THE EFFECTS OF PIPERINE ON THE JUMPING INDUCED BY NALOXONE IN MORPHINE DEPENDENT MICE

ALI AKBAR MOGHADAMNIA AND ELHAM AFRAZE

Department of Pharmacology, Babol University of Medical Sciences, Babol, Iran

ABSTRACT

Black pepper has been used in traditional medicine as an analgesic. In this investigation, the effects of piperine, an alkaloid derived from black pepper seeds on the jumping induced by naloxone were studied on morphine dependent mice. This experimental study was conducted on case (piperine) and control (saline) groups of mice. Mice were made dependent to morphine using Marshall method. For evaluation of dependency, the number of jumps after naloxone injection was counted in a period of 30 minutes. There was a significant difference between number of jumps of mice in saline (10 ml/kg, IP) and drug groups (piperine 25, 50, 75 mg/kg, IP), as well as significant differences in latency period for jumping behavior in two groups. Based on these results, piperine may affect the intensity of morphine dependency.

Key words: Black pepper, Piperine, Morphine dependency, Analgesia

INTRODUCTION

Medicinal plants have been used in many countries especially China, India, Iran and Egypt (1). Black pepper is one of the famous plants, used as a pungent food additive, gastrointestinal stimulant and a palliative agent for headache (2). In Islamic herbal medicine, black pepper has been used as sedative, cough palliative, carminative, appetite stimulant, antiseptic for GI and urinary tract and for management of toothache (1-3). Piperine, an alkaloid derived from black pepper (4-6), has important effects on adrenergic and serotonergic nervous system (6). Some investigations have indicated that the analgesic effect of piperine is similar to that of capsacine, which affects the function of substance P and potassium channels in nociceptive nerve endings and opioid system (7-10). On the basis of these studies, it has been suggested that piperine may affect opioid receptors and it has an impact on morphine dependency. This study was carried out to examine the effect of piperine on morphine dependency in mice.

MATERIALS AND METHODS

Animals:

Male albino mice weighing 20-30gr were used in all experiments. The mice were used 6 per box at room temperature 21±2 °c and they were allowed ad libitum access to food and water. There was a condition of 12hr light and 12hr dark for all subjects. All experiments were initiated at 9:00 am. Mice were randomly allocated in control and sample groups. In each group there were 6 mice.

Materials:

Black pepper (seeds of *pipper nigrum* from Rezaeian herbarium, Tehran), ethanol (Merck), potassium chloride (Merck) and Morphine sulfate (Tolidaru, Iran) were used in this study.

Piperine was extracted from pepper seeds with ethanol and was precipitated by addition of potassium chloride The identity of the product was confirmed by melting point and UV spectrophotometery (11).

Morphine dependency test:

Animals of the control group received saline (10 mg/kg) and animals of the test groups received peperine (25, 50 and 75 mg/kg) intrapritoneally.

All mice in two groups were made dependent to morphine by Marshall method in three sequential days. Morphine dependency was induced by a cumulative subcutaneous dose administration in a three-dose schedule (50, 75 and 100 mg/kg, sc, dose interval; four hour) for three days. Withdrawal syndrome was induced in each mouse after naloxone (1mg/kg) injection at the forth day two hours after 50 mg/kg of morphine as a final dose. Counting the number of jumps was considered for evaluation of intensity of dependency (12).

Correspondence: A.A. Moghadamnia, Department of Pharmacology, Babol University of Medical Sciences, Babol, Iran
Tel & Fax: +98 11 2227667, E-mail: moghadamnia@yahoo.com

Statistics:
Data were analyzed by using t-test and Newmann-Keuls post ANOVA test and difference between data in each point was considered significant at $p<0.05$.

RESULTS

Data are shown in two sections. The first; data associated with the effects of piperine on jumping induced by naloxone and the second; data associated with the effect of piperine on jumping latency period before its onset. There was a clear decrease in the number of jumping in piperine pre-treatment group in comparison with saline group. It is obvious that such a decrease is dose dependent and at a dose of 50mg/kg reduction in jumping is less than other doses ($p<0.001$, figure 1). During all stages of experiments, there were differences in jumping latency period after naloxone injection. There was a significant difference in jumping latency period between piperine and saline groups (figure 2).

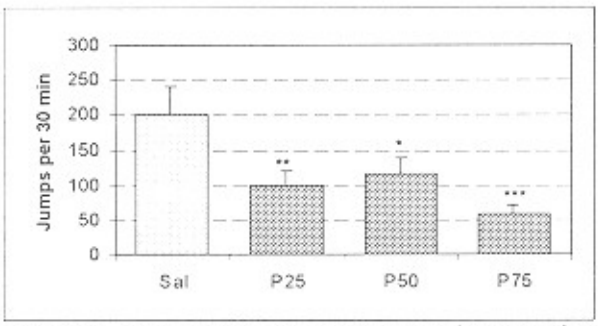

Figure 1. The mean ± SEM of count of jumps after naloxone in control (saline, Sal) and treated groups (peperine 25mg/kg, P25), (peperine 50mg/kg, P50), and (peperine 75mg/kg, P75) in morphine dependent mice. Each bar represents mean ± SEM of six mice. *P<0.01, **P<0.001, ***P<0.0001.

DISCUSSION

Effect of piperine (N-1-peperoyl piperidine) as a main alkaloid of black pepper on morphine dependent mice has been studied. Piperine did dependently reduce the jumping in morphine dependent mice. The effects of piperine on analgesia have been investigated previously (13) but there are not sufficient data about its effects on morphine dependency.

It seems that analgesic effects of piperine and its effect on morphine dependency could be mediated by similar mechanisms. The effect of piperine on analgesia is similar to capsaicine an active substances of red pepper (13). It seems that these effects are due to

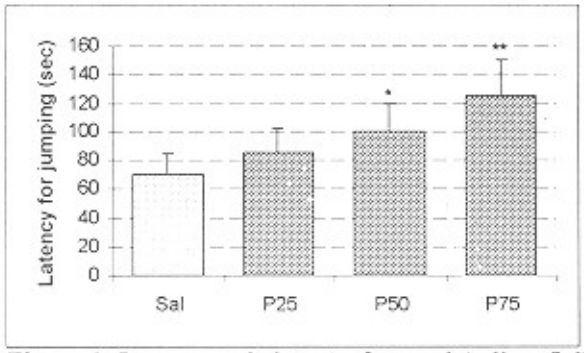

Figure 2. Latency period (sec) of control (saline, Sal) and treated groups (peperine 25mg/kg, P25), (peperine 50mg/kg, P50), and (peperine 75mg/kg, P75) in naloxone induced jumping in the morphine dependent mice. Each bar represents mean± SEM of six mice. *P<0.05, **P<0.01

desensitization of c-fibers of nociceptors and systemic use of piperine like capsaicine (13,14) has antinociceptive effects on some animal models in controlling the intensity and quality of pain. There are similarities in effects of these agents and morphine, and these effects are blocked by naloxone (15). It is suggested that piperine can reduce the effect of substance P (13) in nociceptive pathways. Some investigations support the idea that piperine is able to prolong latency period of tail-flick test (13), and some investigators have shown that administered piperine and capsaicine topically can reduce the intensity of superficial pain. It has been suggested that these effects might be mediated through counter irritation by substance P mediator (16). These responses could be inhibited by naloxone (16, 7). While according to the previous data effects of piperine are mediated by opioid system (15). By results of this investigation it is difficult to explain different effects of various doses and it requires more studies. In addition, piperine could increase the latency time for jumping after naloxone. According to the previous data, this may result from a special mechanism with which opioid receptors system interference (15, 17, 18). It seems that piperine not only can intensify and potentiate the effect of morphine but also it inhibits the effect of naloxone dose dependently on the jumping. The results of this study suggest that piperine can affect morphine withdrawal syndrome.

ACKNOWLEDGMENT

The authors gratefully acknowledge Mrs. M. Hashemi for her helpful laboratory assistance and Mr. G. Asadollah Zadeh for his assistance.

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