Quantifying allodynia with Von Frey monofilaments
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Quantitative Sensory Testing with Von Frey monofilaments in patients with allodynia: what are we quantifying?

Chapter 8

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Abstract
The International Association for the Study of Pain (IASP) defines allosthenia 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. However, does “normally painful” mean “any stimulation of nociceptors” or “the subjective pain response”?
We argue that “normally painful” should not mean “any stimulation of nociceptors”, as Von Frey monofilaments may evoke a pricking sensation – which implies the involvement of nociceptors – without necessarily leading to a subjective pain perception. In this paper, we propose that the diagnosis of either allosthenia or hyperalgesia should be based on the patient’s report, i.e. painful vs. not painful, rather than on the (sub)type of afferent fibre involved.

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8.1. Introduction

Quantitative sensory testing (QST) is routinely performed in patients with neuropathic pain in order to quantify stimulus-evoked pain. Stimulus-evoked pain is a phenomenon that can be frequently observed in these patients and can be further subdivided in allodynia and hyperalgesia [Woolf and Mannion, 1999; Macres et al., 1999; Bridges et al., 2001]. As we will describe below, the use of these terms may be misleading, possibly frustrating the interpretation of research in the field of quantitative sensory testing. For example, multiple definitions for the term ‘hyperalgesia’ are currently used (see Table 1).

<table>
<thead>
<tr>
<th>Source</th>
<th>Hyperalgesia</th>
</tr>
</thead>
<tbody>
<tr>
<td>IASP; [Merskey and Bogduk, 1994]</td>
<td>An increased response to a stimulus which is normally painful</td>
</tr>
<tr>
<td>Adams and Victor’s Principles of Neurology; [Victor and Ropper, 2001]</td>
<td>An increased sensitivity and a lowered threshold to painful stimuli</td>
</tr>
<tr>
<td>Textbook of pain, [Wall and Melzack, 1999]</td>
<td>A lowered threshold for pain and pain to suprathreshold stimuli is enhanced</td>
</tr>
<tr>
<td>Stedman’s Medical Dictionary, 27th ed. 1997</td>
<td>Extreme sensitivity to painful stimuli</td>
</tr>
</tbody>
</table>

Table 1. Four different authors, four different descriptions of the concept ‘hyperalgesia’.

In 1994, the Subcommittee on Taxonomy of the International Association for the Study of Pain (IASP) formulated a widely accepted definition of pain and its associated symptoms (see Table 2). In our opinion, the IASP-definition of hyperalgesia gives rise to a dilemma; does “normally painful” mean (1) any stimulation of nociceptors or (2) the subjective pain response? Both interpretations are possible. Cronje and Williamson (2006) wrote an interesting article on this topic, in which they expressed their surprise that the word ‘normal’ is ubiquitously used in the IASP Pain Terminology, while its precise definition is not determined [Cronje and Williamson, 2006].

<table>
<thead>
<tr>
<th>Concept</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Pain</td>
<td>An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage</td>
</tr>
<tr>
<td>Allodynia</td>
<td>Pain due to a stimulus which does not normally provoke pain</td>
</tr>
<tr>
<td>Hyperalgesia</td>
<td>An increased response to a stimulus which is normally painful</td>
</tr>
</tbody>
</table>

Table 2. Definitions of pain, allodynia and hyperalgesia according to the IASP Pain Terminology [Merskey and Bogduk, 1994].
In this paper we address what we perceive to be the semantic ambiguity regarding the concepts 'hyperalgesia' and 'allodynia'. We argue that the difference between the two becomes less obvious in clinical practice, where the boundary between painful and non-painful is less clear-cut.

The main objective of this paper is to invite clinicians and researchers to carefully examine the semantics of the terms 'allodynia' and 'hyperalgesia' and to join us in the discussion.

8.2. Hyperalgesia or allodynia?

To illustrate our point, we refer to the results of a study that we performed in a group of patients suffering from stimulus-evoked pain [Keizer et al., 2007]. In this study, we tried to determine a mean pain threshold with Von Frey monofilaments in 22 patients who were suffering from unilateral stimulus-evoked pain due to a neuropathic pain syndrome. We applied the Von Frey monofilaments of variable stiffness on the affected and on the contralateral non-affected skin, according to the Method of Limits protocol. We asked the patients to indicate whether they perceived the application of the monofilament as painful or not. We also included 5 healthy subjects for QST according to the same protocol. Further details on the procedure are to be found in the original paper.

As an interesting, additional finding we discovered that, while in 20 of the 22 patients a pain threshold could be determined on the affected skin, none of the Von Frey monofilaments were regarded as painful when applied on the non-affected skin. As a result, we concluded that we had provoked pain with a stimulus that is normally not painful and had therefore measured allodynia. This conclusion, however, does not agree with the leading opinion in medical literature [Ochoa, 2003; Treede et al., 2004], which implies that QST with Von Frey monofilaments measures (punctate) hyperalgesia.

As mentioned before, the IASP defines allodynia as pain due to a stimulus which does not normally provoke pain. The light stroking of the skin is an example of such an innocuous stimulus, which may be perceived as painful on allodynic skin. In contrast, hyperalgesia is defined as an increased response to a stimulus that is normally painful [Merskey and Bogduk, 1994]. According to these definitions, it is therefore the nature of the stimuli, normally painful vs. normally non-painful, which determines the difference between the two. Although this appears to be straightforward, one question arises: what exactly is “a normally painful stimulus”? During the execution of our study, which was originally intended to measure pain thresholds in patients with stimulus-evoked pain, we noticed that none of the Von Frey monofilaments elicited a pain response on healthy skin; neither in the patients nor in the control subjects. Although a mild pricking sensation was generally present upon the application of thicker Von Frey monofilaments, the patients and subjects clearly indicated that they did not regard this as painful. The IASP definition of pain, states explicitly that “experiences which resemble pain but are not unpleasant, e.g., pricking, should not be called pain”. We therefore could not, in the absence of algesia, identify hyperalgesia. Pain is not merely the consequence of the stimulation of nociceptors; pain is a complex sensory and emotional experience [Merskey and Bogduk, 1994].
8.2.1. Different subtypes of stimulus-evoked pain

Most of the research in the field of QST has focused on hyperalgesia, which has led to the distinction of three different subtypes during the 1990s: dynamic, static and punctate hyperalgesia (see below) [Koltzenburg et al., 1992 + 1994; Handwerker and Kobal, 1993; Ochoa and Yarnitsky, 1993; Kilo et al., 1994; Woolf and Mannion, 1999]. The subdivision of hyperalgesia into these three different subtypes has been based mainly on differences in the postulated underlying pathophysiological mechanisms.

Dynamic hyperalgesia: Stimuli that can be administered to provoke dynamic hyperalgesia include the light stroking of the affected skin [Ochoa and Yarnitsky, 1993]. Since this form of cutaneous stimulation is certainly non-painful on normal skin, this dynamic hyperalgesia is also referred to as ‘brush-evoked allodynia’ or ‘low threshold mechanoreceptor mediated allodynia’.

Dynamic hyperalgesia is thought to be mediated by low threshold (Aβ) afferent fibres, with the perception of pain being the consequence of sensitisation and misinterpretation in the central nervous system [Torebjörk et al., 1992; Koltzenburg et al., 1992 + 1994; Kilo et al., 1994]. On the other hand, it may also be mediated by sensitised nociceptors (high threshold Aδ- and C- afferent fibres), which would normally respond only to noxious, high intensity stimulation [LaMotte et al., 1991; Ochoa, 2003]. Consequently, the pain resulting from the light stroking of the skin may be the result of stimulation of either type of afferent fibre.

Several aspects of the concept dynamic hyperalgesia need further consideration. ‘Allodynia’ is often referred to as a synonym for ‘dynamic hyperalgesia’ [Magerl et al., 1998; Woolf and Mannion, 1999; Ziegler et al., 1999; Treede et al., 2004]. According to the IASP definition of hyperalgesia, however, any method of QST to test hyperalgesia should also be normally painful, i.e. painful on corresponding, non-affected skin. Obviously, the light stroking of the skin is not normally painful. As a result, this method of QST does not test hyperalgesia, it tests allodynia. We argue that there is no place for the concept ‘dynamic hyperalgesia’ in the field of quantitative sensory testing.

Static hyperalgesia: Stimuli that can be administered to provoke static hyperalgesia include applying firm pressure, pinching, stretching or squeezing to the skin [Koltzenburg et al., 1992; Ochoa and Yarnitsky, 1993; Kilo et al., 1994]. Static hyperalgesia is thought to be mediated mainly by Aδ- and C- nociceptors and results from sensitisation of these peripheral nociceptors [Ochoa and Yarnitsky, 1993; Warncke et al., 1997; Woolf and Mannion, 1999]. However, input from Aδ-nociceptors may also be exaggerated within the central nervous system [Ziegler et al., 1999; Treede and Magerl, 2000]. Furthermore, stimuli that provoke static hyperalgesia, e.g. firm pressure on the skin, will inevitably activate low threshold Aβ-fibres. Thus, multiple neurophysiological mechanisms may underlie the clinical phenomenon of static hyperalgesia.

Punctate hyperalgesia: Punctate hyperalgesia can be evoked by applying a pin or Von Frey monofilaments onto the affected skin [Magerl et al., 1998; Ziegler et al., 1999]. Punctate hyperalgesia is thought to be mediated mainly by Aδ- nociceptors [Kilo et al., 1994; Ziegler et al., 1999]. Von Frey monofilaments (VFM)s are frequently used to test punctate hyperalgesia. Thin VFM-s stimulate Aβ-afferents, however, thick VFM-s will stimulate Aδ-fibre nociceptors as well, due to the sharp edges of the monofilaments [Ziegler et al., 1999; Graven-Nielsen et al., 2001]. In case of peripheral sensitisation, C-fibre nociceptors may also be involved [Warncke et al., 1997].

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et al., 1997; Gottrup et al., 1998; Woolf and Mannion, 1999; Ziegler et al., 1999; Graven-Nielsen et al., 2001]. As we mentioned above, there is evidence for an exaggerated response to Aδ-nociceptive input at spinal level, suggesting that central sensitisation also plays a role in punctate hyperalgesia [Ziegler et al., 1999]. Hence, when Von Frey monofilaments are used to quantify punctate hyperalgesia, it cannot be determined to what extent these different pathophysiological mechanisms are involved.

In conclusion, current stimulation methods are too crude to be able to discriminate between the three subtypes of hyperalgesia on the basis of the underlying pathophysiological mechanisms, of which our knowledge is still incomplete. Furthermore, it does not automatically suffice to identify any clinical or neurophysiological phenomenon that involves nociceptors as hyperalgesia.

8.3. Quantification of hyperalgesia and allodynia

Different pathophysiological mechanisms often coexist in neuropathic pain. The clinical symptoms that correspond with the two concepts allodynia and hyperalgesia are therefore likely to co-occur in patients with neuropathic pain. However, with the careful use of QST, a distinction between the two subtypes of stimulus-evoked pain can well be made, based on clinical findings rather than based on the assumed underlying pathophysiological mechanisms.

In order to quantify the intensity of stimulus-evoked pain in general, the pain threshold is determined on affected skin, e.g. using the Method of Limits [Peripheral Neuropathy Association, 1993; Gruener and Dyck, 1994; Dotson, 1997]. The pain threshold can then be expressed as the intensity of the stimulus needed to evoke the subject’s verbal pain response.

In order to quantify hyperalgesia, the (subjective) pain intensity following a stimulus that also evokes pain on healthy skin needs to be assessed with a VAS or NRS. After all, the stimulus intensity needed to evoke a pain response is not abnormal; it is the pain response that is exaggerated.

In order to quantify allodynia, the lowest intensity of a non-painful stimulus needed to evoke a pain response on the affected skin, i.e. pain incidence, can be measured [Baumgärtner et al., 2002; Treede et al., 2004]. This option implies the measurement of stimulus intensity, not pain (e.g. degrees Celsius as with thermal QST [Verdugo and Ochoa, 1992]). The advantage of this method is that allodynia can be quantified objectively, since the subjective response of the patient is reduced to either “yes (it was painful)” or “no (it was not painful)”.

Taking the above into account; is hyperalgesia a valuable additional parameter in clinical QST with Von Frey monofilaments or a source of semantic confusion and of limited clinical value?

8.4. Conclusion

Quantitative Sensory Testing of hypersensitive skin in patients with neuropathic pain is important for both clinicians and researchers. Ideally, with QST, stimulus-evoked pain should be quantifiable with a reasonable degree of objectivity, in a reliable and reproducible manner. Furthermore, it is important that it should be clear which subtype of stimulus-evoked pain is quantified, in order to avoid ambiguous results.

We observed that Von Frey monofilaments that evoked a pain response in patients suf-
ferring from stimulus-evoked pain did not evoke a pain response when applied on healthy, unaffected skin, even though this sensation was frequently described as pricking. None of the patients or healthy subjects, however, regarded this pricking sensation to be painful. Thus, we diagnosed the stimulus-evoked pain in our patients to be allodynia, since stimulation of normal skin with Von Frey monofilaments is not painful.

We have found that the leading opinion in medical literature states that with Von Frey monofilaments (punctate) hyperalgesia can be measured. This opinion is based on evidence that punctate stimuli, as with Von Frey monofilaments, stimulate Aδ-nociceptors. The main idea behind this opinion is that ‘normally painful’ implies the involvement of nociceptors, rather than the subjective pain response. In other words; hyperalgesia is increased pain following stimulation of nociceptors, while allodynia is pain following stimulation of Aβ-fibres.

What are we suggesting?

First, there is no need to alter current QST technique, but in view of the abovementioned points we propose to adjust the interpretation of the results. When pain is elicited on the affected skin, it is unlikely that Aβ-, Aδ- or C-fibre afferents can be stimulated selectively with the current methods of QST. Therefore, the difference between allodynia and hyperalgesia should not be diagnosed on the basis of the primary afferent that is assumed to be stimulated. Instead, the diagnosis of either allodynia or hyperalgesia should be based on patients’ report following stimulation of the affected skin, i.e. painful or not painful, whereby corresponding, non-affected skin is used as the reference standard. Allodynia and hyperalgesia are clinical phenomena, not neurophysiological diagnoses.

Secondly, multiple definitions and interpretations of the clinical phenomenon hyperalgesia are currently used in the medical literature. In this respect, the IASP definition of hyperalgesia should be the gold standard, however, we argue that it is of limited use for clinical QST. Needless to say, in day to day medical practice, diagnostic procedures to obtain a better understanding of the pathophysiological mechanisms of neuropathic pain should entail more than just QST, such as an accurate history and a thorough physical examination. Nevertheless, QST of stimulus-evoked pain is a valuable tool in the diagnosis of neuropathic pain and it can be deployed to monitor the effect of therapeutic interventions in the treatment of neuropathic pain.
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