Assessment of the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia and neuropathic pain. A pilot study

Chapter 7

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Abstract
Allodynia is a common and disabling symptom in many patients with neuropathic pain. Whereas quantification of pain mostly depends on subjective pain reports, allodynia can also be measured objectively with quantitative sensory testing (QST). In this pilot study, we investigated the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients with allodynia as a consequence of a neuropathic pain syndrome, by means of correlating subjective pain scores with pain thresholds obtained with QST. During a four-week trial we administered a cannabis extract to 17 patients with allodynia. We quantified the severity of the allodynia with Von Frey monofilaments before, during and after the patients finished the trial. We also asked the patients to rate their pain on a Numeric Rating Scale at these three moments. We found that most of the effect of the cannabis occurred in the last two weeks of the trial. In this phase, we observed that the pain thresholds, as measured with Von Frey monofilaments, were inversely correlated with a decrease of the perceived pain intensity. These preliminary findings indicate clinical relevance of QST with Von Frey monofilaments in the quantification of allodynia in patients with neuropathic pain, although confirmation of our data is still required in further studies to position this method of QST as a valuable tool, for example in the evaluation of therapeutic interventions for neuropathic pain.
7.1. Introduction

In many patients with neuropathic pain, the presence of allodynia can be observed [Macres et al., 1999; Woolf and Mannion, 1999; Bridges and Thompson, 2001]. Allodynia, defined by the International Association for the Study of Pain (IASP) as pain caused by a stimulus that would not normally evoke pain, can be demonstrated when, for example, lightly rubbing the affected skin is found to be painful [Merskey and Bogduk, 1994]. It is a very disabling physical symptom that frequently co-occurs with hyperalgesia in neuropathic pain syndromes [Hansson et al., 2001; Backonja, 2002]. Allodynia can be produced by the action of low threshold Aβ-fibres on an altered central nervous system, but it may also be the consequence of hyperexcitation of nociceptor terminals in the periphery [Woolf and Mannion, 1999]. To determine the exact underlying pathophysiological mechanisms of a patient’s allodynia is difficult if not impossible in clinical practice.

As spontaneous stimulus-independent pain is always subjective; evaluation of the efficacy of analgesic treatment thus depends on a subjective effect size, such as a Visual Analogue Scale (VAS) or Numeric Rating Scale (NRS). This single-dimension subjective scaling does not differentiate between sensory and affective components of pain and addresses the complex nature of the experience as a whole [Chapman and Syrjala, 1990; Atcheson, 2001].

In patients with neuropathic pain, the presence of stimulus-evoked pain, such as allodynia, can be used to evaluate the sensory-discriminative aspects of pain more specifically with quantitative sensory testing (QST). QST can thus be used to evaluate treatment outcome more objectively [Edwards et al., 2005].

Methods for the quantification of stimulus-evoked pain should ideally be simple to execute and yield standardized, validated and reproducible results [Peripheral Neuropathy Association, 1993]. Furthermore, the method used should be clinically relevant.

In this pilot study, we investigated the clinical relevance of quantitative sensory testing with Von Frey monofilaments in patients suffering from allodynia as a consequence of a neuropathic pain syndrome. Despite its heterogeneity, the clinical symptom allodynia can be quantified within a narrow range of deviation using Von Frey monofilaments [Keizer et al., 2007]. Importantly, QST with Von Frey monofilaments is simple in clinical practice and yields reliable and reproducible results [Bell-Krotoski and Tomancik, 1987; Mikkelsen et al., 2004]. We calculated the correlation between a change in the clinical pain (NRS) and changes in QST responses during a therapeutic intervention (see below). A relation between an improvement of the perceived pain and an increased pain threshold would imply clinical relevance of QST with the monofilaments [Edwards et al., 2005].

In order to achieve intra-individual variation of the intensity of alldynia, we chose to administer a whole-plant cannabis extract to the patients. Cannabis has been shown to improve alldynia and hyperalgesia in animal studies and in one study with experimental neuropathic pain in humans [Campbell et al., 2001; Kumar et al., 2001; Iversen and Chapman, 2002; Rukwied et al., 2003]. During a four-week period, we administered this cannabis extract to 17 patients who suffered from alldynia as a consequence of a unilateral neuropathic pain syndrome.
7.2. Methods

Twenty patients suffering from unilateral neuropathic pain and allodynia participated in this study after giving their informed consent. The study was approved by the Medical Ethics Committee of the University Medical Centre Groningen. In these patients, history and physical examination revealed the presence of neuropathic pain and allodynia. Neuropathic pain was diagnosed in all the patients, as there was no tissue damage or nociception that caused the pain; the pain was located in the distribution area of specific nerves or in one or more dermatomes and there was stimulus-evoked pain. Allodynia was diagnosed when the light stroking of the skin was reported as painful on the affected skin.

Patients suffering from polyneuropathy or diabetes mellitus were excluded, as those conditions are associated with hypoesthesia and may subsequently influence the outcome of QST. Drug addiction and psychiatric conditions were also considered as exclusion factors. All patients were Caucasian, Dutch was their native language. The patients continued their usual (analgesic) medication and they and their doctors were asked not to change medication or dosage without consulting one of the members of our research team.

During the first visit ($T_0$) the procedure was explained, QST with Von Frey monofilaments was performed and three grams of whole-plant cannabis were given in three separate envelopes. The patients were instructed to suspend a tea ball containing one gram of cannabis for twenty minutes in one litre of boiling water. Each night, just before sleeping, the patients drank 200 ml of this tea. They were free to choose whether they preferred the tea warm or cold, and with or without sugar or milk. The remaining tea was preserved in the refrigerator.

Two weeks later ($T_1$), the patient was asked if he had noticed any effects caused by the use of cannabis, either analgesia or side effects. If the patient had not noticed any effect, the dose was doubled, which meant an extra cup of cannabis-tea to be taken each morning. QST with Von Frey monofilaments was then performed, as well as at the end of the trial two weeks later ($T_2$), when the cannabis was discontinued.

7.2.1. Experimental setting

All patients underwent the measurements in a quiet room with a constant temperature of 20 - 22 °C. Each of the examinations was carried out by the same investigator (DK). To acclimatise, the patients were present in the room for about 10 minutes prior to the actual investigation. During this time the patients were informed about the procedure and the monofilaments were demonstrated to familiarise the patients with the procedure. Subsequently, the patients were investigated while lying comfortably on an examination table. The patient was asked to point out the skin area where allodynia was perceived as the most intense. The punctum maximum of the allodynia was marked with a little square (±1 cm²) drawn on the skin. The corresponding spot on the contralateral side of the body was marked similarly. These locations were documented in the patient’s medical record for the subsequent measurements two and four weeks later.
7.2.2. **Subjective pain scores**

The patient was asked to indicate the severity of the pain of that moment on a Numeric Rating Scale (NRS), which implied that the patient attributed a number to the perceived pain on the affected skin, ranging from 0 (no pain) to 10 (worst pain imaginable).

7.2.3. **Quantitative Sensory Testing**

A kit consisting of twenty nylon Von Frey monofilaments with increasing diameter of the firm Touch Test™ (North Coast Medical, Inc.) was used for QST. When applied on the skin, monofilaments exert a constant force, as the monofilament bends. This bending reduces measurement outcome artefacts resulting from movement or trembling of the examiner’s hand [Bell-Krotoski and Tomancik, 1987].

The monofilaments are calibrated in a logarithmic scale from 0.008 to 300 grams (0.08 – 2943 mN.), within a 5% standard deviation. Numbers on each monofilament ranging from 1.65 to 6.65, represent the common logarithm of 10 times the force in milligrams [Voerman et al., 2000].

The monofilaments were applied in increasing thickness (method of limits) on the affected and non-affected side successively, in a randomised sequence, until a pain threshold was detected. The patient was asked to give a clear verbal signal when the stimulus was perceived to be painful. Each monofilament was applied three times, with approximately 10 seconds between two successive stimuli, to avoid temporal summation [Price et al., 1989; Gruener and Dyck, 1994]. Subsequently, the procedure was repeated on the contralateral side.

The monofilament was applied perpendicularly to the skin surface for approximately 2 seconds, until a bending of 3-5 mm of the monofilament was produced. Patients kept their eyes closed during the investigation to avoid visual feedback concerning the stimuli.

The pain threshold was defined as the logarithmic number on the monofilament in which at least two out of three applications on the affected side resulted in the perception, and subsequent reporting of pain, the so-called “appearance”- threshold [Peripheral Neuropathy Association, 1993; Dotson, 1997]. Once a pain threshold was reached, QST was stopped. QST of the unaffected side was also performed to obtain baseline values.

The duration of the procedure was 10 - 15 minutes. We assumed that no significant loss of attention occurred during this procedure.

7.2.4. **Cannabis extract**

We used standardised whole plant cannabis produced by the firm Maripharm®, (Rotterdam, The Netherlands). This cannabis has been sterilized for microbial contamination by means of gamma-irradiation. According to European Pharmacopoeia (EP)-requirements, the cannabis contains an acceptably small quantity of pesticides and metalloids. In our hospital’s department of pharmacy, we measured the tetrahydrocannabinol (THC), cannabinol (CBN) and cannabidiol (CBD) contents in the cannabis (18 samples) and the extract (6 samples) by a validated GC-MS method. The mean concentration for THC in the cannabis was 6% ± 0.9% (mean ± SD) and in the cannabis-extracts 1% ± 0.2% (mean ± SD). CBN and CBD were found neither in the tea bags nor in the extract.
7.2.5. Statistical analysis

For the subjective (NRS) scores as well as the pain thresholds measured with the monofilaments, difference scores were calculated between the various time points ($T_0$, $T_1$, and $T_2$). To investigate the relation between the change in pain thresholds and the change in NRS scores, two-tailed Pearson correlation coefficients were calculated. For all statistical calculations in this study, $p$-values smaller than 0.05 were considered statistically significant.

7.3. Results

7.3.1. Baseline characteristics of the patients

Initially, the selected group of patients consisted of 6 males and 14 females. Three patients were lost to follow-up; one because of the development of oedema in both legs and two other patients because of insufficient ability to co-operate. The data of the remaining 17 patients (5 males, 12 females) were analysed. Their mean age was 47.1 years (range 27 – 61 years). The duration of their underlying pain syndromes varied strongly and differed from only a few months to several decades (see Table 1). The neuropathic pain was either the result of surgery (12), trauma (2), stroke (1), or had a (pseudo)-radicular origin (2).

At the time of inclusion, five patients did not use any medication, two patients used a non steroidal anti-inflammatory drug (NSAID) and ten patients used a tricyclic antidepressant and / or an antiepileptic drug, sometimes in combination with other analgesic drugs (Table 1).

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Age</th>
<th>Sex</th>
<th>Neuropathic pain due to:</th>
<th>Duration of pain (months)</th>
<th>Use of medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>52</td>
<td>F</td>
<td>surgery</td>
<td>60</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>F</td>
<td>surgery</td>
<td>5</td>
<td>none</td>
</tr>
<tr>
<td>3</td>
<td>27</td>
<td>F</td>
<td>surgery</td>
<td>100</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>(pseudo)-radicular irritation</td>
<td>22</td>
<td>none</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>M</td>
<td>surgery</td>
<td>72</td>
<td>gabapentin</td>
</tr>
<tr>
<td>6</td>
<td>41</td>
<td>M</td>
<td>surgery</td>
<td>300</td>
<td>none</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>F</td>
<td>surgery</td>
<td>54</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>8</td>
<td>56</td>
<td>F</td>
<td>surgery</td>
<td>19</td>
<td>gabapentin/tramadol</td>
</tr>
<tr>
<td>9</td>
<td>43</td>
<td>F</td>
<td>surgery</td>
<td>54</td>
<td>amitriptyline/temazepam</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>F</td>
<td>stroke following head trauma</td>
<td>25</td>
<td>gabapentin</td>
</tr>
<tr>
<td>11</td>
<td>48</td>
<td>F</td>
<td>surgery</td>
<td>30</td>
<td>gabapentin</td>
</tr>
<tr>
<td>12</td>
<td>59</td>
<td>F</td>
<td>surgery</td>
<td>65</td>
<td>naproxen/tramadol</td>
</tr>
<tr>
<td>13</td>
<td>52</td>
<td>F</td>
<td>surgery</td>
<td>60</td>
<td>morphine</td>
</tr>
<tr>
<td>14</td>
<td>31</td>
<td>F</td>
<td>surgery</td>
<td>15</td>
<td>amitriptyline/paracetamol/codeine/gabapentin</td>
</tr>
<tr>
<td>15</td>
<td>37</td>
<td>M</td>
<td>trauma</td>
<td>10</td>
<td>gabapentin/tramadol</td>
</tr>
<tr>
<td>16</td>
<td>46</td>
<td>F</td>
<td>(pseudo)-radicular irritation</td>
<td>35</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>17</td>
<td>61</td>
<td>M</td>
<td>surgery</td>
<td>500</td>
<td>none</td>
</tr>
</tbody>
</table>

Table 1: Characteristics of included patients; age, gender, diagnosis, duration of pain and medication use are displayed.
7.3.2. **Subjective effects and side-effects**

At \( T_1 \), two of the 17 participating patients indicated to perceive less pain and experienced an improved sense of well being. In these patients the dose was not increased. In the remaining 15 patients the dose was increased, as they described no subjective effect of the cannabis at that moment.

None of the patients that enrolled in this study dropped out because of side-effects. In most patients (15/17) no side-effects occurred at all. However, when side-effects did occur (2/17), they were considered as mild by the participating patients. One patient described a mild transitory redness of the eyes; the other patient had experienced a mild dizziness. Seven patients described an improved sense of well being after completing the trial.

7.3.3. **Quantitative sensory testing and subjective pain report**

\( T_1 - T_0 \): For the first two weeks of the study, the correlation between the change in pain thresholds and the change in subjective pain scores was 0.008 (\( p = 0.976 \)), indicating no relation between the measured difference in pain thresholds and the difference in the reported pain.

\( T_2 - T_0 \): For the whole four-week period, the correlation between the change in pain thresholds and the change in subjective pain scores was –0.426 (\( p = 0.088 \)).

\( T_2 - T_1 \): During the last two weeks of the study, the correlation between the change in pain thresholds and the change in subjective pain scores was –0.501 (\( p = 0.040 \)) indicating a relation that is statistically significant (see Figures 1a,b and c).

![Figure 1: In the first two weeks of the trial no relation between the pain thresholds and subjective pain scores was observed (a). During the last two weeks of the trial, the increase in pain threshold correlated significantly with a decreased NRS-score (c). The correlation that was calculated for the whole four-week period did not reach statistical significance (b).](image)

On the contralateral, unaffected side no pain threshold could be determined in 16 of the 17 patients at any time in the study. One patient, with post-operative neuropathic pain as a result of paramedian abdominal surgery, also experienced the application of thick Von Frey monofilaments on the contralateral healthy skin as painful. She rated her pain of the affected skin to be 10 on the NRS on \( T_0, T_1 \), and \( T_2 \).
4. Discussion

Pain is always subjective [Merskey and Bogduk, 1994]. The subjective nature of pain poses pain researchers and clinicians involved in the treatment of pain for the problem of how to quantify pain in order to evaluate therapeutic interventions as objectively as possible. In the case of neuropathic pain, concomitant symptoms such as allodynia and hyperalgesia can be used to quantify the severity of the pain by means of quantitative sensory testing [Edwards et al., 2005].

Our pilot study indicated clinical relevance of QST with monofilaments of allodynia in patients suffering from neuropathic pain, since the measured pain threshold is negatively associated with a decrease of the perceived pain intensity. These results are in agreement with other studies in which a relation between QST responses and clinical pain was found [Sorensen et al., 1997; Edwards et al., 2005].

Several aspects of this study need further consideration. With respect to terminology, we used the IASP definitions of allodynia and hyperalgesia in this study. We realise that many authors use the term ‘punctate hyperalgesia’ to indicate the pain following the application of Von Frey monofilaments. However, we did not use the word ‘hyperalgesia’ since the application of the monofilaments on unaffected skin was not considered painful by the control subjects and in all patients except one. We therefore preferred the term ‘allodynia’.

We chose to use a cannabis-extract to influence the severity of the patients’ allodynia, as animal studies show that cannabinoids are capable of decreasing the intensity of certain types of stimulus evoked pain, i.e. hyperalgesia and allodynia. In rats, low dose cannabinoids are even capable of reducing allodynia and hyperalgesia, without producing unacceptable side-effects [Martin et al., 1999; Kumar et al., 2001; Iversen and Chapman, 2002; Farquhar-Smith, 2002]. In human subjects, the topically administered synthetic cannabinoid agonist HU210 attenuated capsaicin-induced touch-evoked allodynia [Rukwied et al., 2003]. Of all cannabinoids, the efficacy of (Δ9)-THC against allodynia and hyperalgesia has been studied most extensively. In order to change the patients’ allodynia, we needed to use a THC-containing cannabis-extract.

Three patients were lost to follow up during the study. One female patient was excluded during the trial, because of aggravation of pre-existing oedema in both legs that influenced sensory function. She was referred to back her general practitioner for diagnostic work-up. Two other patients were excluded due to insufficient co-operation. One of these patients failed to comply with the protocol due to hypochondriasis, while the other patient was unable to produce the cannabis-extract adequately. The latter is an obvious disadvantage in general; although not difficult, the complexity of this procedure can lead to mistakes.

As stated earlier, a relation between an improvement of the clinical pain and an increased pain threshold would imply clinical relevance of QST with the monofilaments. In this study, we found a clear increase of the pain thresholds, however, the decrease of the clinical pain was not statistically significant. Probably, the number of patients that participated in this study was too small, or the quantity of ingested cannabinoids may have been inadequate, to detect this effect. The change in pain thresholds - as measured with the Von Frey monofilaments - and NRS scores, predominantly occurred in the last two weeks of the trial (see below). It was in this period (∆T2 - T1) that we found a statistically significant correlation between QST
responses and pain report.
Our finding that the change in pain thresholds and pain report mainly occurred in the last two weeks of the trial, may be explained by a delayed efficacy of the cannabis. Another possibility that cannot be ruled out is habituation to the testing procedure. However, we regard the latter possibility to be unlikely, since the patients had been familiarised with the testing procedure prior to the actual study. Furthermore, the measurements took place only three times in total, with two-week intervals. A delayed efficacy of cannabis as an explanation for the change in pain thresholds and pain report is more likely, and may be caused by rapid redistribution of cannabinoids in the body. As a consequence, an effective plasma level of THC is reached only after repeated dosage. Cannabinoids have a long elimination half-life of up to multiple days, due to extensive uptake in the fatty tissues from where slow release takes place [Mather, 2001]. In comparison, many drugs with a known analgesic effect against neuropathic pain, e.g. tricyclic antidepressants, also exert a therapeutic effect with a delayed onset of a few days to several weeks [Macres et al., 1999]. Finally, the placebo-effect may also account for the change in pain thresholds and pain report, as no control group was included in this study.
In conclusion, we demonstrated that an increased pain threshold correlated significantly with a decreased report of pain in this pilot study. We conclude that these preliminary findings suggest that quantitative sensory testing with Von Frey monofilaments is a clinically relevant method in patients with allodynia and neuropathic pain, although larger studies are needed for further proof.

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