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Published in:
Journal of Oral Rehabilitation

DOI:
[10.1111/j.1365-2842.2009.01960.x](https://doi.org/10.1111/j.1365-2842.2009.01960.x)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2009

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Tjakkes, G. -H. E., De Bont, L. G. M., van Wijhe, M., & Stegenga, B. (2009). Classification of chronic orofacial pain using an intravenous diagnostic test. *Journal of Oral Rehabilitation*, 36(7), 469-475.
<https://doi.org/10.1111/j.1365-2842.2009.01960.x>

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Classification of chronic orofacial pain using an intravenous diagnostic test

G.-H. E. TJAKKES*, L. G. M. DE BONT*, M. VAN WIJHE[†] & B. STEGENGA[‡]
**Department of Oral and Maxillofacial Surgery, [†]Department of Anesthesiology, [‡]Department of Oral and Maxillofacial Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands*

SUMMARY The aim of this study was to evaluate the ability of a preliminary intravenous diagnostic test to classify chronic orofacial pain patients into different subgroups. Patients with chronic orofacial pain conditions that could not be unambiguously diagnosed. A retrospective evaluation of series of conducted pharmacodiagnostic tests, consisting of the consecutive intravenous administration of drugs. Visual analogue scale scores were retrieved from all patients, based on which they were classified into different responder groups. In total, 46 pain profiles were analysed. Of these, 16 patients (35%) could be classified into one or more pain categories, while 30 patients (65%) could not be classified into

any pain category. The pain duration or medication use did not influence the classification. Based on the results of this retrospective study, it seems that classification into subgroups is possible after intravenous testing in a minority of clinically unclassifiable patients. In patients where there is a substantial need for additional diagnostic information, these results may be of value. Recommendations are made for further research, which should include validation in patients with known pain mechanisms.

KEYWORDS: chronic orofacial pain, pain diagnosis, pharmacological diagnostic test

Accepted for publication 26 April 2009

Introduction

Orofacial pain, referring to pain experienced in the mouth and facial area, is very common in medical and dental practice (1). A median prevalence of 13% has been described based on epidemiological studies (2). Facial pains include odontogenic pains, painful diseases of the oral mucosa and salivary glands, temporomandibular disorders, and neurological (e.g. neuralgia) and vascular pains (e.g. temporal arteritis, migraine). The diagnosis of these orofacial pains is usually straightforward, the majority being acute or transient in nature. Pain associated with temporomandibular disorders and neurovascular mechanisms may, however, be more persistent (3, 4).

Chronic orofacial pain conditions are often difficult to diagnose and manage. Pains that cannot be readily diagnosed are frequently referred to as 'atypical',

implying that typical facial pains have been excluded (4). In the classification of the International Headache Society, a subgroup 'persistent idiopathic facial pain' exists, which includes atypical facial pain and atypical odontalgia (5). Others proposed the term 'chronic idiopathic orofacial pain', which should include atypical facial pain, atypical odontalgia, masticatory pain, temporomandibular joint disorder pain and oral dysesthesia (6). The term 'atypical orofacial pain' has also been suggested as a diagnostic term, describing an ongoing, continuous, more or less constant intense chronic pain disorder, frequently of burning quality. Atypical tooth pain is sometimes referred to as 'atypical odontalgia', and when the oral mucosa is involved, terms like 'oral dysesthesia' and 'burning mouth syndrome' are commonly used. Characteristically, an obvious nociceptive substrate is absent (7). Psychological problems are associated in these forms of pain, although whether

these problems are causative or secondary is still a subject of debate (8). Persistent idiopathic facial pain is currently thought to be neuropathic in nature, especially when the pain is accompanied by paresthesia (8). It has also been suggested to be maintained by autonomic sympathetic influences.

Patients with chronic orofacial pain frequently undergo numerous dental procedures that fail to eliminate their symptoms (9). Interventions that cause tissue damage, such as endodontic therapy and surgery, may even exacerbate and perpetuate pain symptoms, causing these patients to use (high doses of) analgesics, sometimes even more than considered safe, as well as antidepressants and anxiolytics (7). Thus, patients with chronic orofacial pain are commonly characterized by multiple diagnoses and inadequate management by multiple disciplines (4).

When the patient's daily life begins to be dictated by pain, psychological changes and restrictions in lifestyle result in limiting the innate capabilities. Therefore, there is a need for early detection of the mechanism(s) underlying the pain state as a basis for rational treatment. As stated by Woolf: 'Perhaps, in the future, when the analgesic armamentarium includes drugs that act on specific mechanisms, it might be possible to judge patient-response to these therapies as diagnostic of underlying mechanisms' (10). The aim of this pilot study was to evaluate the result of a preliminary intravenous diagnostic test based on the response of intravenous administration of different pharmacological probes as possible initiative to distinguish between different pain mechanisms in chronic orofacial pain patients.

Material and methods

Patients

Data for this study were retrieved from the files of consecutive patients with chronic orofacial pain with an ambiguous diagnosis who had attended the Pain Clinic between February 1998 and January 2004 to receive a pharmacodiagnostic test. Standard examination included history-taking with intra- and extra-oral examination. When a dental origin of the pain was suspected, periodontal probing, pulp vitality testing (combining Chloroethyl as cold test and hot gutta-percha as warmth test applied to suspicious teeth) and tooth percussion test were performed, diagnostic local

anaesthesia was given and dental radiographs were taken. When mucosal problems were suspected, periodontal probing was performed, wherever applicable, diagnostic local anaesthesia was given and radiographs were taken. When temporomandibular disorders were suspected, a functional examination was performed; radiographs were taken and as applicable (intra-articular or intra-muscular), local anaesthesia was performed. All these diagnostic tests that were performed were inconclusive for precise diagnosis.

A total of 49 subjects were tested (46 female patients and three male patients; mean age at the time of pharmacological testing 43.7 years, s.d. = 11.4). The average pain duration was 8.0 years (s.d. = 6.2), ranging from 1 to 25 years. Of the 49 patients, 11 patients did not use any medication. Medication used by the other 38 patients varied from paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) to opioids and combinations of medication. In Table 1, information on the types of medication used has been depicted.

Procedure

To perform the pharmacological test, patients were hospitalized for 1 day in the University Medical Center Groningen. The test was performed based on a standardized protocol. The following agents were administered intravenously in fixed doses and in a specific order with a 10-min interval:

Saline (NaCl 0.9%)
Saline

Table 1. Types of medication used with number of patients

Type	Number of patients
Paracetamol	5
Paracetamol/codeine	4
Paracetamol/anti-convulsant	5
Non-steroidal anti-inflammatory drug (NSAID)	4
NSAID/tricyclic antidepressants	3
NSAID/paracetamol	2
NSAID/anticonvulsant	3
Tricyclic antidepressants	4
Anticonvulsant	1
Opioid	4
Other	3
Total	38

Phentolamine (5 mg in 5 min)

Saline

Thiopental (50 mg in 3 min)

Saline

Fentanyl 50 µg, followed by naloxone 400 µg

Saline

Lidocaine titration (200 mg in 60 min)

Pain ratings were taken before the test and after each drug or placebo delivery at fixed intervals. Pain intensity was measured using a 100-mm Visual Analogue Scale (VAS) (11), the endpoints of which are designated as 'no pain' and 'worst pain imaginable'. In addition, possible side-effects occurring during this test were monitored.

Criteria for pharmacological classification of the patients

Pain changes were measured by comparing the baseline VAS with the VAS score after each administration. In our study, patients were classified as:

1. *placebo responders* when 33% or more decrease of pain occurred after at least two placebo administrations;
2. *phentolamine responders* or *lidocaine responders* when there was 33% or more decrease of pain after phentolamine or lidocaine administration, respectively, without any or with minimal effect in response to placebo administration;
3. *opioid responders* when they showed 33% or more decrease of pain after fentanyl administration and increase of pain after subsequent naloxone administration, with no or minimal impact on placebo administration.

When a decrease of pain of 33% or more was measured in two or more active agents, patients were classified into multiple groups. Patients who showed a response of <33% to any of the agents administered were classified as non-responders.

To study whether pain medication influenced the classification, patients who used medication were compared with the group without medication. In addition, to study whether classification was influenced by pain duration, the percentage of non-responders for different pain durations was calculated. An analysis of variance for repeated measures was performed to study the stability of all placebo injections.

Results

All included patients were tested without any notable side-effects. VAS-scores from the patients were analysed,

Table 2. Types and numbers of responders

Type responder	Number of responders
Fentanyl	3
Lidocaine	3
Thiopental	1
Phentolamine	2
Fentanyl-lidocaine	1
Pentotal-fentanyl-phentolamine	1
Pentotal-phentolamine-lidocaine	1
Placebo-pentotal-fentanyl-lidocaine	1
Pentotal-fentanyl-phentolamine-lidocaine	1
Placebo-fentanyl-phentolamine-pentotal-lidocaine	2
Fentanyl-pentotal-placebo	0
Pentotal-fentanyl-lidocaine	0
Placebo-phentolamine	0
Non-responders	30
Total classified	46

sed, combining the responses to intravenous pharmacological agents with the above-mentioned criteria. When applying the above-mentioned criteria and because of missing baseline VAS scores of three patients, 46 VAS-scores were available. Sixteen of these 46 patients could be classified as responder to one or more agents. The remaining 30 patients could not be designated as responder. Data are given in Table 2.

No significant differences were found when the VAS scores following all placebo injections were compared within all subjects ($P = 0.95$). Average VAS scores after placebo infusions are shown in Fig. 1. Following the same, Fig. 2 shows VAS scores after drug infusions.

The percentage of non-responders in the available pain-duration ages is shown in Fig. 3. Non-responsiveness occurred in patients with pain duration varying from 1 to 21 years.

Of the 'non-medication' group, four of 11 patients could be classified (36%). Of the patients who did consume pain medication, 12 could be classified (34%). Types of medication used are described in Table 1.

Discussion

In the management of patients with chronic pain, history-taking and physical examination will largely contribute to the establishment of a diagnosis. However, when this is not sufficient and additional information is necessary; other means of differentiation are to be devised. This study attempted to differentiate

Fig. 1. Average Visual Analogue Scale (VAS) scores at baseline and after placebo infusions with 95% confidence interval (95% CI).

Fig. 2. Average VAS scores after drug infusions with 95% CI.

Fig. 3. Percentage non-responders per available pain duration group.

patients with chronic pain (who could not be differentiated by means of history-taking, physical information and other additional diagnostic tests alone), based on the response to a battery of pharmacological agents. In this study, 16 patients (35%) could be classified into one or more responder groups. The majority (65%), however, could not be classified when using the baseline VAS as reference for classification. Although the percentage of responders may seem disappointing, in this category of patients any additional diagnostic information is of beneficial value. However, because of the retrospective manner of retrieving data, potentially important data, e.g. baseline psychometric measures, were not available in most cases. Baseline data, such as the duration of the pain could be determined for all patients, but did not influence the classification of these patients, as is shown in Fig. 3.

The responses after administration of the different pharmacological agents have been suggested to be used to determine different pain-generating pathophysiological mechanisms (12–16). For instance, fentanyl has been suggested to identify nociceptive pain (17). Fentanyl is a morphine derivative and is 80–100 times more potent as morphine (17–19). Fentanyl produces a peak analgesia after 5 min (19). The effect of fentanyl should be reversed by its antagonist naloxone to confirm opioid responsiveness, as naloxone antagonizes the toxic and clinical effect of opiates (19). In a recent review, studies report mixed results concerning the effect of opioids on neuropathic pain (20). In particular, fentanyl has been shown to relieve non-cancer neuropathic pain, although immediate effects remain unclear (21).

In neuropathic pain, the nervous system itself has changed either structurally or functionally, and lidocaine has been suggested to eliminate this type of pain (22–26). In previous trials, different dosages have been

used, e.g. 100 mg per patient or individual dosage varying from 1 to 5 mg kg⁻¹, either with or without a preceding bolus (26, 27). In a group of patients with post-herpetic neuralgia, no additional benefits were found when 5 mg kg⁻¹ was used instead of 1 mg kg⁻¹ (28). Systemic lidocaine has shown to have no effect on nociceptive pain (29, 30).

Occasionally, the nervous system may be activated by autonomous input (i.e. sympathetically maintained pain). Phentolamine specifically affects this mechanism (31, 32) and thus is the likely drug to selectively modify this pain mechanism. It is a short-acting, competitive alpha adrenergic receptor antagonist, with tachycardia and vasodilatation as clinical effects (19). This sympatholytic procedure was able to predict the effect of subsequent intravenous regional guanethidine treatment with set dosages varying from 5 to 15 mg (32).

Finally, thiopental, a (ultra) short acting barbiturate, is used in a low dose, aiming at centrally mediated pain (33). It rapidly achieves a therapeutic plasma concentration (19).

Although all the aforementioned mechanisms have been suggested to be affected by specific drugs, caution must be taken when interpreting the short-term effects of the intravenous administration of these drugs. When patients respond to agents, the precise clinical consequence remains unclear. Are all suggested mechanisms involved or do these patients respond to any intervention? Until more scientific data are obtained with regard to these effects, it seems more appropriate to refer to the pain relieving effects as 'drug response' rather than influencing specific pain mechanisms.

As the test is done with fixed low doses, again caution must be taken in interpreting the tests' results. These doses may be too low in certain patients to attain a specific effect. In addition, it is not possible to rule out the possibility of carry-over effects, although the VAS scores following all placebo injections remained stable, indicating a similar VAS level prior to all provided drugs and thus suggesting no notable residual effects. Further research should provide further justification for this type of mechanism-based approach in patients with chronic orofacial pain.

Previous studies have used other regiments to come to individual dosages, such as calculation of dosages using the bodyweight, or titration until achieving the desired effect (i.e. pain relief), undesired effects (e.g. side-effects) or a maximum dosage was achieved. However, titration leads to a longer duration of the

test, which may lead to lack of compliance and increased costs. Also, inter-individual differences, in e.g. physiology, likely lead to different reactions after and different effects of drug infusion. This may make out a case for individualization of the dosages using the patients' bodyweight. In future designs, it may therefore be appropriate to start with a standardized test, which may be followed, if necessary, by an individually tailored test. This individual test could be an elaboration of potential effective drugs, which are subsequently titrated until (un)desired effects are achieved.

To study whether patients' current medication use modified the test outcome, we compared the patients who did not use any medication with the patients who did. In both groups, equal proportions of patients could be classified into responder groups. So apparently, medication use did not influence the ability to classify patients. Relative differences in pain were measured in this test and outcomes may be indicative of a pharmacological approach, which is additional to the current medication used. When a critical reappraisal of current pain medication is warranted, one should refrain from medication (if possible) before testing these patients.

We used a cut-off point of 33% pain relief as being sufficient to provide insight in the underlying pain mechanism, as on a numeric scale this reduction was found to be associated with a 'much better' change (34, 35). Farrar and co-workers also proposed the percentage of 33% rather than the more often used 50% in order to prevent underestimation of research results, especially when this cut-off point is used to obtain insight in the effect of a diagnostic test rather than the efficacy of a treatment (35).

The current design of the test was chosen based on face validity (i.e. does the test intend to measure what we want?). To study the construct validity of this pharmacological test for chronic orofacial pain for the purpose of differentiating between different pain mechanisms, patients diagnosed with only nociceptive pain, only neuropathic pain, and only sympathetically maintained pain, preferably in the orofacial region, should be used. Using a control group without pain would complete the validation (by assessing whether pain-free persons perceive pain after injections), although this might be inappropriate from an ethical point of view. In addition, the pharmacological test should be performed twice in a subset of patients to assess intra-individual reliability and consistency.

In summary, with pharmacological testing, disentangling complex chronic orofacial pain problems seems possible in at least a subset of patients. In patients with ambiguous diagnoses, even after thorough examination and/or previous unsuccessful treatment, subtle directions for treatment planning may potentially be provided by this way of testing. Future research should, however, establish the validity and reliability and clinical consequences of the outcomes of this seemingly promising diagnostic tool.

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Correspondence: Geerten-Has E. Tjakkes, Department of Oral and Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, PO Box 30-001, 9700 RB Groningen, The Netherlands.
E-mail: g.h.e.tjakkes@kchir.umcg.nl