Brief Report

Validation of a Fentanyl Transdermal Adhesion Scoring Tool for Use in Clinical Practice

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Abstract

**Context.** The therapeutic efficacy of a transdermal system (TDS) is directly related to the adhesion of the TDS, with partial adhesion resulting in lower plasma concentration. Currently there is no TDS adhesion scoring tool available for use in the clinical setting.

**Objectives.** To validate a U.S. Food and Drug Administration (FDA) scoring system for the adhesion of the fentanyl TDS in cancer patients.

**Methods.** A library of images was created from photographs of fentanyl/placebo TDS placed on patients/volunteers. Thirty photographs, reflecting varying degrees of adhesion, were selected for each of series A and B, with 10 photographs common to both series. Each series was shown to 30 health professionals asked to score the photographs using the FDA scoring system. Validity was assessed using Spearman’s rank correlation and reliability by Cohen’s kappa ($k$). Photo editing software was used to assign control scores to each photograph.

**Results.** Validity was high for both series ($\geq 0.954$). Inter-reliability ($k$) ranged from 0.327 - 0.858 (average 0.547) and 0.433 - 0.910 (average 0.620) in series A and B, respectively. The combined agreement across both series was 0.585. Intra-rater agreement ($k$) of the 10 common images was 0.605. No significant difference was observed between the scoring patterns for those with more than 10 years of working experience.

**Conclusion.** Overall, the TDS adhesion score determined by the participants visually in this study corresponded well to those generated by photo editing software, thus rendering the scoring system highly valid. The FDA scoring system is an adequate tool for assessing fentanyl TDS adhesion in clinical practice.
Key Words: transdermal, TDS adhesion, scoring tool, fentanyl, validation, FDA

Running title: Transdermal Adhesion Tool for Clinical Use

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Introduction

Transdermal systems (TDSs) are designed to deliver a therapeutically effective amount of drug across a patient’s skin. The high lipid solubility and low molecular weight of the opioid fentanyl make it suitable for this mode of administration, for the provision of safe, effective and continuous pain relief in chronic cancer-related pain.\(^1\) Fentanyl TDSs are manufactured such that the amount of drug released is directly proportionate to the surface area of the TDS.\(^2\) A constant TDS-skin contact over the whole application period is essential for consistent delivery and absorption of the drug.\(^3,4\) Therefore, the amount of adhesion of the TDS to the skin is a critical factor, directly related to drug delivery and therapeutic effectiveness. If the TDS lifts or partially detaches, the effective area of TDS-skin contact reduces and changes in drug absorption or therapeutic failure can occur.\(^5\) Factors that can potentially affect the adherence of TDS include excessive sweating,\(^6\) skin placement site, temperature, blood flow, body fat and integrity of the stratum corneum.\(^7-13\)

The degree of TDS adhesion is important not only for therapeutic effectiveness, but also in dose monitoring and pharmacokinetic (PK) studies, because the blood concentration is directly related to the percentage of the TDS that is adhered. If the extent of adhesion is not known, the dose of fentanyl could be incorrectly adjusted and PK studies could be misinterpreted. A validated scoring system, therefore, is needed to assess the degree of adhesion at the time of sampling. The U.S. Food and Drug Administration (FDA) developed a scoring system for use by the pharmaceutical industry for manufacturing purposes (Table 1),\(^14\) but to date there has been no patch adhesion tool for the clinical setting or for PK studies.

Methods
This was a two-part study. Part 1 involved the development of the photo database (survey tool). In Part 2, the survey tool was tested on a number of volunteers to assess the validity and reliability of the FDA scoring system. This study was granted ethical approval by Mater Health Services Human Research Ethics Committee.

**Part 1. Survey Tool Development**

*Recruitment of Patients and Volunteers.* Patients recruited to this part of the study were inpatients and outpatients of an oncology/palliative care service within a metropolitan hospital who were receiving fentanyl via TDS (Duragesic©), at any dose. Volunteers comprised the members of the palliative care research team and/or hospital staff willing to wear a placebo TDS on their chest or arm for a number of days. This was a convenience sample of patients and staff selected to obtain adequate numbers of photographs demonstrating varying levels of adhesion of the TDS. Attempts were made to recruit patients and volunteers demonstrating a range of skin textures, skin colors, propensity to sweat and hair cover.

*Data Collection.* Demographic information was collected to ensure a representative sample of both patients and volunteers. Close-up photographs of consenting patients’ TDSs, or staff members’ placebo TDSs, were taken by research staff and numbered and coded appropriately. Images used in the survey were cropped so that the participant number was not visible and it was not possible to identify the participant from the photographs taken. Photographs were taken until 10 samples were obtained for each FDA adhesion level across a range of participants to build a photo library of 50 photographs reflecting varying degrees of TDS adhesion.

*Calculation of TDS Photo Area.* Photo editing software (Adobe Photoshop C6 Extended, Version 13.0 X64) was used to calculate the TDS adhesion area and assign scores to the
photographs as a control. The software allowed the area of the adhered portion of the TDS to be calculated. This was converted into a percentage of the total TDS area, and assigned a score of 0-4 according to the FDA tool. This was used as the standard comparator against which visual assessment was judged.

Preparation of Survey Tool. The library of 50 photographs was used to create two surveys (survey A and survey B). Ten randomly selected photographs were included in both surveys to determine intra-rater variability. Of the remaining 40 photographs, 20 were included in survey A and the other 20 in survey B, with a spread of difficulty across each adhesion level (Fig. 1). The FDA scoring tool chart and TDS photograph surveys were laminated. A pre-validation pilot study was performed with research staff to ensure that the photographs were of a good quality, easy to view and that the survey could be completed in a time efficient manner.

Part 2. Testing the Tool

Recruitment of Survey Participants. Participants in this part of the study were health care professionals (doctors, pharmacists and nurses) recruited from within an oncology/palliative care service. Inclusion criteria included only the willingness to complete the survey and to provide demographic information such as age and years of experience.

Survey. Each of the 30 consenting staff members were given either survey A or B in random order by research staff. Approximately one week later, they were given the other survey in order to assess intra-observer as well as inter-observer reliability. Participants were asked to score each of the photographs for TDS adhesion according to the FDA scoring tool.

Statistical Analysis

Spearman’s rank correlation was used for validity analysis whereby the participant scores were compared to the control scores obtained from photo editing software. Cohen’s kappa
statistic \((k)\) was used to test intra- and inter-rater **reliability**. Stata/SE v. 12.1 (StataCorp LP, College Station, TX) was used for the calculations. Given that the sample size should be at least five times larger than the total of score categories in validity and reliability studies, our sample size of 30 participants was appropriate.\(^{15}\)

**Results**

Validity was shown to be strong for both surveys (Spearman’s rank 0.954 and 0.978 for survey A and B, respectively; \(P < 0.001\)), where a predefined correlation of 0.7-0.8 was considered sufficient and \(>0.8\) reflects strong correlation for the validity test.\(^{16,17}\) There was no significant difference in the number of years of experience when scoring the level of TDS adhesion (\(<10\) years’ experience 0.964, \(n=13\); \(\geq10\) years’ experience 0.966, \(n=17\)).

Cohen’s kappa statistic \((k)\) was used to test intra- and inter-rater reliability, with \(k >0.75\) considered to be excellent, 0.40 to 0.75 fair to good, and below 0.40, poor.\(^{17,18}\) Intra-rater reliability was fair to good, with the overall \(k = 0.605\) (\(P < 0.001\)) for the two measurements of 10 TDSs common to both surveys scored by each of 30 participants. Inter-rater reliability calculated among the 30 participants was fair to good, with \(k = 0.547\) for survey A, 0.620 for survey B, and 0.585 for both surveys A and B (\(P <0.001\)).

As expected, inter-rater reliability was higher for score 4 (i.e., TDS completely detached), showing an excellent \(k\) of 0.885, than the scores of partial TDS adhesion, namely score 0 (TDS adhesion \(\geq90\%\), \(k = 0.478\)), score 1 (TDS adhesion between 75\% and 90\%, \(k = 0.475\)), score 2 (TDS adhesion between 50\% and 75\%, \(k = 0.392\)) and score 3 (TDS adhesion between 0 and 50\%, \(k = 0.683\)).

**Discussion**
Overall, the TDS adhesion score determined by the participants visually in this study corresponded well to those generated by the photo editing software, thus rendering the scoring system highly valid. Reliability was rated as “fair to good” (i.e., $k = 0.40-0.75$) with an overall $k$ of 0.605 and 0.585 for intra- and inter-reliability, respectively.

Differences in the inter-rater reliability for the individual FDA scores of 0-4 can be explained when considering the nature of the scoring tool. The inter-rater reliability for score “4” (TDS completely detached) was excellent ($k>0.75$), whereas the reliability for partially adhered TDS scores (0-3) were lower. The reason for this is that a TDS that is completely detached (score 4) is understandably much easier to score correctly, than a TDS with score “2” (TDS adhesion between 50% and 75%). Scoring is particularly difficult for those TDSs that are close to the borderline for a particular score, for example 49% or 76% in the case of score “2” above.

In order to make the study more robust, the photograph library was constructed to include a number of photographs that were difficult to score, i.e., very close to the borderline between two scores (Fig. 2). This may have contributed to the lower scores for a partially adhered TDS. There were also limitations with the two dimensional nature of the survey tool. This was highlighted during the prevalidation of the survey tool where it was noted by health care staff that the assessment of a laminated photograph was significantly more challenging than assessment of the degree of adhesion of a TDS in clinical practice.

A recent study assessing genetic, pathological and physiological determinants of transdermal fentanyl pharmacokinetics in over 620 cancer patients found marked variation in serum fentanyl concentrations. The genotypes and clinical factors considered accounted for only a small proportion of variability in the study. The degree of TDS adhesion was not measured in this study and may be an important factor contributing to variation in fentanyl plasma.
concentration, especially as the amount of drug released from a TDS is directly proportionate to the surface area of the attached TDS. A recent Cochrane review included nine randomized controlled trials on the efficacy of transdermal fentanyl for relief of cancer pain, of which none recorded the level of adhesion of the fentanyl TDS.\textsuperscript{20}

In conclusion, the amount of adhesion of the TDS to the skin is a critical factor directly related to therapeutic effectiveness that should be incorporated into all PK and effectiveness studies of fentanyl. The FDA scoring system was found to be highly valid and easily employed by clinical staff. Overall, inter- and intra-reliability were rated as fair to good, and was acceptable given the robust nature of the test used in this study, which included photographs of TDSs where the amount of adhesion was very close to the borderline between two scores. Because it is challenging to score a partially adhered TDS, training programs may have benefit for clinical staff to enhance their scoring ability.

**Disclosures and Acknowledgements**

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**PLS CONFIRM THE PREVIOUS SENTENCE IS ACCURATE**

The authors are grateful to the study participants and those involved in testing the survey tool.

**References**


### Table 1. FDA Scoring System for Patch Adhesion

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Explanation</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>$\geq 90%$ adhered</td>
<td>Essentially no lift off the skin</td>
</tr>
<tr>
<td>1</td>
<td>$\geq 75%$ to $&lt; 90%$ adhered</td>
<td>Some edges only lifting off the skin</td>
</tr>
<tr>
<td>2</td>
<td>$\geq 50%$ to $&lt; 75%$ adhered</td>
<td>Less than half of the patch lifting off the skin</td>
</tr>
<tr>
<td>3</td>
<td>$&gt; 0%$ to $&lt; 50%$ adhered but not detached</td>
<td>More than half of the patch lifting off the skin without falling off</td>
</tr>
<tr>
<td>4</td>
<td>0% adhered - patch detached</td>
<td>Patch completely off the skin</td>
</tr>
</tbody>
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Figure Legends

Fig. 1. Extract of the survey tool showing photographs of TDSs with varying levels of adhesion.

Fig. 2. Examples of closely scored photographs; (A) score 1 (75.8%) and (B) score 2 (73.49%).