Predicting the analgesic effect to oxycodone by ‘static’ and ‘dynamic’ quantitative sensory testing in healthy subjects

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\textbf{A B S T R A C T}

The large inter-individual variability in the magnitude of analgesia in response to opioids and the high prevalence of adverse events associated with their use underline the clinical importance of being able to predict who will or will not respond to opioid treatment. The present study used both static and dynamic quantitative sensory testing (QST) on 40 healthy volunteers in order to test whether this methodology can predict the analgesic effects of oral oxycodone, as compared to a placebo, on latency to onset, pain intensity, and tolerance to the cold pressor test (CPT). Static QST consisted of measuring heat and cold pain thresholds. Dynamic QST included measurements of the magnitude of the diffuse noxious inhibitory control (DNIC)-like effect and of temporal summation (TS). Results showed that oxycodone, but not the placebo, significantly elevated the latency and tolerance to cold pain and significantly reduced pain intensity. The static QST results showed that heat pain thresholds predicted the magnitude of reduction in pain intensity in response to oxycodone treatment ($F_{1,22} = 5.63, p = 0.027, R^2 = 0.17$). The dynamic QST results showed that TS predicted the effect of oxycodone on the tolerance to CPT ($F_{1,38} = 9.11, p = 0.005, R^2 = 0.17$). These results suggest that both static and dynamic QST have the potential to be useful in the prediction of the response to opioid treatment.

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1. Introduction

The magnitude of analgesia in response to opioid administration in patients with a similar clinical condition varies considerably. Furthermore, opioid usage is often associated with adverse events [5]. Therefore, the prediction of responsiveness to opioid treatment is an ongoing medical challenge that carries with it great clinical significance. Various factors have been suggested to be associated with the inter-individual variability in the magnitude of analgesia in response to opioid administration, including gender [6], differences in opioid metabolism [15], heterogeneity in opioid receptors encoding genes [10], and personality traits [13]. Nonetheless, there is relatively scarce literature examining the individual difference factors in opioid analgesia [4,19].

Quantitative sensory testing (QST) has long been used in the study of pain pathways and mechanisms among humans in both experimental and clinical settings. Traditionally, QST has been used in a ‘static’ way in order to detect the threshold to pain onset, the magnitude of pain intensity, or the tolerance to a given stimulus. Recently, more advanced methods of ‘dynamic’ QST have been developed, with stimuli applied repetitively or simultaneously to different body areas. By using paradigms of temporal summation (TS), or diffuse noxious inhibitory control (DNIC), these methods can reveal mechanisms of pain augmentation or descending inhibition control [1].

Since QST can detect inter-individual differences in the response to externally applied stimuli, a few recent studies have tested the ability of both static and dynamic QST to predict the development of pain after surgery. One study showed that the preoperative response to experimental tonic heat pain was correlated with post-cesarean section pain [16]. In another study, a low magnitude of TS prior to surgery was found to be associated with low scores of early post-thoracotomy pain [18]. The results of another study showed that a high degree of preoperative DNIC predicted low scores of chronic post-thoracotomy pain [20].

Similarly, a very small number of studies have tested the capacity of QST to predict the analgesic response to opioids in humans. In one study [4], a greater reduction in pain was observed in patients with post-herpetic neuralgia (PHN), who had exhibited higher heat pain thresholds in an area contralateral to the affected side prior to treatment. A second study [8], found that the pain intensity in response to suprathreshold electrical stimulation correlated...
significantly with the analgesic responses to tramadol + paracetamol in patients with post-amputation pain.

To the best of our knowledge, dynamic QST has not yet been used to predict the response to opioid treatment. The fact that QST can reveal mechanisms of pain facilitation and inhibition through which opioids are believed to exert their analgesic effect, combined with the emerging, yet limited, evidence on the usefulness of QST in predicting the response to opioids, together underline the need to further explore this area of emerging clinical importance. Therefore, the present study was aimed to test whether ‘static’ and ‘dynamic’ QST can indeed predict the response to the administration of oxycodone in healthy volunteers who are exposed to an experimental cold pain model.

2. Methods

2.1. Subjects

The subjects were 40 healthy students, including 21 women and 19 men, ranging in age from 20 to 34 (mean age ± SD 24.5 ± 3.0). Participants were paid volunteers who were enrolled in the study after meeting the following criteria: (1) freedom from pain of any type; (2) no medication use (except for oral contraceptives); and (3) ability to understand the purpose and instructions of the study. The subjects were excluded from the study in cases of pregnancy, allergy to opioids, history of substance abuse, or a diagnosis of Raynaud’s syndrome. Participants were not allowed to consume alcohol or any drugs except for the study medication and were instructed to fast for at least 6 h prior to the trial.

2.2. Instruments and measures

2.2.1. Cold pain model with the cold pressor test (CPT)

The CPT apparatus (Heto CBN 8–30 Lab equipment, Allerod, Denmark) is a temperature-controlled water bath with a maximum temperature variance of ±0.5 °C, and is continuously stirred by a pump. In accordance with the standard protocol, the subjects were asked to place their right hand in the CPT (1 °C) in a still position with their fingers spread wide apart. A stopwatch was simultaneously activated, and the subjects were requested to keep their hand in the cold water for as long as possible. A cut-off time of 180 s was set for safety reasons. Subjects were instructed to indicate the exact point of time when the cold sensation began to elicit pain. This time point was defined as the latency to cold pain onset (sec). The time until spontaneous hand withdrawal was also recorded and was defined as their pain tolerance (sec). The subjects were asked to numerically rate their pain intensity (NPS 0–100) right after immersing their hand in the cold water. Immediately after the hand withdrawal, they were asked to rate the maximal pain intensity they felt during the immersion. In addition, for those subjects who could tolerate the cold stimulation for over 15 s, numerical pain ratings (NPS 0–100) were obtained at the specific time point of 15 s following the immersion.

2.3. Test paradigms

2.3.1. Static QST predictors

2.3.1.1. Thermal pain thresholds. Quantitative cold and heat pain thresholds were determined with the method of limits on a Medoc TSA-2001 device (Medoc, Israel). A Peltier thermode, size 30 × 30 mm, was attached to the skin above the thenar eminence. The baseline temperature was set at 32 °C and was increased or decreased at a rate of 1 °C/s. The Stimulator temperature range was 0–50 °C. The subjects were instructed to depress a switch when the stimulus was first perceived as painful heat or cold. Three read-

ings were obtained for each thermal modality (cold and hot), and their averages were determined as the pain threshold scores.

2.3.2. Dynamic QST predictors

2.3.2.1. DNIC-like effect. In order to induce a DNIC-like effect, heat stimulation was used as the ‘test pain’, whereas cold stimulation was used as the ‘conditioning stimulation’.

Test pain: A TSA thermode of 30 × 30 mm (Medoc TSA-2001 device, Medoc, Israel) was attached to the skin above the left thenar eminence. Four heat stimuli of 47 °C (starting from 37 °C at an increasing and decreasing rate of 10 °C/s) were delivered at an inter-stimulus interval of 12 s, with each pain stimulus lasting for 4 s. After each stimulus, the subjects were asked to report the pain intensity experienced, using a 0–100 numerical pain scale (NPS). The NPS was chosen because rapid ratings of pain intensity were required during the test stimulation, while the subjects had one hand occupied by the CPT.

Conditioning stimulation: The right hand was immersed into the CPT (12 °C) for 30 s.

DNIC-like effect was assessed according to the DNIC test paradigm used in previous studies in our laboratory [14,17]. The first heat stimulation was delivered and the subjects were asked to verbally report the level of pain intensity (NPS) at the point when the temperature reached 47 °C. This was considered as the ‘baseline test pain’ (baseline). The subjects were then instructed to immerse their right hand into the CPT (12 °C). After 15 s, while the hand was still immersed in the CPT, the second test stimulation was delivered and the pain intensity was recorded again (test 1). The subjects were asked to remove their hand from the CPT 15 s later, making for a total time of 30 s of hand immersion in the CPT. Two additional heat stimulations were conducted at 15 and 30 s subsequent to removal of the hand from the CPT (tests 2 and 3, respectively). Upon completion of the session, the subjects were instructed to report the intensity of the pain (NPS) caused by immersing the hand in the CPT (conditioning induced pain intensity). DNIC-like effect was calculated by subtracting the scores of the baseline ‘test pain’ from the scores of the conditioned ‘test pain’.

2.3.2.2. Temporal summation (TS). The TSA thermode was placed on the left volar with a starting temperature of 32 °C. Ten painful phasic heat stimuli were applied at an inter-stimulus interval of 3 s. The end temperature was increased by an additional 6 °C, from 41 to 47 °C, while the rate of increasing and decreasing was 10 °C/s. The subjects were asked to verbally report their level of pain intensity (0–100 NPS) after the 1st, 5th, and 10th heat stimuli.

2.4. Study medications

The study medication employed was the opioid drug oxycodone hydrochloride (Rafa Laboratories Ltd., Jerusalem, Israel) at a dose of 0.3 mg/kg. In addition, an active placebo, chlorpheniramine maleate, was employed in an attempt to mimic the adverse effects of opioids and thus to reduce the risk of un-blinding the study medication. The study medications were administered orally in the form of solutions and were diluted with 50 ml of tap water and 5 ml of grape-flavored syrup.

2.5. Study design

This double-blind crossover trial was approved by Rambam Medical Center’s Helsinki Committee. All the subjects received a detailed explanation of the study design, the pain tests, the pain measures, and the blind administration of the study medications. After giving their written informed consent, the subjects were randomly assigned to the experimental pain models. The first round of
pain tests was considered as training, and its results were not used in the statistical analyses. A second round was conducted 30 min later, and the results were regarded as the baseline measurements. Specifically, these measures were based on the static and dynamic QST predictors (heat and cold pain thresholds, magnitude of the DNIC-like effect, and magnitude of TS), as well as on the CPT tests. Each subject then received either oral oxycodone hydrochloride, 0.3 mg/kg, or active placebo chlorpheniramine maleate, 0.033 mg/kg, in a double-blind fashion. Three additional CPT tests were subsequently performed at 60 min apart (i.e., after 60, 120, and 180 min). Four to seven days later, a second experimental session was conducted in the same manner, but with the administration of the drugs reversed.

2.6. Statistical analysis

Heat and cold pain thresholds, the magnitude of the DNIC-like effect, and the magnitude of TS were regarded as the independent pain variables (predictors), while the changes from baseline in the other CPT pain measures were defined as the dependent variables. All analyses were conducted using the SPSS software for Windows Version 15 statistical package (SPSS, Inc., Chicago, IL). One-way ANOVA was used for examining the differences between the baseline and subsequent measures of DNIC and TS. Two-way repeated measure analysis of variance (RM-ANOVA) was used to test the differences in response to the administered drug (oxycodone vs. placebo), measured at the four time points (i.e., before administration and 1, 2, and 3 h subsequent to administration), for each of the tested pain measures. Significant results underwent repeated contrasts tests. Pearson correlations were conducted in order to examine the relationships between the predictors and the change from the baseline of the dependent variables. Stepwise linear regression analysis was used to identify the independent pain variables that can predict the magnitude of the opioid analgesia in the present experimental setting. A further attempt to confirm the predictive performance of the regression model was made by employing a random sub-sampling cross validation test. A regression was performed on a random half of the sample (“training set”) while keeping the unstandardized coefficients (B). Based on those coefficients, the predicted scores of the second half of the sample (“validation set”) was calculated (by multiplying each variable by its coefficient and adding them all up). The β scores of the entire sample, the “training set” and the “validation set” were compared. The results were considered significant at the 0.05 level. The values are presented as means ± SEM.

3. Results

3.1. Thermal pain thresholds

Thermal (cold and heat) pain thresholds were assessed before each drug administration. The results showed no significant differences between the two assessments for either threshold. Specifically, the mean ± SEM cold pain threshold was 9.7 ± 0.9 and 9.2 ± 1.1 before the administration of oxycodone and the placebo, respectively, whereas the mean ± SEM heat pain threshold was 46.6 ± 0.4 and 46.5 ± 0.4 before the administration of oxycodone and the placebo, respectively.

3.2. DNIC-like effect

The DNIC-like effect was assessed before each drug administration. Results show similar patterns of pain intensities between the two sessions (Fig. 1A). Baseline intensities were significantly higher than all subsequent measures in both oxycodone ($F_{(4,156)} = 30.63, p = 0.0001, \eta^2 = 0.44$) and placebo ($F_{(4,156)} = 18.60, p = 0.0001, \eta^2 = 0.32$) sessions. However, the peak effect in each session was noted after the fifth stimulus. Therefore, all TS related analyses were based on the reduction of the pain scores obtained in test 2 from the baseline pain scores. Hence, the calculated magnitude of the DNIC-like effect (i.e., baseline minus test 2) was 20 points (36% reduction from the baseline) before oxycodone administration and 17 points (33% reduction) before placebo administration.

3.3. Temporal summation

As in the DNIC paradigm, TS was assessed before each drug administration and similar patterns were found. Pain intensities after a train of five and 10 stimuli were significantly higher than those recorded after the first stimuli in both oxycodone ($F_{(2,78)} = 13.10, p = 0.0001, \eta^2 = 0.25$) and placebo ($F_{(2,78)} = 13.74, p = 0.0001, \eta^2 = 0.26$) sessions. However, the peak effect in each session was noted after the fifth stimulus. Therefore, all TS related analyses were based on the differences between the pain scores obtained after the fifth stimulus and the score following the first stimulus (Fig. 1B). Accordingly, the pain intensities were found to increase from 51 ± 3.9 to 59 ± 4.0 (16%) before oxycodone administration and from 49 ± 4.1 to 59 ± 4.0 (20%) before placebo administration.

3.4. Effects of oxycodone and placebo on the CPT

The results of the RM-ANOVA show that the latency to cold pain onset significantly increased from the baseline measurement following the administration of oxycodone, but not following the
placebo (Fig. 2A) \( (F_{1,117} = 6.05, p = 0.001, \eta^2 = 0.13) \). A significant interaction between the drug (oxycodone and placebo) and the time relative to the drug administration was also demonstrated \( (F_{1,117} = 2.75, p = 0.046, \eta^2 = 0.07) \). With regard to cold pain tolerance, a significant increase from the baseline measurement was found following the administration of oxycodone, but not following the placebo (Fig. 2B) \( (F_{1,117} = 6.62, p = 0.0001, \eta^2 = 0.15) \). Likewise, a significant interaction between the drug (oxycodone and placebo) and the time relative to the drug administration was also found \( (F_{1,117} = 6.37, p = 0.0001, \eta^2 = 0.14) \). Maximal cold pain intensity, measured after the hand removal from the CPT, failed to show significant changes from the baseline following both the treatments (Fig. 2C). The measurement of cold pain intensity at 15 s after the hand immersion was obtained only from 23 subjects due to the fact that the other 17 participants withdrew their hand from the CPT earlier than 15 s after immersion. In those 23 subjects, the 15 s recording after oxycodone was significantly lower than their baseline reading \( (F_{1,57} = 3.48, p = 0.022, \eta^2 = 0.16) \). No differences were noted during the placebo session (Fig. 2D). Here too, a significant interaction between the drug (oxycodone and placebo) and the time relative to the drug administration was found \( (F_{1,57} = 3.04, p = 0.036, \eta^2 = 0.14) \).

3.5. Prediction of the magnitude of opioid analgesia

Pearson correlations showed significant relationships between heat pain threshold and the magnitude of pain reduction in response to oxycodone treatment at 15 s in the sub-population of 23 subjects who kept their hand immersed for that long \( (r = 0.452, p < 0.03) \) (Fig. 3A). Significant correlations were also found between the magnitude of TS and the increase in tolerance to the CPT following oxycodone \( (r = 0.44, p = 0.005) \) (Fig. 3B). Stepwise linear regression analyses were used to identify possible predictors for the magnitude of opioid analgesia (baseline values minus post-drug values) for each of the four pain measures (latency to pain onset, pain tolerance, maximal pain intensity, and pain intensity at 15 s induced by the CPT). Each analysis included the independent factors (heat and cold pain thresholds, magnitude of the DNIC-like effect, and magnitude of TS). The results showed that the heat pain threshold significantly predicted the magnitude of pain reduction at 15 s \( (F_{1,22} = 5.63, p = 0.027, \text{Adj. } R^2 = 0.17, \beta = 0.45) \). The results of the sub-sampling cross validation test were as follows: \( \beta = 0.35 \) for “training set” and \( \beta = 0.59 \) for the “validation set”, thus indicating a stable predicting

![Fig. 2.](image-url)  
Latency to cold pain onset (A), pain tolerance (B), maximal pain intensity (C), and pain intensity at 15 s after immersion in the CPT (D). Data are presented as means ± SEM. *p < .01; **p < .001 in the comparisons (RM-ANOVA) of the CPT variables between the baseline measurement and the three hourly measurements subsequent to oxycodone administration.

![Fig. 3.](image-url)  
(A) Correlations between heat pain threshold (°C) and the change in cold pain intensity during immersion (n = 23). NPS – numerical pain scale (0–100). (B) Correlations between the magnitude of TS and the change in cold pain tolerance (n = 40).
performance. In addition, the magnitude of TS significantly predicted cold pain tolerance ($F_{1,385} = 9.11, p = 0.005$, Adj. $R^2 = 0.17$, $\beta = 0.44$). The sub-sampling cross validation tests were $\beta = 0.48$ for “training set” and $\beta = 0.42$ for the “validation set”, indicating again a stable predicting performance.

4. Discussion

The main findings of the present study are that (I) heat pain thresholds predicted the magnitude of pain reduction in response to oxycodone during hand immersion in such a way that higher pain threshold predicted a greater magnitude of pain reduction; (II) TS positively predicted the effect of oxycodone on tolerance to the CPT.

Thus far, the prediction of the analgesic response to opioids by static QST parameters has been studied only to a limited extent. One earlier study found that the heat pain thresholds measured at the affected area and at the corresponding contralateral side predicted the effect of morphine and methadone on pain in patients with PHN [4]. Seemingly, our results and those of the PHN study are similar, because the prediction of opioids analgesia was based on QST parameters which were obtained in a remote area from the painful site. However, previous work has suggested that unilateral PHN may be associated with bilateral peripheral nervous system changes in some patients [12]. Therefore, it is possible that the thresholds measured at the contralateral side in the PHN patients may not represent their actual basal pain sensitivity. In contrast, in our study, heat pain thresholds were measured in healthy subjects and therefore reflect each individual’s actual basal pain sensitivity. This represents a fundamental difference between the two studies. In both studies, the results of the regression analyses indicate that heat pain thresholds explain nearly an identical percentage of the variance in opioid analgesia (10–18% in the PHN study vs. 17% in our study). Taken together, the results of the two studies strongly support the notion that heat pain threshold is likely to be useful in predicting an individual’s response to opioids.

The authors are unaware of a clear physiological explanation for the association between the high heat pain thresholds and the large magnitude of pain reduction in response to opioid treatment. Although according to one theory, it might be related to differences in opioid receptor properties [19], the fact that this association is supported by the findings of the present study calls for further exploration of the possible underlying mechanisms.

A second finding in the present study is that TS predicted the effect of oxycodone on tolerance to the CPT in such a way that in subjects with a higher magnitude of TS, oxycodone exhibited a larger effect on cold pain tolerance. To the best of our knowledge, dynamic QST has not yet been used to predict the response to opioid treatment.

One possible explanation for this finding stems from the mechanisms through which opioids produce their analgesic effects at the level of the spinal cord. At that level, opioids inhibit the ascending transmission of nociceptive information, most likely by acting predominantly at presynaptic sites in the superficial dorsal horn. Repeated or prolonged activation of these synapses leads to the excitation of second-order neurons in the superficial dorsal horn, a phenomenon known as “wind-up” [3]. Thus, it is suggested that in individuals with a high magnitude of TS, opioids have a wide span for their attenuating effect at the spinal cord level, whereas in individuals with little basal TS, opioids have only a limited span for action to begin with.

DNIC had no predictive value for the effect of oxycodone on any of the CPT measures. In addition to their effect at the spinal cord level, opioids enhance central pain inhibition at the supraspinal level by activating the neural circuits that descend from the mid-brain via the rostral ventromedial medulla to the spinal cord dorsal horn. A key mechanism of central pain inhibition is endogenous analgesia (EA), commonly studied by using a DNIC test paradigm [9]. Opioids have been shown to reduce the magnitude of DNIC in both animals and humans [2,14]. As such, it might be reasonable to expect that the magnitude of basal DNIC will also predict opioid analgesia, at least to some degree. We do not have a clear explanation for the fact that such a prediction could not be demonstrated in the present study. Moreover, given the lack of similar studies, it is not clear as to whether this is a generalized phenomenon or a finding specific to the experimental model used in the present study. Further clarification will have to await the results of future research.

It is noteworthy that both heat pain thresholds and TS explained only 17% of the variance in the effect of oxycodone on cold pain intensity and tolerance, respectively. This clearly means that other factors, such as gender, opioid-related gene profiles, opioid metabolism, or personality traits explain a greater proportion of this variance [6,10,13,15]. Additional studies should be conducted in order to further explore the respective role of these various factors.

Notably, consistent with the results of an earlier study [7], the present study results also showed that the administered dose of oxycodone significantly elevated the latency and tolerance to cold pain. Moreover, the oxycodone significantly reduced the pain intensity measured 15 s after the hand immersion in the subgroup of participants who were able to tolerate the CPT for 15 s or more. However, oxycodone had no effect on the maximal cold pain intensity measured upon removal of the hand from the cold water. The placebo had no effect on any of the tested parameters. These results are in line with the results of an earlier study [8].

The concept of “individualized treatment” has only been scarcely employed thus far in the field of pain medicine. Currently, the primary diagnosis of the pain syndrome (e.g., diabetic neuropathy, osteoarthritis, etc.), rather than the patient’s individual characteristics, determine the type of treatment suggested to any given patient. This approach has contributed to the fact that pain relief varies considerably between patients [11]. Therefore, we clearly need tools that can be used to predict and distinguish the ‘responsive’ from the ‘non-responsive’ patients. The results of the present study, as well as those of a small number of other studies, suggest that both static and dynamic QST have the potential to become useful predicting tools to this end. Further studies conducted under other experimental and clinical conditions are needed to confirm these findings.

Conflicts of interest

The authors would like to state that there are no conflicts of interest regarding this work.

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