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An Update on the PDE-5 Inhibitors (PDE-5*i*)

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Phosphodiesterases (PDE) are enzymes that catalyze the degradation of the cyclic nucleotides, cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP), to the corresponding 5' nucleotide monophosphates. Eleven different PDE families have been described to date and are found throughout the body. These enzymes exist as homodimers, and there is structural similarity among the different families. However, they differ in their selectivity for cyclic nucleotides, sensitivity for inhibitors and activators, physiological roles, and tissue distribution. Interest in these enzymes has increased tremendously, both within the medical community and in the general public as a consequence of sildenafil (Viagra), an oral PDE-5 inhibitor (PDE-5*i*) introduced for the treatment of erectile dysfunction (ED).

The discovery of nitric oxide as a neurotransmitter in the cardiovascular system and the role of cGMP in the cascade of events crucial to smooth muscle relaxation in the vessels of the heart led to the study of a potent PDE-5*i* in patients with angina. Although inferior to inexpensive nitrates, it proved to be an effective erectogenic agent. Since 1997, 5 families of PDE enzymes have been discovered, PDE-7 through -11 (Beavo, 1995; Francis, 2001). Each family contains subfamilies and multiple splice variance (Figure 1).

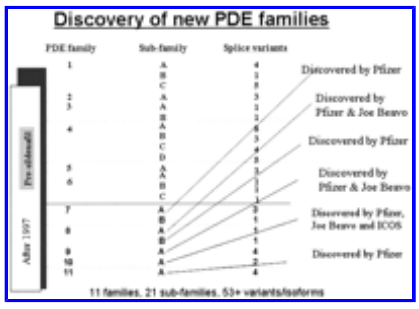

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Figure 1. PDE iso-enzyme families.

Sildenafil was the first in a new class of drug. It was approved in March 1998 as the first oral treatment for ED, and within the next 6 months 2 new PDE-5*i*s are anticipated to be approved in the United States. They were approved in Europe in March 2003.

What Are the Clinical Advances That the New PDE-5i Bring to the Field of ED?

The perfect drug will be highly potent, be 100% selective, have no side effects or drug interaction, be completely safe, and be universally affordable. Financial issues aside, how close do we come to that ideal?

How different are the new PDE-5*i*s? True or perceived differences will be based on 1) the safety which include toleration, extent or safety of experience and drug interactions; 2) the efficacy and reliability; 3) the selectivity; 4) duration; and 5) onset and spontaneity.

The 3 drugs that will be used for the treatment of ED are sildenafil, vardenafil, and tadalafil (Figure 2). All share a chemical structure similar to cGMP with which they compete for the PDE catalytic domain. Caffeine is also a PDE-5*i*, albeit a very weak one.

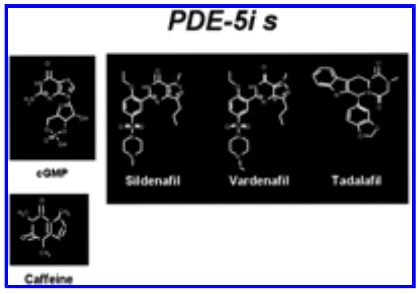

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Figure 2. Molecular structure of PDE-5i.

Let us look at the attributes that are important in defining these medications: 1) potency, 2) selectivity, 3) onset and duration of action or pharmacokinetics, and 4) efficacy.

Potency

PDE*i* method of action is related to the inhibition of the PDE-5, which breaks down cGMP, the second messenger in the enzymatic cascade that results in relaxation of the smooth muscle in the penile vascular spaces as well as the penile vessels. The first messenger in this pathway, nitric oxide, is a gas that crosses the neuromuscular and the vascular spaces and is created by the ubiquitous enzyme nitric-oxide synthase (Figure 3).

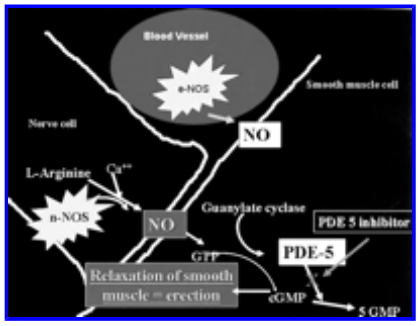

Figure 3. Schematic of mode of action for PDE-5i.

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What does the PDE-5*i* molecule have to do and how might it relate to ultimate potency and efficacy? Many of these steps may vary on an individual basis, resulting in the slight variation in efficacy and side effects from one patient to the next. Published pharmacokinetics represent, after all, an average of the results in many patients.

The PDE enzyme after ingestion needs to exit the stomach in order to get to the small intestine from which it absorbs. The transit out of the stomach can be affected by multiple processes, including the amount of fat content that is within the stomach. It has been well recognized that a fatty meal will delay the gastric emptying time. Ingestion of a high-fat meal delays absorption by approximately 40 minutes, largely through delay in gastric emptying. Other disease processes such as diabetic gastroparesis can likewise affect the presentation of the PDE*i* to the small intestine. After it enters the small intestine, it must be absorbed in the bloodstream, where 96% is bound to circulating proteins (Nichols et al, 2002) and survive the liver, then be transported into the smooth muscle cells of the penile vessels and vascular spaces. Having found its way into the smooth muscle cell, it must negotiate the complexities of the intracellular space to find its way to the cGMP receptor site. Once it finds a receptor site, it must bind to the receptor displacing the cGMP. Once bound to the PDE enzyme, a dynamic process of association and disassociation occurs, which again may vary from one individual to the next. Having produced this desired effect on the PDE-5 enzyme when the concentration is sufficiently low, it will then leave the cell, reenter the vascular space, and be degraded by the liver. The first metabolite of sildenafil will, in fact, be as active pharmacologically as sildenafil, thus repeating the entire scenario of events. Clearly, the mechanism of action of the PDE*i* is quite complex and can be affected by slight individual patient variations.

The efficacy of the medication may be affected by delayed gastric emptying, an overactive or impaired liver metabolism, delayed or poor circulation, deficiency in an neuronal or endothelial nitric oxide synthase (ie, status postradical prostatectomy, diabetes, etc), differences in cell membrane permeability to the PDE*i*, and differences on a molecular level in affinity to the enzyme. The higher the affinity of the drug for its receptor, the lower the concentration of the drug that is required to produce a desired effect, and the higher its potency.

Potency does not mean that a drug has a greater clinical effect, rather, less of the drug is needed for the desired effect. For the PDE-5*i*, less vardenafil is required than sildenafil or tadalafil to achieve the same degree of in vitro PDE-5 inhibition. Vardenafil is, therefore, more potent than sildenafil and tadalafil although not necessarily more efficacious. The concept of potency can be assessed by measuring the concentration of the drug in vitro that inhibits a given enzymatic response by 50%, or IC_{50}. In this case, the enzyme is the PDE-5 enzyme. In contrast, efficacy is based upon the actual in vivo or clinical effect of the drug (Figure 4).

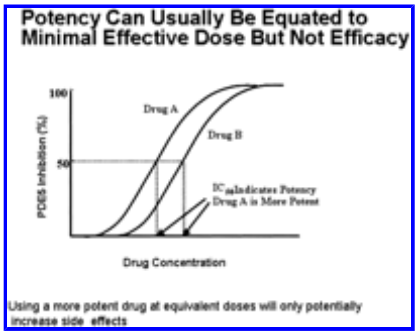

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Figure 4. Pharmacokinetic graphs of PDE-5i with different inhibitory potencies.

How Is the IC_{50} Determined?

The PDE-5 enzyme assay is key (Figure 5). The measurement of cyclic nucleotide hydrolysis is affected by many variables: the enzyme concentration, the origin of the enzyme (whether human or animal), the substrate concentration, the pH and temperature of the enzyme reaction, and the buffer components. The exact conditions of the reaction can vary from one laboratory to the next. This is demonstrated by looking at reported PDE-5 IC_{50} for sildenafil values from various laboratories. Numbers ranging from 0.9 nmol/L to 8.5 nmol/L have been reported. It is, therefore, important not to compare or draw conclusions from results from different laboratories because values can change by an order of magnitude between laboratories. It is more valid to compare values within a single laboratory.

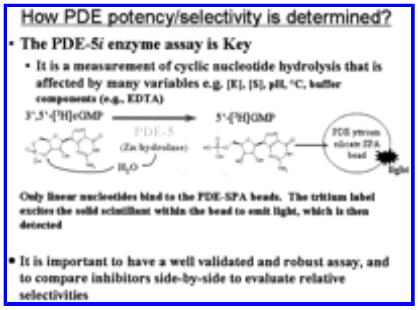

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Figure 5. Schematic for enzymatic assay for PDE-5i.

Having established that small differences in PDE-5*i* potency exist, does this necessarily lead to clinical benefit? Practically speaking, the potency for all three drugs is within the same range; therefore, one might conclude that the clinical benefit is most likely the same. Yet it is possible that small differences in potency may be reflected in minor differences in side effect profile.

Specificity

The specificity is an important attribute because it determines how selective the drug is for the particular enzyme system in which we are interested. To measure selectivity, we compare the IC_{50}s for the index enzyme against other IC_{50}s and compare the multiple of reactivity relative to PDE-5.

This determines the selectivity ratio, the higher the potency, and the less inhibitor it takes to inhibit the enzyme we are investigating. So, the selectivity is then defined as the concentration it takes to inhibit the other PDE-5s over the amount that it takes to inhibit a PDE-5. The higher the selectivity ratio, the less selective the drug is for that isoenzyme vs PDE-5 (Tables 1 and 2) (Corbin and Francis, 2002).

View this table: [in this window] [in a new window]	Table 1. *Selectivity data for comparison of sildenafil, vardenafil, and tadalafil at PDE-1 to -6*[*]

View this table: [in this window] [in a new window]	Table 2. *Selectivity data for comparison of sildenfail, vardenafil, and tadalafil PDE-7 to -11*[*]

Looking at selectivity data, we then find that sildenafil and vardenafil are very similar. A selectivity ratio of greater than 35 is consistent with no clinical interactions. As such, sildenafil and vardenafil react only with PDE-5 and PDE-6. Tadalafil, on the other hand, does not react with PDE-6 but reacts with PDE-5 and PDE-11. Efficacy and safety attributes for vardenafil and sildenafil are likely related to PDE-5 and PDE-6 inhibition. The well-characterized visual effects of PDE-6 inhibition are likely to be shared between vardenafil and sildenafil.

The clinical implications of PDE-11 inhibition are unclear. PDE-11 has been located in the cardiac myocytes by immunohistochemistry and mRNA localization. It has also been found in the pituitary, the heart, and the testes (Baxendale et al, 2000, 2001). No clinical implications to these histological findings have been discovered in any of the clinical trials. There have been no data in any of the clinical trials to suggest an increase in cardiac toxicity in men taking tadalafil (Montorsi et al, 2003).

The presence of PDE-11 in the pituitary and testes has led to some concern about the possibility of detrimental impact in terms of reproductive and sexual-hormonal axes. Animal studies in beagles have suggested testicular vacuolization of the germinal epithelium at pharmacologic doses. These findings have not been duplicated in the PDE-11 knockout model, where changes in sperm capacitation were the only abnormalities that were seen. In extensive human studies in men with normal seminal parameters, exposure of the men to 6 months of dosing of tadalafil have resulted in no demonstrable abnormalities over placebo in follicle-stimulating hormone/luteinizing hormone, testosterone secretion, or any detrimental impact on sperm count, motility, and morphology (Hellstrom et al, 2003). The studies have not been performed in men with marginal or abnormal seminal parameters, thus suggesting that caution be used in men where procreation may be a consideration if they have abnormal seminal parameters.

In summary, vardenafil and sildenafil have excellent selectivity for the PDE-5 vs all PDEs except PDE-6, and both are likely to have visual side effects at the upper end of the dose range. Tadalafil has excellent selectivity for PDE-5 vs all PDEs except for PDE-11. At therapeutic doses, the consequences of PDE-11 inhibition in long-term studies have yet to be determined. Comparative trials are needed to properly compare these agents.

Pharmacokinetic Parameters

The pharmacokinetic parameters of interest are the time to maximum serum concentration and the half life of the molecule. All 3 molecules have high protein-binding and lipophyllic qualities. Sildenafil and vardenafil have similar half lives, whereas tadalafil has a longer time to maximum concentration (T max) and a half life that is 4 to 5 times that of sildenafil and vardenafil. This increased half life may translate to longer clinical efficacy of the medication, but the trade off is, of course, possible longer exposure and the potential risk for drug interactions.

Much emphasis has been placed on onset of duration. The reality is that the onset of action is not affected by the dose of the drug. Drugs with comparable T max should have comparable onset of action. All drugs that are absorbed in the small intestine will have their onset delayed by stomach emptying.

How fast and how long does the medication really have to last? In a recently presented sexual-health telephone survey, in United Kingdom men with and without ED (Eardley, 2002), the time from when the man first thought of intercourse to the time when the couple decided to have intercourse was investigated. It was broken into 3 categories: 1) the time from when the man first thought of intercourse to the time when the couple decided to have intercourse, 2) the time between when the couple decided and when foreplay began, and 3) the time from when foreplay began to when intercourse began.

Surprisingly, for men with and without ED, approximately 60 minutes elapsed from the first thought of intercourse to the beginning of intercourse. With this in mind, all 3 drugs seem to fit the sexual health patterns of the general population.

In addition to onset of action, the duration of action of the medication is important. To have the efficacy of the medication wear off before sexual intimacy is started is not desirable. With this in mind, the degree of sexual frequency within a 24-hour period was investigated. The statistics for men with and without ED were roughly comparable. Approximately 80% of men were sexually active at most once within a 24-hour period, another 10% were sexually active multiple times within 4 hours, and approximately 10% were sexually active multiple times in a 24-hour period but beyond a full hour. On the basis of the survey, all 3 drugs would meet the needs of over 90% of the sexually active couples. Tadalafil might confer an advantage in men desiring to have sexual experiences beyond a 24-hour period because of the prolonged half life.

The increased duration of action or half life may, in fact, be a double-edged sword. The mechanism of the increased half life is unclear. Little is known about the effects of prolonged PDE-5 or PDE-11 inhibition. Up-regulation of the PDE-5 enzyme is unlikely with a drug with a 4-hour half life. In vitro studies with sildenafil have shown that serum levels equivalent to consuming 2800 mg of sildenafil are necessary for up-regulation of the PDE-5 enzyme. No such studies have been performed with tadalafil. In addition, the longer the medication is in the body, the higher the risk for potential for drug-drug interactions.

Side Effects

All PDE-5*i*s share common side effects, which include headaches, flushing, rhinitis, dyspepsia, and myalgia. Unlike sildenafil and vardenafil, tadalafil has not been shown to have any visual disturbances (Hellstrom et al, 2003; Montorsi et al, 2003) (Table 3).

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Table 3. *Adverse event profile of PDE-5 inhibitors*[*]

It is highly probable that all the new PDE-5*i*s will be contraindicated with the administration of nitrates because of potentiation of the hypotensive effect of the nitrates, as is sildenafil (Lue, 2000).

Safety

The safety of sildenafil is supported by 5 years of clinical experience in over 20 million men. It has been shown to be safe in men with heart and vascular disease, in men after having radical surgery, in men with diabetes, in men on multiple hypertensives, in men on dialysis, in men after transplantation (both kidney and liver), in men on protease inhibitors, in men after receiving spinal cord injury, and in elderly men. The incidence of myocardial infarction (MI) and death in men taking sildenafil is less than the age-adjusted incidence in the general population. There have been no such studies to suggest any increased risk in sildenafil in any category of men other than men with advanced cardiac disease and men on nitrates (Zusman et al, 1999). It appears that a 24-hour period after the injection of nitrates is safe for the administration of sildenafil. Although the safety experience with tadalafil and vardenafil is not nearly as great as with sildenafil, many of the clinical trials suggest a comparable safety profile. It is unwise to make far-reaching conclusions about a class safety until a more extensive experience is developed.

Efficacy

All PDE-5*i*s share a common mechanism, and one should expect comparable efficacies. Likely, small differences in clinical efficacies that are currently reported are due to trial entry criteria and individual pharmacodynamic variations. No comparative studies are reported to date, and in view of the small likely differences between the medications, it is unlikely that well-controlled trials will ever be published. It is important to realize that without contemporary comparator studies, it is unfair to draw conclusions in differences in efficacy. Selection factors affecting the outcome of a study can include the era of recruitment, the age of the patients, the dosage of the medications used, the period of ED, the exposure and responsiveness to previous agents, and the severity of ED. Exclusion criteria can dramatically reflect the results with excluding PDE-5*i* failures or including only responders and altering the mix of patients with severe ED.

The future for the use of PDE-5*i* is bright. New indications being investigated include female sexual dysfunction, female infertility, pulmonary hypertension, diabetic gastroparesis, and prevention of endothelial disease progression.

Summary

A pure PDE-5 does not exist because tadalafil trades off the well-described PDE-6 effects of sildenafil for unknown PDE-11 effects, and vardenafil shares the similar PDE-6 inhibition as sildenafil. Small differences in PDE-5 potency are of unclear clinical benefit. In noncomparative trials, sildenafil, vardenafil, and tadalafil have similar safety and efficacy results. Tadalafil's unique long duration of action may present a clinical benefit, yet it presents a potential of unclear long-term safety risks.

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