609-611.

25. **Dickinson, L., S. Khoo, and D. Back.** 2008. Differences in the pharmacokinetics of protease inhibitors between healthy volunteers and HIV-infected persons. Curr. Opin. HIV. AIDS. **3:**296-305.

26. **Gomez, C. M., J. J. Cordingly, and M. G. Palazzo.** 1999. Altered pharmacokinetics of ceftazidime in critically ill patients. Antimicrob. Agents Chemother. **43:**1798-1802.

27. **Stockley, I. H.** 2002. General considerations and an outline survey of some basic interaction mechanisms, p. 1-14. *In* I. H. Stockley (ed.), Stockley's Drug Interactions, 6th ed., Pharmaceutical Press.