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Phosphodiesterase Type-5 Inhibitors: A Critical Comparative Analysis

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Abstract

All three PDE5 inhibitors are targeting the same site of action e.g. PDE5 and this is why a quite similar efficacy and safety profile could be expected and was finally proven in many controlled studies. The efficacy as assessed by the endpoint successful intercourse with maintenance of erection (SEP3) ranges between 65 and 75% in broad-spectrum ED populations with clearly lower success-rates of 40–50% in patients with involvement of the penile nerve supply such as diabetics or patients after pelvic surgery. Generally speaking the drug-related adverse events are principally comparable except visual disturbances being more frequently reported after sildenafil and back pain/myalgia more often occurring after tadalafil.

Considering the pharmacokinetic profile tadalafil distinguishes itself from sildenafil and vardenafil by its long half-life ($T_{1/2} = 17.5$ h) resulting in the majority of patients in successful coitus attempts even after $1\frac{1}{2}$ days. As a rule of thumb the clinical efficacy of the respective PDE5 inhibitors corresponds pretty well to the 2.5–3-fold half-life time. In terms of onset of action as mirrored by the T_{max} vardenafil has the shortest one (40 min) followed by vardenafil (60 min) and tadalafil (120 min) As efficacy and side-effects may be differently perceived in the same individual patient with each of the three PDE5 inhibitors it seems reasonable to grant the couples the opportunity to try all drugs sequentially.

Keywords: Erectile dysfunction; Impotence; Phosphodiesterase (PDE) 5 inhibitors; Sildenafil; Tadalafil; Vardenafil

1. The phosphodiesterase (PDE): system

Currently the PDE system includes 11 families with a total of more than 50 splice variants (isoforms) [1–5]. The distribution and density of PDEs varies among the different tissues. The PDEs catalyse the breakdown either of cyclic guanosine monophosphate (cGMP) or of cyclic adenosine monophosphate (cAMP), which are both second messengers with specific physiologic functions. By hydrolysing the phosphodiesterase bond of cAMP or cGMP, respectively, these second messengers are converted to the biologically inactive monophosphates with subsequent termination of their physiological functions.

In addition to PDE5, which is the most abundant one in the corpus cavernosum, to date at least 13 other PDEs were identified in the cavernous bodies: PDE1A, PDE1B, PDE1C, PDE2A, PDE3A, PDE4A, PDE4B, PDE4C, PDE4D, PDE7A, PDE8A, PDE9A, PDE10A [6].

2. The three phosphodiesterase-5 inhibitors: sildenafil, tadalafil and vardenafil

2.1. Pharmacodynamics, potency, selectivity, pharmacokinetics

2.1.1. General considerations

A head to head comparison of the different PDE5 inhibitors is only possible and provides valuable and comparable data when all the three drugs were assessed under the same conditions. The IC_{50} values are in particular dependent on the following parameters:

Species and tissue being investigated, enzyme assay applied, substrate concentration (should be 10-fold

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lower than the target PDE), pH (buffer used?) of the milieu, in which the investigations were conducted.

The differences in the respective IC_{50} values and therefore in the selectivity ratios as they were reported by several authors for the same PDE5 inhibitor are due to the fact that the aforementioned investigational conditions were varying among the authors.

2.1.2. Pharmacodynamics

The term pharmacodynamics covers all actions of a drug on the different body organs and in turn their functions (for example, blood pressure, heart rate, vision). The pharmacodynamic interactions of any drug are influenced by the number of receptors available in the target organ and the affinity of the compound to the receptors in question. The most important parameters concerning the pharmacodynamc properties of a drug are its biochemical potency and its organ (PDE) selectivity.

2.1.3. Biochemical potency

In PDE inhibitors the biochemical potency is defined as the inhibitory effect on the enzyme of interest, e.g. in PDE5 inhibitors on the PDE5 which is the main PDE enzyme in the cavernous bodies. The biochemical potency is generally expressed as inhibitory concentration 50, the so-called IC_{50}.

IC_{50} is defined as the concentration of a PDE5 inhibitor, required to reduce the activity of PDE5 by 50%. The IC_{50} values provide an overview on the efficacy of a PDE5 inhibitor. Generally speaking the lower the IC_{50} values the more potent and therefore more effective a compound is for this enzyme. For the clinical setting this means that with a PDE5 inhibitor with low IC_{50} values less dosage is needed to yield the same effect namely to inhibit 50% of the enzyme.

2.1.4. Clinical efficacy

The clinical efficacy of a PDE5 inhibitor is related to its ability to produce a rigid and reliable erection enabling the couple to engage satisfactorily in sexual intercourse. In the clinical trials efficacy of the PDE5 inhibitors were measured with the following efficacy tools:

General Assessment Question (GAQ): Has the treatment you have been taking improved your erections? This efficacy tool is the weakest one among all the efficacy tools used in ED trials as it does not say anything whether this improvement in erection was sufficient for sexual intercourse or not

International Index of Erectile Function (IIEF): In terms of this world-wide mostly accepted and used efficacy tool the following questions are used either as primary or secondary efficacy endpoints:

- *Question 3:* When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
- *Question 4:* During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?

Both questions are using the same response options with a score system from 0 to 5:

0 = did not attempt intercourse,
1 = almost never/never,
2 = a few times (much less than half the time),
3 = sometimes (about half the time),
4 = most times (much more than half the time),
5 = almost always/always.

EF-domain of IIEF: As mentioned in the chapter diagnosis of ED this domain addresses erectile function and covers Questions 1–5 and 15 of the IIEF [7]. The maximum score achievable in the EF domain is 30 with 26 or more points indicating that erectile function has converted to normal.

Sexual encounter profile (SEP): The sexual encounter profile relies on the recordings of the patients in the patient diaries distributed to the patients with the study-medication and collected at each study visit. The SEP comprises the following five questions:

- *Question 1:* Were you able to achieve at least some erection (some enlargement of the penis?)
- *Question 2:* Were you able to insert your penis into your partner's vagina?
- *Question 3:* Did your erection last long enough for you to have successful intercourse?
- *Question 4:* Were you satisfied with the hardness of your erection?
- *Question 5:* Were you satisfied overall with this sexual experience?

2.1.5. Selectivity: profile of the PDE5 inhibitors

The selectivity of a drug such as a PDE5 inhibitor provides data on to how selective a compound is in regard to the enzyme (here PDE5), on which the efficacy is desired compared to other enzymes (PDEs 1–4 and 6–11), on which an efficacy has to be regarded undesirable.

Therefore the selectivity of a PDE inhibitor is assessed by comparing its potency (IC_{50}) to inhibit a PDE in question (here PDE 1–4 and 6–11) and its potency to inhibit the PDE desired (here PDE5) (see Table 1).