

TEMPE (Topical Eutectic-Like Mixture for Premature Ejaculation)

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INTRODUCTION

Premature ejaculation (PE; also known as rapid or early ejaculation) is one of the most common sexual problems experienced by men, and it is estimated that PE symptoms are experienced by over 30% of the male population [1]; higher than that of erectile dysfunction (ED). However, in contrast to ED, there is no approved pharmacological therapy.

The commonly used DSM-IV definition of PE is "a lifelong persistent or recurrent ejaculation with minimal sexual stimulation before, upon or shortly after penetration and before the patient wishes it" [2]. However, more recently, the **International Society for Sexual Medicine (ISSM)** has used an evidence-based approach and defined PE as;

'a male sexual dysfunction characterised by ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration; and inability to delay ejaculation on all or nearly all vaginal penetrations; and negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy' [3].

This definition includes the constructs of time to ejaculation; inability to delay ejaculation; and negative consequences of PE. It is supported by consideration of objective evidence for men with lifelong PE who engage in vaginal intercourse; although it is considered that this definition is also likely to apply to men who engage in other sexual activities. The ISSM considers that there are insufficient objective data for an evidence-based definition for acquired PE.

Men with PE might exhibit abnormal autonomic reflex pathways for the ejaculatory process. These include: lower penile vibratory threshold, shorter bulbocavernosus latency time and higher bulbocavernosus evoked potentials [4]. This provides a therapeutic rationale for the use of local anaesthetics (LA) in the treatment of PE. If the sensory input from the glans penis is reduced with desensitising agents, there may be an improvement in intravaginal ejaculatory latency time (IELT), without adversely affecting the sensation of ejaculation.

To date, the application of cream-based local anaesthetic EMLA[®] (Eutectic Mixture of Local Anaesthetics, AstraZeneca) to the penis has shown promising results in terms of prolonging IELT [5,6]. However, the application of EMLA requires the use of a condom to retain the cream for 20-30 minutes prior to intercourse and the shaft of the penis may also become anaesthetised.

TEMPE

TEMPE[®] (Topical Eutectic-Like Mixture for Premature Ejaculation, Plethora Solutions) (figure 1) is a proprietary metered dose aerosol that delivers 7.5mg of lidocaine and 2.5mg prilocaine in their base forms per actuation, dissolved in a non-CFC propellant (hydrofluorocarbon 134a).



Figure 1: The TEMPE aerosol spray

The metered dose delivery system allows the desensitising agents to be deposited in a dose-controlled, concentrated film. This produces a monofilament layer of LA molecules, unlike the cream formulation where the contact of the molecules with the surface is hindered by the cream vehicle (figure 2); thus, the time to onset of action is reduced with TEMPE.

TEMPE forms a clear, odourless, slightly oily film which doesn't require the use of a condom and is easily wiped off prior to intercourse. As it is only applied to the mucosa of the glans penis, sensation in the shaft of the penis is retained.

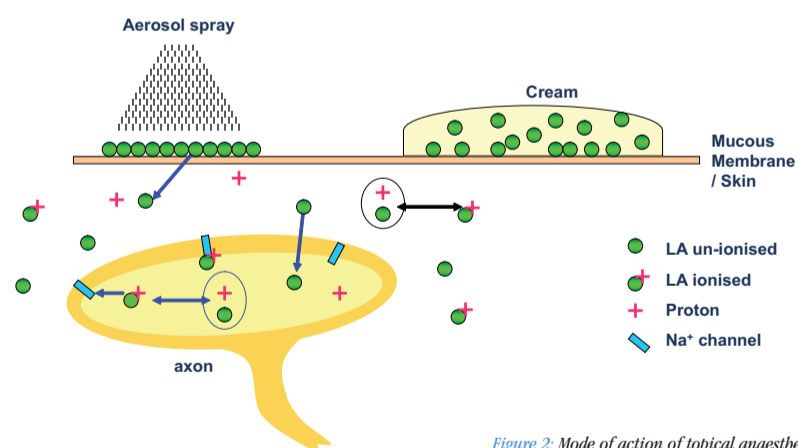


Figure 2: Mode of action of topical anaesthetics

EFFICACY AND TOLERABILITY OF TEMPE

The efficacy of TEMPE has been evaluated in a multi-centre, double-blind, randomised, placebo-controlled, parallel group study in men with PE.

Methods and Objectives

Fifty-four men with PE (defined via DSM-IV criteria) aged between 18–75 years, with a history of primary PE ≥ 6 months duration were enrolled. Patients recorded their baseline, treatment-free IELT using a stopwatch on three consecutive sexual encounters. Patients were then randomised to TEMPE or placebo sprays (three actuations) for use prior to sexual intercourse on four, preferably consecutive occasions. Each sexual encounter was separated by an interval of 24 hours or more. The primary endpoints were the mean change in IELT from baseline and the proportion of men responding to treatment (defined as having at least 2 sexual encounters where the IELT was ≥ 4 minutes). Secondary endpoints included changes in Index of Ejaculatory Control (IEC) and Sexual Quality of Life Questionnaires (SQoL) for patients and partners.

RESULTS

Men with PE were able to increase their IELT from a mean baseline of ~ 1.0 min to 4.9 min using TEMPE, compared to 1.6 min in the placebo group. Log transformed data were used to calculate geometric means, as IELT data were not normally distributed. The post-treatment geometric means for the TEMPE and placebo groups were 2.50 min and 1.04 min respectively ($p < 0.01$ for between-treatment comparison of change from baseline), indicating that TEMPE was 2.4-times more effective at prolonging IELT than placebo (table 1).

	IELT (minutes)		Treatment comparison
	TEMPE (n=20)	Placebo (n=23)	
Baseline Mean	1.0	0.9	
Follow-up	4.9	1.6	
Observed change from Baseline to Follow-up	3.8	0.7	
Geometric Mean change* [95% CI]	2.50 [1.60 - 3.89]	1.04 [0.69 - 1.55]	Increase 2.4 times greater for TEMPE vs placebo ($p < 0.01$)

* adjusted for baseline and centre

Table 1: The mean IELT change from baseline for TEMPE and placebo-treated patients

The number of responders (IELT ≥ 4 minutes on 2 occasions) was greater with TEMPE (25%) than placebo (13%) but the difference between treatments was not statistically significant.

There was a trend towards greater efficacy in TEMPE-treated patients compared with the placebo-treated group in the number of patients who achieved IELT responses ≥ 2 , ≥ 3 or ≥ 4 minutes during at least two sexual encounters (figure 3).

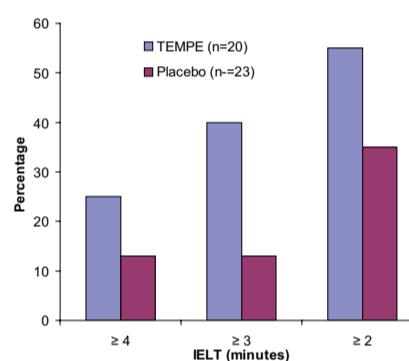


Figure 3: Percentage of men who achieved IELT ≥ 2 minutes on 2 encounters

Men in the TEMPE group also reported improvements in the IEC. SQoL scores for both patients and partners were improved, despite only using TEMPE on four occasions over the course of a month, which might generally be considered insufficient usage to expect a significant change. Patient-reported outcomes are being evaluated further in longer-term studies.

The treatment was considered easy to use and although three patients experienced hypoesthesia and one patient experienced erectile failure on a single occasion, there were no treatment discontinuations. TEMPE was also well tolerated by the female partners, with no reports of numbness of the vagina, and only one partner experiencing a mild burning sensation during intercourse each time her partner used the spray, although this did not result in discontinuation of treatment.

PHARMACOKINETIC DATA

The safety and pharmacokinetics of TEMPE were investigated in double-blind, parallel group, placebo-controlled study in healthy male volunteers. TEMPE was applied to the glans penis daily for 21 days. A single dose (3 sprays; 22.5mg lidocaine and 7.5mg prilocaine) was applied on days 1-6, 8-13 and 15-21, and on days 7 and 14, 3 doses were applied, 4 hours apart. Plasma samples for TEMPE and its metabolites were taken on Day 0 (pre-dose) and Dosing Days 1 and 21 (table 2).

Parameter (Unit)	Lidocaine	Prilocaine
C _{max} (ng/mL)	56.110 (33.519) (n=12)	7.179 (2.457) (n=8)
t _{max} (hr)	2.694 (1.026) (n=12)	2.521 (0.964) (n=6)
t _{1/2} (hr)	3.677 (0.527) (n=3)	2.858 (0.079) (n=3)

Table 2: Mean (SD) pharmacokinetic parameters on day 21 after daily dosing with TEMPE

On Dosing Days 7 and 14 a single plasma sample was taken at 1.5 hours after the third dose of TEMPE. The mean maximum lidocaine concentrations (n=12) on Day 7 and 14 were 84.31 ng/mL and 88.96 ng/mL, respectively and for prilocaine 10.05 ng/mL and 9.99 ng/mL, respectively. All these maximum plasma concentrations are well below the toxic plasma levels (toxic levels $> 5,000$ ng/mL for lidocaine and $> 6,000$ ng/mL for prilocaine).

SUMMARY

TEMPE is a convenient, safe, well tolerated, on-demand treatment for patients with PE. It has a statistically and clinically significant effect on IELT, and positive influence on IEC and SQoL. Its easy mode of application; fast onset of action; and that TEMPE is less likely to penetrate keratinised skin (so sensation in the shaft of the penis is retained) makes it an attractive treatment option for PE.

References

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