

Ondansetron does not inhibit the analgesic effect of alfentanil

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Summary

5-Hydroxytryptamine (5-HT) causes antinociception via presynaptic 5-HT₃ (5-HT subtype 3) receptors on primary afferent nociceptive neurones in the spinal cord dorsal horn. Therefore, ondansetron (a 5-HT₃ receptor antagonist) may increase the perception of a noxious stimulus or decrease the effects of concurrently administered antinociceptive drugs. Using a randomized, double-blind, crossover study design, we have tested this hypothesis in eight healthy volunteers who, on three different days, received either ondansetron and placebo, ondansetron and alfentanil or placebo and alfentanil. Experimental pain was induced with heat, cold, mechanical pressure and electrical stimulation. Ondansetron alone did not change the response to any of the experimental tests, but alfentanil and the combination ondansetron–alfentanil significantly changed the response compared with ondansetron alone. There was no difference between alfentanil alone and the combination ondansetron–alfentanil. We conclude that ondansetron does not change the response to pressure, heat, cold or electrical nociceptive stimuli or antagonize the analgesic effect of alfentanil. (*Br. J. Anaesth.* 1994; **73**: 326–330)

Key words

Analgesics opioid, alfentanil. Vomiting, antiemetics.

The new antiemetic drug, ondansetron, has selective antagonistic effects on 5-hydroxytryptamine subtype 3 (5-HT₃) receptors [1]. These are located both peripherally (vagal nerve endings) and centrally (chemoreceptor trigger zone) [2]. 5-HT causes antinociception via presynaptic 5-HT₃ receptors on primary afferent nociceptive neurones in the spinal cord dorsal horn [3]. Therefore, a 5-HT₃ receptor antagonist might increase the perception of a noxious stimulus or decrease the effects of antinociceptive drugs.

Glaum, Proudfit and Anderson [4] found that intrathecal serotonin produced antinociception in the rat and that this effect could be antagonized by tropisetron, another selective 5-HT₃ receptor antagonist. In a clinical investigation, Pitkänen and co-workers [5] studied the effect of tropisetron on nausea and analgesia after intrathecal morphine and could not find any effect of tropisetron on post-operative pain.

The aim of the present study was to see if ondansetron could reduce the analgesic effect of alfentanil on experimentally induced pain. Experimental methods have the advantage that pain can be induced in a controlled, standardized way. Using different stimulation modalities it is possible to assess different aspects of pain perception [6,7].

Subjects and methods

We studied eight healthy volunteers (seven male, one female, mean age 25 (range 20–28) yr) who were not receiving any medication and did not have any allergies. Written informed consent according to the Helsinki Declaration was obtained and the study was approved by the Ethics Committee of Århus, Denmark. On three different days, with an interval of at least 2 days, the volunteers received one of the following three regimes according to a randomized, double-blind, crossover study design: ondansetron–placebo: ondansetron 8 mg in 100 ml of saline i.v. followed 40 min later by saline 0.06 ml kg⁻¹ i.m.; ondansetron–alfentanil: ondansetron 8 mg in 100 ml of saline i.v. followed 40 min later by alfentanil 30 µg kg⁻¹ i.m.; placebo–alfentanil: saline 100 ml i.v. followed 40 min later by alfentanil 30 µg kg⁻¹ i.m.

In order to avoid the circadian variation in pain sensitivity [8], each volunteer was always tested at the same time of the day. The pain tests were explained to the volunteer and a trial testing of all techniques was performed in order to familiarize the volunteer with the procedures. Each test series lasted about 15 min. After a baseline test series, the volunteer received ondansetron or placebo (saline) i.v. according to the randomization: 25 min elapsed before the second test series was performed. Then alfentanil or placebo (saline) was given i.m. and 15 min thereafter [9] the third test series was performed. A last test series was performed 75 min after the alfentanil–placebo injection. The following experimental tests were applied to assess pain.

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ARGON LASER PAIN TOLERANCE

The volunteer rested comfortably and wore laser protective goggles. The output from an argon laser (Spectra Physics 168) was transmitted to the skin via a single 1-mm quartz fibre. The beam of the fibre diverges and was adjusted to 1 cm on the skin with a spacer. The output was adjusted to 2 W (controlled with an external power meter). A continuous stimulus was applied to the dorsum of the left hand (stimulation of the same area was avoided) and a counter was started at the onset of the laser stimulation. The time until the volunteer wanted the stimulation to be stopped was defined as the pain tolerance threshold. If the pain tolerance threshold was not reached within 30 s, stimulation was discontinued (in order to avoid skin damage) and the pain tolerance threshold in such cases was defined as 30 s.

ICE WATER TEST

A 2-min ice water test was used [10,11]. During these 2 min, the right hand was immersed in ice saturated water (1.5 ± 1.0 °C). Pain intensity was rated continuously with an electronic visual analogue scale (VAS) coupled to a pen recorder. The area under the pain intensity–time curve was calculated. If the pain was considered intolerable before 2 min had elapsed, the volunteer could withdraw the hand, and for calculation of the area under the curve, the pain intensity at withdrawal was presumed constant to the end of the 2-min period.

MECHANICAL PRESSURE PAIN DETECTION AND PAIN TOLERANCE THRESHOLDS

Pressure pain detection and pain tolerance thresholds were determined on the centre of the pulpa of the third finger of the left hand with an electronic pressure algometer (Somedic AB, Stockholm, Sweden) [6,12,13]. A probe with a surface area of 0.28 cm² was used and the pressure was increased at 30 kPa s⁻¹. Pain detection threshold was defined as the point when pressure turned into pain and pain tolerance as the point when the volunteer did not want the pressure to be increased further. For determination of the pain detection threshold, the mean of three consecutive measurements was used. Pain tolerance thresholds were determined only once, in order to avoid damage and hence sensitization of the area.

NOCICEPTIVE FLEXOR REFLEX

The sural nerve was stimulated behind the right lateral malleolus with a 25-ms train of five 0.25-ms square-wave impulses through felt electrodes soaked in saline (inter-electrode distance 3 cm). Electromyographic reflex responses were recorded with surface electrodes placed midway over the biceps femoris and rectus femoris. Eight reflexes were recorded, averaged and the root mean square (RMS)

value in the 80–180-ms interval after the stimulus was calculated. After each recording the volunteer rated the perceived pain on a visual analogue scale.

Statistical analysis was performed with the software package SigmaStat Ver 1.01 (Jandel Scientific GmbH, Erkrath, Germany). For statistical analysis, all values were calculated as percentage of baseline values. Friedman's test for repeated measures analysis of variance on ranks and the Student–Newman–Keuls test for multiple comparison were used to test for differences in the reactions to the pain tests in the ondansetron–placebo group for the four tests and to determine differences between the ondansetron–placebo, ondansetron–alfentanil and placebo–alfentanil groups at the testing performed 15 min after administration of alfentanil or placebo i.m. For calculation of confidence intervals, a bootstrapping [14] (5000 replications of eight values) was performed for each pain test and each measurement. A similar bootstrapping was performed to calculate the difference (and confidence intervals) between the ondansetron–alfentanil and placebo–alfentanil groups. To test the validity of the experimental pain tests, the reactions of the placebo–alfentanil group to the tests 15 min after administration of alfentanil i.m. were analysed and compared with baseline using Wilcoxon's signed rank test. $P < 0.05$ was considered significant.

Results

There was no statistically significant change with time in the response to any of the tests in the ondansetron–placebo group (table 1). Fifteen minutes after i.m. administration of alfentanil or placebo, the reactions to the pain tests of the placebo–alfentanil group and the ondansetron–alfentanil group were significantly different compared with the ondansetron–placebo group. The difference in mechanical pressure pain thresholds did not reach statistical significance. No differences were found between the ondansetron–alfentanil group and the placebo–alfentanil group (table 2). Alfentanil alone significantly changed the reaction of all of the experimental pain tests (except for mechanical pressure pain threshold). The largest changes in the median values were observed in the pain tolerance to argon laser heat stimulation, which increased by 42%, and in the ice water test, where the area under the pain intensity–time curve was reduced by 41%. The VAS pain score to electrical stimulation of the sural nerve was reduced by 25% and the RMS of the flexor reflex by 27%. The pain tolerance to mechanical pressure was increased by 18%.

Discussion

This study showed that ondansetron alone did not change the reactions to any of the experimental pain tests. The reactions were changed significantly by alfentanil, but no significant difference could be found between alfentanil given after placebo compared with alfentanil given after ondansetron. The

Table 1 Median (95% confidence intervals calculated with the bootstrapping method) results of the experimental pain tests in the ondansetron-placebo (O-P), ondansetron-alfentanil (O-A) and placebo-alfentanil (P-A) groups. Values are expressed as percentage change from baseline (100%). * $P < 0.05$ compared with O-P group

Pain test	25 min	55 min	115 min
Heat pain tolerance			
O-P	94.8 (72.0-109.6)	95.3 (67.3-100.0)	87.3 (80.7-100.0)
O-A	93.3 (87.4-100.0)	115.0 (100.0-144.2)*	89.4 (67.9-100.0)
P-A	100.9 (100-127.3)	135.8 (100.0-205.0)*	100.0 (83.7-129.3)
Ice water pain tolerance			
O-P	113.4 (97.9-124.0)	102.5 (86.5-119.0)	105.4 (97.7-123.5)
O-A	96.6 (92.0-119.3)	48.8 (21.2-84.2)*	100.2 (83.0-115.7)
P-A	96.9 (84.8-110.0)	60.0 (12.2-73.0)*	93.1 (87.4-99.4)
Mechanical pressure pain detection			
O-P	104 (86.0-109.0)	95.5 (93.0-98.0)	97.4 (87.0-117.0)
O-A	96.7 (87.0-109.0)	138.1 (116.0-156.0)	98.6 (80.0-116.0)
P-A	95.3 (67.0-103.0)	121.7 (101.0-144.0)	84.7 (71.0-95.0)
Mechanical pressure pain tolerance			
O-P	94.8 (92.0-102.0)	97.9 (91.0-119.0)	97.5 (75.0-117.0)
O-A	99.6 (90.0-123.5)	128.4 (110.0-182.0)*	104.6 (93.0-124.0)
P-A	91.5 (86.0-95.0)	115.7 (102.0-168.0)*	102.2 (85.0-121.0)
Nociceptive flexor reflex (RMS)			
O-P	85.8 (52.3-127.9)	65.5 (49.6-117.5)	89.9 (79.2-124.4)
O-A	83.0 (52.8-105.0)	35.8 (22.8-79.9)*	75.4 (39.8-104.2)
P-A	98.0 (88.6-142.2)	47.9 (19.8-76.5)*	75.9 (51.9-135.1)
VAS—electrical stimulation			
O-P	101.3 (92.4-120.7)	100.2 (75.0-113.0)	100.0 (89.6-120.5)
O-A	105.2 (97.2-120.0)	57.7 (37.0-80.3)*	76.9 (74.6-127.2)
P-A	100.0 (100.0-118.5)	75.5 (39.4-97.5)*	112.7 (96.6-121.0)

Table 2 Comparison between the ondansetron-alfentanil (O-A) and placebo-alfentanil (P-A) groups for each pain test at 55 min. All values were calculated using the bootstrapping method and are median (95% confidence intervals) of the difference between the two groups

Pain test	Diff. (O-A minus P-A)
Heat pain tolerance	-11.2 (-64.7-18.1)
Ice water pain tolerance	1.9 (-12.4-28.4)
Pressure pain detection	17.5 (-32.0-57.0)
Pressure pain tolerance	24.0 (-58.0-66.0)
Nociceptive flexor reflex (RMS)	9.3 (-16.6-22.2)
VAS—electrical stimulation	-4.5 (-24.3-16.8)

hypothesis that the 5-HT₃ receptor antagonist ondansetron antagonizes antinociception was not supported by the present study.

We studied only eight volunteers, repeatedly, and although the variances of the measured variables were generally not large, the possibility of a type II error must be considered. However, the small differences between ondansetron and placebo varied in direction in the various tests. The increased heat pain tolerance after alfentanil was reduced slightly by pretreatment with ondansetron, whereas ondansetron caused a slight additional effect on the alfentanil-induced increase in tolerance to mechanical pressure pain, electrically induced pain and decrease in cold pain. Furthermore, a bootstrapping analysis of the difference between the ondansetron-alfentanil and the placebo-alfentanil groups at 55 min also showed a non-significant difference between the two groups, as zero is included in the confidence interval for all tests. These findings support our conclusion that ondansetron cannot have a major influence on antinociception in acute pain.

This conclusion is also supported by other studies. Hammond [15] reviewed studies examining the effect

of selective alterations in serotonergic systems or pathways on morphine-induced antinociception and found very little consensus on the role of serotonergic neurones in morphine-induced antinociception. Dershwitz and co-workers [16] studied the effect of ondansetron on opioid-induced ventilatory depression and sedation during steady state infusion of alfentanil and found that ondansetron did not produce any change in ventilatory depression or sedation.

In several clinical studies where ondansetron was used to prevent postoperative nausea and vomiting (PONV), no increase could be found in the amount of opioid medication administered to the group receiving ondansetron compared with placebo [Glaxo database, personal communication]. Leiser and Lip [17] gave ondansetron 16 mg orally before operation, followed by the same dose after operation, 8 h after the first dose, and found no difference in the total opioid analgesic doses given during the first 24 h to the ondansetron-treated group compared with the placebo group. However, ondansetron has a relatively short half-life of about 3.5 h [18], and so an antianalgesic effect of ondansetron in the first 6-12 h might escape observation if only the total accumulated dose within the first 24 h is recorded. Scuderi and co-workers [19] studied ondansetron 1, 4 or 8 mg in the treatment of PONV after outpatient surgery and found no increase in the percentage of patients given opioids in the postanesthetic care unit in any of the ondansetron groups compared with placebo. We used ondansetron 8 mg which is considerably less than the 2 × 16 mg doses used in the study of Leiser and Lip. Recent studies [19-21] have shown that 4 mg and even 1 mg may be effective in the prevention and treatment of PONV. Thus ondansetron 8 mg used in the present study is a clinically relevant dose.

The antinociceptive or analgesic-sparing effect of metoclopramide was observed by Lind and Breivik [22] in 1970, and recently rediscovered by Rosenblatt and co-workers [23,24]. Metoclopramide has a partial 5-HT₃ receptor antagonistic effect, but has a more potent antidopaminergic effect. As ondansetron is a selective 5-HT₃ antagonist, the antinociceptive effect of metoclopramide must be caused by a mechanism different from its 5-HT₃ antagonistic effect [25].

The pain tests used in the present study have been shown to be specific and sensitive tests for various antinociceptive drugs. The analgesic effects of alfentanil were verified in the present study with experimental pain tests in volunteers. Thermal stimulation has been used to demonstrate the analgesic effect of i.v. morphine [26], extradural morphine [7], i.v. fentanyl [27] and i.m. alfentanil [9]. In the latter study, brief argon laser pulses (200 ms) covering a small area (3 mm diameter) were used to determine pain detection thresholds. We used a continuous laser light with a fixed intensity, covering a larger area, and measured the time to pain tolerance. The modified 2-min ice water test was described by Jones and co-workers [11]; they found the test to be sensitive to opioids. The pressure algometer used in the present study has been evaluated by Brennum and co-workers [12] and has been used to demonstrate the analgesic effect of extradural morphine [7] and i.v. morphine [13]. Willer [28], and Chan and Dallaire [29] found a linear relation between the amplitude of the nociceptive flexor reflex and perceived pain. I.v. morphine reduces the nociceptive reflex and the associated pain report [30]. Extradural morphine 3 mg for postoperative pain relief resulted in a 40% decrease in the nociceptive reflex 30 min after injection [31]. In the present study, alfentanil 30 µg kg⁻¹ i.m. significantly changed the reaction to all of the experimental pain tests, except for mechanical pressure pain thresholds, thus supporting the validity of the pain tests at this dose of alfentanil. The largest changes were observed in the pain tolerance to argon laser heat stimulation and in the ice water test. Smaller changes were observed with electrical stimulation of the sural nerve and with mechanical pressure. The nociceptive flexor reflex is composed of both sensory and motor components; alfentanil might affect not only the sensory component.

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