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Study of a combined percutaneous local anaesthetic and the TDS® system for venepuncture

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Summary

Transdermal Delivery System (TDS®) is a liquid formulation which can be applied to the skin via a metered pump spray to deliver drug across skin. This placebo controlled, double blind trial compared anaesthetic properties of two TDS® systems (TDS®α and TDS®β) with placebo. The active and placebo treatments were applied to the dorsum of the hands, bilaterally and simultaneously for 5 min on 100 healthy volunteers. Following cannulation, pain perception was measured using the verbal rating score (VRS) and visual analogue score (VAS). Lidocaine plasma levels were assessed at 0 and 2 h. The VRS and VAS results show that TDS®β significantly decreased pain score compared to placebo ($p < 0.02$). Blood lidocaine at 2 h post application was also higher for TDS®β than for TDS®α, suggesting that a 5 min application of TDS®β was effective in delivering local anaesthetic and accelerating the onset of skin anaesthesia prior to venous cannulation in adults.

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The pain caused by common minor procedures such as venepuncture and minor surgery is often ignored by clinicians. While it may be a trivial problem in adults, for young people, especially children, the pain is significant and can lead to the development of 'needle phobia', an intense fear of needles that triggers immediate anxiety. This also affects some adults. Local anaesthetics are normally given through injection and used to reduce the pain by inducing a loss of feeling (numbness) of skin and mucous membranes. To avoid the pain and anxiety of venepuncture, topical anaesthetics have been in use to provide needleless induction of local anaesthesia.

Current topical local anaesthetics such as EMLA® (Astra Pharmaceuticals Ltd, Luton, UK) [1] and AMETOP® gel [2] (Smith & Nephew Healthcare Ltd, Hull, UK), whilst effective, require institutional support. One hour prior application of EMLA® [3] and 30–45 min prior application of AMETOP® [4] limit clinical and patient acceptance. Thus, topical anaesthetics are excluded from the procedures requiring acute anaesthesia, as well as those outside the institutional environment. The development of a topical delivery system with faster time of anaesthetic onset would be helpful in emergency cases and to increase the number of surgical day cases seen, especially in paediatrics.

The Transdermal Delivery System (TDS®) is a patented process for creating a formulation to deliver drug across skin using a liquid vehicle, measured by unit dose or metered pump spray. The dose is routinely compounded into approximately 1 ml of very stable fluid. There is no patch or application appliance required other than unit dose packaging or metered pump sprayer. The system is composed of substances that are nutritional and/or neutral and harmless at their respective concentrations. TDS® systems are typically composed of a compatible solvent, supplemented by other excipients that enable a sufficient dose of the drug to be put into a relatively small volume of liquid. TDS® also contains excipients designed to support the skin and maintain the integrity of the barrier and the health of the skin. A TDS® may also contain excipients that can affect the rate of absorption of the drug. The TDS® is usually designed to enable extremely rapid delivery and bioavailability of drugs

equivalent to needle injection, with the added benefit of design, which enables rapid physiological response and blood levels equivalent to oral dosing.

The TDS® has been successfully tested in preclinical models with the following diverse molecules: cystamine, hydroxyzine, acyclovir, morphine sulphate, ibuprofen (three studies), paracetemol (two studies), imidazolinium methyl sulphate, testosterone, progesterone and the peptide alpha melanocyte-stimulating hormone. These drugs vary with molecular weights from the low 100 Da to nearly 2000 Da, both hydro- and lipophilic compounds and doses of 1–500 $mg.ml^{-1}$ of TDS® drug product. The safety of TDS® systems has been evaluated and confirmed by the Institute for In Vitro Sciences in Gaithersburg, Maryland, USA, for primary dermal irritation, skin sensitisation and toxicity. In this study, two TDS® local anaesthetic systems (TDS®α and TDS®β) have been evaluated for their speed of onset of anaesthesia, and drug penetration into the circulation.

Method

Study materials

Study materials were supplied by Transdermal Technologies Inc., Florida.

1 TDS®α Anaesthetic System (alcohol based) containing 4% w/v lidocaine and 2% w/v tetracaine.
2 TDS®β Anaesthetic System (water based) containing 4% w/v lidocaine and 2% w/v tetracaine.
3 TDS®α and TDS®β placebo.

Study design and subjects

This study was prospective, double blinded and placebo controlled, with a 1-week washout period, involving 100 healthy volunteers. Based on our previous study [5], 100 subjects recruited in this study would have an 80% power to detect a difference of 25% in the primary outcome measures at $p < 0.05$. Prior to enrolment, each subject was screened for standard blood biochemistry, drugs of abuse, and answered a questionnaire for demographics. Skin was assessed for erythema, oedema, itching, broken skin, or other signs of pathology. Body mass, height, body mass index, systolic and diastolic blood pressure, and heart rate were recorded. Subjects outside the age range of 20–40 years, with signs of skin pathology, haematology 'out of standard limits' or with positive drug abuse tests were excluded. Subjects were not permitted any form of analgesia within 1 week of the trial. The study was approved by the East London and City Authority Research Ethics Committee and received a Doctors and Dentists Exemption Certificate (DDX) from the MHRA (Medicines and Healthcare Products Regulatory Agency, UK). Subjects were admitted to the investigation having been provided with a verbal and written explanation and signed a consent form.

Admission and procedure

Subjects were admitted to the Study Unit having fulfilled all the inclusion criteria. Blood pressure and heart rate were measured after subjects rested for 10 min. A sample was taken from an antecubital vein to establish a baseline measurement of plasma lidocaine concentration. All subjects were dosed according to the randomisation schedule. In the Phase 1 study, TDS® (active) was applied to the dorsal surface of a randomly selected hand and the TDS® (placebo) was simultaneously applied on the contralateral hand. Administrations of the formulations were achieved by metered pump spray of 1 ml to the area of 4 cm^2. Five minutes after application, the hands were routinely cleaned using alcohol wipes prior to venepuncture.

A vein on each hand within the treatment area was then cannulated using a 20G butterfly needle. The success of cannulation was confirmed by the ability to withdraw 1–2 ml of blood. Two methods of pain assessment, Verbal Rating Score (VRS) and Verbal Analogue Score (VAS), were used to assess the pain of the procedure. Both systems have been fully validated in the literature [6, 7] and the investigators trained in their use [5]. Following successful bilateral cannulation, a VRS pain classification was used for each hand. The volunteers were asked the following question: 'How strong was the pain of the procedure?' and provided with a choice of five categories:

1 no pain
2 minimal sensation
3 mild pain
4 moderate pain
5 severe pain

The volunteer selected one answer for each hand by circling the number.

In the VAS assessment, a 100 mm horizontal line with endpoints that are anchored by descriptors 'no pain' and 'severe pain' was used. For each hand, the volunteer was asked 'What did the procedure feel like?' and then requested to make a vertical line on the horizontal line which represented the intensity or unpleasantness of their pain by the procedure. Values were measured in millimetres from the left hand edge of the horizontal line.

Two hours after the treatment application, another blood sample was taken to assess the systemic level of lidocaine. The plasma was transferred to cryo-vials and stored at − 20 °C until analysis. All the procedures, including treatment applications, bilateral cannulation and data recording were each performed blindly by separate investigators. One week later, the volunteers repeated the above procedure using the second formulation (TDS®β).

Analytical method

Plasma concentration of lidocaine was analysed by using the liquid chromatography-mass spectrometry (LC-MS/MS) method. Sample separation and detection was achieved on a Supelcosil LC-Si 10 cm column and PE SCIEX API 2000 mass spectrometer. The method was validated to demonstrate adequate sensitivity, specificity, accuracy and precision. The lower limit of quantification (LOQ) was 0.5 ng.ml^{-1} and bupivacaine was used as an internal standard.

Statistical analysis

All the data were analysed using GraphPad Prism 4.0 (http://www.graphpad.com/prism/Prism.htm) and Minitab 14 statistical software (http://www.minitab.com/). The active treatments were compared to the placebo control using Wilcoxon's Signed Rank test. The lidocaine concentrations at 2 h for TDS®α and TDS®β were compared using Student's paired *t*-test.

Results

One hundred healthy volunteers were successfully recruited, and the demographics data are presented in Table 1. Of the 100 subjects, 65 were Caucasian, 22 Asian, four African/Caribbean, and nine from other ethnic groups. The cannulation procedures were successfully completed at the first attempt for all 100 volunteers. All the subjects tolerated the procedure well and complied with the study protocol.

The median for VRS and VAS scores were different between active and placebo for both TDS®α and TDS®β. In the VRS pain classification, the active treatment of TDS®α was not significantly different from the placebo (p = NS; Fig. 1). However, the active treatment of TDS®β resulted in a significant reduction in pain response to cannulation compared to the placebo treatment ($p < 0.02$; Fig. 2).

Similarly, the VAS also showed no significant difference between placebo and active treatment with TDS®α but was significantly different for TDS®β ($p < 0.02$; Fig. 3). The distribution of scores of the active treatment group in Phase II (TDS®β) was generally shifted from the two highest scores (moderate and severe) to the lower

Table 1 Demographic data of study volunteers.

Parameter	Mean (SD)	Median [range]
Sex; M : F	41 : 59	
Age; years	26.45 (5.2)	25.0 [20–40]
Body mass index (BMI)	23.3 (3.9)	22.6 [15.2–37.5]

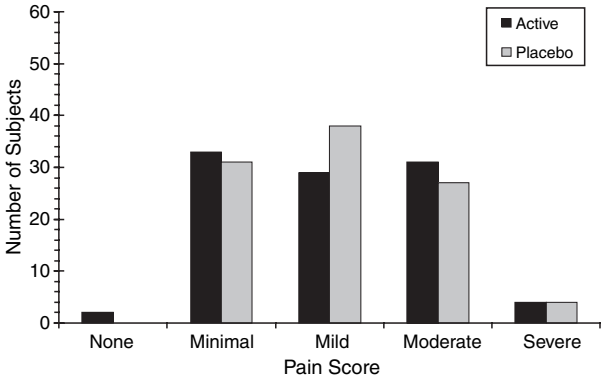

Figure 1 Verbal Rating Score (VRS) for TDS®α. Values are subjects percentage vs. categories; $n = 100$; p = NS, Wilcoxon's Signed Rank test.

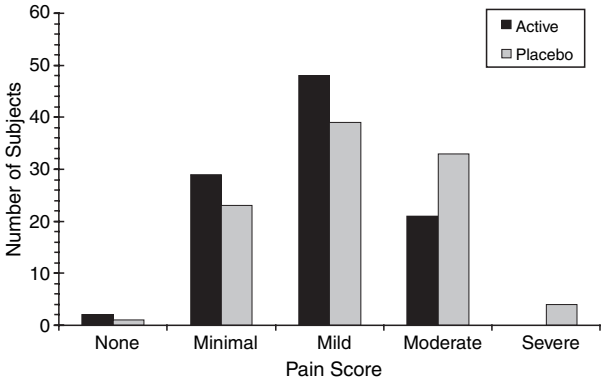

Figure 2 Verbal Rating Score (VRS) for TDS®β. Values are subjects percentage vs. categories; $n = 100$; $p < 0.02$, Wilcoxon's Signed Rank test.

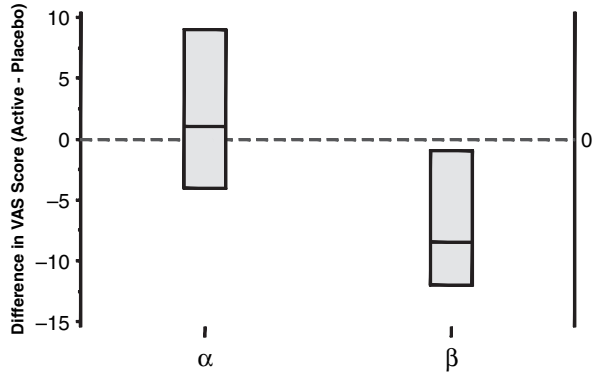

Figure 3 The median differences in VAS score of active and placebo (α = TDS®α and β = TDS®β). Values are median ± 95% CI; $n = 100$; p = NS for TDSα and $p < 0.02$ for TDS®β, Wilcoxon's Signed Rank test.

level of score (mild), with no subjects on active treatment rating the pain as severe. There was a reduction of those who scored the pain as moderate by 36.4% (Fig. 2).

The above result was further supported by the plasma lidocaine concentrations 2 h after the active treatment was applied. Lidocaine was detected in plasma for almost all subjects at 2 h post dose. Although the level of lidocaine was not significantly different between TDS®α and TDS®β ($p = 0.287$, NS; paired *t*-test), the mean plasma level for TDS®β was slightly higher than TDS®α: mean (SD) [range] 3.51 (9.31)[0–64.5] $ng.ml^{-1}$ and 2.51 (6.8)[0–55.9] $ng.ml^{-1}$, respectively.

Discussion

The result from this exploratory study suggests that immediately following application of a TDS® anaesthetic system, there is a fast onset of effective anaesthesia for the venous cannulation in adults. The fact that 5 min application of TDS® anaesthetic system can produce an acceptable level of anaesthesia is a major advance in the anaesthetic system compared to EMLA® and AMETOP® gel, which must be applied 1 h and 30–45 min, respectively, before cannulation is attempted. For operational reasons, randomisation was only performed within the treatment between active and placebo and not between the two systems (TDS®α and TDS®β). However, the first treatment (TDS®α) could not have affected the second treatment (TDS®β) due to the 1 week washout period. This gave more than enough time for the lidocaine to clear from the body and made carry over effects highly unlikely.

Between the two TDS® systems tested, the water based anaesthetic system was more effective than the alcohol based product in providing both transdermal delivery of local anaesthetic and anaesthesia. The TDS® anaesthetic system can thus be manipulated to adjust the onset and degree of topical anaesthesia, and will be used as a basis for investigations into application periods and increased levels of anaesthesia. Other TDS® anaesthetic systems, such as those using alternative combinations of local anaesthetic agents rather than the lidocaine/tetracaine used in this study, are currently under investigation. The development of a rapid onset topical local anaesthetic would enable the replacement of invasive methods of local anaesthesia, and free this procedure from the institutional environment.

Conclusion

In conclusion, topical application of the TDS® local anaesthetic system was effective in providing skin anaesthesia for dorsal hand vein cannulation in healthy subjects, after 5 min of application. TDS®β (water based) was found to be more effective than TDS®α (alcohol based) and can be used for further development of this system. These findings also indicate the rapid transdermal drug delivery by the TDS® system.

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