International Journal of Medicine and Medical Sciences Vol. 3(2), pp. 22-31, February 2011
Available online http://www.academicjournals.org/ijmms
ISSN 2006-9723 ©2011 Academic Journals

Review

Pharmacokinetic drug interactions of phosphodiesterase-5 inhibitors mediated by cytochrome P450 3A4 isoform

Srinivas Pentyala[1,2,*], Aleef Rahman[1], Supriya Mishra[1], Sowmya Muthiki[1], Emily Hughes[1], Abhishek Bikkani[1], Kathleen Cervo[1], Christopher Maruso[2] and Sardar Khan[2]

[1]Departments of Anesthesiology, School of Medicine, Stony Brook University Medical Center, Stony Brook, New York
[2]Departments of Urology, School of Medicine, Stony Brook University Medical Center, Stony Brook, New York.

Accepted 9 November, 2010

Novel drugs for Erectile Dysfunction (ED) must be assessed for their interactions with other already approved medications that are processed through similar metabolic pathways. The cytochrome P450 enzyme family, in particular 3A4 isoform, is ubiquitously used to oxidize azole antifungals, erythromycin, and HIV protease inhibitors. Administering multiple medications using cytochrome P450 CYP3A4 (3A4) as a primary metabolic route may cause unexpected toxicological effects in patients. Current U.S Food and Drug Administration (FDA) approved ED drugs such as sildenafil (Viagra), tadalafil (Levitra), and vardenafil (Cialis), all Phosphodiesterase-5 inhibitors, are also metabolized by 3A4. The overlapping metabolic pathways for the above mentioned PDE-5 inhibitors are known, however it is still imperative to discover any negative clinical manifestations that may arise from their concomitant use or their use with other substrates that are metabolized by 3A4 enzyme. Worldwide, approximately 150 million men are struggling with ED, making this research a valid obligation. Consequently, interaction of the widely prescribed ED drugs and their interactions with 3A4 enzyme are discussed in this review.

Key words: Cytochrome P450, 3A4, erectile dysfunction, Viagra, Cialis, Levitra.

INTRODUCTION

The cytochrome P450 super family is a family of enzymes that is widely expressed across all living species, from archaebacteria to advanced eukaryotes such as humans (Danielson, 2002). There are over 2000 known genomic cytochrome P450 sequences, including 75 gene sequences and 19 pseudogenes that have been identified in humans in particular (Guengerich, 2001; Danielson, 2002). This enzyme family derives its name for the unique absorbance at 450 nm that is seen in its microsomal carbon monoxide bound species in early studies of rat and pig microsomal protein fractions (Omura, 1999). The cytochrome P450 super family is involved in a wide variety of reactions in human metabolism (Wang et al., 2009). These include; the synthesis of endogenous low-molecular-weight substances such as steroids, prostaglandins, thromboxanes, fatty acid derivatives and derivatives of retinoic acid (Ito et al., 1998; Lewis, 2003), and metabolism of xenobiotics derived from foreign chemicals, pollutants, carcinogens, and therapeutic drugs.

STRUCTURE OF P450

In humans, cytochrome P450 enzymes are about 500 amino acids long and are best characterized by their heme group bound by four ligands, which is conserved across all cytochrome P450s. This iron containing heme group is likely to be the active site for its metabolic catalytic activity. When this active site is bound with

*Corresponding author. E-mail: srinivas.plenty@stonybrook.edu. Tel: 631-444-2974. Fax: 631-444-2907.

carbon monoxide, this creates the 450 nm absorbance peak that led to the naming of this protein as cytochrome P450. A highly conserved Thr residue and neighboring Glu residue are important to the heme group and play a role in proton transfer to the heme group to aid in heterolytic cleavage of the O-O bond (Guengerich, 2001), a key step in several important reactions that are catalyzed by these enzymes. All members of the cytochrome P450 super family share a common globular to triangular structural framework that is rich in alpha helices and beta sheets at the carboxy-terminus and amino-terminus, respectively(Jang et al., 2010). These enzymes are membrane bound by an amino terminal anchor sequence by the endoplasmic reticulum in micro-somes of the liver and in the mitochondrial membrane. A unique cytochrome P450 was reported as a cytosolic variant that is common in prokaryotic species, but extremely rare in eukaroyotes. In eukaryotes, the cytochrome P450s are expressed in several tissues including, but not limited to, the gastro-intestinal tract, the kidneys, and of most importance the liver, one of the main sites of xenobiotic metabolism.

BIOCHEMISTRY / METABOLISM / XENOBIOTIC PROCESSING

One of the primary roles of the cytochrome P450 family is xenobiotic processing. In this role, the enzymes catalyze a multitude of reactions, some common and uncommon reactions that result in normal metabolism and or lead to chemical toxicity, respectively. Although cytochrome P450 catalyzes a multitude of reactions such as deaminations, epoxidations, N-oxidations, peroxidations, sulfoxidations, dehalogenations, etc., the most important reaction is the oxidative hydroxylation of lipophillic xenobiotics (McKinnon and McManus, 1996; Guengerich, 2001; Liska et al., 2006).

This occurs during phase one of xenobiotic metabolism and results in a hydroxylated product that is more polar and thus more likely to be excreted. Cytochrome P450 enzymes also conjugates with endogenous products by reacting with the hydroxy substituent during phase two metabolism reactions. The hydroxylation reaction requires the incorporation of one atom of molecular oxygen into the substrate and another oxygen atom into a molecule of water. The generalized reaction follows the basic equation:

$$NAD(P)H + O_2 + SH + H^+ \rightarrow NAD(P)^+ + SOH + H_2O \quad (1)$$

This reaction type, although just one of many others, is the primary one used for oxidative metabolism of xeno-biotics by the microsomal fractions and mitochondrial cytochrome P450s. Although the general characteristics of catalysis are widely agreed upon, there is a plethora of alternate reactions and mechanisms that the cytochrome P450s can carry out.

DRUG INTERACTIONS

Because of the role that the cytochrome P450 enzymes play in drug metabolism, their activity will determine the pharmacokinetic behavior of the majority of therapeutic drugs that are taken today. The incidence of drug interactions is increased when there is competition between two or more drugs for oxidation by the same P450 enzyme (Murray, 1992; Danielson, 2002). This becomes a topic of interest in dealing with cytochrome P450 enzymes and in particular will have important bearing on one cytochrome P450, the 3A4.

3A4 and its significance in xenobiotic metabolism

Of the many cytochrome P450 isoforms that exist in the human, 3A4 is widely regarded as the most important in xenobiotic metabolism (Thummel and Wilkinson, 1998; Danielson, 2002; Lewis, 2003). First, it is the most abundant of the cytochrome P450 isoforms in the liver, the primary organ of xenobiotic metabolism. Secondly, partially due to the enzyme's broad substrate specificity and flexible active site (Lewis, 2003), it is responsible for the metabolism of the majority of therapeutic drugs in the human. It is suggested that up to 40 to 50% of all drugs that are taken by humans are metabolized to some extent through the action of 3A4 (Thummel and Wilkinson, 1998).

Although this suggestion is based to a large extent on *in-vitro* studies, though actual *in-vivo* effects may be different, it is still apparent that 3A4 plays a major role in the xenobiotic metabolism of drugs in the human body. If we consider that 3A4 plays such an important role in the xenobiotic metabolism of such a broad spectrum of drugs, we must also take into account possible drug interactions that could occur. Administration of multiple drugs that are metabolized by a single enzyme primarily can result in disruption of key metabolic processes. The likelihood of such a situation happening is increased to a great extent with 3A4, because of the plethora of drugs that are metabolized by cytochrome P450 enzyme (Lewis, 2003).

Drug interactions occur primarily via inhibition or induction of the 3A4 enzyme. Although certain reactions have been characterized as inductions of 3A4 leading to unwanted toxicological effects, the focus of this report will be on the inhibition of 3A4 as it is more broadly characterized and pertains more to the drugs related to the treatment of Erectile Dysfunction (ED). The substrate with higher affinity will bind to 3A4 first, when two competing drugs that are both metabolized by 3A4 are co-administered. Depending on the substrate, several mechanisms can then potentially block the enzyme (3A4) from acting on the second substrate. This in turn, could result in elevated levels of that substrate, creating the possibility of increased and unwanted pharmacological and toxicological effects. 3A4 has been examined in

many research studies, and the major mechanisms of drug-interaction inhibition that could cause unwanted pharmacological effects are under strict scrutiny. Inhibition drug patterns can abide by certain mechanisms such as competitive inhibition, non-competitive inhibition, and uncompetitive inhibition (Ito et al., 1998). These interactions have been applied to 3A4 in particular. Previous research has shown, the inhibition of 3A4 abides by several main mechanisms (Thummel and Wilkinson, 1998):

Competitive or non-competitive binding

In this type of interaction, the inhibition mechanism is direct and is rapidly reversible. It depends on the binding constants of the substrate versus the inhibitor, and also depends on the relative concentrations of each of the species. Some of the inhibitors of 3A4 that use this mechanism of inhibition include azole antifungal agents, some HIV protease inhibitors such as nelfinavir mesylate (Lillibridge et al., 1998), and antihypertensives such as Diltiazem (Sutton et al., 1997).

Formation of metabolic-intermediate (MI) complexes

The formation of an MI complex results from inhibitors that have an N-alkyl substituent - a common feature on many therapeutic drugs. After the inhibitor binds, it is oxidized by 3A4 and the resultant oxidized species of the inhibitor remains complexed with the reduced heme group of 3A4 forming a complex (MI complex) that is slowly reversible. Macrolide antibiotics are well known 3A4 inhibitors that use this mechanism of inhibition.

Mechanism based inhibition

In mechanism based inhibition, the metabolite that results from the oxidation of the substrate by 3A4 becomes irreversibly and covalently bound to 3A4 thus leading to a permanent activation of the enzyme. 17α substituted steroids; ethinylestradiol, gestodene, and levonorgestrol have been found to inactivate 3A4 in this fashion. Recently resveratrol, one among a number of non volatile red wine components, have been shown to irreversibly inactivate 3A4 in this way (Piver et al., 2001).

Despite a good amount of knowledge that exists on inhibitors of 3A4 and their clinical manifestations, the nature of the interactions is still being studied in more detail. Clinical pharmacokinetics of erectile dysfunction drugs has been extensively studied(Gupta et al., 2005) and inhibitions based on these mechanisms have been well characterized but some studies also show that they can be more complex and interaction is not simply based on the inhibitor at hand, but is also substrate dependent (Nishime et al., 1999). Additionally, certain inhibitors only augment the concentration of certain substrates possibly due to multiple binding sites of 3A4 (Galetin et al., 2002).

Through clinical experience, only a few inhibitors have shown to result in significant negative clinical manifestation (Thummel and Wilkinson, 1998). For clinically negative effects to occur, one needs co-administration of 3A4 inhibitor with another drug whose major elimination/ metabolism pathway is 3A4. And with these conditions only, certain strong 3A4 inhibitors have been shown to induce pharmacological effects. Azole antifungals are potent 3A4 inhibitors and this family includes ketoconazole, itraconazole, and fluconazole (Thummel and Wilkinson, 1998). Macrolide antibiotics are common medications that are strong inhibitors of 3A4 as well (Thummel and Wilkinson, 1998). This family includes drugs such as erythromycin troleandomycin and clarithromycin. Serotonin reuptake inhibitors such as nefazodone and fluvoxamine have also been characterized to inhibit 3A4 (Thummel and Wilkinson, 1998). Because of the characterization of many of the 3A4 inhibitors through *in vitro* studies, the dynamics of many drug interactions can be predicted, and thus, possible co-contaminant use of interacting drugs can be avoided. Studies have investigated these effects and their results urge the public to prevent possible drug interactions through warnings of adverse effects. For example, the co-administration of 3A4 inhibitors with Simvastatin could increase the risk of myopathy (Gruer et al., 1999) and co-administration of HMC-CoA inhibitors can increase the risk of rhabdomyolysis (Martin and Krum, 2003). In general, the strong 3A4 inhibitors administered with other drugs, whose primary metabolism is 3A4, warrants close watch of dose titration to prevent any possible negative effects.

Although many drug interactions cannot be understood until clinical trial of a drug, the well known interactions with known 3A4 inhibitors can be predicted before co-administration. This must be taken into account with new drugs coming into the market. In addition, the ability of a newly approved drug to bind 3A4 and augment its activity or inhibit its activity must be investigated as well, to prevent adverse pharmacokinetic and toxicological effects. Characterization of 3A4 inhibitors among new drugs could also prevent drug interactions from occurring in patients unnecessarily. These results could provide critical warning for patients about possible drug interactions and in doing so could prevent negative clinical effects such as toxicity and unwanted pharmacological effects. This issue is also important with all new drugs pending approval by the FDA, and attention should be focused on the PDE-5 inhibitor class of drugs whose interaction with 3A4 must be scrutinized.

ERECTILE DYSFUNCTION AND PHOSPHODIESTERASE-5 INHIBITORS

Erectile dysfunction (ED) is the inability to achieve and maintain an erection adequate for satisfactory sexual

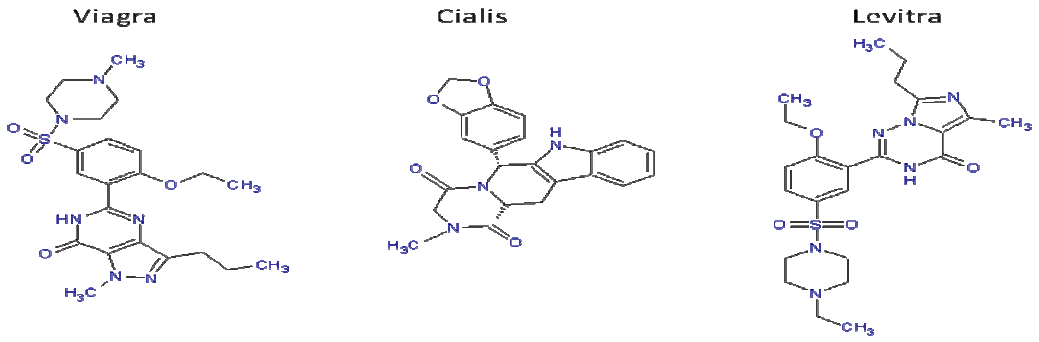

Figure 1. Chemical structure of PDE- 5 inhibitor used for treating ED.

performance. Over 150 million men worldwide are struggling with ED (McKinlay, 2000). The etiologies of erectile dysfunction can be psychological and physical factors, although in most cases both mechanisms interplay. Psychological factors include depression, relationship issues, sexual ignorance, fear of failure, performance anxiety, and childhood or adult sexual abuse. Physical factors may be vasculogenic as in diabetes, hypertension, hypercholesterolaemia and smoking, neurogenic as in spinal injuries, endocrinal as in hypogonadism and hypothyroidism, and local penile tissue factors as in Peyronie's disease. Recent studies have shown the association of erectile dysfunction with metabolic syndrome and cardiovascular disease. Erectile dysfunction is now considered a marker for these conditions and consequently the management of erectile dysfunction now concentrates on screening for, and preventing, cardiovascular diseases as well as treating the condition itself (Raheem and Kell, 2009).

Before 1998, several treatments existed for erectile dysfunction, including intercavernous injection therapy such as Caverject and Edex (both being alprostadil injections), use of a vacuum erection device, and penile prosthesis; each with its own individual reports of efficacy. With the introduction of the phosphodiesterase-5 (PDE-5) inhibitor class of drugs, sildenafil (Viagra) revolutionized the treatment for erectile dysfunction and brought the disease into mainstream attention.

PDE-5 specific inhibitors allow penile tumescence to remain. In the penile erectile response, sexual stimulation induces nonadrenergic and noncholinergic nerve terminals to release nitric oxide (NO) in the corpus cavernosa of the penis. Nitric oxide (NO) then positively activates guanylate cyclase, an enzyme that converts guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). cGMP is a neurotransmitter which induces smooth muscle relaxation, in the corpora cavernosa, increasing arterial blood flow into the penis. This results in penile tumescence and erection. The tumescence is lost and the penis becomes flaccid when PDE-5 catalyzes the breakdown of cGMP. The inhibitors of PDE-5 prevent this breakdown from occurring, increasing the effect of cGMP.

SILDENAFIL (VIAGRA)

By 2002, four years after it was approved by the Food Drug Administration, more than 16 million men received over 100 million prescriptions of sildenafil worldwide (Corbin and Francis, 2002). To a certain extent, the widespread use of sildenafil is an affirmation to the efficacy and safe use of the drug. Sildenafil has been found to be a significantly effective treatment for erectile dysfunction improving erections in affected men from multiple etiologies in multiple double blind, placebo controlled trials with differential doses (Fagelman et al., 2001; Palumbo et al., 2001). The efficacy of sildenafil can be ensured even further through comprehensive and proactive measures by physicians who ensure proper patient education regarding drug dosage, even in patients who have not experienced success with sildenafil treatment (McCullough et al., 2002). On one hand, sildenafil has been associated with side effects including headache, flushing, dyspepsia, nasal congestion, abnormal vision, dizziness and rashes (Lim et al., 2002). However, these effects are usually transient and tolerable to most patients (Lim et al., 2002).

In addition to its excellent efficacy profile, the pharmacological profile of sildenafil has also been well characterized and studied. Highly selective for PDE-5, sildenafil (Figure 1) has a mean half-life of 3.7 h reaching a maximum serum concentration at 0.8 h with a C_{max} of 560 ng/ml (Corbin and Francis, 2002). Sildenafil is contraindicated with nitrates or nitrites use (Krenzelok, 2000). The combination of the two substances could possibly cause profound hypotension due to the synergistic effect between the drugs which itself could lead to further complications, including death. This synergistic effect with nitrates is the only combination that is outright contraindicated at the present time.

Sildenafil is metabolized primarily by the cytochrome P450 enzyme 3A4 (Krenzelok, 2000; Warrington et al., 2000; Burgess et al., 2008), which is the principle enzyme responsible for the oxidative metabolism of the majority of drugs that are taken today. With this in mind, one must take into account the interaction between sildenafil and other drugs that are also metabolized by

3A4, because enzymes that compete with sildenafil for 3A4, especially those that are inhibitors of the enzyme, could cause unwanted pharmacological effects such as elevated and prolonged serum concentrations of sildenafil.

There is a mutual pharmacokinetic interaction between bosentan (an endothelin receptor antagonist used for the treatment of pulmonary arterial hypertension) and sildenafil that may influence the dosage of each drug in a combination treatment (Burgess et al., 2008). How-ever, co-administration of sitaxentan (endothelin receptor antagonist) with sildenafil has been reported to clinically insignificant (Stavros et al., 2010). Clinical research on strong inhibitors of cytochrome P450, specifically, co-administration of sildenafil with potent 3A4 inhibitors such as azole antifungal agents, macrolide antibiotics, and protease inhibitors, suggest caution with dosing (Krenzelok, 2000; Corbin and Francis, 2002; Jetter et al., 2002). Even inhibitors of 3A4 that exist in grapefruit juice have been shown to alter sildenafil biometabolism.

This result urged physicians to practice cautioning of patients who are experimenting with such a combination (Jetter et al., 2002). Strong inhibitors of 3A4 can overburden and inhibit the enzyme, resulting in elevated sildenafil serum concentration (Muirhead et al., 2000; Corbin and Francis, 2002) and could enhance pharma-cological and toxicological effects (Corbin and Francis, 2002).

It is suggested that administration of sildenafil with inhibitors of 3A4 should consider using a lower starting dose (Krenzelok, 2000; Corbin and Francis, 2002; Jetter et al., 2002) and yet others suggest that those on 3A4 inhibitors should not exceed the usual minimum dosage of 25 mg in any 48 h period (Krenzelok, 2000). Dosage of sildenafil with 3A4 inhibitors has demanded some extent of caution. In the absence of absolute contrain-dications regarding co-administration with nitrates, the use of sildenafil has proven to be extremely safe under proper conditions (Krenzelok, 2000).

Sildenafil itself is a weak inhibitor of 3A4 (Lim et al., 2002), and may occasionally interfere with the degra-dation of substrates cleared by that enzyme system. However, because of the weak inhibition it exhibits, this interaction does not have significant clinical manifesta-tions and rather the interaction of sildenafil with inhibitors with a stronger affinity for the 3A4 enzyme draws greater agony.

TADALAFIL (CIALIS)

Tadalafil is approved by the Food and Drug Administration to be taken once daily. It is a selective PDE-5 inhibitor that has shown in some studies to have promising efficacy, tolerability, and goodshort-term safety for the treatment of erectile dysfunction of varying etiologies. In a study published in 2002 (Brock et al., 2002), 5 randomized, double blind, placebo controlled, parallel group trials conducted the efficacy and tolerability of tadalafil at differential doses for two years in over 1000 men. Tadalafil significantly improved erectile response in these men and was well tolerated among the patients in the study with the main adverse side effects being headache and dyspepsia.

One of the main things that set tadalafil apart from the other PDE-5 inhibitors is its broad therapeutic window of response due to its distinctive structure (Figure 1). Studies have shown that men with erectile dysfunction under tadalafil treatment have been able to successfully complete sexual intercourse attempts with proper sexual stimulation after 36 h following initial dosing. With its T_{max} of 2 h, tadalafil shows effect within 16 to 60 min after intake (Brock et al., 2002). This is due to the long $T_{½}$ of 17.5 h, which is more than four times the half-life of sildenafil ($T_{½}$ sildenafil = 3.7 h). The long half-life of tadalafil allows the patient greater opportunity to engage in sexual activity more than once after a single dose of tadalafil, and possibly up to 1.5 days after tadalafil was initially taken. In addition there is no interaction between food and alcohol and the absorption of tadalafil. These unique characteristics of the drug may contribute to a more spontaneous sexual activity (Montorsi et al., 2003a) for men with erectile dysfunction under tadalafil treatment because of less stringency with timing of dosage and prior food or drink intake. With the widespread use of sildenafil, one might expect that a similar trend with tadalafil will be seen in terms of use. However, despite its convenient usage, the pharmacokinetics of the drug that is solely responsible for prolonged erection are the exact effects that should demand careful caution due to possible metabolic complications and drug interaction.

With regard to its unique pharmacokinetics, in one report, tadalafil has been reported to have a C_{max} of 378 ngml, a T_{max} of 2.0 h, a $T_{½}$ of 17.5 h and an area under the curve for plasma concentration (AUC) of 8066 ng*h/ml (Corbin and Francis, 2002). It should be noted that C_{max} depends upon dose and distribution volume and varies with each subject. Tadalafil is also primarily metabolized by the cytochrome P450 3A4, similar to sildenafil, which brings into question once again the potential drug interactions with competing drugs for the enzyme. Despite such evident risk possibility, currently there is limited or no information on potential drug interactions with tadalafil (Corbin and Francis, 2002).

Drugs that are eliminated by hepatic metabolism such as 3A4 (inclusive of tadalafil) require some type of consideration in regard to drug interactions and even more careful consideration for PDE-5 inhibitors that have a long $T_{½}$ (Corbin and Francis, 2002). This could possibly require even more careful dosing intervals. With exten-sive studies on sildenafil, precautions have already been characterized to a great extent, and dosing suggestions have been outlined regarding the co-administration with 3A4 inhibitors. No such dosing precautions exist for

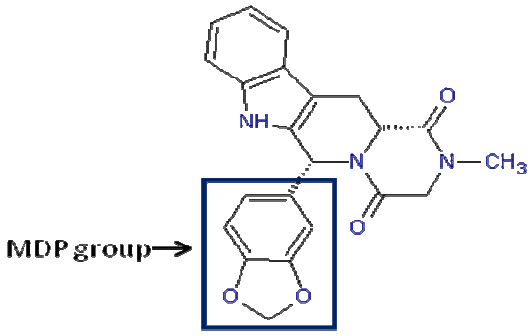

Figure 2. Tadalafil with MDP group.

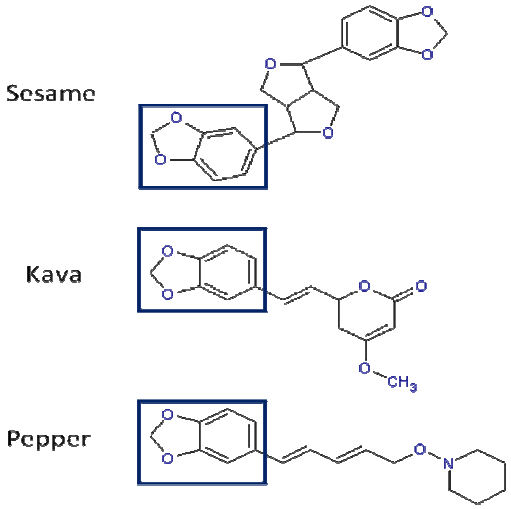

Figure 3. MDP found in oils and spices.

tadalafil at the present time.

Tadalafil also exhibits a greater AUC versus time. A greater AUC may be valuable for a longer therapeutic effect in the case of tadalafil (the AUC of tadalafil is 4 times greater than that of sildenafil), but could be harmful if adverse effects need to be limited (Corbin and Francis, 2002).

In addition to the considerations regarding dose caution with tadalafil when co-administered with already well characterized 3A4 inhibitors inclusive of macrolide anti-biotics, azole antifungals, and HIV protease inhibitors, the inhibition of 3A4 by tadalafil itself has yet to be characterized. Sildenafil is a weak inhibitor of 3A4. Tadalafil's chemical structure is very different from that of sildenafil, thus suggesting it may have different binding properties in terms of interacting with 3A4 and inhibiting the enzyme. A key substituent group that is also present on tadalafil is the methylenedioxyphenyl (MDP) group (Figure 2). It is suggested that MDP compounds, found in some oils, spices, (Figure 3) and new therapeutic drugs, are of considerable toxicological significance because of their capacity to inhibit and induce CYP enzymes in mammals (Murray, 2000). The presence of MDP group on tadalafil could indicate great ability to bind and inhibit the activity of Cytochrome P450 (Murray, 2000). Although currently there is insufficient evidence regarding the effect of MDP on human cytochrome P450, it has been characterized as a strong modulator of several mammalian cytochromes including CYP3A. There are multiple mechanisms that these MDP compounds use to inhibit cytochrome P450 and new therapeutic drugs with this group are under scrutiny for potential adverse reactions. This interaction warrants further study with human 3A4. This further challenges the long term side effects tadalafil could have on patients, not only through interaction with well known inhibitors of 3A4, but also by its intrinsic ability to bind CYP itself, since it is a MDP compound.

Tadalafil shows promise in terms of its ability to treat erectile dysfunction, however, its pharmacological profile, regarding its interaction with 3A4 inhibitors, as well as its own ability as an MDP compound to alter 3A4 and possibly inhibit it, must be further examined. Such discoveries are necessary to prevent any adverse drug reactions in long term use of tadalafil from occurring.

VARDENAFIL (LEVITRA)

Vardenafil (Figure 1) was introduced in 2005 as a highly potent PDE-5 inhibitor that is highly selective with an IC_{50} of 0.7 nm. Although sildenafil has the same metabolic profile, vardenafil was found to be more effective at doses with equivalent clinical efficacy to that of sildenafil (Bischoff, 2004; Bandel, 2001). Sodium nitroprusside, a NO donor, increases cGMP in human cavernosal tissue with the administration of vardenafil (Bischoff, 2004). With a maximum plasma concentration of 0.7 to 0.9 h, and terminal half-life of more than 4 h, when examined in doses of 10, 20, and 40 mg, vardenafil significantly increased the quality and the duration of erections with ED patients. In a randomized, double-blind, placebo-controlled study over the course of 12 weeks, vardenafil showed high efficacy and low adverse events. Primary endpoints studied were Q3 (vaginal penetration) and Q4 (maintenance of erection) of the International Index of Erectile Function (IIEF). In the intent-to-treat population, the changes from baseline vardenafil were all improved over placebo for Q3 and were similarly improved for Q4 compared to placebo. Vardenafil improved all IIEF domains compared to placebo and success rate was reported to be around 75%. A few frequent treatment-emergent adverse events like headache, flushing and up to 7% for dyspepsia or rhinitis, with no cardiovascular problems, were reported (Porst et al., 2001).

Since the release of NO achieves and maintains a penile erection, vardenafil inhibits PDE-5 by augmenting the effect of NO and inducing smooth muscle relaxation. As a result, cGMP levels rise, enhancing the vasodilatory

effect of NO in the corpus cavernosum. The major substrate of vardenafil is cytochrome P450-3A4. Therefore, it is suggested that concomitant administration of vardenafil with other PDE-5 inhibitors reduce vardenafil clearance. Administration of vardenafil with indinavir, ritonavir and ketoconazole is contraindicated because they are all strong inhibitors of 3A4. In a study where ritonavir and ketoconazole were co-administered with vardenafil, significant increase in vardenafil AUC was observed. This implies a general rule - if other PDE-5 inhibitors are taken with vardenafil, careful monitoring of patient health and strict dosage intervals must be followed to avoid detrimental health risks (McCullough, 2004). Additionally, in clinical trials, it was shown that vardenafil has five times the PDE-5 inhibitory effect than sildenafil (Gresser and Gleiter, 2002). Such a difference emphasizes the importance of specifically studying the different drug interactions between vardenafil and other PDE-5 inhibitors. Due to the higher inhibitory effect, dosage intervals for vardenafil may be more stringent than sildenafil, when administered with other PDE-5 inhibitors. There are still many unknown drug interactions between vardenafil and other PDE-5 inhibitors such as the azole antifungals, erythromycin and other HIV protease inhibitors because all are metabolized by cytochrome P450 (Nishime et al., 1999). Drug-drug interactions with alpha-1 adrenergic blockers and anti arrhythmic agents were also reported for vardenafil (Bailey and Dresser, 2004). However, co-administration of silodosin and maximum therapeutic doses of sildenafil or tadalafil in healthy men caused no clinically important orthostatic changes in blood pressure or HR and no orthostatic symptoms (MacDiamid et al, 2010). Therefore, it would be vital to examine the detailed effects and function of vardenafil in individuals who are also consuming other drugs and PDE-5 inhibitors.

Other ED treatments

Current studies show that DA-8159, a new phosphordiesterase 5 inhibitor, was assessed for its erectogenic potential by a penile erection test in rats. Specifically, a variety of measures such as the relaxation of isolated rabbit corpus cavernosum (CC), and estimation of the intracavernous pressure (ICP) in the anesthetized dog, were examined (Yu et al., 2005). It is clear that researchers have continued to study PDE-5 inhibitors; they are still aiming to eventually manufacture the one inhibitor that works effectively with minimal adverse effects from the clash of similar metabolic path-ways. In addition to the PDE-5 inhibitors, they are also examining other substances that use a distinct pathway against ED. Apomorphine sublingual is the first centrally acting agent officially approved for the treatment of erectile dysfunction (Montorsi et al., 2003b). It was licensed in the UK as a sublingual therapy and it was prescribed in general medical practice in England as a treatment for ED (Maclennan et al., 2006). It stimulates a central dopamine receptor in the brain to enhance sexual response. Overall, it is these oral treatments; sildenafil, tadalafil, vardenafil and apomorphone that are minimally invasive and the favored treatments. The PDE-5 inhibitors are effective but have shown possible detrimental effects when considering drug metabolism via 3A4. Apomorphine does not use the cytochrome P450-3A4 enzyme, it uses SULT1A1 as the major enzyme responsible for hepatic apomorphine metabolism (Thomas and Coughtrie, 2003). However not only does apomorphine cause nausea in a minority of men, it is not as effective as the PDE-5 inhibitors. Previous research demonstrates that sildenafil was superior to apomorphine in the open-label crossover study of men with ED who were naive to therapy (Eardley et al., 2004). In addition Maclennan et al. (2006) showed that a high percentage of ED patients in the study reported the low effectivity for apomorphine (Maclennan et al., 2006). Futhermore, other drugs such as Yohimbine, an alpha-receptor antagonist, is effective in some placebo-controlled trials, but not adequate for treatment of most ED. Intracavernosal injection of drugs such as prostaglandin E1, papaverine, and phentolamine may be effective but it is an invasive treatment. As a last resort, when patients do not respond to oral treatment or counseling, alternative treatments such as testosterone, vacuum-pump treatment, surgery, and surgical implants may be suggested by the Physician (Dinsmore, 2005). Increased research in this field has open doors for us to grasp the physiological principles of penile erection, and it has allowed the development of novel oral pharmacological therapies. These agents offer a potential benefit because they provide a broader range of treatment options for patients with varying clinical situations.

CONCLUSION

The cytochrome P450 family is important in drug metabolism, in particular 3A4 isoform, which is responsible for metabolism of the majority of drugs used by humans. The breadth of drugs that 3A4 metabolizes brings into question possible drug interactions associated with taking multiple medications using 3A4 as a primary metabolic route. Drug interactions occurring through CYP mostly involve P-glycoprotein. Both 3A4 and P-glycoprotein are represented in human gut and so and hence drug-drug interaction may occur in the gut before it occurs in liver (Kim, 2002). Certain drugs such as azole antifungals, macrolide antibiotics, HIV protease inhibitors, and many others have been well characterized as 3A4 inhibitors and caution is warned about administration of those drugs with other drugs metabolized by 3A4 (Table 1). Such warnings exist with sildenafil. Co-administration of sildenafil with 3A4 inhibitors requires careful monitoring

Table 1. Dosage range based on concurrent drug dose and combinations.

Drugs	Metabolism	Standard dosage amounts	Administrations based on disease conditions	PDE5 inhibitor once daily administrations based on concomitant drugs	Drug interactions	Stated disease conditions with/no controlled clinical data for PDE-5 inhibitor usage
Sildenafil (Viagra)	3A4 (major), CYP2C9 (minor)	25 mg, 50mg, 100 mg, Once daily	Geriatric patients older than 65 years, Recommended 25 mg; Hepatic impairment, 25 mg . Severe renal impairment, 25 mg	3A4 inhibitor: Ritonavir(25 mg) *Ketoconazole(25 mg) Itraconazole(25 mg) Erythromycin(25 mg) Saquinavir(25 mg) Nitrates: (Sildenafil is not recommended at any dose) *Alpha-blockers(25 mg)	3A4 inhibitor (Ritonavir), Nitrates, Alpha blocker, HIV protease inhibitors, nonspecific CYP inhibitor (Cimetidine), alcohol	Severe hepatic impairments, myocardial infarction, severe arrhythmia, hypotension (BP<90/50), hypertension (BP>170/110), Cardiac Failure, Coronary artery disease (unstable Angina), retinitis Pigmentosa
Vardenafil (Levitra)	3A4 (major), CYP2C (minor), CYP3A5 (minor)	2.5 mg, 5 mg, 10 mg, 20 mg Once daily	Geriactric patients, Recommended dose 5 mg for ≥ 65 Years); Hepatic impairment, Maximum dose: 10 mg Renal Impairment, no Dose Adjustment Required	3A4 Inhibitor: Ritonavir (2.5 mg) Indinavir (2.5 mg) Saquinavir (2.5 mg) Atazanavir(2.5 mg) *Ketoconazole (2.5 mg-5 mg) Itraconazole(2.5 mg) Clarithromycin(2.5 mg) *Alpha-blocker: (2.5 mg-5 mg)	3A4 inhibitors, alpha blockers, Nitrates, HIV protease inhibitors (Indinavir), non-specific CYP 450 inhibitor(Cimetidine), alcohol	Severe hepatic impairments, hypertension, hypotension, stroke, myocardial infarction, retinitis pigmentosa, servere cardiac failure, end stage renal disease
Tadalafil (Cialis)	3A4	2.5 mg, 5 mg, 10 mg, 20 mg Once daily	Renal insufficiency: Mild (no dose adjustment) moderate to maximum (2.5 mg); Severe: (Tadalafil not recommended); Hepatic impairment child pugh class A/B (10 mg); child pugh class C (Tadalafil not recommended) Geriatric (No dose adjustment is required >65 years of age)	Nitrates: Tadalafil is not recommended All 3A4 Inhibitors (2.5 mg max)	3A4 Inhibitors (Ketoconazole, Ritonavir, Itraconazole), 3A4 Inducers (Rifampin), alpha blockers, Nitrates, antihypertensives, alcohol, antacids, H2 antagonists(Nizatidine), HIV protease inhibitors	Hepatic insufficiency, myocardial infarction within 90 days, unstable angina, uncontrolled arrhythmias, hypotension (<90/50 mmHg), hypertension (>170/100mmHg), stroke within 6 months

Table information is based on prescribing information by respective pharmaceutical manufacturers of sildenafil, tadalafil and vardenafil.

and reduction of dosage. Studies have shown that sildenafil does not inhibit 3A4 strongly. With that, sildenafil is a safe drug with respect to 3A4 metabolism.

Vardenafil has the same metabolic profile as sildenafil, but it has been found to be more clinically effective. It has been well-characterized that vardenafil is primarily metabolized by 3A4; however, the extent to which it inhibits 3A4 enzymes is not yet known. Administration of vardenafil is contraindicated in those taking indinavir, ritonavir, ketoconzaole, due to the strong inhibitory effects that these drugs have on 3A4. Since vardenafil is significantly more potent than sildenafil, further study of its effects on 3A4 and other cytochrome P450 enzymes is crucial. The interactions between vardenafil and azole antifungals, erythromycin, and HIV protease inhibitors must be examined before prescribing it to patients. If vardenafil is to be administered to patients taking other PDE-5 inhibitors, patients should be given a low dose and dosage intervals must be stringently monitored to avoid drug interactions and liver damage (Table 1).

Despite its promise as a treatment for erectile dysfunction in terms of efficacy and tolerability, there is little to no knowledge of the effect of tadalafil on 3A4 metabolism and possible drug interactions. The extended half life and AUC, in conjunction with the fact that tadalafil is also metabolized by 3A4 metabolism, could possibly lead to increased toxicological effects when tadalafil is co-administered with 3A4 inhibitors. In addition, some early studies show that the MDP substituent on tadalafil, which is uncommon among drugs, has a great effect on 3A4 as an inhibitor and in some cases as an inductor. Taking these points into account, there could be an increased risk of pharmacological and toxicological effects of tadalafil based on its pharmacokinetic characteristics. These mechanisms must be thus studied in detail before negative manifestations arise clinically and have an effect on the patients that may take tadalafil in the future. Knowing that the CYP complement of a particular organ will affect pharmacological and toxicological effects in that organ, one might theorize that these possible interactions could arise in the liver, the organ where 3A4 is expressed the most.

It is suggested that users of tadalafil and other PDE-5 inhibitors that interact with 3A4 could develop liver toxicity due to these possible interactions. Only through further in depth research about the nature of the interaction between ED drugs and 3A4 and on the interaction between these drugs and 3A4 inhibitors, predictions can be made about drug interactions. The goal in this field is to prevent negative clinical manifestations, such as the “lover’s liver” from arising in patients who will need to rely on these drugs in the future.

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