African Journal of Pharmacy and Pharmacology Vol. 6(1), pp. 24-29, 8 January, 2012
Available online at http://www.academicjournals.org/AJPP
DOI: 10.5897/AJPP11.340
ISSN 1996-0816 ©2012 Academic Journals

Full Length Research Paper

Antinociceptive effect of *Matricaria chamomilla* on vincristine-induced peripheral neuropathy in mice

Mir Hadi Khayate Nouri[1] and Ali Namvaran Abbas Abad[2]*

[1]Department of Pharmacology and Toxicology, Faculty of Veterinary Medicine, Tabriz branch, Islamic Azad University, Tabriz, Iran.
[2]Young Researchers Club, Tabriz Branch, Islamic Azad University, Tabriz, Iran.

Accepted 30 December, 2011

Vincristine-induced peripheral neuropathy is a major dose limiting side effect and thus, effective therapeutic strategy is required. In this study, the antinociceptive effect of *Matricaria chamomilla* (MC) hydroalcoholic extract and morphine on vincristine-induced peripheral neuropathy model in mice has been investigated. Experiments were performed on 60 Naval Medical Research Institute (NMRI) male mice. Mouse subsequently received daily intraperitoneal and intravenal injections of vincristine sulfate, saline and MC hydroalcoholic extract over 12 days, immediately following behavioral testing. For assessment of pain, formalin test was preformed. The effects of MC, morphine and vehicle (saline) 30 min before formalin test on vincristine-induced neuropathy were evaluated. Administration of MC before formalin injection showed significant ($P < 0.05$) decrease of pain responses in both phases. Administration of vincristine produced significant ($Pm < 0.05$) increase in pain response in second phase of formalin test. Injection of MC and vincristine together has shown that MC is able to decrease the vincristine induced pain significantly ($P < 0.05$). Morphine decreased vincristine induced pain test significantly ($P < 0.05$). In comparison, morphine has analgesic effects in the first phase and MC has anti-inflammatory effects in the second phase of formalin test significantly ($P < 0.05$). These results suggest that MC may be an alternative approach for the treatment of vincristine-induced peripheral neuropathic pain.

Key words: *Matricaria chamomilla*, vincristine, antinociception, neuropathic pain.

INTRODUCTION

Painful peripheral neuropathy is one of the main side effects induced by diverse classes of chemotherapeutic agents, including vincristine (Namvaran et al., 2011b; Postma et al., 1993; Quasthoff and Hartung, 2002). Vincristine is one of the most common chemotherapeutic drugs used to treat a wide variety of malignancies, including leukemia and lymphoma, and prevents tumor cell replication through alteration of cytoskeletal structure and disorientation of microtubules (Himes et al., 1976; Owellen et al., 1976). However, vincristine may also induce painful peripheral neuropathy. The chief clinical manifestation of vincristine induced peripheral neuropathy is disturbance in both sensory and motor function (Casey et al., 1973; Weiden and Wright, 1972). Sensory disturbances range from mild tingling to spontaneous painful burning paresthesia and hypersensitivity to painful stimuli (Forman, 1990). Vincristine-induced painful peripheral neuropathy is the major dose-limiting side effect and requires discontinuation of treatment, greatly impacting on the survival of cancer patients (Sandler et al., 1969). Moreover, the resulting symptoms, which frequently include moderate to severe pain, can often be disabling and cause significant loss of functional abilities and decreased quality of life (Wolf et al., 2008).

Although it has been hypothesized that vincristine induced neuropathic pain is due to neuronal toxicity and/or neurological disorder (Ogawa et al., 2000; Topp et

*Corresponding author. E-mail: ali.namvaran@gmail.com. Tel: +98 914 413 73 58. Fax: +98 411 542 43 68.

al., 2000), the exact mechanism responsible is still unknown. Recently, Weng et al. (2003) suggested a state of central sensitization develops in spinal wide dynamic range neurons with repeated vincristine treatment that contributes to the neuropathic pain (2003).

Unfortunately, neither prophylactic strategies nor symptomatic treatments of this chemotherapy-induced peripheral neuropathy (CIPN) have proven useful yet. Aspirin, ibuprofen and celebrex are commonly prescribed to patients to treat CIPN but show limited efficacy (Lynch et al., 2004). Furthermore, gabapentin, lamotrigine, nortriptyline and amitriptyline studies were disappointing in treating CIPN (Kaley and Deangelis, 2009), and there have been no trials of opioids in patients with CIPN.

Data concerning the effectiveness of opioids on neuropathic pain have been controversial (Arner and Meyerson, 1988). However, animal models (Dellemijn, 1999) and controlled patient trials (Obara et al., 2007) suggest that μ-opioid receptor agonists are effective at attenuating neuropathic pain. Recently, opioid analgesics were recommended as second-line treatment that can be considered for first-line use in certain clinical circumstances (Eisenberg et al., 2005).

Nowadays herbal treatment including usage of supplement and total extract is common around the world. Increasing number of patients uses medicinal herbs or seeks the advice of their physician regarding their use. More than one third of Americans use herbs for health purposes, yet patients (and physicians) often lack accurate information about the safety and efficacy of herbal remedies (Khayat Nouri, 2011; O'Hara et al., 1998). Previous study have shown that Matricaria Chamomilla could be useful in Cisplatin-induced neurotoxicity (Namvaran et al., 2011a)

Matricaria Chamomilla (MC) is the herb that is used for sedation, pain management, antispasmodic, anti-convulsant, anti inflammatory, antipyretic, wound healing, and antioxidant agent in traditional medicine (Berry, 1995; Kyokong et al., 2002; Mills, 1991; Namvaran and Khayate, 2011; Namvaran et al., 2011c; Norman, 2001; Trease and Evans, 1982; Wong et al., 1998). MC powder is aromatic, yellowish green in color and bitter taste. Its essence called chamazulene is the reason of smelling. Apigenin and Trihydroxyflavone are glycosides that cause bitter taste. They also contain two important flavonoids called Cyranosid and Pituitrin (Berry, 1995; Norman, 2001; Trease and Evans, 1982). It seems that flavonoids are important in antispasmodic effects and main parts of essence such as bisabolol, chamazulene and α– Bisabolol have anti-inflammatory effects (Viola et al., 1995).

Therefore, because of synthetic and chemical drug's unwanted side effects, nowadays finding new analgesic agents especially herbal drugs is popular (Coderre et al., 1990; Ivey, 1986; Murray and Brater, 1993).

In this study, the antinociceptive effect of Matricaria Chamomilla and morphine on the vincristine induced peripheral neuropathy model in mice was investigated.

MATERIALS AND METHODS

Animals

Experiments were performed on 25 to 30 g adult male Naval Medical Research Institute (NMRI) male mice in their 8 to 9 week, purchased from Razi Institute. Animals were acclimated to the laboratory environment for 5 to 7 days before being used in the study. Animals were housed 6 per cage in a temperature and humidity controlled environment under a 12-hour light/dark cycle (lights on at 7 am). Food and water were available *ad libitum*. The National Institutes of Health guidelines for care and use of animals and Guidelines on Ethical Standards for Investigation of Experimental Pain in Animals were followed (Zimmermann, 1983). All efforts were made to minimize the number of animals which were used and their suffering degree.

The vincristine-induced peripheral neuropathy model induced by intravenal (IV) injection was used in this experiment. Animals subsequently received daily IV injections of either vincristine sulfate (100 μg/kg/day), saline (0.1 ml/kg/day) MC hydroalcoholic extract (25 mg/kg/IP), immediately following behavioral testing. The treatment paradigm consisted of five daily injections, followed by a 2-day interval where no injections were administered, followed by five subsequent daily injections, as described previously (Weng et al., 2003).

Animals were divided into 6 groups randomly, the first group received saline normal (saline group), the second group received MC hydroalcoholic extract (25 mg/kg/IP) (MC group) (Gomaa et al., 2003), the third group received vincristine (100 μg/kg/IV/day) (Vin group) (Bujalska and Gumulka, 2008), the forth group received MC hydroalcoholic extract and vincristine, fifth group received morphine (10 mg/kg/IP 30 min before formalin test) and sixth group received vincristine and morphine, and then formalin test was preformed.

Formalin test

Behavioral experiments were done in a quiet, temperature controlled (20 to 22°C) at room between 10 am and 4 pm. Formalin test was preformed based on Dubission and Dennis method. They were placed in observation container for 15 min to get used to the new environment, then 20 μl of attenuated formalin (5%) was injected in hind paw skin with insulin syringe in restrainer. After injection, animals were returned to observation container immediately and were viewed, the time of injected hind paw biting and licking time were measured in 5 min interval for an hour (Namvaran et al., 2011b; Shibata et al., 1989).

Chemicals

Formalin was purchased from Merck Company. Vincristine was purchased from Tocris Cookson Ltd., Bristol, Avon, UK.

Administration of test agent

Vincristine (100 μg/kg) was administered intravenously via tail vein. Formalin used in the study was administered into the hind paw via the intradermal route. The volume was adjusted to 1 ml/kg for intravenous and 5 ml/paw for intradermal administration. Dose selection of each agent was based on the results of previous studies (Aley and Levine, 2002; Joseph and Levine, 2004, 2006; Park et al., 2010).

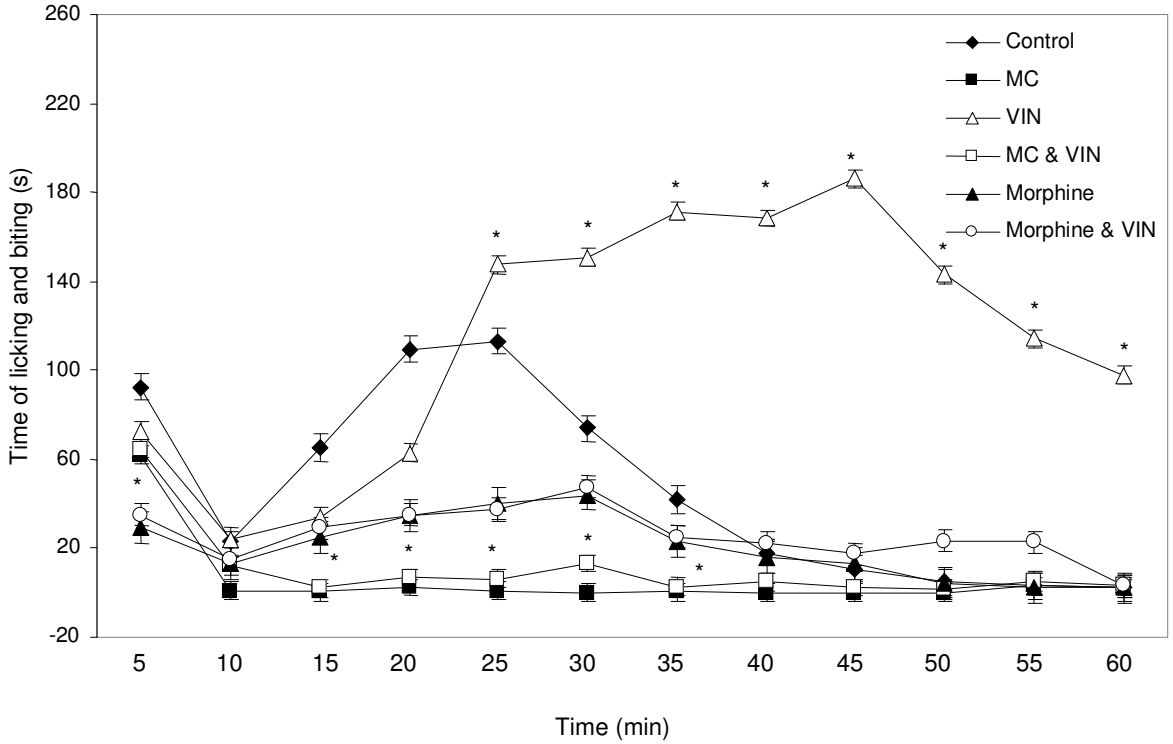

Figure 1. Time course of paw licking and biting response to formalin injection. Comparison between MC, morphine, vincristine and MC- vincristine, morphine-vincristine administration in formalin hind paw injection first and second phase of pain responses. Each line represents mean ± SEM of 10 mice. *P < 0.05, versus control group.

Extracting method

A dry MC flower (*Matricaria chamomilla*) from Esfahan pharmaceutical company was purchased and drenches method was used for extraction. For this purpose, flowers were mildly powdered. 20 g of MC powder and 200 ml of 70% ethylic alcohol were mixed and after 48 h (container were motivated for 5 min with 12 h withdrawal time). The mixture was leached and solvent extracted in rotary was adjusted in 70°C in medium round speed. The caliginous fluid was spread on a window and in 50°C oven, and after drying, the powder was gathered and was used in this experiment (Norman and Max, 2001).

Data analysis

Group data are presented as mean ± standard error of the mean (SEM) and are analyzed statistically using student test. Time course data for vincristine was analyzed using one-way ANOVA followed by Tukey's post hoc test. The level for statistical significance was set at a P value of < 0.05.

RESULTS

Formalin injection to hind paw after intraperitoneal injection of normal saline induced significant (P < 0.05) pain response in the first, second, third, fourth, fifth, sixth, seventh and eighth 5 min in comparison with other 5 min (Figure 1), as results show formalin induces biphasic pain response (the first phase: 0 to 5 min and the second phase 15 to 40 min after injection).

Intraperitoneal injection of MC, 30 min before hind paw injection of formalin showed significant (P < 0.05) decrease of pain responses (time of licking and biting of injected paw), in the first phase (first 5 min) and the second phase (third, fourth, fifth, sixth and seventh5 min) (Figure 1).

Intraperitoneal injection of morphine, 30 min before hind paw injection of formalin showed significant (P < 0.05) decrease of pain responses (time of licking and biting of injected paw), in the first phase (first 5 min) and the second phase (third, fourth, fifth, sixth and seventh 5 min) (Figure 1).

Intravenous administration of vincristine caused significant (P < 0.05) increase in second phase of formalin test (Figure 1).

Injection of MC and vincristine together (MC and Cis group), before formalin test have shown that there is significant change in the second phase of vincristine induced pain significantly (P < 0.05). This decrease was similar to MC group and they do not have significant change, this means that MC could decrease vincristine induced pain response as we have in MC group (Figure 1) Injection of morphine and vincristine together as described in the method, before formalin test have shown.

that there is significant decrease in first and second phase ($P < 0.05$). In comparison, morphine has analgesic effects (first and second phase) and MC has antiinflammatory effects in second phase of formalin test, that is, MC has anti-inflammatory effects more than morphine significantly ($P < 0.05$) (Figure 1).

DISCUSSION

Treatment with many cancer chemotherapies is limited by their dose-related peripheral nervous system toxicity, a small-fiber painful peripheral neuropathy. The most frequently reported agents include many older commonly used chemotherapeutic agents, such as platinum drugs, taxanes, epothilones and vinca alkaloids, but also newer agents, such as bortezomib and lenolidamide (Abrey and Correa, 2005; Kaley and Deangelis, 2009; Stillman and Cata, 2006; Sul and Deangelis, 2006; Wolf et al., 2008). The choice of chemotherapeutic agent, dosing schedule, type of cancer and presence of concomitant medical problems all affect the incidence and severity of chemotherapy-induced neuropathy (Cata et al., 2006; Polomano and Bennett, 2001). Better understanding of the underlying mechanisms is critical to allow identification of therapeutic targets, especially if these drugs produce their neurotoxic effects by mechanisms different from those by which they kill tumor cells (Park et al., 2010). Thus, although it is generally held that the therapeutic effects of vincristine is preventing tumor cell replication through alteration of cytoskeletal structure and disorientation of microtubules (Himes et al., 1976; Owellen et al., 1976), the mechanism by which they produce painful peripheral neuropathy, a major dose-limiting side effect for this class of therapeutic agents, is not well understood (Park et al., 2010).

Results of the present study have shown that vincristine increases the second phase of formalin pain test responses. Formalin test has two phases; early phase and delayed phase. It seems that early phase is induced by C-fiber activation and peripheral stimulates. But inflammatory reactions in peripheral tissues and action change in dorsal root of spine are the main reasons of delayed phase. The main reason of pain in second phase is because of inflammatory reactions (Sahley and Berntson, 1979; Shibata et al., 1989).

In this study, we examined if two compounds would have an antinociceptive effect on neuropathic pain induced by vincristine. These analgesic compounds were selected because morphine is the reference opioid compound, and is the most effective drug in pain especially in formalin test for both phases, while MC extract has antiinflammation effects.

Recently, animal models and controlled patient trials suggest that μ-opioid receptor agonists are effective at attenuating neuropathic pain (Dellemijn, 1999; Obara et al., 2007). In this study, systemic morphine significantly decreased pain responses in both phases of formalin in vincristine induced neuropathic test of 10 mg/kg, that is, similar results have been published with other models of neuropathic pain (Bulka et al., 2002; Erichsen et al., 2005; Park et al., 2010). In contrast, another study found opioid agonists, such as morphine (5 mg/kg, i.p.) administered alone on 5 consecutive days, did not modify hyperalgesia (Bujalska et al., 2009). This discrepancy could be due to differences in study protocol and animal model.

The results of this study have shown that MC extract can induce analgesia in mice. Also, it shows that MC has analgesic effects in both phases of formalin test that indicate that MC could have central nervous system (CNS) and local effects (Aceto et al., 1980; Murray and Brater, 1993; Phan et al., 1973; Sahley and Berntson, 1979). Studies on laboratory animals have shown that MC extract has antiinflammatory, antispasmodic and antidisquiet effects that are predicted in traditional medicine (Besson and Chaouch, 1987; Viola et al., 1995). In other studies, scientists have shown that MC extract has sedative and antianxiety effects (Nmecz, 2000).

MC contains apigenin, that is, a kind of flavonoid, and it has efficacy to attach to benzodizepin receptors (Viola et al., 1995). It can interact with histaminergic system (Miller et al., 1996). Apigenin can control dose dependant dermal inflammation (Gerritsen et al., 1995), and prevent drug, stress and alcohol dependent gastric ulcer (Szelenyi et al., 1979). *In vitro* studies have shown that MC oil extract has antioxidant activities (Rekka and Kourounakis, 1996). Main mechanism of extracts and essences in controlling the lipids oxidative stress and peroxidation is not well understood, but it is possible they act in starting stage of none stratified fatty acids (Chevalier et al., 1999; Joseph et al., 2008).

The result of the present study is same as that of the previous study on tail flick test (Carstens and Wilson, 1993). Studies have shown that systemic administration of MC extract could decrease the pain responses in sacral spinal part to tail heating and chronic pain response related to formalin test. This is almost like morphine analgesic effects that act in sensory part of lumbar spinal cord that is in accordance with previous studies (Douglass and Carstens, 1997; Einspahr and Piercey, 1980; Wheatley, 2005).

Results of the present study and previous researches proved that MC extract has analgesic effects on inflammatory pain (second phase) of formalin test. Preventing in syntheses of prostaglandin and decrease of formalin induced inflammation are suggested for MC analgesic mechanism (McCall et al., 1996). Aley and Levine (2002) have shown that apigenin that is extracted from MC can decrease production of cytokines from lipopolysaccharides *in vivo* and *in vitro*, so it can control inflammation. Also it is possible that an analgesic effect of MC is due to reducing inflammatory parameters

production (Aley and Levine, 2002).

Our results showed that morphine has the ability to decrease the first and second phase of formalin test, but MC has antiinflammatory effects more than morphine in the second phase. Also, MC extract has less analgesic effects in comparison with morphine, but it was able to control the inflammatory effects of vincristine.

Analgesic and antiinflammatory effects of MC extract is proved in human. Results of Ramos-e-Silva et al. (2006) have shown that MC aqueous extract could be useful for mouth ulcer and other mouth painful ulcers without any side effects reported. They reported that after 5 to 15 min analgesic, effects of MC extract begin and it has 82% remarkable and in the other 18% it has fine analgesic activity. They found that it is useful in 97% of patients and could improve life quality of mouth ulcer patients (Ramos-e-Silva et al., 2006). Burns et al. (2000) have shown that MC essence can decrease pain during parturition in 8058 pregnant women.

Conclusion

Conclusively, systemic MC extract and morphine have an analgesic effect on the vincristine induced peripheral neuropathy model in mice. MC extract and morphine may therefore offer an alternative approach to the treatment of vincristine induced neuropathic pain states. However, similar studies on various animal models are required to obtain a reliable oversight of the effect of these drugs on vincristine induced neuropathic pain in a clinical setting.

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