

# Azole antimycotics and drug interactions in the perioperative period

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## Purpose of review

A beneficial effect of antifungal prophylaxis on the prevention of invasive fungal infections has increased the use of azole antimycotics in intensive care and during the perioperative period. At the same time more severe illnesses are treated and multiple drug therapies are employed. Thus, the potential for severe drug–drug interactions has increased. Previous studies have shown that azole antimycotics increase the risk of many clinically significant drug interactions with potentially hazardous consequences.

## Recent findings

A recent pharmacoepidemiological study has found a more than five-fold incidence ratio in the adjusted rate of sudden death from cardiac diseases among those patients who were given simultaneously inhibitors of cytochrome P450 (CYP) enzymes and their substrates. Although new triazole antifungals are well tolerated, they still cause significant inhibition of CYP enzymes.

## Summary

This review focuses on azole antimycotics and anesthetic drugs being used during the perioperative period and discusses the possible clinically significant drug–drug interactions. Azole antimycotics are amongst the strongest inhibitors of CYP-mediated drug metabolism. Anesthesiologists must be aware of the interaction potential of azole antimycotics to be able to adjust their perioperative strategies according to the patient's condition and concomitant medication.

## Keywords

azoles, benzodiazepines, drug interactions, intravenous hypnotics, opioid, pharmacokinetics

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## Introduction

Many drugs used in the perioperative period are eliminated mainly by metabolism. Cytochrome P450 (CYP) enzymes are of major importance for the metabolism of these drugs [1\*,2]. Inhibition of the CYP-mediated metabolism of a drug by another drug may result in a rise in the plasma drug concentrations, which in turn may cause an exaggerated effect and/or an increased incidence of adverse effects. Thus, concomitant therapy with drugs inhibiting CYP enzymes may affect the safety and clinical efficacy of drugs used in the perioperative period. The risk of receiving potentially interacting drugs is strongly correlated with the concomitant use of multiple drugs [3,4]. The number of drugs prescribed annually is growing constantly, increasing the risk for drug–drug interactions as has been pointed out by many authors [4,5].

New antifungal agents have been introduced into clinical practice during the last decade. A beneficial effect of antifungal prophylaxis on the prevention of invasive fungal infections and reduction of total mortality has been recently shown in nonneutropenic critically ill patients [6,7]. Antifungal prophylaxis with azole antimycotics is therefore commonly used in patients at an increased risk of invasive fungal infections. Azole antimycotics are increasingly used during the perioperative period and in ICUs [8\*], and the consumption of broad-spectrum antibiotics has been shown to be positively correlated with the total antifungal consumption [9]. Polytherapy is often required to manage critically ill patients appropriately, and drug interactions must be considered of notable importance during the perioperative period especially in critically ill patients. Azole antifungal agents significantly inhibit CYP-mediated metabolism [10\*] and previous studies have described

many clinically significant drug interactions with potentially hazardous consequences [11–13,14<sup>•</sup>].

The review covers the interactions of azole antimycotics with drugs commonly used by anesthesiologists. We have therefore no intention to give an exhaustive presentation of all possible drug–drug interactions which the azoles may have during the perioperative period. Only human studies are reviewed since the extrapolation and prediction of drug–drug interactions from in-vitro studies is difficult and complex [15]. Readers with a wider interest in drug interactions should consult two excellent reviews published recently: one summarizing the clinically relevant CYP-mediated drug interactions in intensive care [1<sup>•</sup>] and another thoroughly listing the pharmacokinetic interactions of azole antifungals with other coadministered drugs [16<sup>••</sup>].

### **Pharmacology and pharmacokinetics of azole antimycotics**

Azole antifungal agents inhibit the synthesis of ergosterol, the major sterol component in fungal plasma membrane. This leads to depletion of ergosterol and the accumulation of 14- $\alpha$ -sterols which distract the integrity and function of the fungal membrane. Cross-inhibition of CYP-dependent enzymes involved in mammalian biosynthesis is evident as a result of the nonselective nature of the therapeutic target. However, new triazole antifungals cause fewer and less severe toxic effects than the older compounds [17]. The pharmacokinetic properties of the azole antimycotics currently used perioperatively are summarized in the Table 1.

#### **Ketoconazole**

The first oral triazole, ketoconazole, was introduced in the USA in 1981 and it provided an alternative to amphotericin B for the treatment of fungal infections. Ketoconazole is a very potent inhibitor of human steroidogenesis and it has several CYP3A-mediated hazardous drug interactions with the substrates of CYP3A (see [22]). Ketoconazole has successively been replaced by the more tolerable itraconazole. However, in regard to

triazole-related drug interactions via the cytochrome P450 system, experience with ketoconazole can be used to extrapolate to structurally related triazoles.

#### **Itraconazole**

Itraconazole is a triazole antifungal agent first brought onto the market in 1990. It is available for oral use only in the form of capsules and solution. It is used for prophylaxis and treatment of many systemic as well as for superficial fungal infections [23]. Itraconazole is extensively metabolized in the liver and the major metabolite, hydroxyitraconazole, has a similar antifungal activity to the parent drug. It is predominantly metabolized by CYP3A, which is also inhibited by itraconazole [18].

#### **Fluconazole**

Fluconazole is a water-soluble molecule which is available in oral and intravenous form. Renal excretion is the main pathway for fluconazole elimination and approximately 80% of fluconazole is recovered in urine in unchanged form. Only 11% of the dose is metabolized [24]. Renal insufficiency prolongs the elimination half-life of fluconazole, necessitating dosage adjustment which is proportional to creatinine clearance [19]. Fluconazole is a weaker inhibitor of CYP3A than other triazoles. However, several significant drug–drug interactions have been described [24–26].

#### **Voriconazole**

Voriconazole is the first second-generation triazole antifungal agent and it is available as an intravenous infusion, tablets and suspension for oral administration. The pharmacokinetics of voriconazole is nonlinear in adults with a greater than proportional increase in plasma concentration with dose escalation [27]. Variability between individuals in plasma voriconazole concentration is high, whereas within individuals the variation is low [28,29]. Dose adjustment is needed for patients with chronic hepatic impairment but no adjustment of oral voriconazole is needed in individuals with renal dysfunction as voriconazole is exclusively metabolized in the liver [30,31]. Voriconazole is extensively metabolized by

**Table 1 Pharmacokinetic parameters of perioperatively used triazole antifungal agents**

Parameter	Itraconazole	Fluconazole	Voriconazole	Posaconazole
Formulations	i.v. Infusion, p.o. capsules, oral solution	i.v. Infusion, p.o. capsules, oral solution	i.v. Infusion, p.o. capsules, oral suspension	p.o. Suspension
Bioavailability (%)	≥55	80–90	96	Dose-dependent
Elimination half-life (h)	15–46	22–37	6	20–66
Protein binding (%)	>99	12	98	58
Clearance (ml/min)	381	17–19	100–333	192–363
Volume of distribution at steady state (l/kg)	10.7	0.7–0.8	4.6	25
CYP metabolism	CYP3A	–	CYP2C19, 2C9, 3A	–
CYP inhibition	CYP3A, 2C9	CYP2C9, 3A, 2C19	CYP3A, 2C9, 2C19	CYP3A

Data from [18–21].

various CYP enzymes and it is a potent inhibitor of CYP3A and CYP2C enzymes [32].

### Posaconazole

Posaconazole is the newest azole antimycotic and has been introduced to clinical practice in many countries. It is well tolerated during both short and long-term use, with the most commonly reported adverse events being mild-to-moderate gastrointestinal disturbances. There seems to be a relationship between posaconazole plasma concentrations and prophylactic efficacy. However, plasma concentrations are influenced by several factors, which necessitates therapeutic drug monitoring on a regular basis [33]. Posaconazole is not metabolized by CYP enzymes, but drug interactions arising from CYP3A inhibition have been reported [34,35]. Since posaconazole is available only as an oral formulation, its use in critically ill patients is limited.

### Mechanisms of drug–drug interactions

Many drugs in common therapeutic use are lipophilic, facilitating their passage through the biological membranes. However, their excretion from the body is slow unless they are converted to more water-soluble forms. This biotransformation is catalyzed by a sequence of enzyme-mediated reactions, divided into phase I and phase II reactions. Oxidation is the most important phase I reaction involving the CYP enzymes

CYP enzymes [36] consist of a superfamily of hemthiolate mono-oxygenases, which are divided on the basis of amino acid similarities into families and subfamilies [36]. Many CYP enzymes are primarily involved in the synthesis of steroids and bile acids; others take part mainly in the metabolism of xenobiotics. Collectively, CYP enzymes are involved in approximately 80% of oxidative drug metabolism.

CYP2 is the largest CYP family in mammals, and consists of 13 subfamilies and 16 members [36]. It constitutes up to 30% of total liver CYP protein, of which the subfamily CYP2C accounts for about 20% [37]. Human CYP2 enzymes, especially those belonging to the CYP2C subfamily (namely CYP2C8, CYP2C9 and CYP2C19), metabolize more than half of all frequently prescribed drugs [36]. Considering the perioperative period, CYP2D6 is particularly important because it metabolizes 20–25% of known drugs [38<sup>\*</sup>], although it constitutes only about 2% of total liver CYP content [37].

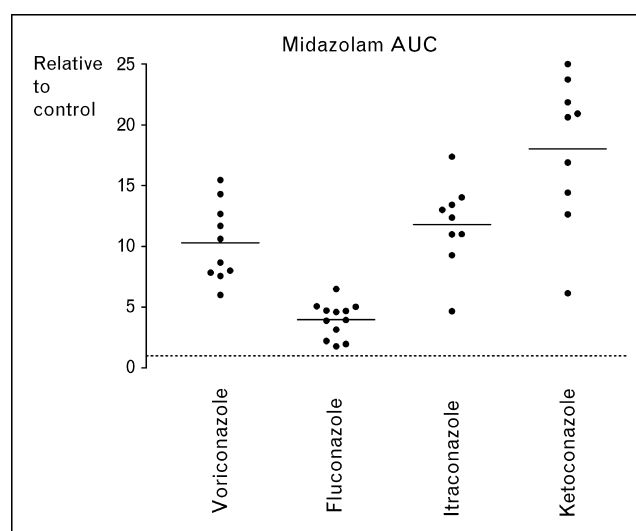
CYP isoforms belonging to the CYP3A family account for the majority of drug-metabolizing enzymes present in adult human tissues, constituting approximately 40–50% of the total CYP content in adult human liver. In addition to hepatic expression, CYP3A4 and CYP3A5 are present

in extrahepatic tissues, for example small intestine [39]. Intestinal CYP3A is an important factor in drug metabolism since the biotransformation in the gut wall substantially contributes to the overall first-pass metabolism of many orally ingested CYP3A4 substrates.

The CYP3A subfamily family is shown to metabolize more than 120 frequently prescribed drugs, and endogenous substrates such as steroids and bile acids. It is estimated that the metabolism of more than 40–50% of drugs in current clinical use involves CYP3A [40]. Azole antimycotics are among the most potent inhibitors of CYP3A, and many clinically significant drug interactions have been reported after their concomitant use with CYP3A substrates (e.g. [11–13,14<sup>\*</sup>,41]).

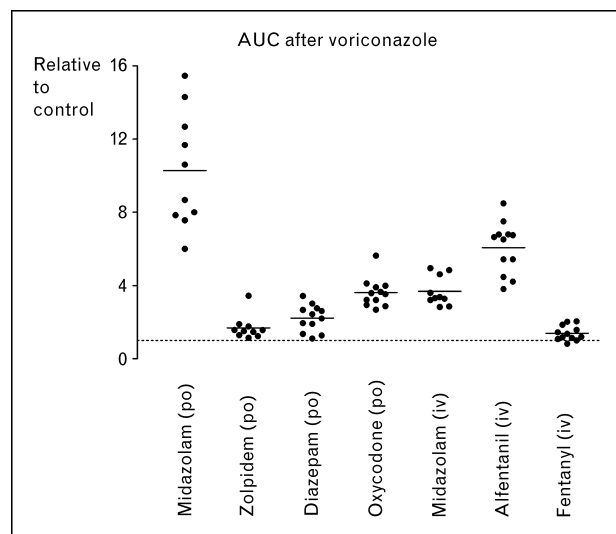
The inhibition of CYP enzymes has been recognized as the pivotal cause of drug–drug interactions in everyday clinical practice. An interaction may alter systemic drug disposition, and the first-pass metabolism of an orally administered drug [2]. Clinically significant CYP inhibition occurs only when the inhibited enzyme is responsible for a major elimination pathway. The magnitude of a drug–drug interaction depends also on the mechanism of inhibition. There are major differences between the separate azoles and the interacting substrates of CYP enzyme inhibitors. This is demonstrated in Figs 1 and 2, which show the relative inhibitory potential between different triazoles (Fig. 1) and the susceptibility of some substrates to the CYP-mediated inhibition (Fig. 2).

**Figure 1** Effect of CYP-mediated inhibition by azole antimycotics on midazolam exposure to orally administered midazolam



Individual values (mean) in healthy volunteers given 7.5 mg of midazolam. AUC, area under the plasma concentration–time curve. The dashed line shows the mean AUC in the control phase without the administration of antimycotics. Data from [11,13,42].

**Figure 2** Effect of azole antimycotic voriconazole on the exposure to various perioperatively administered oral or intravenous hypnotics and opioid analgesics



Studies were conducted in healthy volunteers. AUC, area under the plasma concentration–time curve; i.v., intravenously; p.o., orally. The dashed line shows the mean AUC in the control phase without the administration of antimycotics. Data from [13,14\*,43–45].

### Clinically significant drug interactions involving triazoles in the perioperative period

Antifungal prophylaxis is employed increasingly during the perioperative period. At the same time, the number of other drugs used by severely ill patients is also increasing. This gives rise to an increased potential of clinically significant drug–drug interactions during the perioperative period.

#### Hypnotics

The metabolic pathways of the drugs used for the induction of anesthesia remain rather poorly characterized. Propofol is metabolized mainly by glucuronidation by uridine diphosphate-glucuronosyltransferases and by hydroxylation by CYP2B6 and CYP2C enzymes [46,47]. No studies have suggested that azole antimycotics or any other drugs affecting the activity of CYP enzymes would affect the pharmacokinetics of propofol. The same is true also for etomidate, which is eliminated by ester hydrolysis [48], and for thiopental, which is almost completely metabolized by oxidation with only a small proportion being excreted unchanged in urine [49]. CYP enzymes responsible for its metabolism are unknown. If a drug is given only for the induction of anesthesia, clinically significant pharmacokinetic drug interactions are extremely unlikely.

Ketamine is extensively metabolized in the liver by CYP 3A, 2B6 and 2C9 enzymes [50,51]. Owing to its oxidative

metabolism, ketamine is prone to pharmacokinetic drug interactions which may influence its clinical effects. Ketamine is mainly given by the intravenous route, but for chronic pain the oral route may be useful. Clarithromycin strongly increases the plasma concentrations of oral S-ketamine by inhibiting its CYP3A-mediated N-demethylation [52]. These results may also most likely be extrapolated to other inhibitors of CYP3A. The inhibitors of CYP3A are likely to affect the pharmacokinetics of intravenous ketamine too, but clinically significant drug interactions for a drug with a high extraction ratio are unlikely.

Midazolam is used in anesthesiology and intensive care medicine for its anxiolytic, sedative, hypnotic, and amnesic effects. It is the most widely used CYP3A probe, and its clearance shows significant dependence on CYP3A activity [41]. The interaction of midazolam with the inhibitors of CYP3A has been shown in multiple in-vitro and in-vivo studies. *In vivo*, the inhibition of CYP3A by the azole antifungals results in clinically significant drug interactions with midazolam, as has been demonstrated in healthy volunteers (Fig. 1, Table 2). Strong inhibitors of CYP3A forcefully increase the concentrations of oral midazolam, whereas the concentrations of intravenous midazolam are increased only moderately.

Diazepam metabolism involves primarily CYP2C19 and CYP3A4, and it is likely to have interactions with drugs affecting these enzymes. Itraconazole, a strong inhibitor of CYP3A4, has only a minor effect on the pharmacokinetics of oral diazepam [60]. Thus far, no clinically significant drug interactions with diazepam and CYP3A4 inhibitors have been published. On the contrary, the inhibitors of CYP2C19 have stronger interactions with diazepam. Pharmacokinetics of oral diazepam is markedly affected by concomitant voriconazole or fluconazole [44]. A considerable delay in the elimination of diazepam is seen while the absorption of diazepam is unchanged. Consequently, 2.5 and 2.2 times higher exposure to diazepam is seen after voriconazole or fluconazole, respectively, compared with the control values.

#### Opioid analgesics

Alfentanil and fentanyl are synthetic opioid analgesics widely used in anesthesia. As alfentanil has a low extraction ratio, inhibitors of CYP3A can impair its clearance. Previous studies have shown that ketoconazole and fluconazole reduce, on average, the clearance of alfentanil by 82 and 55%, respectively [26,61]. The increased concentrations were reflected also in the alfentanil-induced subjective effects. Plasma clearance of intravenous alfentanil decreases by 85% after voriconazole and this increase is also associated with a significant prolongation of the elimination half-life [43]. There is no

**Table 2** Effects of some CYP3A inhibitors on the pharmacokinetic (PK) and pharmacodynamic (PD) parameters of midazolam

Inhibitor	PK effects		PD effects <sup>a</sup>	Reference
	Increase in AUC ( <i>n</i> -fold)	Decrease in CL (%)		
Ketoconazole	15.9	NA	DSST, VAS, MW	[11]
Itraconazole	5.8	NA	DSST, VAS, CFFT	[53]
	10.8	NA		[11]
	6.6	69		[42]
	10.3	72	DSST, VAS, MW	[13]
Fluconazole	3.6	51	DSST	[42]
	3.7	NA	DSST, CFFT	[25]
Terbinafine	NS	NS	NS	[53]
Erythromycin	4.4	54	DSST	[54]
Clarithromycin	3.6	62	DSST, CFFT, VAS	[55]
	7.0		Sleep time	[56]
Diltiazem	3.7	NA	DSST, VAS, MW	[57]
Verapamil	2.9	NA	DSST, VAS, MW	[57]
Saquinavir	5	56	VAS	[58]
Grapefruit juice	1.5	0	DSST	[59]

AUC, area under the plasma concentration–time curve; CFFT, critical flicker fusion test; CL, clearance; DSST, digit symbol substitution test; MW, Maddox wing test; NA, not available; NS, nonsignificant change; VAS, visual analog scale.

<sup>a</sup>PD tests showing significant changes compared with the control values are listed.

published information on the effect of itraconazole or posaconazole on the pharmacokinetics of alfentanil.

Conventional pharmacokinetic theories anticipate that the rate of hepatic elimination of a drug with a high extraction ratio, such as fentanyl, is more dependent on the liver blood flow than on the changes in its intrinsic clearance. However, based on the well stirred model of hepatic elimination [62], clinically significant reductions in systemic clearance would occur with a 65% decrease in fentanyl intrinsic clearance. Voriconazole and fluconazole, administered at typically used clinical doses, significantly affect the pharmacokinetics of fentanyl [24]. Voriconazole reduces, on average, the clearance of fentanyl by 28% and this change is associated with a significant prolongation of the elimination half-life. Although itraconazole is a strong inhibitor of the CYP3A enzymes responsible for metabolism of fentanyl *in vitro*, it does not affect the pharmacokinetics of intravenous fentanyl in humans [63]. Ketoconazole is *in vitro* capable of inhibiting the metabolism of fentanyl [64] but there are no *in-vivo* studies confirming this finding. There are no published reports on the effect of posaconazole on the metabolism of fentanyl.

Oxycodone is a semi-synthetic  $\mu$ -opioid receptor agonist widely used in the treatment of acute and chronic pain. Oxycodone is metabolized mainly in the liver by oxidative metabolism by CYP3A and, to a lesser extent, by CYP2D6, making it prone to pharmacokinetic drug interactions [65]. Voriconazole increases the exposure to oral oxycodone by 260% by inhibiting the CYP3A4-mediated metabolism of oxycodone [14\*]. Similar results have been observed with itraconazole, another strong inhibitor of CYP3A4. Inhibitors of CYP3A4 simultaneously reduce

the concentrations of noroxycodone [66]. The inhibition of CYP2D6 by quinidine has no statistically significant effect on the plasma concentrations of oxycodone, but it effectively inhibits the formation of the CYP2D6-dependent metabolite oxymorphone [67]. The minor effect of CYP2D6 inhibition on oxycodone kinetics was also demonstrated in a recent study in which healthy volunteers were given paroxetine prior to oxycodone. When a combination of paroxetine and itraconazole was used to inhibit CYP2D6 and 3A4 simultaneously, the exposure to oxycodone increased greatly [68]. The induction of CYP3A4 by rifampicin strongly reduces the exposure to oral oxycodone by almost 90% [69].

#### Muscle relaxants

There is no information on the effect of azole antimycotics on the metabolism of nondepolarizing muscle relaxants. Benzylisoquinoline muscle relaxants (cisatracurium, atracurium and mivacurium) are metabolized by ester hydrolysis and/or Hoffman elimination and are not prone to metabolic drug interactions with the azoles. Steroidal muscle relaxants (rocuronium, vecuronium and pancuronium) are assumed to be metabolized, at least in part, by CYP enzymes. Strong inducers of CYP enzymes increase the dose requirement of vecuronium, but the involvement of different CYP enzymes is lacking [70].

#### Local anesthetics

Itraconazole has practically no effect on the pharmacokinetics of ropivacaine [71] or intravenous [72] and inhaled [73] lidocaine. However, the concentrations of oral lidocaine are almost doubled by itraconazole [74]. There is no evidence about the effect of other antimycotics on the pharmacokinetics of local anesthetics.

## Clinical considerations

Triazole antifungals are potent inhibitors of CYP3A *in vitro*. A beneficial effect of antifungal prophylaxis on preventing invasive fungal infections and reducing mortality has increased the use of antimycotic agents in the operating room and ICUs [6,7]. Therefore, the risk for drug interactions with CYP3A substrates is increased. A recent pharmacoepidemiological study has found a more than five-fold incidence ratio in the adjusted rate of sudden death from cardiac diseases among those patients who concurrently used strong inhibitors of CYP3A4 and erythromycin [75].

Several studies involving healthy volunteers have shown that azole antimycotics have clinically significant interactions with benzodiazepines and opioid analgesics. Administration of benzodiazepines, especially oral midazolam, along with azole antimycotics may result in deep and long-lasting hypnotic effects (Table 1). Therefore concomitant administration of azole antimycotics with oral midazolam should be avoided or greatly lower doses of midazolam should be used. The effects of bolus doses of intravenous midazolam may not be increased to a clinically significant degree. Long-term infusions of midazolam should be titrated according to the effect in patients receiving systemic azole antimycotics.

Many of the results cited here are obtained in healthy volunteers and therefore cannot be extrapolated uncritically to elderly patients or patients with critical illness. However, azole antimycotics are usually administered in critically ill patients with extensive fungal infections, and these patients can be very sensitive to the CNS-depressant effects of anesthetic drugs. Thus, for instance, the interactions between voriconazole and fentanyl as well as between fluconazole and fentanyl are of potential clinical significance. There is a risk of respiratory depression if the dose of fentanyl during infusion or transdermal administration is not reduced and the patients are not monitored closely. Of note is that the transdermal absorption of fentanyl continues for several hours after release of a transdermal fentanyl patch [76]. This warrants a careful monitoring of patients, when voriconazole or fluconazole have been added to their drug regimen. Similarly, patients having continuous epidural infusions with fentanyl during voriconazole treatment require careful monitoring and possibly a dose adjustment for fentanyl.

## Conclusion

Azole antimycotics are amongst the strongest inhibitors of CYP-mediated drug metabolism. Previous studies have described many clinically significant CYP-mediated drug interactions with azole antifungal agents and drugs used perioperatively with potentially hazardous consequences.

Because both the use of antifungal prophylaxis during the perioperative period and the number of other drugs used by severely ill patients has increased, there is an increased potential of clinically significant drug–drug interactions. Thus, anesthesiologists must be aware of the basic principles of drug interactions to be able to adjust their perioperative strategies according to the patient's condition and concomitant medication.

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- of special interest
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