“Role of the Phosphodiesterase-5 Inhibitor (Tadalafil) In Morphine Induced Analgesia in Rats”

Summary

The current study addressed two important concerns, one pertinent to the impact of PDE-5 inhibitor (tadalafil) on morphine-induced analgesia and the second relevant to its influence on morphine-induced oxidative stress in two different pain models, the the tail-flick test (representing an acute thermal phasic pain model) and the formalin test (representing an inflammatory tonic pain model). This study was performed in adult male albino rats treated with morphine in the absence or presence of tadalafil, a PDE-5 inhibitor, L-NAME, a non selective nitric oxide synthase inhibitor and methylene blue, a guanylyl cyclase inhibitor, to investigate the effect of these interventions on morphine-induced analgesia and oxidative stress. The former was evaluated through measurement of tail-flick latencies (represented as MPE) and hind paw flinches (represented as AUC) in both tail flick test and formalin test, respectively. The latter was detected through assessment of various biochemical parameters in the rat liver homogenates including GSH, total GPX activity and MDA.

The main findings and conclusions can be summarized as follows:

1- The obtained results revealed that per se administered tadalafil exhibit differential antinociceptive effects, depending on the pain model used. In the formalin test, tadalafil showed a significant analgesia in both phases in comparison to the control group. This effect was abolished by the administration of both L-NAME and methylene blue. Whereas, tadalafil did not modified the thermal threshold of male rats in the tail-flick test.
2- The present study was in accordance with several previous studies, that showed the importance of the L-arginine/NO/cGMP/PKG/K<sub>ATP</sub> pathway in mediating antinociception evoked by morphine. Inhibiting of the PDE-5 by tadalafil resulted in a significant potentiation of the antinociceptive effect of morphine only in the formalin test, which was remarked by decreasing the number of flinches. Moreover, this potentiation was attenuated by the administration of both L-NAME and methylene blue. In the tail-flick test tadalafil did not show any effect on the morphine induced analgesia.

3- The data obtained in this study reflected the effectiveness of per se administered tadalafil on oxidative stress. Tadalafil at a dose of 5 mg/kg provokes oxidative stress in both animal models as indicated by lower value of defensive antioxidants, GSH and GPX activity and higher level of hepatic MDA, as compared to those of control. However, this oxidative effect induced by tadalafil was reversed by the co-administration of L-NAME and methylene blue.

4- This study also provides pharmacological evidence for the involvement of L-arginine/NO/cGMP pathway in the toxic oxidative stress induced by morphine. As compared to morphine-treated rats, tadalafil co-administration with morphine at a high dose of 50 mg/kg resulted in a significant potentiation effect, confirmed by the attenuation of GSH and GPX activity and a significant enhancement of the MDA level in both pain models. Whereas, this effect was reversed in the presence of L-NAME and methylene blue.

5- In conclusion, an increase in morphine dose can potentially increase the negative side effects such as: nausea, vomiting, constipation, respiratory depression, tolerance and dependence. Therefore, if a combination of
lower, inactive doses of the opioids and PDE-5 inhibitors can be used to achieve similar analgesic results to that of morphine alone, the dose of morphine will be decreased and hence, its side effects will be lessened. This work present evidence that PDE-5 inhibitor contribute to the analgesic effect of morphine against inflammatory pain, so this combination may provide a new therapeutic strategy for the treatment of persistent inflammatory pain. Further implication of the current observations is the necessity of dosage regimen adjustment of morphine in patients suffering from pulmonary hypertension placed on sildenafil or those suffering from coronary heart disease placed on organic nitrates, when managing severe pain. Although a benefit can be obtained from this combination, but it may have some adverse clinical implications. Clearly, these interesting findings need further testing on humans and under clinical conditions.