American Pain Society
RESEARCH
EDUCATION
TREATMENT
ADVOCACY
PUBLISHED BY ELSEVIER

The Journal of Pain, Vol 12, No 7 (July), 2011: pp 764-773
Available online at www.sciencedirect.com

Topical High-Concentration (40%) Menthol—Somatosensory Profile of a Human Surrogate Pain Model

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Abstract: Cold hyperalgesia is 1 of the characteristic signs in neuropathic pain. Topical application of menthol has been proposed as model to study cold hyperalgesia. The aim of this psychophysical study was to characterize the human surrogate of neuropathic pain of topical menthol application by using a standardized and validated protocol of quantitative sensory testing (QST). Additionally, we assessed the course of the signs elicited by menthol application over time. High-concentration 40% L-menthol was applied topically on hairy skin in 12 healthy subjects. Standardized psychophysical tests (QST) assessing 13 parameters including thermal and mechanical detection and pain thresholds were obtained before and every 45 minutes after menthol removal up to 4 hours after menthol application. Menthol decreased the cold pain threshold, mechanical pain threshold, and increased the mechanical pain sensitivity in all subjects displaying cold and mechanical pinprick hyperalgesia. In all subjects, an area of secondary pinprick hyperalgesia could be determined. Within the observation time, the decreased cold pain threshold increased continuously, whereas the signs of primary and secondary pinprick hyperalgesia remained stable. The data suggest that topical 40% menthol application is a useful model for studies of cold hyperalgesia and pinprick hyperalgesia in humans.

***Perspective:** This study establishes the topical application of high-concentration 40% menthol as a useful stable model for studies of cold hyperalgesia and pinprick hyperalgesia in humans. The provided long-term data are important for psychophysical and pharmacological research in humans and provide us with insights on experimental cold and mechanical hyperalgesia.*

***Key words:** Cold hyperalgesia, mechanical hyperalgesia, quantitative sensory testing, model stability.*

Human experimental pain models play an important role in studying mechanisms of neuropathic pain.[23,45,58] These so-called human surrogate models of neuropathic pain share similar symptoms and signs, eg, thermal hyperalgesia, of typical neuropathic pain syndromes such as postherpetic neuralgia and posttraumatic neuralgia.[5] Thus, these models are widely used to explore pathophysiological mechanisms, to perform proof-of-concept studies in the development of new analgesics, and translational neuroscience to verify results of animal studies in humans.[12,15,24,33] Capsaicin, a compound of the hot chili, has been extensively used in the past to induce burning pain, heat, and mechanical hyperalgesia and mechanical allodynia.[31] This is achieved by capsaicin as a potent TRPV1 receptor agonist on nociceptive neurons that are sensitized.[9,10] Recently, topical application of menthol has been introduced as a surrogate model of cold hyperalgesia.[18,36,59] Menthol is an agonist on the TRPM8 receptor,[33] causing a sensitization of nociceptive C-fibers leading to cold hyperalgesia and mechanical (pinprick) hyperalgesia.[59] As in the capsaicin model, topical application of menthol leads to sensitization of cutaneous nociceptors. The zone of application (primary zone) is characterized by cold and mechanical

Received August 5, 2010; Revised December 3, 2010; Accepted December 31, 2010.

This study is a part of the Europain project, funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU; www.imi.europa.eu) Grant no 115007 and was financially supported by BMBF (01EM0504) and an unrestricted financial grant from Pfizer Germany.

A.B. received honoraria for lectures from Grünenthal, Allergan, Astellas, Pfizer and payment for development of educational presentations from Pfizer. M.S. received honoraria for lectures from Grünenthal and Pfizer. R.B. has consultancies with and received honoraria from Pfizer, Genzyme, Grünenthal, Mundipharma, Allergan, Sanofi Pasteur, Medtronic, Eisai, UCB, Lilly, and Astellas; received grants from Pfizer, Grünenthal, Genzyme; and received payment for development of educational presentations from Pfizer, Medtronic. G.W. received honoraria for lectures from Grünenthal, Medtronic, Pfizer, and Mundipharma.

The authors declare that the sources of financial support had no influence on data assessment, analysis and interpretation and disclose potential conflicts of interest.

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1526-5900/$36.00

doi:10.1016/j.jpain.2010.12.013

hyperalgesia. Additionally, as a result of ongoing primary afferent nociceptor activity from the zone of primary hyperalgesia, centrally located neurons are sensitized. This central sensitization leads to mechanical (but not thermal hyperalgesia) and inconsistently dynamic mechanical allodynia in the zone of secondary hyperalgesia (secondary zone) surrounding the primary zone.

However, stability of a human surrogate model of pain is crucial, being the prerequisite of gaining reliable symptoms and signs over time that can be assessed, e.g, by quantitative sensory testing (QST), and in particular when testing pharmacological interventions.[3] This goal has been achieved by introducing a long-lasting stable model, the heat/capsaicin sensitization model,[41] enabling the investigator to rekindle heat hyperalgesia, mechanical hyperalgesia, and allodynia by repetitive heating of the capsaicin-pretreated skin. However, no study so far assessed the symptom and sign stability of the menthol surrogate model, ie, a cold hyperalgesia and mechanical hyperalgesia in humans. Moreover, the methods of quantitative sensory testing used to characterize the menthol model varied between the previous studies regarding the set of tests and test algorithms used. In 2006, a standardized QST protocol has been validated in healthy volunteers and provides now the opportunity to characterize the somatosensory profile in a standardized way.[44]

Thus, aim of this study was first to determine the somatosensory profile of the menthol pain model by using a standardized and validated QST protocol; and second, to explore the stability of different symptoms and signs of the menthol-induced surrogate model of neuropathic pain over time. Thereby, we assessed time ranges for stable psychophysical testing, its different symptoms and signs, and the suitability for pharmacological interventions.

Methods

Subjects and Study Protocol

12 male healthy right-handed volunteers (mean age 25.3 ± 1.61 years) were consecutively assigned to the study. All subjects were free of pain and medication at the time of testing.

At baseline, quantitative sensory testing (QST) parameters were assessed using the standardized protocol of the German Research Network on Neuropathic Pain (DFNS) within the previously marked prospective application area at the dorsum of the right hand (Fig 1).[44] Afterwards, menthol was applied topically for 20 minutes.[59] During application time, cold sensation, spontaneous pain (both every minute), and pain quality (McGill Pain Questionnaire; every 5 minutes) were obtained. After removal of the menthol patch, the QST parameters were assessed immediately ("post menthol") and every 45 minutes up to 225 minutes after menthol patch removal, ie, 245 minutes after menthol application (Fig 1). Additionally, the area of dynamical mechanical allodynia and mechanical hyperalgesia was assessed after each QST (Fig 1). All experiments were performed in a supine position in a quiet room.

The study was approved by the Ethics Committee of the Medical Faculty of the Christian-Albrechts-University Kiel and conducted according the Declaration of Helsinki. The volunteers gave written informed consent after being adequately informed before entering the study.

Assessment of Skin Temperature

To control for possible interactions in the determination of thermal perception and pain thresholds, the skin temperature (IR-1000L, VoltCraft, DE) at the test area was measured before and after menthol application and every time before QST hereafter.

Quantitative Sensory Testing (QST)

In all volunteers, the dorsum of the right hand was investigated using the QST-protocol of the German Research Network on Neuropathic Pain (DFNS) as described previously.[44] This protocol has been recently validated in 180 healthy volunteers[44] and includes a standardized QST battery measuring 13 parameters (a detailed description in[44]). Summarizing, the mechanical detection threshold (MDT) and vibration detection threshold (VDT) represent a large-fiber function (thickly myelinated A-beta fibers). Cold detection threshold (CDT), cold pain threshold (CPT), warm detection threshold (WDT), heat pain threshold (HPT), thermal sensory limen (TSL), mechanical pain threshold (MPT), and pressure pain threshold (PPT) represent a small-fiber function (unmyelinated C fibers and thinly myelinated A-delta fibers). Paradoxical heat sensations (PHS) represent a dysfunction of A-delta cold fibers. Wind-up ratio (WUR) is a frequency-dependent increase in excitability of spinal cord neurons and pain. Within stimulus/response functions, mechanical pain sensitivity (MPS) for pinprick stimuli and dynamic mechanical allodynia (DMA) was assessed. All parameters were determined by repeated measurements as outlined within the standardized QST protocol,[44] and mean values were calculated before statistical analysis. All QST tests were always performed in the same order and within the menthol application area. As known from previous studies, it was expected that due to central sensitization mechanisms, dynamic mechanical allodynia and mechanical hyperalgesia may be detected beyond the primary application site (secondary zone). Thus, we assessed additionally the possibility of mechanical (pinprick) hyperalgesia and dynamic mechanical allodynia.

Assessment of the Area of Mechanical Hyperalgesia and Dynamic Mechanical Allodynia

The area of mechanical hyperalgesia and dynamic mechanical allodynia was quantified with a pinprick mechanical stimulator with a fixed stimulus intensity (flat contact area of .2-mm diameter) that exerted a force of 128 mN and a standardized brush exerting ~200 to 400 mN (Somedic, SE), respectively. Stimuli were applied according to the QST protocol along 8 linear paths arranged horizontally and vertically around the