Original Experimental

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Oxaliplatin causes increased offset analgesia during chemotherapy – a feasibility study

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Abstract

Objectives: Offset analgesia (OA) is the phenomenon where the perceived pain intensity to heat stimulation disproportionally decreases after a slight decrease in stimulation temperature. The neural mechanisms of OA are not fully understood, but it appears that both peripheral and central temporal filtering properties are involved. Chemotherapy with oxaliplatin often causes acute peripheral sensory neuropathy, and manifests primarily as a cold induced allodynia. The aim of this exploratory patient study was to investigate if OA was affected by the neurotoxic effects of adjuvant oxaliplatin treatment.

Methods: OA was assessed in 17 colon cancer patients during 12 cycles of adjuvant oxaliplatin treatment. The OA response was estimated as the decrease in pain intensity caused by a temperature decrease from 46 °C to 45 °C. Changes in the OA during the treatment period was estimated using a mixed linear model and corrected for multiple comparisons by Sidak's test.

Results: OA was increased significantly when assessed before the 2nd, 3rd, 5th, 6th, 9th, and 10th treatment cycle compared to the first (baseline) treatment ($p<0.05$).

Conclusions: OA is generally decreased in persons suffering from chronic pain or peripheral neuropathy as compared to healthy controls. But in the present study, OA increased during chemotherapy with oxaliplatin. The underlying mechanism of this unexpected increase should be further explored.

Keywords: chemotherapy induced peripheral neuropathy; offset analgesia; oxaliplatin

Introduction

Offset analgesia (OA) is a manifestation of the temporal filtering mechanisms of human pain perception [1, 2]. OA is a still scarcely understood endogenous pain modulatory mechanism and is often evoked by a slight decrease in a tonic painful heat stimulation that in turn manifests as a disproportionally strong decrease in pain intensity [3, 4].

The OA phenomenon appears to be the result of both peripheral and central neural mechanisms that works to temporally filter the noxious input before it emerges as pain perception [5–7]. OA can be elicited even when painful heat stimulation is applied to different skin areas [5] or with temporally discrete stimuli [7] thus demanding some central integration, and OA can also be evoked by painful electrical stimulation, and is thus not dependent on the heat transduction mechanisms [8]. Several studies have shown that individuals suffering from pain conditions tends to exhibit decreased OA effect (for review see: Hermans et al. [4]). A recent meta-analysis on the modulation of OA showed that OA is resilient to centrally acting neuromodulating drugs [9].

However, the OA effect has not been investigated on patients during chemotherapy and in patients with chemotherapy induced peripheral neuropathy. Oxaliplatin is one

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of the most neurotoxic chemotherapeutical agents and is used e.g., as adjuvant treatment of colon cancer and reduces the risk of cancer recurrence [10]. Oxaliplatin often causes peripheral neuropathy which constitutes the most frequent side effect leading to dose reduction [11]. Oxaliplatin induced peripheral neuropathy (OIPN) manifests with acute signs and symptoms that often include cold induced allodynia mainly in the hands and perioral area. The acute neuropathy has been thought to resolve during the first week after each chemotherapy cycle [12]. However, studies indicate that the acute neuropathy may last for more than the two weeks which is one of the most commonly used interval between oxaliplatin containing chemotherapy cycles [13]. Oxaliplatin also causes persistent neuropathy that outlasts the treatment. The signs and symptoms of persistent OIPN affects both hands and feet and includes decreased touch, pin, thermal, and vibration perception, as well as ataxia and may emerge even after completion of oxaliplatin treatment and may last for several years [12, 14].

In a recent study, we investigated the excitability changes of large sensory nerve fibers using perception threshold tracking as well as the functional integrity of the peripheral nerve fibers using QST [15]. The study confirmed that altered sensory nerve fiber function and excitability could be observed two weeks after oxaliplatin infusion.

The aim of the present exploratory patient study was to investigate if chemotherapy with cycles of oxaliplatin would also alter the OA response.

Methods

Patients and oxaliplatin treatment

This is an exploratory study of the secondary outcome from the prospective and observational study where data was collected between April 2014 and September 2015. The study population has been reported in detail elsewhere [15], but in short 23 patients who underwent radical surgery for histopathologically confirmed stage III colon cancer were included in the study. These patients were eligible for the actual standard adjuvant combination chemotherapy with modified FOLFOX 6 (mFOLFOX6): folinic acid, fluorouracil, and oxaliplatin. The treatment was administered as 12 cycles with 14 days interval. Three patients withdrew their consent at the beginning of the study and three patients had the oxaliplatin dose reduced during the first six cycles due to hematologic toxicity and were excluded; thus, data from 17 patients was included in the analysis. All patients provided written informed consent for the procedures which were conducted in accordance with the Helsinki Declaration of 1975 and approved by the Local Ethics Committee (approval number: N-20140024).

Study design

The OA paradigm and QST measures were performed 1 h before each of the 12 chemotherapy cycle. The patients were seated in an inclined hospital bed.

CTCAE grades of peripheral sensory neuropathy and dose modifications

Symptoms of OIPN were assessed according to the CTCAE v. 4.0 scale prior to each treatment cycle using the following grades: grade 1 (Asymptomatic; loss of deep tendon reflexes or paresthesia); grade 2 (Moderate symptoms; limiting instrumental ADL); grade 3 (Severe symptoms, limiting selfcare ADL); grade 4 (Life-threatening consequences – urgent intervention indicated). According to the department's clinical guidelines, the dose of oxaliplatin was reduced by 25 % if a grade ≥2 CTCAE score was present at any time between cycles. Oxaliplatin was discontinued in the event of a recurrent grade CTCAE score ≥2 or if symptoms of OIPN persisted between the treatment cycles.

Quantitative sensory tests

A battery of QST were performed during the same session as the OA assessment. The development of the QST measures and their interrelation was reported elsewhere [15]. The QST tests consisted of pinprick stimulation, vibration threshold (VTH), warmth detection threshold (WDT), cold detection threshold (CDT), heat pain threshold (HPT), and cold pain threshold (CPT). The tests were performed in this order.

The VTH was assessed as the minimal perceived vibration amplitude for a vibration of 100 Hz. A vibrometer (Somedic, Sweden) was applied to the dorsal side of the third metacarpal bone of the left hand and the amplitude was increased until the patient indicated to perceive the vibration. The average of three measurements was used as the VTH.

Thermal perception and pain thresholds were assessed using a 9 cm^2 thermode (TSAII, Medoc, Ramat-Yishai, Israel). The thermode was placed on the inner side of the wrist of the left arm. The baseline temperature was set to 32 °C and temperature changes were applied with a rate of 1 °C/s. The CDT was assessed by decreasing the temperature until the patient indicated perception by pushing a button. The WDT was assessed increasing the temperature until the patient indicated perception by pushing a button. The CPT was assessed by decreasing the temperature until the patient indicated perception of cold became painful by pushing a button. The HPT was assessed by increasing the temperature until the patient indicated perception of warmth became painful by pushing a button. The average of three tests was used for all thermal thresholds.

Calibrated pinprick stimulators (custom made at Aalborg University) were applied to the dorsum of the hand. The 12.8 and 60 g pinprick weights with a blunt tip with a diameter of 0.2 mm were used. The pinpricks were applied for 1 s and the patients were asked to rate the pain perception on a 10 cm electronic VAS scale anchored as 0 being non-painful sensation and 10 being the worst imaginable pain intensity (custom made at Aalborg University). Each test was applied three times and the average was used for further analysis.

Stimulation paradigm for the offset analgesia (OA)

A 9 cm^2 thermode (TSAII, Medoc, Ramat-Yishai, Israel) was placed on the inner side of the wrist of the left arm. The baseline was set to 32 °C. The OA paradigm consisted of three stimulation periods; the temperature was increased to 45 °C and maintained for 5 s (T1), then the temperature was increased to 46 °C and maintained for 5 s (T2), then the temperature was decreased to 45 °C and maintained for 20 s (T3), before returning to baseline. Temperature changes were performed at rates of 1 °C/s (See Figure 1). The patients were asked to continuously rate the perceived pain intensity on an electronic VAS scale during the entire OA stimulation period (Medoc, Ramat-Yishai, Israel). The VAS scale was anchored as 0 being non-painful sensation and 100 being the worst imaginable pain intensity.

Data analysis

The OA response occurring as the temperature was decreased by 1 °C between T2 and T3 was estimated as the maximal VAS score during T2 minus the minimal VAS score during T3 in each test. A possible onset hyperalgesia effect was estimated as the increase in pain perception when the temperature was increased by 1 °C from T1 to T2 by subtracting the maximal VAS score during T2 from the maximal VAS score during T1.

Statistical analysis

The development of OA during the oxaliplatin treatment period was analyzed with a Mixed Linear Models (MLM); The OA response was used as the dependent factor and the oxaliplatin cycle number as within-subject categorical independent factor. When a session effect was observed, sidak correction for multiple comparison was used for comparing the OA response at the first session (baseline) to all the consecutive sessions. A series of similar MLMs were made to analyze the development of the VAS score during T1, T2, and T3 and the onset hyperalgesia response.

A three-step multiple linear regression model was made to investigate the relation between the OA response and the QST measures. First, a series of univariate simple linear regression models was established with the OA effect as the dependent factor and each of the QST measures as the independent factor. Second, a multiple linear regression model was established with the OA response as the dependent factor and all the QST measures as independent factors. Third, factor stepwise reduction was performed on the multiple linear regression model to identify the QST measures that were independently correlated to the OA response.

Statistical analyses were performed using SPSS v. 27 (IBM Corp., Armonk, NY) Results were reported as mean values and their 95 % confidence interval (CI). p-values less than 0.05 were considered statistically significant.

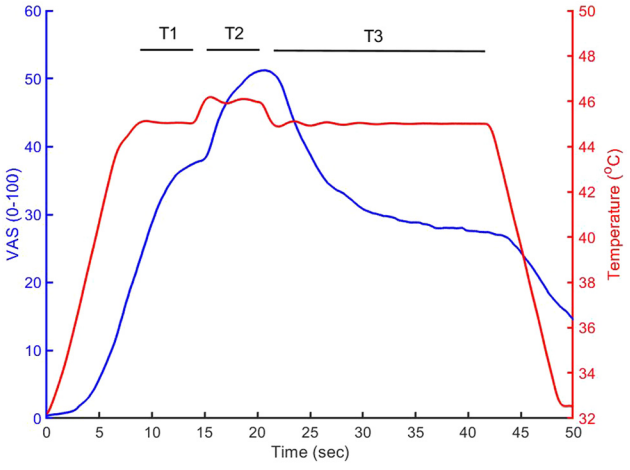

Figure 1: The mean VAS score (blue) across all patients and sessions showed an increase to the temperature (red) increase with a few second's delay. The mean VAS score increased throughout T1 and with a steeper increase following the temperature increase from T1 to T2. The VAS score decreased as the temperature was decreased from between T2 and T3 and continued to decrease throughout T3.

Results

The OA test could not be completed in three of the 204 tests due to voluntary withdrawal of the arm from the thermode. The OA test was not repeated during that session but was performed in the following sessions. The mean VAS score across patients and sessions are depicted together with the stimulation temperature profile in Figure 1.

A significant difference of the OA-effect was observed between cycles (MLM, p<0.042). The OA-effect increased compared to the first session (pre-treatment baseline) when assessed before the 2nd (p<0.012; 19 [2–36]), 3rd (p<0.041; 20 [0:39]), 5th (p<0.024; 23 [1–44]), 6th (p<0.004; 27 [5–48]), 9th (p<0.016; 24 [2–46]), and 10th (p<0.026; 23 [1–45]); Sidak adjusted pairwise comparison based on estimated marginal means; Figure 2.

The maximal VAS score during T1 (p=0.289) and T2 (p=0.280), the minimum VAS score during T3 (p=0.170) and

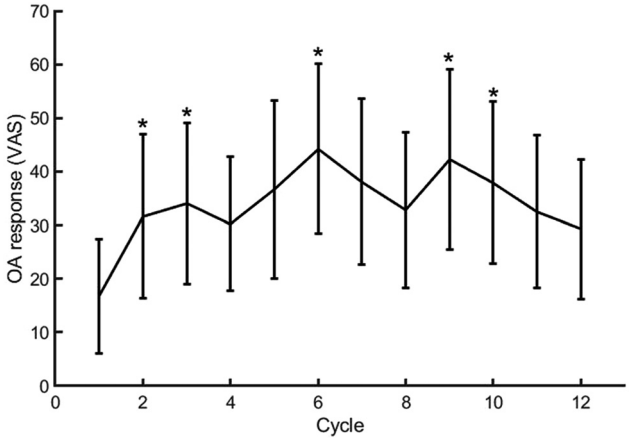

Figure 2: A significant increase of the offset analgesia (OA) response from before the first cycle oxaliplatin treatment (baseline) to the 2nd, 3rd, 6th, 9th, and 10th cycle was observed (MLM, p<0.042).

Table 1: Relation between quantitative sensory tests and the offset analgesia (OA) response. The univariate linear regression model showed that the heat pain threshold (HPT) was negatively related to the OA response, and that the static mechanical stimulation with 12.8 g pinprick and 60 g pinprick with calibrated pinpricks were positively correlated to the OA response. The common toxicity scale for adverse events (CTCAE) score, vibration threshold (VTH), warmth detection threshold (WDT), cold detection threshold (CDT), and the cold pain threshold (CPT) were not related to the OA response in the univariate linear regression models. The multiple linear regression model showed that HPT and the pinprick 60 g were independently correlated to OA response. This was maintained during the stepwise factor reduction procedure.

	Univariate regression		Multiple regression		Multiple regression with factor reduction	
	Standardized coefficients	p-Value	Standardized coefficients	p-Value	Standardized coefficients	p-Value
CTCAE	0.059	0.408	0.044	0.511		
VTH	0.053	0.459	0.117	0.093		
WDT	0.081	0.256	0.016	0.833		
CDT	−0.095	0.183	0.017	0.819		
HPT	**−0.258**	**<0.001**	**−0.203**	**0.041**	**−0.167**	**0.013**
CPT	**0.177**	**0.013**	−0.058	0.530		
12.8 g pinprick	**0.321**	**<0.001**	0.086	0.272		
60 g pinprick	**0.431**	**<0.001**	**0.348**	**<0.001**	**0.383**	**<0.001**

p-Values <0.05 are highlighted in bold.

the onset hyperalgesia (p=0.671) were not significantly different between cycles (MLMs).

Although the CTCAE score and the OA-response both differed between treatment cycles, they were not correlated (r=0.06, p=0.408, simple linear regression). The OA response was negatively correlated to the HPT and positively correlated to the pinprick scores and the CPT. Adjusting for co-linearity between the QST measures showed that the OA response was independently correlated to the 60 g pinprick score as well as independently and negatively correlated to the HPT (Table 1).

Discussion

This is the first study to investigate the OA phenomenon during chemotherapy with oxaliplatin and showed an increased OA response during the oxaliplatin treatment. Moreover, this is the first study to show an increased OA response per se, as OA is generally reduced when assessed in patients with peripheral neuropathy.

OA in patients with chronic pain

Brain imaging studies have shown activation in the periaqueductal grey and rostral ventromedial medulla during the OA [16, 17]. These brain areas differ from areas involved in the more commonly studied conditioned pain modulation effect and it must thus be concluded that these endogenous pain modulatory phenomena do not share fundamental mechanisms [18].

Several studies have shown that the OA is not affected by centrally acting drugs [9], with exception of spinal anaesthesia which reduced the OA [19]. OA is decreased in persons with neuropathic pain [20] and diabetic neuropathy [21]. The dysfunctional OA mechanism in chronic pain patients has recently been ascribed to disrupted OA-modulated functional connectivity in the descending pain modulatory system, the default mode network and emotional network brain systems [17].

The neurotoxic effect of oxaliplatin

The mechanisms-of-action causing neurotoxic side effect of oxaliplatin is not fully understood, however several mechanisms have been proposed. Previous studies have indicated that OIPN is closely related to alterations of the gating properties of voltage gated sodium channels [22, 23]. Oxaliplatin also affects the voltage gated potassium and calcium as well as temperature sensitive transient receptor potential channels Kang et al. [15]. These changes in the ion channel properties may be the cause of the observed increased excitability of large sensory nerve fibers both in this cohort of patients [15] and others [24, 25]. The excitability of the small sensory nerve fibers, including the heat sensitive nerve fibers, has not been investigated, but it seems likely that similar excitability changes occur. Unlike the cold pain threshold, the heat pain threshold does not seem to change during the oxaliplatin treatment [15, 26–28]. In addition, the reported VAS score to the painful heat stimulation did not changes during the treatment either. The observed increased OA response can therefore not be explained by a

simple gain of heat sensitivity. However, a weak but significantly negative correlation between the heat pain threshold and the OA effect was observed in the present study. Usually, no relation between OA and the heat pain threshold have been observed. E.g. differences in OA between migraine patients and healthy controls has been observed but no difference in heat pain thresholds [29]. Similarly, differences in OA between a group of persons how have had cerebellar infarction compared to healthy controls was observed, whereas the heat pain thresholds were not significantly different but pinprick sensitivity was [30], and OA was observed to be different between genders but heat pain threhsolds was not [31]. Likewise, no correlation between heat pain thresholds and the OA effect was observed [32]. This underscores the rather unique neurotoxic side effects of oxaliplatin as pain perception was sensitized while the endogenous pain modulatory effects are enhanced. The present study was performed during chemotherapy treatment, therefore, these effects may not be extrapolated to persons experiencing persistent or chronic OIPN, where it seems likely that the endogenous pain modulatory functions have become deficient.

The cold pain threshold decreases during acute OIPN [15, 26–28], which may cause the often reported cold induced allodynia. The cold induced allodynia may cause an increased response at the temperature decrease from T2 to T3 as the thermode is actively cooled during the temperature decrease. This would effectively cause an attenuation of the heat perception, assuming that perceived heat pain is a result of the difference between cold and heat fiber barrage of the spinal cord. This explanation would require activation of cold sensitive nerve fibres when the temperature was decreased from 46 °C to 45 °C at the transition from T2 to T3. The transient receptor potential melastatin 8 (TRPM8) channel is activated by temperatures less than ~25 °C, and applying menthol increases the activation threshold to ~30 °C [33]. It seems unlikely that oxaliplatin should be able to increase the activation threshold to 45 °C, though this has not been studied directly. Therefore, it seems unlikely that the increased OA response is be caused by altered activation properties of the TRPM8 channel.

Onset hyperalgesia

Onset hyperalgesia has been defined as a disproportionate increase in pain intensity at a given stimulus intensity when this intensity is preceded by a rise from a lower intensity [32]. Onset hyperalgesia constitutes a temporal filtering phenomenon similar to OA, but enhances the response to an increased stimulus, rather than a decreased stimulus. Onset hyperalgesia appears to cause a smaller increase in pain perception compared to the decrease in pain perception during OA [1]. However, when adjusting for habituation, the onset hyperalgesia effect seems to be of similar magnitude as the OA response [32]. In this study, we quantified the onset analgesia effect as the increase in pain perception caused by the temperature increase from T1 to T2. Unlike the OA, the onset hyperalgesia effect was not affected by the oxaliplatin treatment.

Limitations

This study has several limitations, and the conclusion should be considered with some caution. This study reports a secondary outcome from a study intended to assess the excitability of peripheral nerve fibers during oxaliplatin treatment [15]. Therefore, the study has no control groups nor control condition. The lack of a non-treatment control group could affect the conclusion that OA changed during the oxaliplatin treatment, however there is no indications that a potential non-treatment control group would increase OA over the cause of several weeks as was observed during oxaliplatin treatment in this study. The OA was measured at baseline for each patient, and this measurement acted as control measurement. This study has no control condition i.e., a test with constant temperature equal to the temperature of the T3 period. Therefore, this study does not prove that the pain response to the temperature decrease is 'disproportional'. However, the OA phenomenon has been validated in several studies and should be considered validated [4, 9].

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Research ethics: The study complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and was approved by the Local Ethics Committee (approval number: N-20140024).

Informed consent: All patients provided written informed consent to the procedures which were conducted.

Author contribution: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: Authors state no conflict of interest.

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