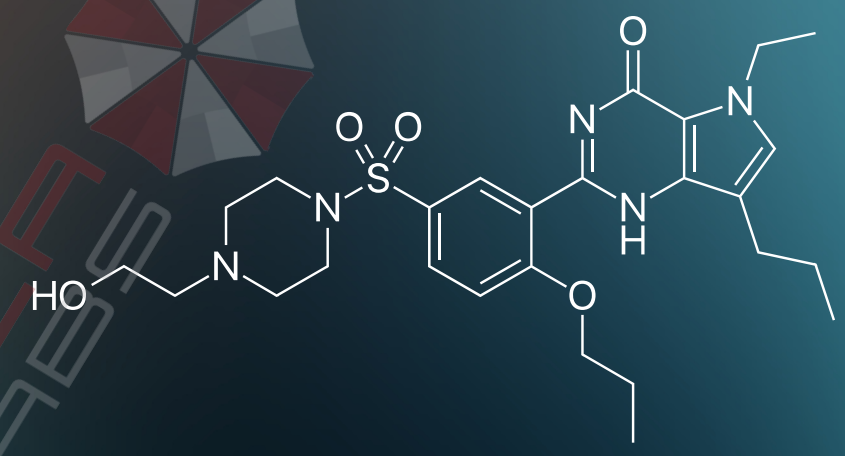

Mirodenafil: Pharmacology and Pharmacokinetics of a Selective PDE-5 Inhibitor

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History

Mirodenafil appeared in the scientific landscape in the year 2008.[1] It was developed by Janssen in Korea. It is also approved there for the treatment of erectile dysfunction, but there are no other countries in which it is in clinical use. Clinical studies have shown that it may be used for other indications, mostly urogenital disorders. However, it has never been approved for other conditions.

Mechanism of Action

Mirodenafil is a close structural analog of sildenafil (Viagra) and only differs from it in few atomic positions. It hence belongs to the same class of compound, the PDE-5 inhibitors, which are well known to induce dilation of blood vessels in male genitalia. Other classes of PDE-inhibitors lead to the same effect, but in other organs, for example PDE-3 inhibitors can dilate blood vessel in the heart. The compound blocks the breakdown of cAMP, increasing its intracellular concentration. cAMP acts as second messenger in various tissues and its effects vary with tissue type.

Pharmacokinetics

Animal experiments showed that compared to sildenafil, mirodenafil remains longer in blood and penile tissue and hence has a longer lasting effect.[2] A review concluded that mirodenafil exhibits better PDE5 selectivity than existing molecules, but another molecule within the PDE-5 inhibitors was described as overall superior (Vardenafil).[3]

As primary metabolites, the two molecules SK3541 and SK3544 were identified in rats after intravenous and oral administration. After oral administration of mirodenafil, approximately 2.59% of the oral dose was not absorbed. The plasma binding of mirodenafil to rat plasma was 87.8%.[4,5]

Mirodenafil inhibited the molecule metabolizing enzymes CYP3A4, CYP2C19 and CYP2D6 activities with IC50 values of 15.6, 38.2 and 77.0 μM, respectively, in human liver microsomes. However, it is very unlikely that mirodenafil will significantly alter the clearance of other compounds metabolized by those CYPs because the maximum plasma concentration of mirodenafil is 0.55 μM after oral dosing of mirodenafil (100 mg) in male volunteers.[6–8]

Analysis

Highly sensitive methods to determine mirodenafil and its major metabolite SK-3541 in human plasma have been

developed.[9]

Preclinical Studies

In cell cultures, one study investigated the effects of Ginkgo biloba extracts on the smooth muscle relaxing properties of mirodenafil. After pre-treatment with 0.03 mg/ml of GBE, the relaxant effects of mirodenafil were increased at all tested concentrations, which was attributed to an additional outflow of potassium from the muscle cells, which leads to stronger muscle relaxation. This shows that Gingko extract may increase the effect of mirodenafil if taken together.[10]

After its initial reported use of erectile dysfunction in humans was established, it was later investigated further in the treatment of Alzheimer's disease, as it was known that mirodenafil was able to cross the blood brain barrier. In a mouse model it was shown that mirodenafil could improve cognitive performance in an Alzheimer mouse model.[11] A similar, disease elevating effect of Alzheimer's disease was also seen in different genetic model of mice, which expressed Apolipoprotein E4, which constitutes one of the mayor genetic risk factors was Alzheimer's in humans.[12]

Mirodenafil was also shown to increase the recovery of rats which suffered from strokes. Effects were seen in a dose-dependent manner up to 1 mg/kg mirodenafil. The benefits of mirodenafil treatment increased with longer treatment duration, and the largest improvements over control were typically observed on the last assessment day.[13]

Mirodenafil also prevented bladder dysfunction induced by chronic bladder ischemia in rats at a dose of 4 mg/kg.[14]

In rabbits, with spinal cord injury (which prevents erection in humans), mirodenafil was evaluated as agent to treat erectile dysfunction caused by such an injury. Penile erections were induced at 0.3, 1 and 3 mg/kg of mirodenafil but sildenafil only showed an erectile response at 3 mg/kg. The effects of 1 and 3 mg/kg of mirodenafil were significantly increased by intravenous injection of sodium nitroprusside (SNP), a nitric oxide donor.[15]

Clinical Studies

In its first clinical study, mirodenafil was used in 50mg and 100 mg doses was shown to decrease the self-reported signs of erectile dysfunction in 223 subjects. Most treatment-associated adverse events were of mild intensity, resolving spontaneously.1 Another study 5 years later with only 50 mg in all subjects showed the same results.[16]

Another small scale clinical study investigated the interactions of mirodenafil with the antifungal agents ketoconazole and the antibiotic rifampicin. It was found that both molecules had significant interactions with the breakdown of mirodenafil in the body. Ketoconazole increased the exposure by 3-fold, while rifampicin reduced it by almost 95%.[17] The co-administration of alcohol did not result in clinically significant changes, however.[18] In patients taking blood-pressure regulation medication together with mirodenafil, it did also show positive effects on erectile dysfunction while inducing double treatment related side-effects.[19] Similar results were found in diabetic men.[20]

Most of the available clinical studies have reported that adverse effects (up to 53.7%) caused by 50 and 100 mg mirodenafil are mild or moderate in severity, with headache (1.8–14.8%) and flushing (6.7–24.1%) being the most common. Due to the pharmacodynamic profiles of mirodenafil, its tolerability is expected to be somewhat better than those of the other PDE-5 inhibitors.[21]

Interestingly, PDE-5 inhibitors such as mirodenafil can also be used to treat chronic prostatitis, as the enzyme PDE-5 is also present in prostatic tissue. And indeed, a study showed a reduction in symptom burden for a combination of the antibiotic levofloxacin together with mirodenafil (50 mg/day) in 88 male patients.[22] Benign prostatic hyperplasia (which is extremely common in older males) was also symptomatically reduced by a combination of mirodenafil in combination with α1- blockers (which are often used to treat benign prostatic hyperplasia).[23] α1-blockers are a concern because they can induce blood pressure drops, especially of taken together with other medication that affects blood vessels, like PDE inhibitors.

However, no significant drop in blood pressure was found when mirodenafil (100 mg) in healthy male Korean volunteers when coadministered with α1-blocker tamsulosin (0.2 mg).[24]

Additional clinical studies showed mirodenafil was also able to increase sexual performance if treated patients suffered from lifelong premature ejaculation.[25]

Conclusion

Clinical studies consistently demonstrate that mirodenafil is effective at oral doses of 50 mg and 100 mg, with both regimens improving erectile function across diverse patient groups with several comorbidities. The molecule exhibits a favorable pharmacokinetic profile, with sustained tissue presence and high selectivity for PDE- 5, which contributes to its therapeutic effect. Importantly, while molecule–molecule interactions with strong CYP3A4 inhibitors or inducers require clinical consideration, mirodenafil generally shows a predictable safety margin, and co-administration with alcohol or common blood pressure medications does not result in clinically significant complications. Most adverse effects are mild and transient, with headache and flushing being the most commonly reported.

Compared to other PDE-5 inhibitors, mirodenafil offers several advantages. Its relatively long tissue retention may support a longer duration of action, while its high PDE-5 selectivity improves tolerability by limiting off-target effects. Emerging clinical and preclinical data also suggest potential utility beyond erectile dysfunction, such as in chronic prostatitis, benign prostatic hyperplasia even premature ejaculation.

Some preclinical evidence also hints at a potential use of mirodenafil in neurodegenerative disorders, mostly in the treatment of Alzheimer's disease. However, more studies (especially clinical studies) are needed to confirm these effects.

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