volunteers. We performed a population pharmacokinetic-pharmacodynamic analysis and constructed utility functions. Utility functions are objective assessments of the probability of analgesia relative to the probability of respiratory depression. The morphine steady-state plasma concentration causing 25% ventilatory depression was 11±2 ng/mL (median±SE) and for concentration causing a doubling of the pain tolerance 34±10 ng/mL; the equivalent values for Oliceridine were 27±4 ng/mL (ventilation) and 28±5 ng/mL. The values indicate a 2.5-fold greater morphine respiratory potency compared to Olicerdine while equipotency was observed for analgesia efficacy of the two opioids. Additionally, Oliceridine equilibrates more rapidly than morphine with its effects compartment. The two utility curves that were constructed, i.e. the probability of analgesia minus the probability of respiratory depression and the probability of analgesia without respiratory depression, were all in favor of Oliceridine compared to morphine, indicating that following treatment with Oliceridine the probability of analgesia exceeds that of respiratory depression, over the dose range studied. In contrast, the probability of respiratory depression exceeded that of analgesia following morphine treatment.

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DIETARY ASCORBIC ACID RESTRICTION IN GNL/SMP30-KNOCKOUT MICE UNVEILS THE ROLE OF ASCORBIC ACID IN REGULATION OF CA_{3.2}-DEPENDENT PAIN

A. Kawabata1, M. Tsubota1, K. Uebo1, K. Miki1, F. Sekiguchi1, A. Ishigami2
1Kindai University, Pharmacology & Pathophysiology, Faculty of Pharmacy, Higashi-Osaka, Japan, 2Tokyo Metropolitan Institute of Gerontology, Molecular Regulation of Aging, Tokyo, Japan

Background and aims: Ca_{3.2} T-type calcium channels, expressed in the primary afferents, play a pronociceptive role, and their function is regulated by a variety of extracellular substances; e.g. Zn^{2+} reduces Ca_{3.2} activity by binding to His^{191} in Ca_{3.2}, an effect cancelled by L-cysteine and H\_2S, a gasotransmitter. Interestingly, ascorbic acid (vitamin C) suppresses Ca_{3.2} activity through metal-catalyzed oxidation of the Zn^{2+}-binding His^{191}. The present study thus examined the role of ascorbic acid in nociceptive processing, using the mice lacking gluconolactonase (GNL)/SMP30, an enzyme essential for ascorbic acid biosynthesis.

Methods: T-type calcium channel-dependent currents (T-currents) were determined in NG108-15 cells that abundantly express Ca_{3.2}. GNL/SMP30-KO and wild-type mice were subjected to dietary ascorbic acid restriction. Ascorbic acid levels were measured by HPLC. Somatic allodynia and referred hyperalgesia were assessed by von Frey test.

Results: NaHS, an H\_2S donor, enhanced T-currents in NG108-15 cells, an effect abolished by ascorbic acid. The somatic allodynia and referred hyperalgesia following intraplantar and intracolonic NaHS, respectively, and paclitaxel-induced neuropathic allodynia in wild-type mice were suppressed by ascorbic acid or T-type calcium channel blockers. Dietary ascorbic acid restriction caused systemic ascorbic acid deficiency in GNL/SMP30-KO, but not wild-type, mice. The ascorbic acid restriction enhanced the NaHS-induced somatic and visceral hypersensitivity and paclitaxel-induced neuropathy in GNL/SMP30-KO mice, while it had no such effect in wild-type mice.

Conclusions: Our data unveil the critical role of ascorbic acid in regulating Ca_{3.2}-dependent somatic and visceral pain hypersensitivity.

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TOPICAL MORPHINE FOR THE TREATMENT OF CANCER-RELATED PAINFUL MUCOSAL AND CUTANEOUS LESIONS: A DOUBLE-BLIND, PLACEBO-CONTROLLED CROSS-OVER CLINICAL TRIAL

A. Ciałkowska-Rysz1, T. Dzierzanowski2
1Medical University of Lodz, Laboratory of Palliative Medicine, Lodz, Poland, 2Medical University of Warsaw, Warsaw, Poland
Background and aims: Painful mucosal and cutaneous lesions are often less responsive or even refractory to systemic opioid analgesics. There is evidence that suggests the effectiveness of topical morphine be restricted to inflammatory pain. The aim of this study was to assess the effectiveness and safety of the topical morphine for the pain related to mucosal lesions and skin ulcers.

Methods: The study was a 14-days randomized placebo-controlled cross-over trial with a 28-days follow-up open phase (OP). The trial was conducted in adult patients with localized cancer-related pain and treated with systemic opioids. The patients administered 0.2% gel on the mucosal lesion or 0.2% ointment on the skin lesion by themselves. The primary measurements were mean pain intensity (MPI) and mean pain relief (MPR) in NRS 0-10, and ITT analysis was performed.

Results: 35 patients were randomized to the RCT, and all of them finished 14-day observation. The MPI before the treatment was NRS 5.9 and decreased to 2.5 after morphine (p < 0.0001 vs. placebo). The MPR was 57% after morphine, and 77% of the patients using topical morphine reached clinically significant (at least 50% of the starting value) pain relief, statistically different to placebo. The analgesic effect sustained over the 28-day OP period (p = 0.00001). No side effects were reported, except for two cases of moderate pruritus.

Conclusions: Topical morphine appeared fast-acting, highly effective, and safe medication for mucosal and skin lesions in palliative patients, with sustainable pain relief effect over the 28-day observation period.

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THE ASSOCIATION BETWEEN ACCEPTANCE AND PSYCHOLOGICAL AND PHYSICAL FUNCTION IN PORTUGUESE WOMEN IN CHRONIC PAIN DUE TO ENDOMETRIOSIS

A. Rosa¹, A. Ferreira-Valente²,³, A. Pereira¹

¹University of Aveiro, Education and Psychology Department, Aveiro, Portugal, ²ISPA - Instituto Universitário, William James Center for Research, Lisbon, Portugal, ³University of Washington, Department of Rehabilitation Medicine, Seattle, United States

Background and aims: Endometriosis is a significant chronic health condition, affecting about 10% of adult women worldwide. One major symptom of this illness is chronic pain. Both endometriosis itself and pain associated to it greatly impact these patients’ well-being. Previous research shows that mindfulness-based interventions may be effective in increasing the well-being in women with endometriosis. This cross-sectional study sought to examine: (a) the association between acceptance and awareness, on one hand, and psychological and physical function, on the other; (b) the moderation effect of acceptance and awareness in the association between physical and psychological function, in a sample of women with chronic pain due to endometriosis.

Methods: A sample of 189 Portuguese adult women with endometriosis completed measures of acceptance and awareness, psychological function, pain and physical and social impact of the condition.

Results: Participants presented a mild depression, a moderate level of anxiety and severe distress. Acceptance, but not awareness, was significantly negatively correlated with psychological function. Physical and psychological function were significantly positively correlated. Neither acceptance nor awareness moderated the association between physical and psychological function.

Conclusions: These results suggest the need to rethink the clinical intervention with women with endometriosis. Psychological intervention programs should promote acceptance as a resource for promoting psychological adjustment. Future research should examine the role of meaning attributed to the condition and associated pain, as well as the role of the social support network.

Keywords: Endometriosis, Chronic pain, Acceptance, Psychological function, Physical Function