Quantifying allodynia in patients suffering from unilateral neuropathic pain using Von Frey monofilaments

Chapter 6

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Abstract:
Objectives: The aim of this study is to investigate whether quantitative sensory testing with Von Frey monofilaments can be used for the quantification of allodynia in patients with chronic neuropathic pain, and how the pain threshold of affected skin differs from healthy skin.

Methods: Using Von Frey monofilaments, we aimed to determine the pain threshold in 22 patients suffering from allodynia as a consequence of a chronic unilateral neuropathic pain syndrome. We performed quantitative sensory testing according to the Method of Limits protocol. We used the patient’s own contralateral side and 5 healthy control subjects to obtain reference values.

Results: On the affected side, we found in 20 out of 22 patients that the pain threshold could be determined with the monofilaments. On average, these 20 patients indicated pain upon the application of monofilament with logarithmic nr. 4.56, whereas no pain threshold could be determined on the contralateral, unaffected side and in the healthy control subjects for any monofilament.

Discussion: We showed that although aetiology and pathophysiology of allodynia vary individually, with Von Frey monofilaments the clinical symptom allodynia can be quantified in a simple and practical fashion in almost all patients.
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6.1. Introduction

About 1 – 1.5% of the population in western countries suffers from some form of neuropathic pain [Chong and Bajwa, 2003]. Neuropathic pain is a common symptom of various conditions, ranging from diabetic polyneuropathy to the nerve entrapment by tumours. The pathophysiology of neuropathic pain is extremely complex and differs amongst various pain syndromes.

Stimulus-evoked pain is a phenomenon that can be frequently observed in patients with neuropathic pain and includes allodynia and hyperalgesia [Verdugo and Ochoa, 1992; Woolf and Mannion, 1999; Macres et al., 1999; Bridges et al., 2001]. The International Association for the Study of Pain (IASP) defines allodynia as pain due to a stimulus, which does not normally provoke pain, and hyperalgesia as an increased response to a stimulus, which is normally painful [Merskey and Bogduk, 1994]. Allodynia may well be one of the most disabling physical symptoms in neuropathic pain [Hansson et al., 2001; Backonja, 2002]. Allodynia is manifested in pain resulting for example from contact between clothing and skin, or between water and skin when taking a shower.

The clinical symptoms allodynia and hyperalgesia can be used to evaluate the effect of therapy aimed to reduce neuropathic pain. Neuropathic pain is notoriously difficult to alleviate, especially when compared with nociceptive pain [McQuay and Moore, 1998a+b]. In general, evaluation of the effect of therapeutic interventions is complicated by the fact that the variable, i.e. pain, is subjective in nature. Whereas subjective pain scores can be obtained by means of the Visual Analogue Scale (VAS) or the Numeric Rating Scale (NRS), more objective information concerning the severity of neuropathic pain can be obtained with quantitative sensory testing (QST) of allodynia or hyperalgesia.

Von Frey monofilaments (VFMs) are frequently used as a means of quantitative sensory testing to assess perception thresholds (PT) of sensory function at specific body sites, e.g. for quantifying hypoesthesia in diabetic polyneuropathy [Olaleye et al., 2001; Perkins et al., 2001]. In pain research, VFMs can be used to administer painful stimuli on hypersensitive skin in human experimental pain conditions or to determine the size of the hypersensitive skin area [LaMotte et al., 1991; Mayhöfner et al., 2005; Zambreanu et al., 2005]. In rodents the withdrawal responses of painful hind paws can be determined with VFMs [Martin et al., 1999; Johanek et al., 2001].

When used in a standardised fashion, application of Von Frey monofilaments provides the clinical investigator with practical, reproducible and reliable test results [Bell-Krotoski and Tomancik, 1987; Bell-Krotoski et al., 1995]. The most important condition is that measurement with VFMs should occur according to a uniform and standardised protocol [PNA, 1993]. In the presence of stimulus-evoked pain of the skin, apart from the perception threshold, a pain threshold can be determined as well.

The aim of this study is to investigate whether quantitative sensory testing with Von Frey monofilaments can be used to quantify stimulus-evoked pain in patients with chronic neuropathic pain, and how these thresholds differ from the healthy skin. Quantitative sensory testing with VFMs can be used for measuring stimulus-evoked pain irrespective of the underlying pathophysiological mechanisms. Whereas thin Von Frey monofilaments stimulate low threshold
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Aβ-fibres, thick VFMs also recruit Aδ-fibre nociceptors or even C-fibre nociceptors [Warncke et al., 1997; Gottrup et al., 1998; Woolf and Mannion, 1999; Ziegler et al., 1999; Graven-Nielsen et al., 2001]. The extent in which the different nerve fibres are involved in the – subjective – sensation that is perceived by the subject cannot be ascertained. We present the mean value of pain thresholds, as determined with VFMs using the Method of Limits [Gruener and Dyck, 1994; Dotson, 1997], in 20 patients suffering from stimulus-evoked pain as a consequence of a unilateral neuropathic pain syndrome. We will argue that this stimulus-evoked pain is in accordance with the IASP definition of allodynia. The pain threshold is defined as the logarithmic number of a Von Frey monofilament, which expresses the force exerted by this VFM that is reported as painful by the subject. QST on the patient’s own contralateral, unaffected side was performed to acquire appropriate reference values [PNA, 1993]. Furthermore, to exclude the possibility that a relative hypoalgesia might occur on the unaffected skin, we also performed QST in five healthy subjects. To our best knowledge, a mean pain threshold of allodynia in patients with chronic neuropathic pain has not been published thus far.

In this study we demonstrate that the symptom of allodynia, irrespective of the underlying pathophysiological mechanisms, is quantifiable in a simple and practical way with the use of Von Frey monofilaments.

6.2. Materials and methods
6.2.1. Patients and control subjects

Twenty-two patients suffering from unilateral neuropathic pain and stimulus-evoked pain participated in this study after giving their informed consent. The study was approved by the Medical Ethics Committee of the University Hospital in Groningen. In these patients, history and physical examination revealed the presence of allodynia, which was regarded to be present when a normally non-painful stimulus of any kind was considered painful by the patient. At the time of the inclusion, no distinction was made in type of stimulus-evoked pain or in medical diagnosis as a result of which the pain syndrome had arisen or in duration of the pain syndrome.

Patients with polyneuropathy and or diabetes mellitus were excluded, as those conditions may influence the outcome of QST. Drug addiction or psychiatric diseases were also considered exclusion factors. Subjects continued their (analgesic) medication.

Five control subjects, who did not suffer from pain of any kind and did not use any medication, were also included after they signed an informed consent. Originally, we intended to include 10 healthy subjects, however, after the study had been performed in 5 subjects, there was no variation of the results, therefore we decided to include no more subjects.

6.2.2. Experimental setting

All patients underwent the experiment in a quiet room with a constant temperature of 20 - 22 °C. Each of the examinations was carried out by the same investigator (D.K). To acclimatise, the patients were present in the room for 10 – 15 minutes prior to the actual quantitative sensory testing procedures. During this time they were informed about the procedure
and the monofilaments were demonstrated to familiarise the patients with the procedure. Subsequently, the patients underwent the experiment lying on an examination table. The patient was asked to point out the skin area where the stimulus-evoked pain was perceived as the most intense. The punctum maximum was marked by a little square (±1 cm²) drawn on the skin. The corresponding spot on the contralateral side of the body was marked similarly.

QST of the control subjects was performed on the dorsum of the hand above the first interosseus muscle on the left or right hand; allocated at random. Again, measurements took place within a square drawn on the skin, in the same manner as the patients.

6.2.3. Quantitative Sensory Testing with Von Frey monofilaments

A set consisting of twenty nylon Von Frey monofilaments with constant length and increasing diameter of the firm Touch Test™ (North Coast Medical, Inc.; Morgan Hill, USA) was used. When applied, these VFMs exert a constant force onto the tested skin. The bending of the VFM reduces measurement outcome artefacts resulting from movement or trembling of the examiner’s hand [Bell-Krotoski and Tomancik, 1987]. The VFMs 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 VFMs were applied in increasing thickness on the affected and non-affected side successively - in a randomised sequence - until a pain threshold was detected. This method is called the ‘Method of Limits’ [Gruener and Dyck, 1994; Dotson, 1997]. The patient was asked to give a clear verbal signal when the stimulus was perceived as painful. We asked the patients to pay specific attention to the pricking sensations evoked by stimulation with the monofilaments; would they consider this sensation to be painful or not? Each VFM was applied three times, with approximately 10 seconds between two successive stimuli, to avoid temporal summation [Price et al., 1989; Warncke et al., 1997; Leung et al., 2001]. Subsequently, the procedure was repeated on the contralateral side. The VFM was applied perpendicularly to the skin surface for approximately 2 seconds, until a bending of 3-5 mm of the VFM 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 VFM 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 [PNA, 1993; Dotson, 1997; Bohm-Starke et al., 2001]. Once a pain threshold was reached, we asked the patients to rate the amount of pain that was induced by the stimulus on a NRS. Next, QST was stopped. To exclude interference of learning effects, the side on which the examination began was randomised.

6.2.4. Data analysis

The mean value of the pain threshold, as measured with VFMs was determined, as well as the standard deviation. The pain threshold is expressed as the number of the logarithmic scale mentioned earlier.
6.3. Results
The group of included patients consisted of 6 males and 16 females, with a mean age of 49.2 years (range 24 – 78 years). The duration of their underlying pain syndromes varied from only a few months to several decades. The neuropathic pain was either the result of trauma, surgery or herpes zoster, or was due to chronic complex regional pain syndrome (CRPS) type 1 (see Table 1). The group of 5 control subjects consisted of 2 males and 3 females, with a mean age of 40.0 years (range 25 – 50 years), see also Table 1.
At the time of inclusion, six patients did not use any medication, eleven used a tricyclic antidepressant and / or an antiepileptic drug, sometimes in combination with analgesics. None of the control subjects were under the influence of medication at the time of inclusion. In the case of the patients, the procedure of QST took approximately 5 - 10 minutes, which was about twice as long compared to the control subjects.
In two of the 22 patients a pain threshold could not be measured using VFMs. Although the presence of stimulus-evoked pain had been demonstrated during the examination of the affected skin area, no pain threshold was reached with the application of any VFM.

Figure 1 is a bar diagram that illustrates the various pain thresholds as determined in the remaining 20 patients. All pain thresholds were above VFM log nr. 4.08 (9.8 mN) and under VFM log nr. 4.93 (78.5 mN). A pain threshold could neither be determined on the non-affected side for any VFM, nor in any of the control subjects.
The patients indicated that the transition from non-painful sensation to painful sensation was clearly noticeable; the NRS scores of the stimulus-evoked pain averaged 6.8 (range 4 – 9).
Table 1: Characteristics of participating patients. In the last two patients (nr. 21 and 22) no pain threshold could be measured with Von Frey monofilaments.

<table>
<thead>
<tr>
<th>Patient nr.</th>
<th>Age</th>
<th>Sex</th>
<th>Location of pain</th>
<th>Neuropathic pain due to</th>
<th>Duration of pain (months)</th>
<th>Severity (NRS)</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>41</td>
<td>M</td>
<td>lower abdomen</td>
<td>appendectomy</td>
<td>300</td>
<td>4</td>
<td>none</td>
</tr>
<tr>
<td>2</td>
<td>59</td>
<td>F</td>
<td>left ankle</td>
<td>bimalleolar fracture</td>
<td>65</td>
<td>6</td>
<td>naproxen/tamadol</td>
</tr>
<tr>
<td>3</td>
<td>34</td>
<td>F</td>
<td>right flank (side)</td>
<td>nephrectomy</td>
<td>55</td>
<td>5</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>4</td>
<td>69</td>
<td>F</td>
<td>right Th4 dermatome</td>
<td>herpes zoster</td>
<td>4</td>
<td>6</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>F</td>
<td>dorsal right upper arm</td>
<td>excision melanoma</td>
<td>5</td>
<td>7</td>
<td>none</td>
</tr>
<tr>
<td>6</td>
<td>27</td>
<td>F</td>
<td>left dorsal foot</td>
<td>excision neurofibroma</td>
<td>100</td>
<td>7</td>
<td>ibuprofen</td>
</tr>
<tr>
<td>7</td>
<td>54</td>
<td>M</td>
<td>C2 dermatome right</td>
<td>excision fibroma</td>
<td>72</td>
<td>4</td>
<td>gabapentin</td>
</tr>
<tr>
<td>8</td>
<td>39</td>
<td>F</td>
<td>left leg</td>
<td>CRPS type I</td>
<td>44</td>
<td>7</td>
<td>diclofenac/acetaminofen</td>
</tr>
<tr>
<td>9</td>
<td>57</td>
<td>F</td>
<td>right area of infraorbital nerve</td>
<td>orbital fracture</td>
<td>38</td>
<td>8</td>
<td>tramadol/oxycodone/amitriptyline/gabapentin</td>
</tr>
<tr>
<td>10</td>
<td>56</td>
<td>M</td>
<td>right C6 dermatome</td>
<td>spontaneous</td>
<td>22</td>
<td>8</td>
<td>none</td>
</tr>
<tr>
<td>11</td>
<td>58</td>
<td>M</td>
<td>left leg</td>
<td>CRPS type I</td>
<td>30</td>
<td>9</td>
<td>none</td>
</tr>
<tr>
<td>12</td>
<td>24</td>
<td>F</td>
<td>right leg</td>
<td>CRPS type I</td>
<td>115</td>
<td>6</td>
<td>none</td>
</tr>
<tr>
<td>13</td>
<td>56</td>
<td>F</td>
<td>right upper thorax and upper arm</td>
<td>amputation right mamma</td>
<td>54</td>
<td>9</td>
<td>amitriptyline</td>
</tr>
<tr>
<td>14</td>
<td>40</td>
<td>F</td>
<td>left arm</td>
<td>CRPS type I</td>
<td>6</td>
<td>7</td>
<td>amitriptyline/tramadol/acetaminofen</td>
</tr>
<tr>
<td>15</td>
<td>48</td>
<td>F</td>
<td>area of n. cut. fem. lat. sup.</td>
<td>surgery in right groin</td>
<td>30</td>
<td>7</td>
<td>gabapentin</td>
</tr>
<tr>
<td>16</td>
<td>72</td>
<td>F</td>
<td>left armpit</td>
<td>excision lymphnode</td>
<td>7</td>
<td>5</td>
<td>acetaminofen/ibuprofen/amitriptyline/temazepam</td>
</tr>
<tr>
<td>17</td>
<td>26</td>
<td>F</td>
<td>right wrist</td>
<td>CRPS type I</td>
<td>18</td>
<td>7</td>
<td>diclofenac/acetaminofen/ibuprofen</td>
</tr>
<tr>
<td>18</td>
<td>72</td>
<td>F</td>
<td>right Th8 dermatome</td>
<td>herpes zoster</td>
<td>16</td>
<td>8</td>
<td>acetaminofen/tramadol/gabapentin/oxazepam</td>
</tr>
<tr>
<td>19</td>
<td>28</td>
<td>F</td>
<td>left leg</td>
<td>CRPS type I</td>
<td>1</td>
<td>8</td>
<td>tramadol/amitriptyline/gabapentin</td>
</tr>
<tr>
<td>20</td>
<td>78</td>
<td>F</td>
<td>right L3 dermatome</td>
<td>herpes zoster</td>
<td>8</td>
<td>8</td>
<td>gabapentin</td>
</tr>
<tr>
<td>21</td>
<td>54</td>
<td>M</td>
<td>left laterale heel</td>
<td>fracture both calcanei</td>
<td>43</td>
<td>8</td>
<td>amitriptyline/clomipramine</td>
</tr>
<tr>
<td>22</td>
<td>53</td>
<td>F</td>
<td>right shoulder and upper arm</td>
<td>amputation right mamma</td>
<td>115</td>
<td>7</td>
<td>amitriptyline</td>
</tr>
</tbody>
</table>
In this study we found a mean pain threshold corresponding with the logarithmic number 4.47, (SD = 0.25) on the affected skin, which signifies that patients suffering from stimulus-evoked pain will on average experience VFM with log nr. 4.56 (39.2 mN) as painful (see Figure 1.). The standard deviation of 0.25 corresponds with two VFMs thinner or thicker than the VFM with log nr. 4.56.

6.4. Discussion

Despite the heterogeneous character of the patients and their neuropathic pain syndromes, we showed that stimulus-evoked pain is quantifiable using Von Frey monofilaments - within a narrow range of deviation - in 20 of 22 of the patients. On average, these 20 patients indicated pain upon the application of VFM with log nr. 4.56, whereas no pain threshold could be determined on the contralateral, unaffected side for any VFM or in any of the control subjects. Several aspects of this method of QST need further consideration. Although thick VFMs evoke a pricking sensation on unaffected skin, none of the patients or control subjects described this pricking sensation as pain. Therefore, we decided to call the patient’s stimulus-evoked pain ‘allogynia’ instead of (pinprick or punctate) ‘hyperalgesia’. The IASP definition of pain also explicitly states that “experiences which resemble pain but are not unpleasant, e.g. pricking, should not be called pain” [Merskey and Bogduk, 1994].

Despite the presence of allogynia, which had been established during history taking and physical examination, a pain threshold could not be determined in 2 of the 22 patients.
Several explanations may account for this finding. First, a primarily psychogenic cause of allodynia or insufficient co-operation may frustrate the outcome of quantitative sensory testing by inconsistent reporting [Dotson, 1997]. Second, it is not exactly known to what extent the different subtypes of afferent nerve fibres - Aβ, Aδ or C fibres - are stimulated by the various VFMs [Warncke et al., 1997; Gottrup et al., 1998; Woolf and Mannion, 1999; Ziegler et al., 1999; Graven-Nielsen et al., 2001]. Since the involvement of one of these subtypes of afferent nerve fibres may predominate in a patient’s clinical symptom of allodynia, it is possible that the dominant subtype of afferent fibre is not activated sufficiently with VFMs in order to reach a pain threshold. To elucidate the extent in which the different types of afferent fibre are involved in the perception of the different VFMs, future studies using differential nerve blocks would be needed.

We think that wind-up-like pain or temporal summation did not influence the outcome of our measurements, due to the intervals of over 10 seconds between stimuli with the successive stimuli (0.1 Hz). Wind-up-like pain, lowering of the pain threshold, has shown to be evoked when stimuli are applied at a frequency of 0.3 Hz or higher [Price et al., 1989; Warncke et al., 1997; Leung et al., 2001]. We assumed that no significant loss of attention occurred during the brief period when QST was performed.

Apart from quantitative sensory testing, Von Frey monofilaments have also been deployed for investigating the qualitative aspects of sensory function, i.e. to determine the presence of hyposensibility or hypersensibility. In patients with diabetic polyneuropathy, VFMs can be used to assess whether nerve function is compromised, as is described by Olaleye et al. (2001) and Perkins et al. (2001). In these two studies, the hallux of each foot was stimulated with one specific Von Frey monofilament, while the patient was asked to respond if the stimulus was perceived. This screening method enables clinicians to rapidly assess the presence of impaired sensory function. However, no information is obtained concerning the severity of the sensory impairment.

The severity of sensory dysfunction can be determined in various manners. The first method is to measure or ‘map’ the area of altered sensibility, by changing the location where the VFM is applied on the skin. A change in the size of the skin area where the stimulus-evoked pain is located, can aid in evaluating the effect of therapeutic interventions [Leung et al., 2001; Wallace et al., 2002a; Koppert et al., 2005; Schulte et al., 2005].

An alternative method to quantify the severity of stimulus-evoked pain, is to apply a stimulus following which the patient is asked to rate the severity of pain on a Visual Analogue Scale or Numeric Rating Scale [Belfrage et al., 1995; Wallace et al., 2002a+b]. The major disadvantage of this method of QST, however, is that VAS and NRS scores are highly subjective.

Finally, the smallest stimulus intensity needed to evoke a response can be determined. For example, Voerman et al. (2000) measured sensory detection thresholds in patients with chronic cervicobrachialgia, by applying VFMs of increasing thickness on the skin according to the Method of Limits protocol, after these patients had undergone a diagnostic dorsal root blockade. The patients were asked to respond as soon as the stimulus was felt. The detection threshold was expressed as the physical force exerted by the smallest monofilament that evoked the patient’s response. Similarly, Wallace et al. (2002a) measured both sensory detec-
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tion thresholds and pain thresholds with Von Frey monofilaments after infusion of analgesics in healthy subjects in whom pain had been induced with intradermal capsaicin injections. Although we used a comparable design in our study, several differences in methodology warrant further discussion. Wallace and co-workers used Von Frey monofilaments to measure both sensory detection thresholds and pain thresholds; we only measured pain thresholds. They selected the monofilaments at random, whereas we applied always the same ascending order of monofilaments. In both studies, the pain threshold was expressed as the smallest force needed to evoke a response from the subject, however, Wallace and co-workers measured sensory thresholds with a methodology that appears to be more complex than the Method of Limits. Finally, Wallace and co-workers asked their subjects to report “discomfort”, rather than “pain” as we did [Wallace et al., 2002a].

A mean pain threshold measurement with VFM's according to the Method of Limits protocol, in patients with alldynia as a consequence of a neuropathic pain syndrome, has not been published before. In this study, we showed that, although the aetiology and pathophysiology of alldynia vary, quantification of this symptom with VFM's using the Method of Limits is simple and practical in almost all the patients with alldynia (20 of 22). Future studies are needed to evaluate the response of these pain thresholds to therapeutic interventions, in order to demonstrate that this method of QST can also measure a change in (hyper)sensibility following treatment.
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