TESTING OF ANALGESIC EFFECT OF FLUOXETINE

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Abstract

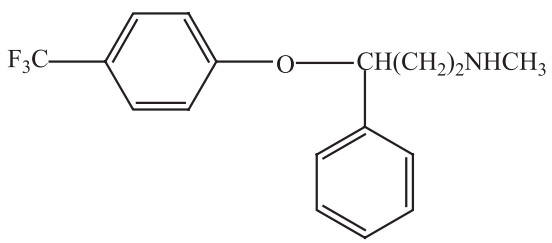
Fluoxetine is used in treatment of depression caused by a variety of different factors and from year to year new indications are being added, especially in conditions followed with strong bouts of pain. Additional flouxetine based therapy that is known to help in improvement of mental state and mood stabilization can significantly increase analgesic effects.
Analgesic effects of fluoxetine as well as of fluoxetine in combination with morphine were analyzed on albino mice of both genders. The sense of pain was induced by thermal stimulus by the method of hot plate. Analgesic effect was measured 30, 60, 90 and 120 minutes after a single i.p. administration of fluoxetine in following dosages: 5, 10 and 20 mg/kg. The control group was treated with 0.1 ml/10 g physiological solution. Test group injected with morphine s.c. (7 mg/kg) was used to observe the effect of fluoxetine in combination with morphine.
Fluoxetine applied in 5mg/kg dosage causes increased pain reaction 60 and 90 minutes ($p=0.049$ and $p=0.002$) (t-test) following application when compared with corresponding values of control group. When fluoxetine is applied in 10 mg/kg dosage duration of pain reaction is significantly increased after 30 ($p=0.01$), 60 ($p=0.001$) and 90 minutes ($p=0.026$), when compared to the control group. When fluoxetine is applied in 20 mg/kg dosage duration of pain reaction is increased 60 and 120 minutes ($p<0.001$) after application when compared to the control group. After application of fluoxetine (5 mg/kg) in combination with morphine, reaction time to pain is significantly extended ($p<0.001$) 60, 90 and 120 minutes after application when compared to the control group injected exclusively with morphine.
Fluoxetine causes analgesic effect in all three applied dosages as well as it significantly increases analgesic effect when applied in 5mg/kg dosage in combination with morphine.
Key words: analgesia, hot plate, fluoxetine.

Introduction

Pain is defined by the International Association for the Study of Pain as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage". Psychological influences have a very important role in definition and description of pain, causing an effect on both pain perception as well as reaction to the pain (1).
Antidepressants are used widely to treat symptoms other than depression, many of which fit into a general category of pain. Adjuvant analgesics are described as any drug that has a primary indication other than pain but can be analgesic in some conditions. The primary role of antidepressants is when pain relief with conventional analgesics is inadequate or when pain relief is combined with intolerable or unmanageable adverse effects. A secondary role of antidepressants in treating chronic pain is their use in addition to conventional analgesics. This can be particularly effective with cancer where there is presence of pain at multiple pain sites, some nociceptive and some neuropathic (2,3,4).

Fluoxetine is an effective and a highly selective inhibitor of serotonin reuptake at the presynaptic neuronal membrane. Fluoxetine-induced inhibition of serotonin reuptake causes increased synaptic concentrations of serotonin in the CNS, resulting in numerous functional changes associated with enhanced serotonergic neurotransmission. When serotonin is released from nerve endings its activity at the receptor is ended by an action of a specific pump mechanism by which serotonin is taken into the membrane. Fluoxetine blocks this action of reuptake of serotonin into the membrane by above mentioned pump mechanism (5,6,7).

Structural formula of fluoxetine



Serotonin plays a very important role in regulation of pain perception i.e. the mechanism of analgesia because it is a very important transmittor in pain-supressing systems. Decreasing the serotonin concentration increases nociceptive stimuli sensitivity (8,9).

Materials and methods

Analgesic effects of fluoxetine as well as of fluoxetine in combination with morphine were analyzed on albino mice of both genders, weighing 25-37 g. The mice were randomized in six groups with six mice in the each group. The sense of pain was induced by thermal stimulus by the method of hot plate. The temperature of the plate was constantly 55°C during the experiment. Analgesic effect was measured 30, 60, 90 and 120 minutes after a single i.p. administration of fluoxetine in following dosages: 5, 10 and 20 mg/kg. The control group was treated with 0.1 ml/10 g physiological solution. Test group injected with morphine s.c. (7 mg/kg) was used to observe the analgesic effect of fluoxetine in combination with morphine.
The study has been conducted with the consent of Ethical Committee and in accordance to provisions of the Declaration of Helsinki.

Results and discussion

Fluoxetine applied in 5mg/kg dosage causes increased pain reaction 60 and 90 minutes ($p=0.049$ and $p=0.002$) (t-test) following application when compared with corresponding values of control group. When fluoxetine is applied in 10 mg/kg dosage duration of pain reaction is significantly increased after 30 ($p=0.01$), 60 ($p=0.001$) and 90 minutes ($p=0.026$), when compared to the control group. When fluoxetine is applied in 20 mg/kg dosage duration of pain reaction is increased 60 and 120 minutes ($p<0.001$) after application when compared to the control group. After application of fluoxetine (5 mg/kg) in combination with morphine, reaction time to pain is significantly extended ($p<0.001$) 60, 90 and 120 minutes after application when compared to the control group injected exclusively with morphine.
It can be observed from obtained results that analgesic effect is shown in all three applied dosages of fluoxetine. The strongest analgesic effect is expressed 90 minutes after the application of 5 mg/kg dosage. The analgesic effect with the longest time duration is obtained with 10 mg/kg (90 minutes) dosage, this dosage is also the fastest acting (30 minutes). Fluoxetine significantly increases analgesic effect when applied in combination with morphine.
Fluoxetine exhibits analgesic activity in some analgesic test systems when administered alone in animals, but the lack of such effects observed in other test systems suggests that demonstration of analgesic activity may be test-dependent. Fluoxetine has potentiated opiate agonist-induced analgesia in most but not all studies, possibly as a result of the drug's ability to enhance serotonergic neurotransmission (10).

Figure 1. Dosage dependent analgesic effect of fluoxetine.

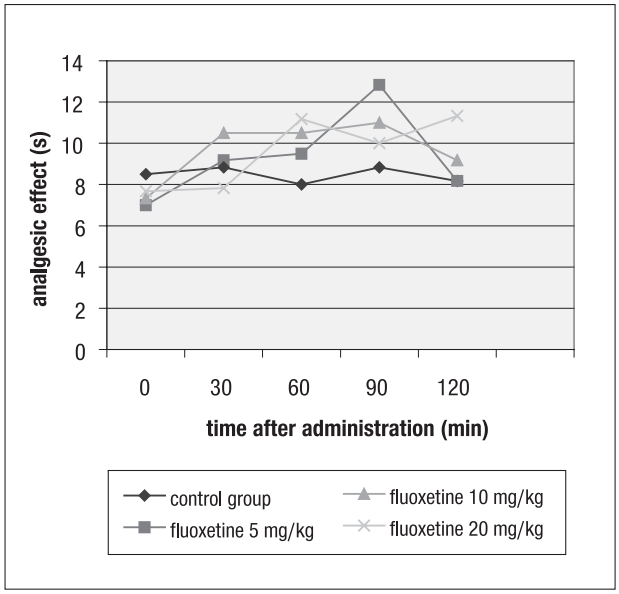
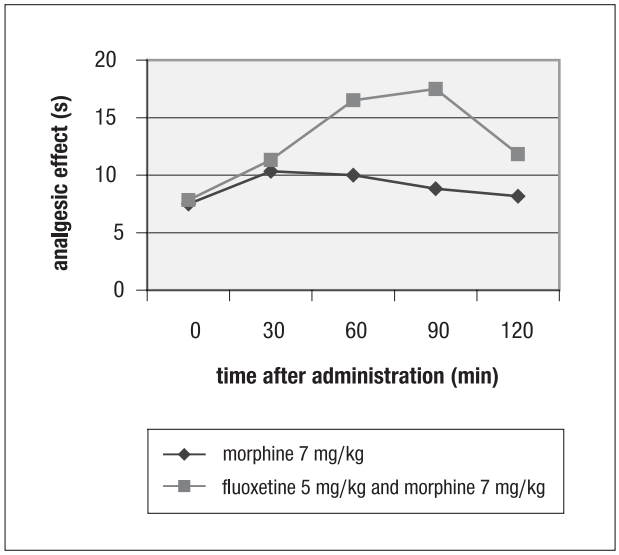


Figure 2. Comparison of increased analgesic effect of fluoxetine from application of fluoxetine in combination with morphine and application of morphine alone.



Conclusions

Fluoxetine shows analgesic effect in all three applied dosages and the best analgesic effect is obtained with 10 mg/kg dosage. Fluoxetine in 5 mg/kg dosage significantly increases analgesic effect when applied in combination with morphine.

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