A Randomised, Single-Dose, Two-Period, Cross-Over Phase I Pharmacokinetic Study to Compare TDS®-Diazepam with Rectal Diazepam in Healthy Adult Subjects

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Introduction

Diazepam is a psychotropic with sedative and hypnotic effects, additionally, it also has anticonvulsive actions. Its action results in inhibitory effect of GABA-nergic transmission.

Diazepam is currently approved for oral, intravenous, intramuscular, or rectal administration. Diazepam is not known to metabolise in the skin and has not been successfully delivered by patch or other topical preparation.

We have developed a transdermal drug delivery system (TDS®, Transdermal Technologies Inc, Florida, USA) which is a liquid formulation that can be combined with drug entity to form a novel and more convenient, patient compliant pharmaceutical dosage form (spray form), to enhance drug delivery through the skin. Recent studies of the TDS system, e.g., TDS-Lidocaine can give acceptable anesthesia in five minutes post application[1], and TDS®-Testosterone was bioequivalent to AndroGel®[2].

Methods

Study materials

TDS®-diazepam was supplied as a liquid formulation, delivered at 0.2 mL per spray metered pump, with each spray containing 2 mg diazepam. Diastat® was supplied as a gel in a unit-dose containing 10mg diazepam.

Study design and treatments

A single-dose, two-period, cross-over phase I (pharmacokinetic) comparative study involving two treatments and two periods with a minimum of a 14 day washout period was conducted.

Subjects

Twelve healthy subjects successfully completed the protocol. The study was approved by St Thomas' Hospital Research Ethics Committee, and received an acceptance from MHRA UK.

Diazepam Analysis

Diazepam and metabolites concentrations were measured in plasma using a HPLC/MS.

Results

	Diazepam	Desmethyl-diazepam
Rectal t½	59.2 (121.7)	
Rectal t_{max}	1.0 (24.3)	33.0 (29.8)
TDS t_{max}	24.0 (56.0)	14.8 (36.2)
TDS - Rectal Difference	10.1% (49.6)	45.0% (33.7)
Rectal C_{max}	3929.3 (25.9)	1714.9 (37.2)
TDS C_{max}	1104.5 (42.9)	753.8 (46.1)
TDS / Rectal Ratio	27.2% (40.8)	44% (43.6)

Table1: Bioequivalence parameters for diazepam and desmethyl-diazepam, TDS diazepam (Test formulation (A)) versus Rectal diazepam (Reference formulation (B))

		-90% CI	Point Estimate%	+90% CI
Diazepam	t_{max}	1.6	32.13	6.75
	C_{max} (A:B)	7.3	10.1	14.0
	C_{max} (B:A)	715.8	990.1	1367.7
	AUC_{0-72}(A:B)	19.7	27.2	37.6
	AUC_{0-72} (B:A)	266.1	367.6	507.8
Desmethyl-diazepam	t_{max}	-20	-4	12
	C_{max} (A:B)	37.6	45.0	53.8
	C_{max} (B:A)	186.0	222.4	266.0
	AUC_{0-72} (A:B)	33.4	44.0	57.8
	AUC_{0-72} (B:A)	172.9	227.5	299.4

Table 2: Derived diazepam and desmethyl-diazepam Geometric mean (CV percentage) for rectal and TDS diazepam (10 mg)

Results continued

Figure 1 and Figure 2 show the plots of mean plasma concentration of diazepam and nordiazepam vs. time. A diazepam concentration was higher in rectal diazepam (Diastat®) in all of the subjects compared to TDS®-Diazepam. The pharmacokinetic parameters AUC, C_{max}, and t_{max} are listed in Table1 for both treatment. The AUC and C_{max} values were calculated for 0 – 72h. And the mean AUC_{0-72} and C_{max} of both treatments are listed in Table 2.

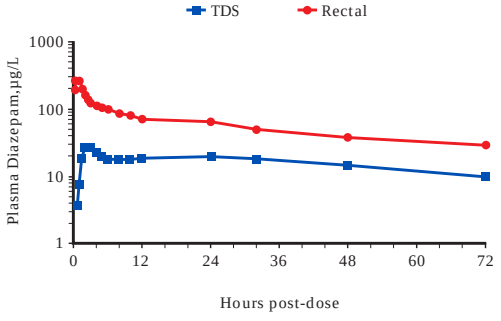

Figure1: Mean plasma diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

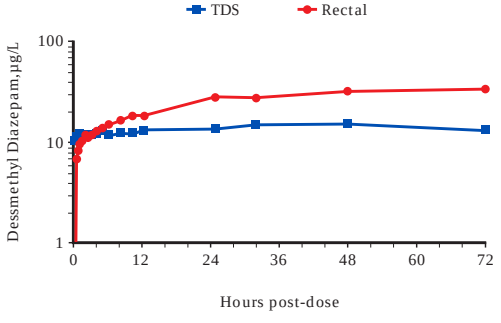

Figure 2: Mean plasma desmethyl-diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

Conclusion

The drug formulations and protocol requirements were well tolerated by all subjects.
This proof of concept study demonstrates that the TDS® preparation successfully delivered diazepam systemically to adults. As expected, the concentration of diazepam following the TDS® application was lower and not bioequivalent to rectal gel. Future development of this unique system will focus on further enhancing the formulation to create a clinically appropriate and preferred alternative to rectal or intravenous diazepam treatments.

Acknowledgement

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References

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