Fundamental Concepts of Azole Compounds and Triazole Antifungals: A Beginner's Review

Nelson Martínez-Matías, MS; José R. Rodríguez-Medina, PhD

Azoles are the most widely used drugs in antifungal therapy. They have a wide spectrum of activity against pathogenic fungi that are clinically relevant. However, they have been associated with adverse reactions and toxicity, both of which can be significant in patients. Compared to diazoles, triazoles discriminate better between their intended molecular target, the fungal CYP51 enzyme, and several enzymes of the human CYP450 system. Over the years, this superior discrimination has led to the favoring of triazoles over diazoles in the treatment of systemic mycoses. Nevertheless, despite their being better able to discriminate between the fungal CYP51 and host CYP450 enzymes, they are still capable of inducing significant toxicity and adverse reactions in the host, especially when taken concomitantly with other therapeutic drugs by patients with compromised immune systems. In this writing, we review some of the fundamental concepts regarding the chemistry and mechanisms of action of azole compounds, as well as the spectrum of activity, pharmacokinetics, and adverse effects of triazole antifungals. In addition, we discuss some of the mechanisms that pathogenic fungi have developed to overcome the cytotoxic effects of therapeutic drugs, with an emphasis on triazoles. [*P R Health Sci J 2018;37:135-142*]

Key words: Fungal CYP51, CYP450 System

Fungal infections have become a worldwide public health issue. According to estimates, they lead to approximately 1.5 million deaths each year worldwide, with *Candida*, *Cryptococcus*, and *Aspergillus spp.* being the most common opportunistic fungi. This is important to consider by clinical practitioners, especially when taking care of patients that have compromised immune systems because of HIV infection, chemotherapy, or otherwise (1), as *opportunistic fungi* take advantage of weaknesses in the host's immune system to establish infection and cause disease (2). From a medical standpoint, the development of novel antifungal agents is imperative. Firstly because, aside from palliative treatment, drug therapy is often the only way to treat a patient once a fungal infection is established. Secondly, with time, fungi develop resistance to the toxic effects of antifungal drugs. Azoles are the most widely used class of antifungal compounds. Among them, triazoles are often used as a first option of treatment for systemic mycoses. In this writing, we review the basic concepts of azole antifungals, their chemistry and mechanism of action, and the spectrum of activity, pharmacokinetics, and adverse effects of triazoles. We also review some of the mechanisms that pathogenic fungi have acquired to overcome the cytotoxic effects of therapeutic drugs, with an emphasis on triazoles.

Chemistry and uses of azole drugs

Azoles are heterocyclic compounds that are structurally related to the 5-membered ring compound *pyrrole*. The molecular structure of *pyrrole* is shown in Figure 1, below, along with the structures of 3 simple azole compounds. In the azoles, 1 or more of the carbon atoms in the pentagonal ring of *pyrrole* are replaced by heteroatoms that can be additional nitrogen, oxygen, or sulfur atoms (3). If the ring has 2 nitrogen atoms, 1 in addition to the equivalent nitrogen atom found in the ring of *pyrrole*, the resulting compound is *imidazole* (rightmost at the top of Figure 1, below). If there are 3 nitrogen atoms, 2 in addition to the nitrogen already found in *pyrrole* replacing carbon in the ring, the compounds are called triazoles. Azole drugs are synthetic or semi-synthetic compounds that can be considered derivatives of the single-ring compounds imidazole or either the 1,2,3 or 1,2,4 isomers of triazole. The structures of imidazole and the triazole isomers are shown in Figure 1. They are classified either as imidazoles or triazoles according to whether their pentagon-like heterocyclic rings have 2 or 3 nitrogen atoms, thus resembling imidazole or either 1,2,3 or 1,2,4 triazole respectively (4). Therefore, if the atom marked X in the leftmost structure of Figure 2, below (top), is also a nitrogen atom, the compound is a triazole, while if it is a carbon atom, the compound is an imidazole (4). Notice that

Department of Biochemistry, University of Puerto Rico Medical Sciences Campus, San Juan, PR

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Address correspondence to: José R. Rodríguez-Medina, PhD, Department of Biochemistry, University of Puerto Rico Medical Sciences Campus, PO Box 365067, San Juan, PR 00936-5067. Email: jose.rodriguez123@upr.edu

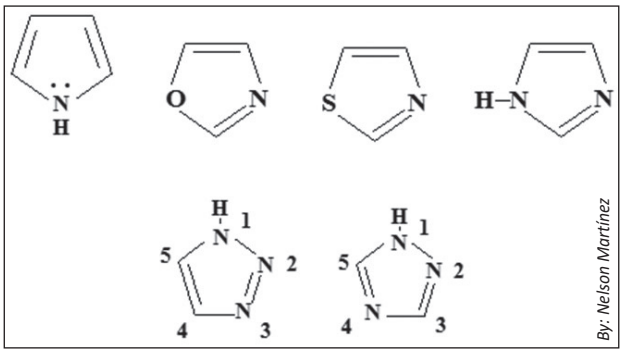

Figure 1. Molecular structures of 4 representative 5-membered single-ring heterocyclic aromatic compounds (above), and of the parent triazole compounds 1,2,3 and 1,2,4 triazole (below). On top, from left to right: pyrrole, oxazole, thiazole, and imidazole (rightmost). Below: 1,2,3 triazole (left) and 1,2,4 triazole (right).

the identity of the resulting azole, whether it is an imidazole or a triazole, depends on the nature of the chemical substituent R. The molecular structures of several azole antifungals, the imidazoles *clotrimazole*, *miconazole*, and *ketoconazole* and the triazoles *fluconazole*, *voriconazole*, and *itraconazole*, are also shown in Figure 2.

As suggested above, azoles are widely used in the medical industry as therapeutic agents against pathogenic fungi; that is, as *antifungal drugs*. It is worth emphasizing, however, that though in this writing we will focus on *medical azoles*, antifungal azoles different from those mentioned in the preceding paragraph are used worldwide in the food and agricultural industries to prevent the infection of crops with common plant fungal pathogens (5). Indeed, azoles are widely used in the industry of materials. They are added to a variety of products, such as paints and coatings that prevent fungal growth (5) and are also used to preserve wood (6).

Mechanism of therapeutic action

Azoles inhibit competitively the fungal CYP51-class cytochrome P450 superfamily enzyme *14a-sterol demethylase* in a dose-dependent manner (7, 8). CYP51 enzymes are essential components of the pathway leading to the synthesis of *ergosterol*, a major sterol of the plasma membrane of most fungi (9). They catalyze the oxidative removal of methyl groups at position 14 of the sterol substrate (10). Inhibition of the fungal CYP51 (codified by the *ERG11* gene in *Saccharomyces cerevisiae* and other fungi) by azole drugs involves binding of the nucleophilic

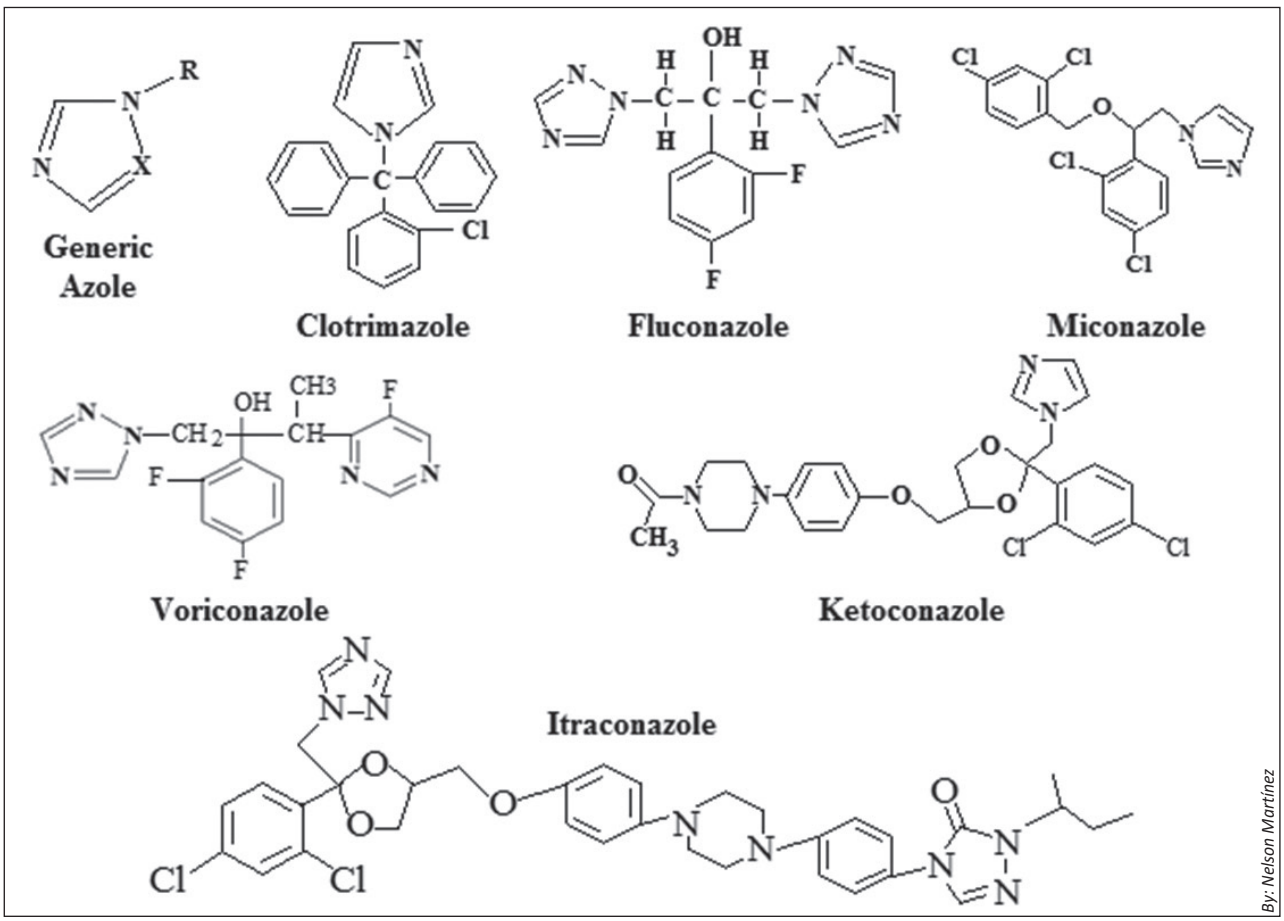

Figure 2. Molecular structures of a general azole compound and of different imidazole and triazole antifungal drugs that have been approved for use in therapy. Clotrimazole, miconazole, and ketoconazole are diazoles, while the remaining compounds are triazoles.

N-4 of the azole ring to the sixth coordination site of the iron atom in the heme group of the enzyme. This causes inhibition when the azole occupies the binding site instead of *lanosterol*, which in most fungi is the normal substrate (11). Interestingly, CYP51 enzymes are essential for sterol synthesis in different eukaryotes besides fungi, having substrates such as *obtusifoliol* in plants, and *24,25-dihydrolanosterol* in mammals (12). Moreover, important bacterial pathogens also have a CYP51 enzyme. For example, *Mycobacterium tuberculosis* also has a CYP51 enzyme whose crystal structure has been determined in complex with fluconazole (12). Azole drugs, especially imidazoles have antimicrobial activity against *M. tuberculosis*. However, the mechanism is still unclear, as imidazoles have been shown to bind multiple P450 molecules in this microbe, some of which have been shown to be non-essential *in vitro* (13). In addition, other azoles have been shown to have bactericidal or inhibitory effects against *Mycobacterium smegmatis* (14). In most fungi azoles exert a dual antimicrobial effect. Firstly, as sterols are essential components that help to maintain the fluidity of membranes, *ergosterol* depletion causes instability of this structure and ultimately leads to the inhibition of growth (15,16). This makes azoles generally *fungistatic* (and not *fungicidal*) against most of their targeted fungi. Secondly, inhibition of the fungal CYP51 causes the accumulation of methylated metabolites different from lanosterol, which are also toxic to the pathogens against which the azole drugs are active. One of them is *14a-methyl-3,6-diol* (16). An abbreviated diagram of the pathway leading to the synthesis of ergosterol is shown in Figure 3, below. Although *allylamines* and *benzylamines* are not the subject of this writing, one should notice from the figure that these drugs also inhibit the synthesis of ergosterol, though at a different level in the pathway. They inhibit the enzyme *squalene epoxidase*, thus interfering with the synthesis of *lanosterol*, which, as we said, is the normal is substrate of CYP51 in most fungi and the precursor of *ergosterol*.

Drug resistance mechanisms

Fungal drug resistance can be *primary* (intrinsic) or *secondary* (acquired). They can be distinguished by the fact that in the former the pathogen is never inhibited, even by high doses of the drug (5). On the other hand, secondary resistance can emerge *de novo* through a selection process when the organism is exposed to the drug for a prolonged period (5). This is important when pathogenic fungi are exposed to a drug for a prolonged time, particularly when the agent is fungistatic. If it is fungicidal, death is usually rapid and thus it is unlikely there is enough time for resistance to emerge. A second feature of secondary resistance is that often the pathogen can still be inhibited *at higher-than-normal levels of a drug*. Examples of intrinsic resistance are found in *Aspergillus fumigatus*, *Candida krusei*, and *Candida glabrata*, which are often resistant to fluconazole (5). In the case of *A. fumigatus*, intrinsic resistance to fluconazole has been proposed to arise from a differential inhibition of its 2 CYP51 isoforms, CYP51A and CYP51B (17). In the case of *C. krusei*, intrinsic resistance is thought to arise largely because of having an alternative pathway for the synthesis of membrane sterols (5). Therefore, whether a fungus has intrinsic resistance to a triazole depends on its physiology and genetics and on the characteristics of the triazole. In contrast, a non-intrinsically resistant fungus such as *Candida albicans* can develop resistance to fluconazole (11). Another example of secondary resistance is that of *A. fumigatus*, which has been shown to *develop resistance* to itraconazole, voriconazole, and posaconazole (18). From now on we will focus on secondary resistance against triazoles.

As a rule, the mechanisms by which fungi develop resistance to a drug depend on the action mechanism of the drug and the number of target sites, among other factors (5). One important mechanism that has evolved in fungi, and with which they circumvent the effect of therapeutic drugs, is mutations in the coding sequence of the molecular target (19). These may lead to the decreased affinity of the drug for the target (11, 16). Two additional mechanisms that have been described are the overexpression of the cellular target and the up-regulation of genes related to drug efflux (20). In *C. albicans*, CYP51 overexpression and mutations in its coding sequence have been described and found to contribute to drug resistance (11). Moreover, the mechanisms are not always mutually exclusive. The simultaneous detection of mutations in CYP51 and the overexpression of efflux pumps have been described for *C. albicans* (21). In this pathogen, the overexpression of CYP51 is known to occur by 2 mechanisms. The first one involves a gain-of-function mutation in the transcriptional regulator Upc2 and the second is an increase in the number of copies of chromosome 5, which contains *ERG11* (11).

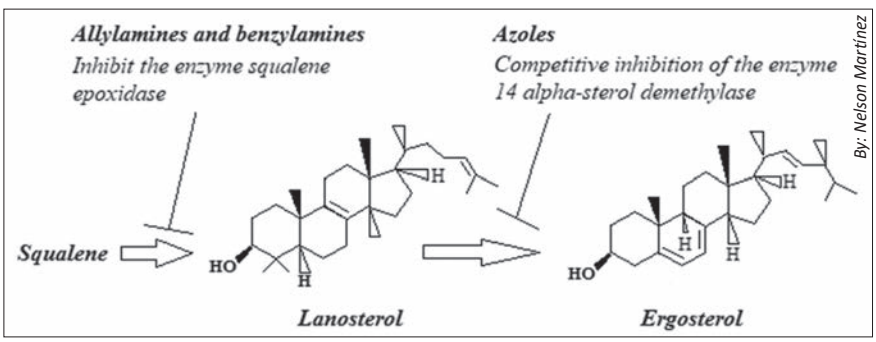

Figure 3. Abbreviated representation of a part of the fungal metabolic pathway leading to the synthesis of ergosterol.

Perhaps the most studied drug resistance mechanism in fungi is mutations in *ERG11* that lead to the decreased affinity of azoles for their target. Some of these mutations lead to amino acid substitutions precisely in the binding site of the enzyme (16). In homozygous strains of *C. albicans*, some of the mutations that have been found to confer

resistance to fluconazole lead to the following single amino acid substitutions: Y132F, K143R, F145L, S405F, D446E, G448E, F449V, G450E, and G464S (11). The mutations lead to phenotypes of augmented *minimum inhibitory concentrations* (MICs) for fluconazole approximately 4-fold. Among these the one at position 132 (including Y132H), which in the sequence of the *S. cerevisiae* CYP51 corresponds to Y140F/H, is the only one that has been observed to yield a fluconazole resistance phenotype when found as a single mutation, while the remaining mutations confer resistance only when combined, and lead to decreased susceptibility phenotypes, otherwise (16). In any case, for this type of mutation to be firmly established, selective pressure needs to be maintained in the fungal population for a prolonged time for resistance clones to be selected. Unfortunately, this is likely to happen in 2 important scenarios. The first is in hospitals or other medical facilities where antifungal drugs, especially triazoles, are used therapeutically in patients over prolonged periods as prophylactic agents to prevent infections (5). This is evident in the case of *A. fumigatus*, whose mechanism of resistance usually involves mutations in the CYP51A gene (18). This is apparent from genotypic analyses of serial strains from patients suffering from chronic aspergillosis. These have revealed essentially the same genotypes before and after the acquisition of resistance, with the only difference being the mutations that confer resistance (18). This suggests that *A. fumigatus* can rapidly adapt to azoles when therapy is given for a long period of time. The second possible scenario occurs when there are open places where susceptible species of pathogenic fungi can thrive under pressure from exposure to agricultural azoles that are present in the environment (5). Indeed, the emergence of azole-resistant strains of *A. fumigatus* (due to exposure to agricultural azoles) is well documented (18). This is not surprising for at least 3 reasons. Firstly, important fungal pathogens such as *A. fumigatus*, *H. capsulatum*, and others usually thrive in an environment that includes crops. Secondly, agricultural and medical azoles share the same mode of action (5). Finally, most fungal pathogens are not endogenous to humans but are acquired from the environment. A good example is some *Aspergillus spp.* whose conidia are dispersed in the air with particles coming from the soil or decaying organic matter (5).

Another mechanism by which resistance to azole antifungals might arise in pathogenic fungi is by preventing the drug from reaching toxic levels inside the cell (17). In principle, this can be achieved in 2 ways. The first one is by increasing the cellular drug efflux rate. This is a well-documented drug resistance strategy that usually involves membrane transporters such as the *ATP-binding cassette* (ABC) and *major facilitator superfamily* (MFS) transporters (17). The second one is by reducing the cellular drug influx rate. Drug import processes in fungi have been less well studied than have those of drug efflux. In *A. fumigatus*, indirect evidence suggesting drug import rate reduction as a potential mechanism for drug resistance first came from the characterization of isolates that show reductions in drug accumulation that are independent of drug efflux (17). Experiments performed with *C. albicans* and *A. fumigatus* using radioactively labeled azoles indicate that defective drug import is indeed a potential mechanism for drug resistance in pathogenic fungi (17), suggesting in turn that passive diffusion is not the only mechanism for the accumulation of azoles inside these pathogens.

Two additional mechanisms for drug resistance in pathogenic fungi are modifications in the drug metabolic degradation and the formation of biofilms (22). However, a discussion of these and other mechanisms for drug resistance in fungi is beyond the scope of this writing.

Finally, in contrast to bacteria, a mechanism for drug resistance that has not been demonstrated until now to exist in fungi is *horizontal transfer of resistance-conferring genes* (5). *Horizontal gene transfer* (HGT), also known as *lateral gene transfer*, is defined as an exchange of genetic information either between different strains of a species or between different species, which exchange is non-transient (23). HGT is different from the usual reproductive transfer of genetic material that flows in only 1 direction, from parent to offspring. Prokaryote to eukaryote HGT is also documented. The best examples arise from the well-known *Agrobacterium*–host plant interaction (24). Indeed, the transference of prokaryotic genes via HGT has also been shown to confer selective advantages to eukaryotes such as amoeba (23), and it has even been suggested that the *URA1* gene in *S. cerevisiae* might have arisen from lactic acid bacteria (24). Despite all that, however, we have not found evidence in the literature for the horizontal transfer of genes *conferring resistance to azoles or to any other antifungal drug class*, from bacteria to fungi. Nevertheless, it is our opinion, in view of the existent evidence supporting the occurrence of HGT from bacteria to fungi, that this possibility cannot be ruled out.

Metabolism and drug interactions

Drug–drug interactions (DDIs) can be categorized as *pharmacodynamic* or *pharmacokinetic* (25). The first type results from the action of the drugs in the organism and can be synergistic, antagonistic, or additive. They may lead to either an increase or a decrease in the frequency or severity of adverse reactions (25). An example of a synergistic interaction is the reported synergistic effect between the immunosuppressive drug tacrolimus and the triazole compounds itraconazole and voriconazole in certain isolates of *Candida glabrata* that are resistant to fluconazole (26). The second type results from changes induced in the absorption, distribution, metabolism, or elimination of a drug. These may lead to anomalous concentrations of the drug or its metabolites (25) and, therefore, the possibility of reduced efficacy or even toxicity depending on the exposure (27, 28). Although most azole-induced DDIs that are highlighted in the literature are pharmacokinetic, pharmacodynamic interactions are also common, as occurs with the concomitant use of azoles and immunosuppressants (28, 29). As the medical use of imidazoles is nowadays mostly

limited to topical mycoses (9), we will focus our discussion on the commonly prescribed triazoles. Moreover, we will mainly discuss pharmacokinetic DDIs induced by the triazoles on the other drug(s). We encourage the reader interested in specific details to study the available references.

In humans, most DDIs induced by triazoles involve the cytochrome P450 (CYP450) enzymes of the intestinal lumen and liver (25). CYP450 is a heme-containing enzyme superfamily existing in almost all living organisms, including humans and fungi, and whose members in mammals are embedded in the membrane of the endoplasmic reticulum (30). CYP450 enzymes participate in the metabolism of xenobiotics such as drugs and contaminants and in the metabolism of endogenous substances such as lipids and prostaglandins (6). CYP450 enzymes are monooxygenases (30) that catalyze phase I redox reactions (31). Fifty-seven CYP450 isozymes are known to exist in humans, and nearly one third of them are only expressed exclusively in the liver (30). Of these the most important for drug clearance belong to the CYP1, CYP2, and CYP3 families (31). Azole antifungals are common substrates and inhibitors of the hepatic CYP450 enzymes. They are known to cause DDIs, mainly via inhibition of CYP3A4 (32). In addition, azoles are also known to interfere with P-glycoprotein membrane transporters and with phase II enzymes involved in conjugation reactions (28). Triazoles are considered potential causatives of many DDIs. This is a consequence of being usually administered for prophylaxis or to treat systemic mycoses in patients that are already in a drug therapy regime for tissue or organ transplant rejection prevention or to treat other conditions (28, 29). DDIs induced by triazoles have been categorized as those in which i) the other drug(s) modify the azole pharmacokinetics, ii) the azole modifies the pharmacokinetics of the other drug(s), and iii) both drugs' pharmacokinetics are modified (28).

The mechanism for pharmacokinetic DDIs is relatively simple to understand in terms of the fate of the different drugs once they get into the human body. Although the following discussion is made regarding the CYP450 enzymes, as DDIs in humans are often mediated by them (30), the same reasoning can be applied regarding other drug-metabolized systems, such as the P-glycoprotein.

Suppose that a drug, X, is predominantly metabolized through CYP3A4 in humans and that it is concomitantly administered with another drug, Y, that is a strong inhibitor of CYP3A4. In this scenario it is likely that the levels and thus the bioavailability of drug X might increase above therapeutic levels because of diminished drug clearance rates provoked by the inhibition of CYP3A4 induced by drug Y. Such an increase in the bioavailability of drug X might be dangerous (33) and could lead to adverse reactions in a patient. Conversely, other things being equal, if Y were a strong inductor of CYP3A4, it is likely that the levels of drug X would decrease below therapeutic levels because of an increased drug clearance rate induced by drug Y, thus possibly causing the therapy with drug X to fail. We leave the reader to conclude what might happen if X were a *pro-drug* instead of a pharmacologically active drug, and finish our discussion taking a glance at the metabolism of the triazole antifungals and considering specific examples of common DDIs induced by these antifungals. Let us begin with fluconazole.

Fluconazole is predominantly excreted via the urine, with 80% of the drug being excreted unchanged, while only about 11% is metabolized, through CYP3A4, in the liver (27). Fluconazole inhibits CYP2C9, CYP3A4, and CYP2C19, non-competitively or by mixed-type inhibition, but to a lesser extent than does itraconazole (28). For this reason, it can interfere with the metabolism of drugs that are substrates of 1 or more of these enzymes, especially the first 2. These include warfarin, midazolam, rapamycin, FK506, cyclosporine, and vincristine, among others (28). The interaction with warfarin is especially important because the anticoagulant is metabolized predominantly through CYP2C9. Fluconazole, being an inhibitor of CYP2C9, has been shown to induce an increase in warfarin levels as high as 38% in patients previously stabilized on warfarin therapy, according to standards (28). Fluconazole also interferes with enzymes involved in glucuronidation (phase II reactions), so it can influence the conjugation and thus the levels of drugs such as acetaminophen, lorazepam, and carbamazepine, among others (28). Importantly, as fluconazale is not predominantly metabolized through the CYP450 system, drugs that induce or inhibit the CYP450 enzymes are unlikely to exert changes in the pharmacokinetic profile of fluconazole (27).

In contrast, itraconazole is predominantly metabolized in the liver through CYP3A4 (27). Interestingly, and contrary to the other azoles, itraconazole has a metabolite with antifungal activity that is comparable to that of the parent compound. A drug whose pharmacokinetic profile has been shown to be significantly influenced by itraconazole is lovastatin (28). This can be explained by the fact that the drug is mainly metabolized through hepatic CYP3A4, and this enzyme is strongly inhibited by itraconazole.

Voriconazole is mainly metabolized through CYP2C19, CYP3A4, and, to a lesser degree, CYP2C9 (28). Voriconazole also inhibits these enzymes, thus potentially interacting with different drugs that are also metabolized by these enzymes. Examples are, among others, warfarin and the immunosuppressants FK506, rapamycin, and cyclosporine (28).

Posaconazole, in contrast to itraconazole and voriconazole, is metabolized predominantly via *uridine diphosphate glucuronosyltransferase* (UGT) pathways instead of by the CYP450 system (28). Therefore, drugs that induce or inhibit the UGT pathways are likely to induce changes in the pharmacokinetic profile of posaconazole. Examples of such drugs are lopinavir and ritonavir (27).

One thing worth mentioning about the drugs tacrolimus (FK 506) and cyclosporine and the triazole antifungals is that a reduction in the dose of the immunosuppressive drugs is advised when either one of them is being concomitantly administered with a triazole (28). In addition, careful monitoring of

renal function parameters and immunosuppressant serum concentrations is recommended.

Another aspect regarding DDIs that is worth mentioning is the following: Besides the direct inhibition of catalytic activity that azole drugs exert on the CYP450 enzymes, especially CYP3A4, azole drugs also influence CYP3A4 and other CYP450 enzymes indirectly (32). This is because azoles exert an influence on the transcriptional activity of the *pregnane X receptor* (PXR) by modulating its ligand-binding properties or by affecting the recruitment of co-activators (32). PXR is a key regulator of the transcription of metabolic enzymes such as CYP3A4. Although important, further discussion of this aspect is beyond the scope of this writing.

Finally, it is important to mention that pharmacokinetic DDIs are much more complex than is apparent from the discussion, as additional factors besides those we have discussed have an influence on the occurrence of DDIs (33). Perhaps the most important one is the occurrence of polymorphisms or genetic variants among individuals in a population (31). Human CYP450 genes are highly polymorphic, leading to variants forms of enzymes with either enhanced or decreased activity, or with almost no activity at all in some cases. Three other factors that exert an influence in the occurrence of DDIs are diet, exposure to environmental chemicals, and lifestyle habits, such as smoking (33). However, a discussion of these and other factors related to the occurrence of DDIs is beyond the scope of this writing.

Spectrum of activity and adverse effects

Triazoles have been shown to discriminate between fungal and mammalian P450 enzymes better than the imidazoles do (34). This makes them safer for humans to use. Nevertheless, though safer when compared to other drugs, triazoles are not completely free of adverse effects (34). As a group, they have been associated with a degree of hepatotoxicity that can be severe in extreme cases (though rarely requiring the ending of the treatment) (34). The first triazoles introduced in the market, the so-called *first-generation* triazoles, *fluconazole* and *itraconazole*, have an improved safety profile compared to *ketoconazole* (9).

Fluconazole

Fluconazole is the first member of the *first-generation* of triazoles. The spectrum of activity of fluconazole includes the dimorphic fungi *Cryptococcus neoformans* and most *Candida spp.* (9). Two *Candida* species that are often insensitive to fluconazole and are thus exceptions to the rule are *Candida krusei* and *Candida glabrata* (5). Fluconazole has been associated with the development of hepatic necrosis, hepatitis, cholestasis, and gastrointestinal disturbances such as abdominal pain, nausea, vomiting, and diarrhea (7). Additional but rare adverse effects associated with the use of fluconazole are fever, hypotension, pulmonary edema, and hematologic disturbances such as anemia and thrombocytopenia (7). In 2011 a safety communication was made by the FDA, announcing that fluconazole given at doses of 400 to 800 mg/day during pregnancy might be linked to birth defects in infants (35).

Itraconazole

Itraconazole is the second member of the *first-generation* of triazoles. It is often the first choice for the treatment of infections caused by *Blastomyces dermatitidis*, *Histoplasma capsulatum*, and *Aspergillus spp.*, and to treat *onychomycosis* (36). The safety and pharmacokinetic profile of itraconazole has limited its use in therapy. Most adverse effects linked to the use of itraconazole are like those associated with the use of fluconazole. However, the incidences of these effects, especially nausea and diarrhea, have been found to increase significantly when it is administered orally (9). Although less common, another serious adverse effect that has been reported is heart failure (36). According to the cited source, itraconazole should not be prescribed to patients with either heart failure or left ventricular systolic dysfunction (36).

Voriconazole

The FDA approved the therapeutic use of voriconazole in 2003 (37). As a rule, it is a relatively safe and well-tolerated drug (38). However, it is not free of adverse effects. Some of the most common are transient visual disturbances (9). *Photopsia*, which may persist after ending treatment, has also been associated with the use of voriconazole (39). In addition, although less common, neurological disturbances have also been reported (38). Reversible visual disturbances include the altered sensing of colors, blurred vision, and photophobia (40), while the neurological disturbances include neurotoxicity, hallucinations, and encephalopathy (38). Additional adverse effects that have been reported are angioedema, which is a transient swelling of the face, dermatologic reactions and hepatotoxicity (41), hypoglycemia, electrolytic disturbances, and pneumonitis (42). Furthermore, voriconazole therapy has been implicated in the development of photosensitivity, aggressive squamous cell carcinoma, and melanoma, when administered for a long term in patients with chronic photosensitivity (43). Pediatric cases in which the drug is used deserve special attention, as reactions of a psychological nature, although apparently transient, have been reported in children as young as 9 years old (38). In addition, pediatric oncology patients have experienced severe skin toxicity when voriconazole is used in prophylaxis concomitantly with a low dose of methotrexate (MTX) (43). In these patients, photosensitivity was apparently enhanced when they were given voriconazole concomitantly with MTX, though the mechanism for this effect was not identified.

Posaconazole

Posaconazole was approved for use in the U.S. in 2006 in an oral suspension formulation. Other drug formulations (delayed-release tablets and an injectable formulation) were approved in 2013 and 2014, respectively, by the FDA (44). Posaconazole

has a spectrum of activity that is like that of voriconazole, but in addition it has limited activity against *Mucorales spp.* (9). In the U.S. it is sold under the name Noxafil®, and its use has been limited to be a prophylaxis agent against *Aspergillus* and *Candida* infections and for the treatment of *oropharyngeal candidiasis*. The adverse reactions profile of posaconazole is like that of fluconazole (9). Interestingly, it has been found to have a lower potential for interaction with other drugs and for adverse events compared to voriconazole and itraconazole. It is contraindicated in patients taking sirolimus (rapamycin), CYP3A4 substrates such as pimozide and quinidine, HMG–CoA inhibitors that are metabolized through CYP3A4, and ergot alkaloids. The levels of these drugs are likely to increase with the concomitant use of posaconazole (44). It is also contraindicated in patients with a known hypersensitivity to azole drugs and in pregnant women. As with adults, in pediatric patients it is indicated as a prophylactic agent against invasive *Aspergillus* and *Candida* infections and for treating *oropharyngeal candidiasis*, the dose of the latter depending on whether the infection is refractory to fluconazole or itraconazole. However, the latter statement holds true only for the *oral formulation of the drug, as the injection formulation has been approved only for patients who are 18 years or older* (44). Importantly, the FDA has not approved the use of posaconazole in children less than 13 years of age. According to the agency, common adverse reactions related to the use of posaconazole in pediatric patients are diarrhea, nausea, fever, vomiting, headache, hypokalemia, and coughing (44).

Future perspectives

Triazoles are still promising as therapeutic agents against pathogenic fungi, and some have been recently under study (15). Yet a new advance has been recently reported that will aid us in the rational design of novel triazole antifungals. It is the determination of the crystal structure of the CYP51 from the model yeast *Saccharomyces cerevisiae* in complex with its substrate lanosterol and with the triazole inhibitors fluconazole and itraconazole (16). Moreover, since the solving of this structure, others have been determined—such as that of the pathogenic fungi *Candida glabrata*—and have been deposited in the protein data bank (www.pdb.org). These newly solved structures will give us insights into the essential interactions involved and how they can be manipulated to develop more effective triazole antifungals.

Conclusions

Triazoles remain the most widely used compounds in the treatment of systemic mycoses. However, despite showing high selectivity for fungal CYP450 enzymes compared to imidazoles, triazoles can still lead to adverse side reactions mostly by interfering with human CYP450 enzymes. Indeed, when used concomitantly with other drugs, triazoles can induce DDIs that might be significant and could lead to adverse reactions that may require the monitoring of drug and/or enzyme levels or even therapy withdrawal, in extreme cases. As the incidence of opportunistic mycoses has been increasing during the last decades, and because pathogenic fungi are able to develop resistance to the current drugs, we need to develop new strategies to fight these infections. Triazoles are still promising for therapy, but novel ones with a higher selectivity for the fungal CYP51 enzymes and that are better able to discriminate between the fungal target and the host must be developed.

Resumen

Los compuestos azoles son ampliamente usados con fines terapéuticos para combatir infecciones causadas por hongos. Estos compuestos muestran un amplio espectro de actividad antimicótica, combatiendo patógenos de relevancia clínica. Los triazoles discriminan mejor comparados a los diazoles entre su objetivo molecular, la enzima CYP51 del hongo patogénico, y varias enzimas del sistema CYP450 humano. Por esta razón su uso ha sido favorecido a través de los años sobre los diazoles en el tratamiento de infecciones micóticas sistémicas. No obstante, a pesar de tener una mayor capacidad para discriminar entre las maquinarias moleculares del patógeno y la del huésped, siguen siendo capaces de inducir toxicidad y reacciones adversas severas en el huésped, especialmente cuando son administrados de manera simultánea con otras drogas terapéuticas a pacientes con un sistema inmunitario comprometido. En este escrito repasamos algunos conceptos fundamentales acerca de la química y mecanismos de acción de los compuestos azoles, así como también espectros de actividad antimicótica, farmacocinética y efectos adversos de los compuestos triazoles. Además, discutimos algunos de los mecanismos emergentes en hongos patogénicos para resistir los efectos citotóxicos de drogas terapéuticas, haciendo énfasis en compuestos triazoles.

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