Sexual Medicine

Pharmacokinetic and pharmacodynamic features of dapoxetine, a novel drug for 'on-demand' treatment of premature ejaculation

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OBJECTIVE

To describe the relationship between the pharmacokinetic and pharmacodynamic properties of dapoxetine, a drug specifically developed for treating premature ejaculation (PE).

METHODS

Data from various stages of the clinical development programme were analysed using validated methods for assessing ejaculatory latency. The clinical characteristics were then compared with the pharmacokinetic profile, determined from measured plasma drug concentrations.

RESULTS

Pharmacodynamic and pharmacokinetic measurements confirm that 'on demand' dapoxetine has a rapid onset of action and is rapidly cleared after sexual intercourse.

CONCLUSION

Dapoxetine may represent the first of a new category of selective serotonin transport inhibitors. Although dapoxetine has pharmacological similarities to other selective serotonin transport inhibitors, its efficacy after acute administration sets it apart and suggests a different mode of action. Its physicochemical and pharmacokinetic properties and its clinical efficacy make dapoxetine suitable for on-demand treatment of PE.

KEYWORDS

dapoxetine, serotonin transport inhibitor, premature ejaculation

INTRODUCTION

Premature ejaculation (PE), also commonly known as rapid or early ejaculation, is defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) [1] as 'the persistent or recurrent onset of orgasm and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it'. The DSM-IV criteria further specify that, for a diagnosis of PE, the condition must also cause marked distress or interpersonal difficulty.

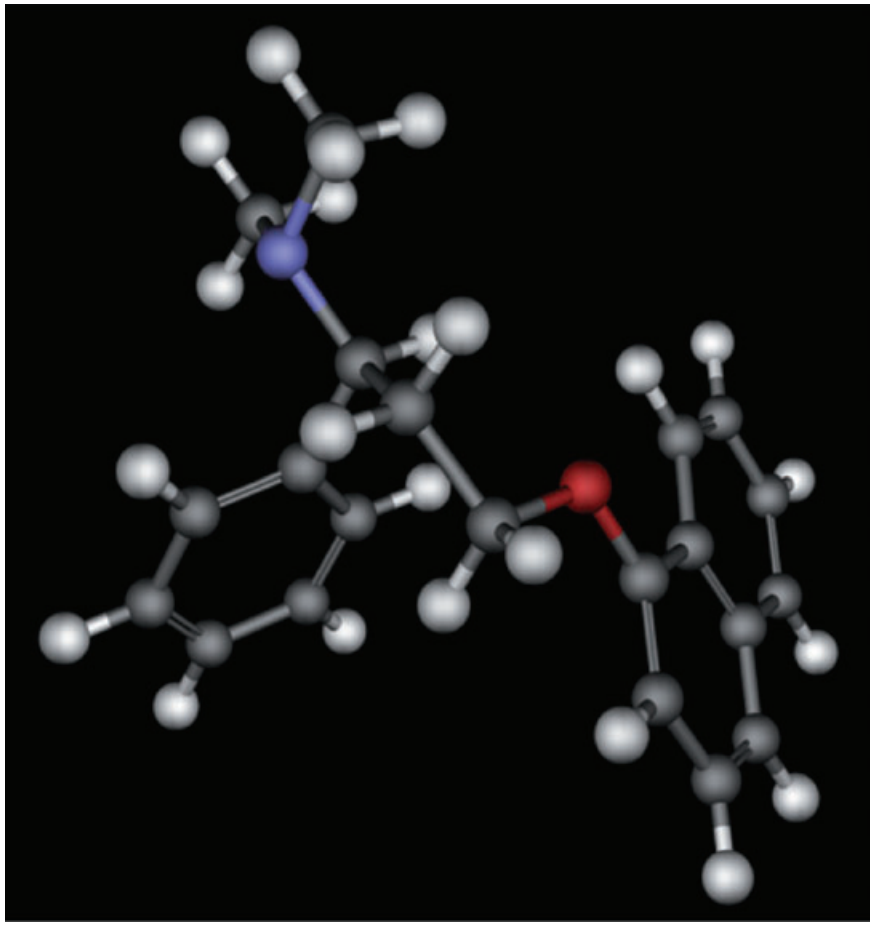
PE is a prevalent sexual dysfunction in men; although the reported values vary among individual studies, depending on definitions used, the prevalence of PE is generally reported to be 25–30% [2–4]. Unusually for such a prevalent condition, there is no firmly established cause. This contrasts with erectile dysfunction, which has an acknowledged association with cardiovascular disease. Nevertheless, there is an increasing understanding that PE may be a biological, as well as psychological, condition [5], and efforts to treat PE should reflect this view.

Ejaculation, consisting of emission and expulsion, is a sympathetically controlled lumbosacral reflex under supraspinal influence from several brain regions, including the stria terminalis, medial preoptic area and nucleus paragigantocellularis (see [6]). The nucleus paragigantocellularis is a serotonergic nucleus. Descending neurones control the spinal ejaculation reflex. Despite a lack of detailed consensus on the cause, it is nevertheless accepted that the physiological control of ejaculation involves central serotonergic neurotransmission and it has therefore been suggested that a serotonergic deficit may underpin PE [7].

In many respects the recognition and diagnosis of PE has been compromised by the absence of a consensus understanding of normal male ejaculatory function. It has been difficult to define PE with no clear normal reference data. A recent study [8] addressed this and compared 'normal' men, i.e. not diagnosed as having PE, with those diagnosed as having PE using the DSM-IV criteria. These populations were readily distinguishable in terms of ejaculatory latency and many other patient and as partner-reported measures of sexual function.

PE remains under-diagnosed and consequently, under-treated. Physicians typically diagnose PE using a variety of criteria, including intravaginal ejaculatory latency time (IELT), perceived ejaculatory control, satisfaction with sexual intercourse, and the degree of distress engendered by the individual's PE. However, physicians can only diagnose those patients who present for treatment. Patients readily self-identify [9] and many use various forms of self-treatment. However, only very few men see a healthcare professional [10]. Although PE causes distress, and this is a powerful driver to seek treatment, there are more impediments.

FIG. 1. The structure of dapoxetine ((+)-(S)-N,N-dimethyl-(a)-[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine).



In particular, the absence of a credible treatment is a significant barrier.

Treatment for PE continues to be given ad hoc, with no strong evidence-base, and only a small percentage of men with PE seek or receive prescribed treatment [10]. Partly this reflects the absence of any approved medications for PE and the limited success of counselling and behavioural modification techniques.

INTRODUCTION TO DAPOXETINE

There are currently no pharmacological therapies indicated and approved for treating PE. Dapoxetine is a new 'designed-for-purpose' agent, currently in development for the treatment of PE, which may address the shortcomings of existing pharmacological therapy. Dapoxetine ((+)-(S)-N,N-dimethyl-(a)-[2-(1-naphthalenyloxy)ethyl]-benzenemethanamine) hydrochloride is a water-soluble, white to off-white powder with a molecular weight of 341.88. Dapoxetine has a pKa of 8.6 and is mainly charged at physiological pH. These characteristics allow rapid distribution in the body.

Pharmacological studies show dapoxetine to be a highly potent serotonin-transporter inhibitor [11]. Although this pharmacological activity is similar to that of clomipramine and conventional selective serotonin reuptake inhibitors (SSRIs), chemical features of the structure of dapoxetine and its pharmacokinetic profile differentiate it from other SSRIs. For instance, and unique among SSRIs, it is not a halogenated compound (Fig. 1), while all other SSRIs contain one or more halogen atoms. The molecular structure of dapoxetine also includes a naphthyl moiety and it is possible that these features underpin the

FIG. 2.
Rapid absorption and clearance of dapoxetine; plasma dapoxetine concentrations vs time after oral administration of 30 or 60 mg dapoxetine.

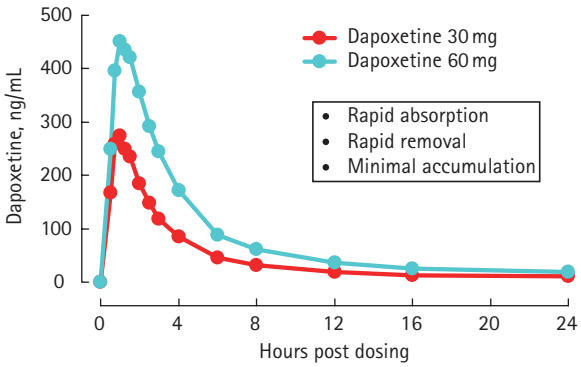
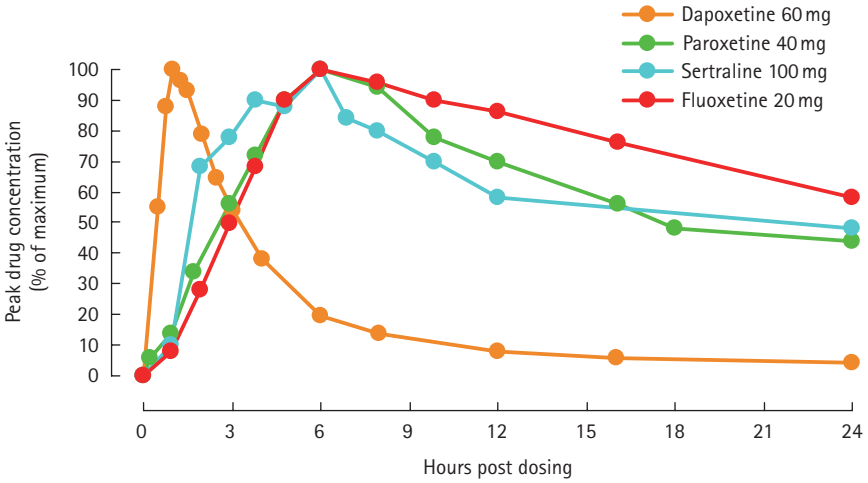


FIG. 3. Dapoxetine has more rapid pharmacokinetics than other SSRIs. Plasma concentrations vs time after oral administration of paroxetine (40 mg), sertraline (100 mg), fluoxetine (20 mg) or dapoxetine (60 mg). The SSRI data are based on Summary Basis of Approval and published reports).



physicochemical and pharmacokinetic properties of the molecule.

The pharmacokinetic, and efficacy and safety data described were generated from the early stages (phase I) of the clinical development programme for dapoxetine. Also included, when relevant, are data from the late development (phase III) programme. Throughout these studies, recognized, validated instruments were used for assessing ejaculatory and sexual function.

DAPOXETINE: PHARMACOKINETIC PROPERTIES

Dapoxetine is rapidly absorbed after oral administration of 30 or 60 mg doses (Fig. 2); the peak plasma concentrations are reached within 60–80 min and are dose-related [12]. Dapoxetine has an absolute bioavailability of 42%. The molecule is 99% protein-bound and has a volume of distribution of 2.1 L/kg. Tissue-distribution studies in animals with radiolabelled dapoxetine showed that the drug distributes widely throughout the body, with peak concentrations in neural tissue close to plasma levels. Dapoxetine is extensively metabolized by many pathways to give ≈40 metabolites. Despite their multiplicity, the dapoxetine metabolites are essentially inactive or are found at pharmacologically insignificant concentrations. Dapoxetine-N-oxide is the main, albeit inactive, human metabolite, reaching peak plasma concentrations about a fifth of those of the parent drug. Others with activity at the serotonin transporter comparable to the parent drug are present at much lower levels: desmethyl dapoxetine concentrations are about 10% of those of dapoxetine, while didesmethyldapoxetine concentrations are 200 times lower than the parent compound. Clinical efficacy resides almost wholly with dapoxetine.

Plasma concentrations of dapoxetine decrease rapidly after peak concentrations are reached; the plasma half-life is ≈90 min, and is the same at both the 30 and 60 mg doses. At 24 h after dosing, plasma levels of dapoxetine are <4% of peak values. Animal studies gave even lower levels at 24 h in neural tissues.

The rapid elimination of dapoxetine from the body (Fig. 3) means that, unlike the conventional SSRIs, there is minimal accumulation after repeated dosing. Repeated daily administration of dapoxetine results in plasma drug concentrations of ≈20% higher than after a single dose. For other SSRIs, accumulation is not only substantial (several fold), but may even be necessary for efficacy both as antidepressants and in PE. For instance, a recent study found that peak plasma sertraline levels were six times higher after repeated administration than after a single dose [13], a pattern typical of the conventional SSRIs.

PHARMACOKINETIC SUMMARY

Among the SSRIs, dapoxetine has a unique pharmacokinetic profile, being both rapidly absorbed, and swiftly and extensively metabolized to inactive compounds. Unlike other SSRIs, dapoxetine is almost completely eliminated from the body within 24 h, showing minimal accumulation after daily dosing [12].

DAPOXETINE: PHARMACODYNAMIC PROPERTIES

In recent Phase III trials, the efficacy of dapoxetine was tested in patients with moderate to severe PE who, at baseline, had a measured mean IELT of <1 min (an IELT inclusion criteria of <2 min was used throughout trials with dapoxetine). In the light of the rapid peak drug concentration, patients were asked to take dapoxetine (30 or 60 mg) or placebo, on-demand, at 1–3 h before anticipated sexual intercourse. This contrasts with other PE studies in which patients were obliged to take their medication daily for several weeks, to detect any benefit [14]. Even those studies that purport to

examine 'on-demand' drug dosing, use long pre-intercourse dosing intervals such as 3–8 h (see [5] for review) or pre-load patients with the trial drug for several weeks [15].

By contrast, dapoxetine (30 and 60 mg) significantly increased the mean IELT by three to four times during the Phase III trials, when taken on demand [16]. Moreover, on-demand dapoxetine caused a significant improvement in IELT relative to placebo on the first dose administered. The 60 mg dose of dapoxetine significantly increased the mean IELT from 55 to 145 s. Dapoxetine is the only drug for PE to be effective at the first dose, when taken 1–3 h before intercourse.

IELT is a pharmacodynamic facet of treatment evaluation in PE. Patient-reported outcomes, e.g. control over ejaculation and satisfaction with sexual intercourse, although more subjective, are increasingly recognized as important dimensions in assessing treatment benefit in PE [8]. A recent observational study of these, and other, patient-reported outcomes showed that they could readily distinguish men with and with no PE [8], and showed their validity as tools to assess treatment benefit.

Dapoxetine dose-dependently improved patient perceptions of control over ejaculation and satisfaction with sexual intercourse. Moreover, and reflecting that interpersonal difficulty forms part of the DSM-IV criteria, dapoxetine improved the partners' satisfaction with sexual intercourse [8].

ONSET AND DURATION OF EFFICACY

The on-demand efficacy of dapoxetine in PE is the key feature that sets the drug apart from other PE treatments. Although various authors have claimed 'on-demand' efficacy for other treatments (e.g. the conventional SSRIs), close inspection of the studies often reveals methodological failings. Often hybrid treatment regimens have been used, comprising periods of chronic drug administration followed by on-demand treatment [15]. Moreover, double-blind, placebo-controlled trials are the exception rather than the rule (see [5]). These idiosyncratic protocols make the results difficult to assess, and true on-demand efficacy has not been convincingly shown for existing agents [17].

The efficacy of on-demand dapoxetine suggests that the drug, despite its biochemical similarities to other SSRIs, may have a different mechanism of action in PE, possibly due to its pharmacokinetic profile or physicochemical properties.

TOLERABILITY/SAFETY

The most common and a dose-dependent adverse effect with both the conventional SSRIs and dapoxetine is nausea [16,18]. Even so, nausea after dapoxetine is mainly mild, transient and related to the presence of dapoxetine in the body. Other adverse effects occurred less frequently and were not consistently dose-related.

One of the largest issues when treating PE with conventional daily dosing of SSRIs is the high incidence of sexual side-effects: chronic treatment with these SSRIs reduces libido and compromises erectile function, possibly due to the adaptive receptor and messenger changes inherent in their actions. Of patients on chronic SSRIs, 30–50% experience sexual side-effects [19]. By contrast, sexual side-effects are infrequent with dapoxetine. On-demand dapoxetine has no significant adverse effects on libido (<1%) or erection (<4%), presumably because it does not persist in the body and thus there are no adaptive changes.

CONCLUSIONS

The nature of PE is such that patients should not have to take potent psychoactive drugs, with long-lasting actions and debilitating side-effects, for weeks before sex to receive any benefit. Sexual intercourse is rarely premeditated and patients need a drug that matches the spontaneity inherent in sexual intercourse, a drug that they can take as needed and one with no prolonged side-effect 'hangover'.

Dapoxetine is a selective serotonin transport inhibitor with pharmacokinetic and pharmacodynamic properties that can account for its clinical effects. Dapoxetine reaches the site of action rapidly, exerts its effect and is then swiftly cleared from the system. Unlike other SSRIs, dapoxetine is effective on the first dose. These properties make dapoxetine suitable for the on-demand treatment of PE.

CONFLICT OF INTEREST

John Mulhall is a consultant to Ortho Urology.

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Abbreviations: **DSM–IV**, Diagnostic and Statistical Manual of Mental Disorders -IV; **PE**, premature ejaculation; **SSRI**, selective serotonin reuptake inhibitor; **IELT**, intravaginal ejaculatory latency time.