Systemic measurement of TDS®-Diazepam, compared with Rectal Diazepam, a pharmacokinetic study in Healthy Adult Subjects

11th International Congress of Therapeutic Drug Monitoring & Clinical Toxicology Montréal, Québec, Canada, October 3-8, 2009

William Harvey Research Institute

Barts and The London NHS NHS Trust

QUEEN MARY AND WESTFIELD COLLEGE UNIVERSITY OF LONDON

F Al-Otaibi [1], A Johnston [1],AT Tucker [1, 2], T Lee [3], R Langford [1, 4], S Ratcliffe [4], C. Alam[5], K.Kirby[6]

[1]Clinical Pharmacology, [5]Experimental Pathology, WHRI, QMUL; [2]Clinical Vascular & Microvascular Unit, and [4]Anaesthetics Department, BLT, [3]Analytical Unit St George's University of London, [6]Langford Research Institute .

1. Introduction

Diazepam is a psychotropic drug, with sedative and hypnotic effects, additionally, it also has anti-convulsive. Its action results in inhibitory effect of GABA-ergic transmission.

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

We have developed 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 TDS-Lidocaine can give acceptable anesthesia, in five minutes post application [1], and the TDS®-Testosterone was bioequivalent to AndroGel® [2].

2. Method

Study materials

TDS®-diazepam was supplied as a liquid formulation, delivered at 0.2 mL per spray metered pump, which 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.

3. Result

Figure 1 and figure 2 show the plots of mean plasma concentration of diazepam and nordiazepam vs time. The diazepam concentration was higher in rectal diazepam (Diastat®) in all of the subjects compared to TDS®-Diazepam. The bioequivalent parameters for AUC, Cmax, and tmax are listed in Table 1 for both treatments. The AUC and Cmax values were calculated for 0 – 72h. And the mean AUC0-72 and Cmax of both treatments are listed in table 2.

4. Result continued

Table 1: Bioequivalence parameters for diazepam and desmethtyl-diazepam, TDS diazepam (Test formulation (A)) versus Rectal diazepam (Reference formulation (B))

	-90% CI	Point Estimate %	+90% CI
Diazepam			
tmax (difference)	1.63	2.13	6.75
Cmax(A:B)	7.3	10.1	14.0
Cmax(B:A)	715.8	990.1	1367.7
AUC0-72(A:B)	19.7	27.2	37.6
AUC0-72(B:A)	266.1	367.6	507.8
Desmethyl-diazepam			
tmax (difference)	-20	-4	12
Cmax(A:B)	37.6	45.0	53.8
Cmax(B:A)	186.0	222.4	266.0
AUC0-72(A:B)	33.4	44.0	57.8
AUC0-72(B:A)	172.9	227.5	299.4

Table2:Derived diazepam and desmethyl-diazepam Geometric mean (CV percentage) for rectal and TDS diazepam (10 mg)

	Diazepam	Desmethyl-diazepam
Rectal t1/2	59.2 (121.7)	--
Rectal tmax	1.0 (24.3)	33.0 (29.8)
TDS tmax	24.0 (56.0)	14.8 (36.2)
TDS tmax	10.1% (49.6)	45.0% (33.7)
TDS - Rectal Difference	3929.3 (25.9)	1714.9 (37.2)
Rectal Cmax	1104.5 (42.9)	753.8 (46.1)
TDS Cmax	27.2% (40.8)	44% (43.6)
TDS/Rectal Ratio	24.0 (56.0)	33.0 (29.8)

5. Result continued

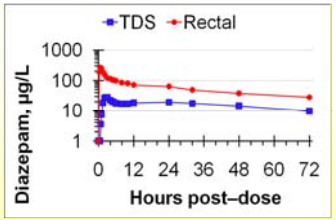

Figure 1:Mean plasma diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

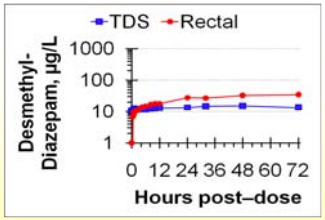

Figure 2: Mean plasma desmethyl-diazepam versus time in 12 subjects following a 10 mg dose rectally (filled red circles) and dermally by TDS diazepam (filled blue squares), logarithmic concentration axis.

6. 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.

7. Acknowledgements

This work was supported by Langford Institute, University of London (QMUL).

8. Reference

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