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Synergistic effect of ultramicronized palmitoylethanolamide and NSAIDs in inflammatory pain

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Abstract

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most used interventions in the treatment of inflammatory pain. Nonetheless, NSAID side effects are still a cause for concern. The inhibition of prostaglandin production may lead to dose-dependent adverse events (e.g., renal and hepatic toxicity, cardiovascular and gastrointestinal complications) especially in frail patients, like the elderly or renal patients and those in polytherapy. Therefore, providing adequate analgesia at the lowest NSAID effective dose is desirable. Palmitoylethanolamide (PEA) is a body's own fatty acid amide, produced on demand in response to damage and involved in pain control [1]. Micron-size formulations of PEA (e.g., ultramicronized, um-PEA) have shown favorable pharmacokinetic properties compared to naïve PEA [2]. Although the advantage of um-PEA in terms of lower use of NSAIDs has already been shown in patients suffering from migraine [3], the synergistic effect of um-PEA and NSAIDs has not been proven yet. The aim of the study is to investigate whether um-PEA synergizes analgesia from two different NSAIDs in a model of inflammatory pain.

Methods

Male Sprague-Dawley rats (200-250 g) were maintained and used in accordance with ARRIVE guidelines, the Italian and European directives. A volume of 50 µL of complete Freund's adjuvant (CFA) or saline solution (control group) was injected between the tibiofibular and tarsal bone of the left paw after light anesthesia with 2% isoflurane. Seven days after injection, animals were administered a single oral dose of either um-PEA (10 mg/kg), diclofenac (3 and 30 mg/kg), meloxicam (3 and 30 mg/kg) or um-PEA combined with the respective low-dose NSAID. The paw pressure test was performed on the ipsilateral paw with the Ugo Basile analgesy meter, before or after 15, 30, 45 and 60 min from treatment. The pain threshold was expressed as the force at which rat withdrew the paw or vocalized. Data were analyzed with the Generalized Linear Mixed Model, followed by Tukey-Kramer correction for multiple comparisons. The area under the curve (AUC) was considered for the analysis of the synergistic effect.

Results

The groups of animals treated with the high- (30 mg/kg) but not low-dose (3 mg/kg) diclofenac or meloxicam showed a significant increase in pain tolerance compared to CFA ($p<0.001$). The combined use of um-PEA (10 mg/kg) significantly increased the pain threshold in animals receiving low-dose diclofenac or meloxicam ($p<0.005$ vs CFA), to the same extent as the respective high-dose NSAID. The analysis of synergy performed on AUC confirmed a synergistic effect between um-PEA and low-dose NSAIDs, with the combined treatment being significantly more effective than the sum of the effects exerted by the individual compounds ($p<0.05$).

Conclusions

Overall, the present study demonstrates that combining um-PEA with either meloxicam or diclofenac enhances the analgesic effect of NSAIDs, allowing a ten-time reduction of the effective dose. Moreover, the study clearly shows that combining um-PEA to NSAIDs exerts a synergistic analgesia, supporting a new strategy for NSAID dose reduction in patients with inflammatory pain.

References

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