

Effects of lisinopril, captopril and losartan alone or in combination with morphine in light tail flick analgesic test

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Abstract

There are controversial reports about the effect of captopril on pain modulation. Also while captopril may potentiate morphine analgesia, enalapril has not such an effect and interaction of morphine with angiotensin II receptor antagonists and other angiotensin converting enzyme inhibitors has not been studied yet. Therefore, this study was designed to assess the effect of captopril, lisinopril and losartan on pain sensation and the possible modifying effect of these drugs on morphine antinociception. Male Swiss mice (25-35 g) in groups of 6 animals per each received vehicle (10 ml/kg), captopril (20 mg/kg), lisinopril (10 mg/kg) and losartan (10 mg/kg) alone or in combination with morphine (5 mg/kg, i.p.) and analgesic response was assessed using light tail flick test. Reaction latencies to a light beam were recorded at 15 minute intervals until 2 hours. The maximum possible analgesic effect was calculated and compared. Lisinopril and captopril when administered alone could not change the pain response but losartan per se induced a hyperalgesic state. Pretreatment with captopril potentiated morphine analgesic response and losartan and lisinopril did not modify morphine analgesia. It is concluded that although angiotensin converting enzyme inhibitors have the same mechanism of action on renin-angiotensin system but they do not have the same interaction with morphine. Also since losartan, an antagonist of angiotensin receptor type 1 did not alter morphine response, it seems that these receptors are not involved in captopril potentiation of morphine analgesia.

Keywords: Lisinopril; Captopril; Losrtan; Morphine; Analgesia

INTRODUCTION

Angiotensin converting enzyme inhibitors (ACEIs) such as captopril, enalapril and lisinopril and angiotensin receptor antagonists (ARAs) including losartan and valsartan are widely used in various cardiovascular disorders (1-4). Since angiotensin converting enzyme (dipeptidyl carboxypeptidase) is also involved in degradation of kinins such as bradykinin and substance P which are potent mediators of pain and inflammation, some investigators have studied the effects of renin-angiotensin system on pain

perception (5-9). Rohit et al. by using thermal and chemical-induced pain models showed that captopril exerted a hyperalgesic state in mice (10). Also Correa and Calixto (1993) reported that pretreatment of mice with captopril significantly increased the first and the second phases of formalin-induced pain (11). On the contrary Takai et al. (1996) reported that captopril had analgesic activity (12). Furthermore although captopril and enalapril have the same mechanism of action and exert same changes on Ang II and bradykinin level, it has been shown that captopril potentiates

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morphine analgesia (13,14) while enalapril has not such an effect (15). According to above reports, controversy is observed regarding ACEIs and pain modulation and therefore the present study was aimed to examine the effect of two well known ACEI drugs and also losartan as the prototype of angiotensin receptor antagonists on pain threshold and their interaction with analgesic activity of morphine.

MATERIALS AND METHODS

Animals

Male Swiss mice (25-35 g) obtained from the animal house of our school were used. They were housed in polypropylene cages under standard environmental conditions and had free access to pellet diet and tap water. For experimentation six animals were included in each group.

Drugs

Captopril, lisinopril and losartan (Abidi Pharmaceutical Co., Iran) and morphine hydrochloride (Daru Pakhsh, Iran) were used in this study. All drugs were dissolved in 0.9% sodium chloride solution and the concentrations were adjusted so that a volume of 10 ml/kg of drugs was used.

Light tail flick test

The analgesic response to morphine was determined by the light tail-flick method (16,17) using a tail flick apparatus (Pooya-armaghan, Iran). Briefly, each animal was placed in a restrainer, 2 min before treatment, and baseline reaction time was measured by focusing a beam of light on the distal one-third portion of the animal's tail. Captopril (20 mg/kg), lisinopril (10 mg/kg) and losartan (10 mg/kg) were administered i.p. 15 min prior to morphine injection (5 mg/kg, s.c.). The post drug reaction time was measured at 15 min intervals until 2 hours. A 12 sec cut-off

time was used in order to prevent tissue damage. The MPE% (percent of maximum possible analgesic effect) was calculated for each time interval according to the following formula. $MPE\% = [(test\ latency - control\ latency) / [(cut-off\ time - control\ latency)] \times 100$

Statistical analysis

The results are presented as mean \pm SD and statistically analyzed by one-way ANOVA followed by the Duncan test.

RESULTS

Three doses of morphine (3, 5 and 8 mg/kg) were administered. As it is seen in Fig. 1 morphine at a dose of 3 mg/kg could not produce a significant analgesia at any time interval. While at a dose of 8 mg/kg, the reaction latencies at 30 and 45 min reached the cut-off time (12 sec) and 100% MPE was obtained. At a dose of 5 mg/kg of morphine, almost half maximum effect was achieved and this dose was recognized suitable for observing possible potentiation or attenuation of morphine response by test drugs.

As it is seen in Fig. 2 lisinopril by itself could not change the baseline of pain perception at all intervals and the analgesic response in lisinopril-treated group was not significantly different from vehicle-treated group. Morphine (5 mg/kg) showed analgesic activity with a peak effect at 30 min interval. The analgesic response was completely lost two hours after its administration. Pretreatment with lisinopril could not exert any significant change on morphine antinociception.

Effect of captopril on pain and morphine analgesia is shown in Fig. 3. Like lisinopril, captopril by itself did not alter pain sensation. However, it potentiated morphine response, so that at 30, 45 and 60 min time intervals the analgesic effect in animals pretreated with captopril was significantly ($P < 0.05$) higher than that of

animals received morphine alone.

Fig. 4 shows the results of losartan. Injection of this drug produced a hyperalgesic state, so that nearly in all time intervals the reaction latencies to light beam decreased in comparison with zero

time (before drug administration) and this resulted in MPE% less than zero. Also when losartan was injected prior to morphine, it could not significantly modify morphine response at any time interval.

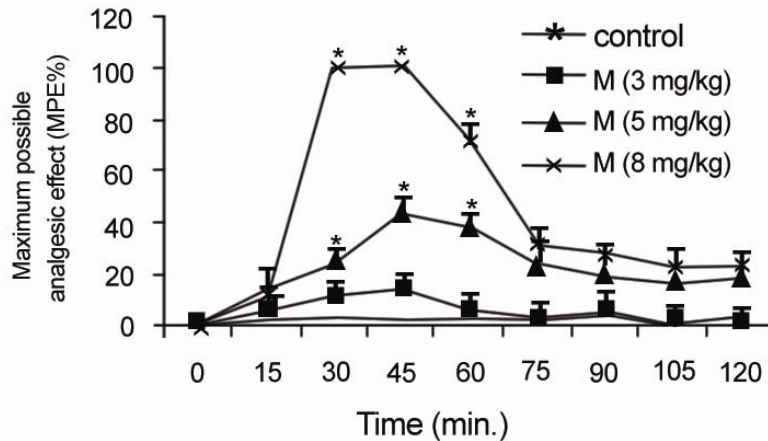


Fig. 1. Analgesic effect of morphine in mice. Control animals received saline (10 ml/kg). The other groups received three different doses of morphine (3, 5 and 8 mg/kg). Light tail flick test was used for assessment of analgesia and values are mean \pm SD of MPE% of six animals in each group. * $P < 0.05$ is considered significant in comparison to control group.

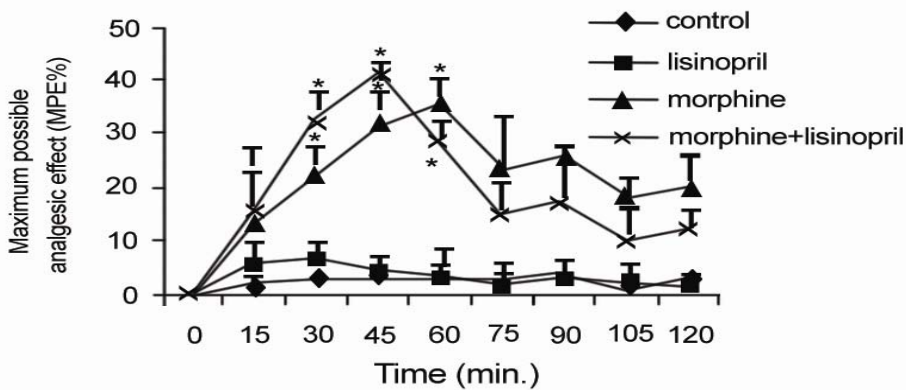


Fig. 2. Effect of lisinopril pretreatment on morphine-induced analgesic response in mice. Control animals received saline (10 ml/kg). lisinopril (10 mg/kg) and morphine (5 mg/kg) alone or in combination were administered to other groups. Light tail flick test was used for assessment of analgesia and values are mean \pm SD of MPE% of six animals in each group. * $P < 0.05$ is considered significant in comparison to control group.

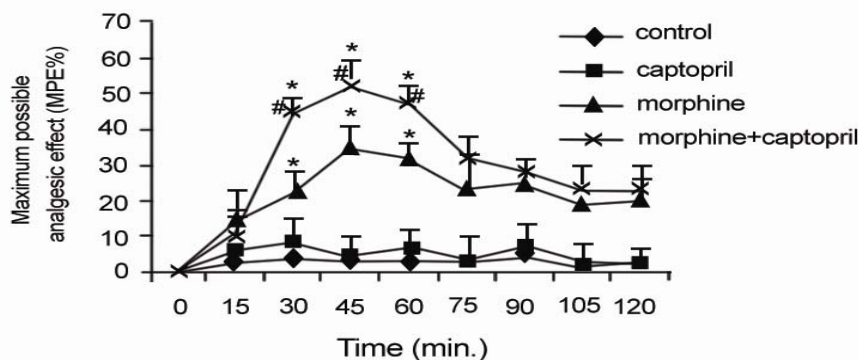


Fig. 3. Effect of captopril pretreatment on morphine-induced analgesic response in mice. Control animals received saline (10 ml/kg). Captopril (20 mg/kg) and morphine (5 mg/kg) alone or in combination were administered to other groups. Light tail flick test was used for assessment of analgesia and values are mean \pm SD of MPE% of six animals in each group. # $P < 0.05$ is considered significant in comparison to group received morphine alone. * $P < 0.05$ is considered significant in comparison to control group.

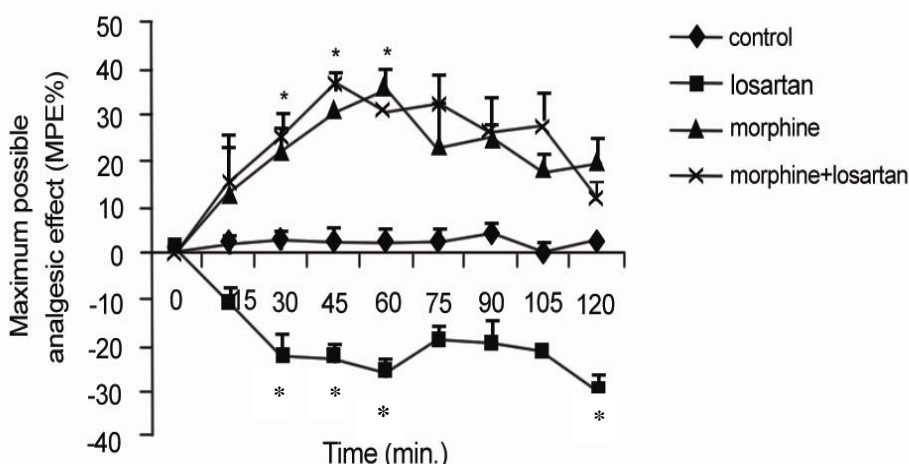


Fig. 4. Effect of losartan pretreatment on morphine-induced analgesic response in mice. Control animals received saline (10 ml/kg). Losartan (10 mg/kg) and morphine (5 mg/kg) alone or in combination were administered to other groups. Light tail flick test was used for assessment of analgesia and values are mean \pm SD of MPE% of six animals in each group. * $P < 0.05$ in comparison to control group.

DISCUSSION

The present study for the first time provides direct evidence that losartan can not enhance the analgesic action of morphine. Our results indicating a hyperalgesic state with losartan alone is in agreement with the results of Rohit et al. (10). Losartan is a well known antagonist of AT1 receptors. It has been shown that i.c.v. administration of angiotensin II elicits antinociception and perhaps the

enhancement of pain response observed in this study is due to blockade of Ang II receptors in CNS.

Captopril and lisinopril by inhibition of ACE reduce Ang II level. They also increase bradykinin and substance P levels which are potent mediators of pain. These drugs unexpectedly per se had no effect on pain perception and at present the reason is not clear for us and further studies are needed to clarify it. Captopril potentiated morphine analgesia and our results confirm previous results (13,14). Unlike captopril,

lisinopril had no effect on morphine analgesia. It has been reported that enalapril, another ACEI did not also modify morphine analgesic response (15). Chemical structure of ACEIs show that captopril structurally differs from other agents in possessing a sulfidryl moiety and it may be the reason why nonsulfidryl ACEI drugs such as enalapril in a previous study (15) and lisiniopril in our study could not affect morphine response. Also since losartan, an antagonist of AT1 could not alter morphine analgesic response; it seems that these receptors are not involved in captopril potentiation of morphine analgesia and further studies are needed to clarify the exact mechanism of captopril-morphine interaction.

In conclusion it seems that all ACEI drugs have not the same interaction with morphine and for patients receiving captopril, if morphine is needed for control of pain, a smaller dose may be needed. Also according to our data indicating a hyperalgesic state with losartan, it seems that it is not a suitable drug for those suffering from both hypertension or congestive heart failure and painful disease such as rheumatoid arthritis.

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