

THE influence of circulating serotonin (5-HT) on the effects of intra-articular administration of granisetron on temporomandibular joint (TMJ) pain was investigated in 11 patients with chronic polyarthritides. An analgesic effect superior to placebo has been shown previously.

The change in TMJ movement pain intensity was negatively correlated to circulating 5-HT; that is, the higher the 5-HT before injection, the greater the reduction of pain intensity. The resting pain intensity reduction was not related to 5-HT.

In conclusion, this study indicates a stronger short-term analgesic effect on TMJ movement pain by intra-articular administration of the 5-HT₃ receptor antagonist granisetron in patients with high levels of circulating 5-HT.

Key words: 5-HT₃ receptor, Arthritis, Blood, Nociception, Pain, Rheumatoid arthritis, Serotonin, Serum, Temporomandibular joint

Influence of serotonin on the analgesic effect of granisetron on temporomandibular joint arthritis

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Introduction

Temporomandibular joint (TMJ) pain is a significant part of the symptomatology and impairment of daily life in patients with TMJ involvement of chronic polyarthritides such as rheumatoid arthritis (RA).¹ The monoamine serotonin (5-HT) mediates pain and hyperalgesia,² and has been found to be associated with TMJ pain upon joint movement and associated impairment of mobility.³ Peripheral 5-HT is mainly stored in thrombocytes, and several signal substances involved in the mediation of inflammation can induce 5-HT release from these cells.^{4,5} In patients with RA, thrombocytes have been found to be increased in number and to release 5-HT.⁴ Richardson and Engel showed that 5-HT participates in the mediation of resting pain from inflamed peripheral tissues by sensitizing or exciting fine afferent units via the 5-HT₃ receptor.⁶ This receptor is peripherally located only on afferent neurons.⁷ In a recent study of patients with RA, intra-articular injection of 1 mg of the 5-HT₃ receptor antagonist granisetron was found to reduce TMJ resting pain for at least 20 min and injection of granisetron into the healthy human masseter muscle reduced pain induced by local administration of 5-HT.^{8,9} It therefore seems probable that the 5-HT₃ receptor is involved in the modulation of musculoskeletal pain. The analgesic effect of granisetron most probably depends on the cell-surface expression of 5-HT₃ receptors on the local nerve

endings and on the local tissue level of 5-HT. However, the influence of circulating 5-HT, which is the major source of tissue 5-HT, on the response to granisetron is unknown. The aim of this study was therefore to investigate the influence of circulating 5-HT on the effects on TMJ pain by intra-articular administration of granisetron in patients with chronic polyarthritides.

Materials and methods

Patients

Eleven patients (10 females and one male) with a median (interquartile range) age of 40 (22) years with signs (localized pain) of TMJ involvement by chronic polyarthritides were included (Table 1). The diagnosis of RA (three patients) was determined according to the 1987 classification criteria of the American College of Rheumatology,¹⁰ while the diagnosis of psoriatic arthritis (one patient), ankylosing spondylitis (one patient), reactive polyarthritis (two patients), Sjögren's syndrome (one patient) or chronic unspecified polyarthritis (three patients) was determined according to the European Spondylarthropathy Study Group's criteria.¹¹

The patients were first referred to the Department of Rheumatology at the University of Tartu, Estonia from general practitioners or rheumatologists in Estonia. After an inclusion examination at the rheu-

Table 1. Demographic and background factors in 11 patients with chronic polyarthritides receiving injections of 3 mg/3 ml of granisetron into the temporomandibular joint (TMJ)

Parameter	Median	Interquartile range
Age (years)	40	22
Duration ^a		
General disease (years)	5	7
TMJ disease (years)	1	2
Pre-injection TMJ pain intensity		
Rest		
Injected side (VAS)	21	22
Contralateral side (VAS)	0	1
Maximum mouth opening		
Injected side (VAS)	39	22
Contralateral side (VAS)	0	2
Background factors		
Number of symptomatic joint regions	3	2
Erythrocyte sedimentation rate (mm/h)	16	26
C-reactive protein (mg/l)	5	12
Thrombocyte particle count (10 ⁹ /l)	265	102
Rheumatoid factor (IU/ml)	0	0
Serotonin		
Serum (nmol/l)	668	531
Plasma (nmol/l)	10	9

VAS, visual analogue scale.

matology clinic, the patients were referred to the Department of Stomatology at the same university. Inclusion criteria were diagnosis of chronic polyarthritides, resting pain localized to the TMJ region and a reduction in TMJ pain intensity upon maximum mouth opening of 35% or more after an auriculotemporal nerve block with 2 ml of 2% lidocaine (20 mg/ml of Xylocain; Astra-Zeneca, Södertälje, Sweden). Exclusion criteria were pregnancy and allergic reactions to granisetron or any other disease that may cause pain in the TMJ region. All patients used non-steroid anti-inflammatory drugs, three patients used oral glucocorticoids and three patients used disease-modifying antirheumatic drugs. The patients had not been subjected to any recent (<3 months) treatment of the TMJ. The study was approved by the local ethics committees at the University of Tartu, Estonia (94/3, 01) and the Huddinge University Hospital, Sweden (151/01). All individuals gave their verbal consent.

Procedures

After the inclusion examination, the current resting pain intensity and the pain intensity during maximum mouth opening of the TMJ were assessed with a 100 mm visual analogue scale (ACO, Stockholm, Sweden) with end-points marked 'No pain' and 'Worst pain ever experienced'. The pain intensities were assessed before the injection as well as at every fifth minute

during the first 30 min and then every 10th min up to 60 min. Three ml of the 5-HT₃ antagonist granisetron (1 mg/ml of Kytril®; F. Hoffman-La Roche Ltd, Basel, Switzerland) was used for the injections. Granisetron was administered into the posterior part of the upper joint compartment of the most painful TMJ during approximately 3 min. The patients were contacted within 1 week after the granisetron injection to record any adverse effect.

Venous blood was sampled prior to the injections to measure the serum concentrations of 5-HT, rheumatoid factor, C-reactive protein, thrombocyte particle count and the erythrocyte sedimentation rate. C-reactive protein concentrations below 10 mg/l and rheumatoid factor concentrations below 20 IU/ml were considered normal.

Analysis

Serotonin was analyzed by a commercially available enzyme immunoassay kit (Immunotech, Marseille, France) with a detection limit of 0.5 nmol/l and a sensitivity of 0.5 nmol/l. The intra-assay coefficient of variation for this assay is <9.4% and the interassay coefficient of variation is <9.9% according to the manufacturer. According to the manufacturer, the normal concentration to be expected for 5-HT in human serum is 300–700 nmol/l for males and 500–900 nmol/l for females.

Statistics

The analgesic effect was expressed by the ratio between the post-injection values of TMJ resting pain and movement pain intensities, respectively, and the corresponding pre-injection values. Friedman's repeated-measures test and Dunn's post-hoc test for compensation of multiple comparisons were used to calculate the significance of the change in pain intensity during the experimental procedure. The significance of correlations between blood variables, pre-injection pain intensities and effects of the injections were tested by the Spearman ranked correlation test. A probability level less than 0.05 was considered as significant.

Results

The serum concentration of 5-HT was above the normal range in four patients (36%) and below it in four patients (36%), while the thrombocyte particle concentration was within the normal range for all patients.

The serum concentration of 5-HT was negatively correlated to the change in TMJ pain intensity upon maximum mouth opening after 60 min ($r_s = -.72$,

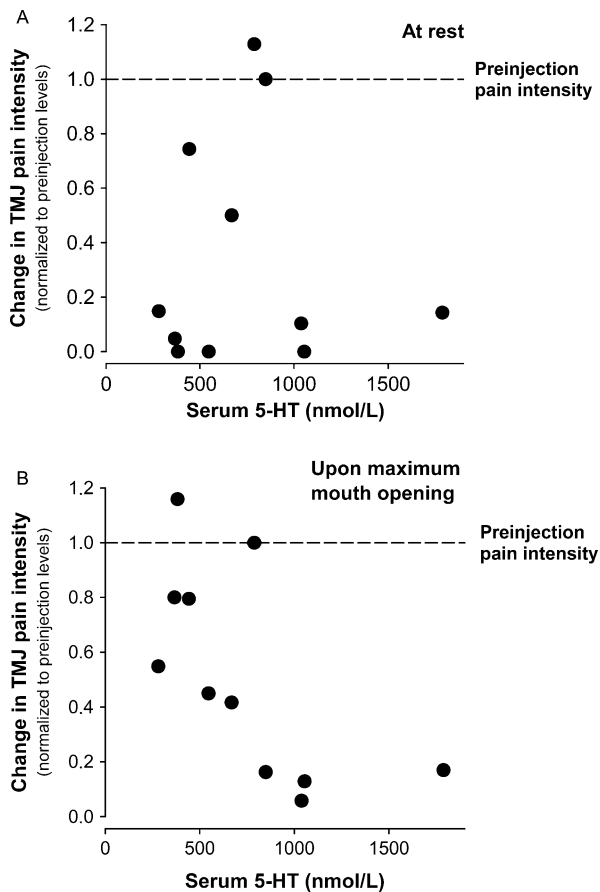


FIG. 1. Scatterplots of the relation between the serum concentration of 5-HT and TMJ pain intensity (A) at rest and (B) upon maximum mouth opening 60 min after intra-articular injection of granisetron (3 mg/3 ml). The pain intensities are shown normalized to the pre-injection level (1.0). For TMJ pain upon maximum mouth opening there was a negative correlation to 5-HT ($r_s = -0.72$, $n = 11$, $p = 0.012$), while no significant correlation was found for TMJ pain at rest ($r_s = 0.06$, $n = 11$, $p = 0.852$).

$n = 11$, $p = 0.012$; Fig. 1); that is, the higher the serum concentration of 5-HT before injection, the larger the reduction of pain intensity. Such a relation was not found for TMJ resting pain intensity and the serum level of 5-HT ($r_s = 0.06$, $n = 11$, $p = 0.852$).

After the granisetron injection, a significant reduction of TMJ pain intensity was present during the whole experimental period (resting pain intensity, $p = 0.007$; movement pain intensity, $p = 0.030$) on the injection side. Neither TMJ resting pain intensity nor TMJ pain intensity upon maximum mouth opening changed significantly on the non-injection side during the observation time period.

The pre-injection levels of the inflammatory markers are presented in Table 1. The C-reactive protein level correlated positively to the erythrocyte sedimentation rate ($r_s = 0.75$, $n = 11$, $p = 0.008$) and to the thrombocyte particle count ($r_s = 0.86$, $n = 11$, $p = 0.001$), but did not influence the analgesic effect of granisetron.

Age was positively correlated to the ratio between TMJ pain intensity upon maximum mouth opening after 60 min and the corresponding pre-injection pain intensity ($r_s = 0.62$, $n = 11$, $p = 0.041$); that is, a larger reduction of movement pain intensity was found in the younger patients. Age and serum concentration of 5-HT were not significantly correlated ($r_s = -0.24$, $n = 11$, $p = 0.498$).

The granisetron injections were well tolerated and there were no adverse effects following the injection during the experimental procedure or thereafter.

Discussion

This study indicates that the analgesic effect of intra-articular administration of granisetron is influenced by the level of circulating 5-HT in patients with chronic polyarthritides.

A higher serum level of 5-HT was associated with a stronger analgesic effect of granisetron on the pain intensity upon maximum mouth opening, which is interesting from three aspects: the anti-nociceptive effect created by block of the 5-HT₃ receptor, the fact that the effect of granisetron seems to be specific for reduction of movement pain intensity, and the relation to serum 5-HT. It is thus very probable that the effect of granisetron after intra-articular administration can be contributed to a specific antagonism of the 5-HT₃ receptor. Richardson and Engel showed that 5-HT participates in the mediation of spontaneous pain from inflamed peripheral tissues by exciting or sensitizing fine afferent units by the 5-HT₃ receptor.⁶ Giordano and Rogers¹² found that 5-HT₃ receptor antagonists had greater analgesic effect on chronic pain than on acute pain in a peripheral animal inflammation model, which indicates the involvement of peripheral 5-HT₃ receptor sites in chronic inflammatory pain and supports our findings about the 5-HT₃ receptor.

Activation of the 5-HT₃ receptor causes a long-lasting sensitization even of high-threshold mechanosensitive units as well as a brief excitation of other mechanosensitive units in joints.¹³ Therefore, this receptor type might be active to specifically elicit TMJ movement pain; that is, pain due to mechanical stimulation of the synovial tissues upon joint movement by activation of mechanosensitive units.

Serum 5-HT, which is the main source for synovial tissue 5-HT, has previously been found to modulate inflammation and TMJ pain in patients with seropositive rheumatoid arthritis.¹⁴ Increased serum and plasma levels of 5-HT would probably cause an immediate increase of the tissue 5-HT level, resulting in increased stimulation of peripheral 5-HT receptors and, in turn, sensitization of nociceptors in the synovial tissues by, for example, the 5-HT₃

receptor.^{4,7-9} Indeed, high synovial fluid levels of 5-HT in the TMJ have been associated with TMJ movement pain.³ It is therefore reasonable to assume that granisetron has the possibility to produce a greater analgesic effect by blocking 5-HT₃ receptor binding of 5-HT when there is a high 5-HT level in the serum and synovial tissues, which could explain the relation between serum 5-HT and the reduction of TMJ movement pain intensity found in the present study.

The anti-nociceptive effect of the granisetron injection found in this study could also, at least partly, be due to an unspecific effect of the injection or injection procedure *per se*. Examples of such unspecific effects could be dilution of endogenous pain mediators in the synovial tissues by the injected solution and placebo effects. However, since the analgesic effect was related to circulating 5-HT levels, a specific analgesic effect of granisetron is likely.

In the present study, the effect of granisetron was not related to the blood levels of inflammatory markers, which suggests that the effect of granisetron is not primarily influenced by disease activity. In addition, the blood levels of inflammatory markers as well as serotonin for the majority of patients were below the upper normal limits, which means that the patients can be considered to have a low inflammatory disease activity. Whether there is a pain-relieving effect of granisetron in more active disease is therefore so far unknown.

In conclusion, this study indicates a stronger short-term analgesic effect on TMJ movement pain by intra-articular administration of the 5-HT₃ receptor antagonist granisetron in patients with high levels of circulating 5-HT.

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