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Short communication

Topical ondansetron attenuates nociceptive and inflammatory effects of intradermal capsaicin in humans

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Abstract

Topical application of the 5-HT_3 receptor antagonist ondansetron (50–250 μg) delivered in a pluronic lecithin organogel vehicle (PLO, 0.5 ml) produced dose-dependent attenuation of nociceptive and inflammatory effects of intradermally injected capsaicin (10 μg/10 μl) in humans. Significant, dose-dependent analgesic effects were produced by 100 μg and 250 μg doses of ondansetron; these doses also reduced mechanical hyperalgesia produced by capsaicin. However, only 250 μg dose of ondansetron diminished capsaicin-induced inflammatory flare.

Keywords: Ondansetron; Pain; Human

In humans, intradermally injected capsaicin produces an inflammatory reaction consisting of flare, a sensation of burning pain and increased nociceptive sensitivity characterized by an area of mechanical hyperalgesia (Simone et al., 1989). These qualities make capsaicin-induced effects a useful human model of acute inflammatory pain. Previously, we have shown that local injection of serotonin 5-HT_3 receptor antagonists produce analgesia against acute and chronic inflammatory pain in animals, apparently by blocking the action of platelet-, mast cell- and/or plasma-derived 5-HT upon 5-HT_3 receptors localized upon C-fiber afferents (Giordano and Rogers, 1989; Giordano and Sacks, 1997). The area of pain and mechanical hyperalgesia surrounding inflammatory pain sites would make delivery of analgesic drugs by local injection clinically impractical in humans. Pluronic lecithin organogels (PLO) have proven to be efficient vehicles for transdermal transport of various drugs and permit topical application which affords local bioavailability with little or no systemic distribution (Willimann et al., 1992).

The present study examined the dose-dependent effects of the 5-HT_3 receptor antagonist ondansetron, topically applied in a PLO base vehicle, against pain, mechanical hyperalgesia and flare produced by intradermally injected capsaicin. All protocols were reviewed and approved by the Institutional Review Board of HealthSouth Rehabilitation Hospital, Beaumont. Twelve (12) subjects provided informed consent and received instruction in sensory magnitude estimation using the 10 cm visual analog scaling method (Scott and Huskisson, 1979). All agents were delivered to the volar surface of the subjects' forearm. Each subject was tested for dose-dependent effects across the dose range of topically administered ondansetron. At least 2 days elapsed before subjects were re-tested. Drug doses and temporal parameters of drug administration and evaluation of effects were established in preliminary experiments. Capsaicin (10 μg/10 μl) was freshly prepared prior to each session of testing. Nociception was assessed using 10-cm VAS according to Scott and Huskisson (1979); mechanical hyperalgesia and inflammatory flare were assessed using methods previously described (Simone et al., 1989). Ondansetron (50, 100, 250 μg) was prepared in a PLO vehicle according to methods described for other compounds by Willimann et al. (1992). Ondansetron (50–

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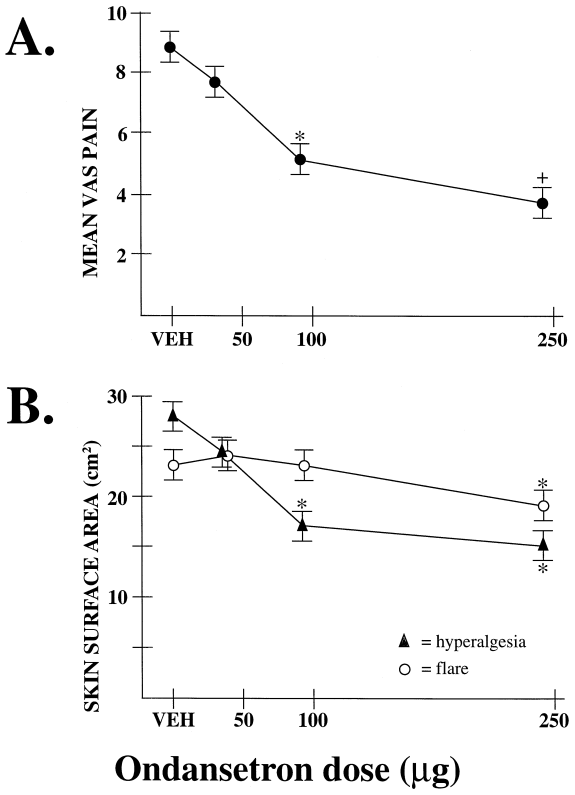

Fig. 1. A: Effects of topically applied ondansetron (50–250 μg) in PLO vehicle (0.5 ml) vs. PLO vehicle alone against acute inflammatory pain produced by intradermal injection of capsaicin (10 μg/10 μl). Ondansetron (or vehicle) was applied 1 min. after capsaicin injection; effects were assessed 4 min. following ondansetron application. Points represent mean visual analog pain scores from 12 subjects (±S.D.). (* = Significant difference from PLO vehicle alone, $P < 0.05$; + = significantly different from PLO vehicle, $P < 0.01$). B: Effects of topically applied ondansetron (50–250 μg) in PLO vehicle (0.5 ml) on capsaicin-induced mechanical hyperalgesia and inflammatory flare. Mean area of maximal hyperalgesia produced by intradermal capsaicin was 28.3 cm^2; mean area of capsaicin-induced inflammatory flare was 24.0 cm^2. Ondansetron (or PLO vehicle alone) was applied 1 min. after intradermal capsaicin injection and effects were assessed 4 min. following ondansetron application. Points represent mean skin area assessments from 12 subjects (±S.D.) (* = Significant difference from PLO vehicle alone, $P < 0.05$).

250 μg/0.5ml) was topically applied to an area of 30 cm^2 surrounding the site of intradermal capsaicin, 1 min after capsaicin administration.

Effects of topically administered ondansetron on capsaicin-induced pain, hyperalgesia and flare were examined at 4 min after ondansetron application. Data were analyzed using analysis of variance (ANOVA) with post-hoc, pairwise comparisons using Student's *t*-test. In all cases, significance was indicated at a level of $P < 0.05$. Preliminary experiments revealed that topical application of PLO vehicle alone or the various doses of ondansetron did not produce nociceptive, noxious or itching sensations when administered in the absence of capsaicin.

Fig. 1A shows that topical ondansetron produced dose-dependent analgesia against capsaicin-induced pain. Effects were first observed at 100 μg ($P < 0.05$), with 250 μg producing significantly greater pain reduction ($P < 0.01$). Fig. 1B illustrates that against capsaicin-induced mechanical hyperalgesia, both 100 μg and 250 μg doses of ondansetron produced significant effects ($P < 0.05$) that did not statistically differ from each other. In contrast, only the highest dose of ondansetron has discernible effects against the flare produced by intradermal capsaicin ($P < 0.05$, Fig. 1B).

These results strengthen the hypothesis for differential involvement of peripheral 5-HT_3 receptors in the processes of inflammatory pain, hyperalgesia and vasodilatory flare. As well, the data suggest the possible clinical utility of topically applied ondansetron against specific types of peripheral inflammatory pain.

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