Prevention of Development of Tolerance and Dependence to Opiate in Mice by BR-16A (Mentat) A Herbal Psychotropic Preparation

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ABSTRACT
Chronic treatment with BR-16A, (Mentat) (20-500 mg/kg) followed by saline on days 1 to 9 failed to produce any significant change in tail-flick latency from the saline-pretreated group in mice. Repeated administration of Mentat (20-500 mg/kg) for 9 days, however, attenuated the development of tolerance to the analgesic effect of morphine (10 mg/kg). Mentat (20-500 mg/kg) also suppressed, in a dose-dependent manner, the development of morphine dependence as assessed by naloxone (2 mg/kg) - precipitated withdrawal on day 10 of testing.

INTRODUCTION
BR-16A (Mentat), a herbal psychotropic preparation, contains the following indigenous ingredients, reputed in the ancient system of Ayurvedic medicine to be useful in the management of nervous disorders: Brahmī (Hydrocotyle asiatica), Shatavari (Asparagus racemosus), Buchh (Acorus calamus), Ashwagandha (Withania somnifera), Giloi (Tinospora cordifolia), Amla (Emblica officinalis), Shankhpushpi (Evolvulus alsinoides), Kuth (Saussurea lappa) and Triphala. Preliminary toxicity studies have shown it to be a safe preparation and no adverse effect ensued its chronic use (unpublished data).

Mentat has been reported to be effective in improving learning ability and behavioural disturbances in mentally retarded children. It is also beneficial in cases of cerebral deficit, behavioural disturbances following postnatal organic lesions of the central nervous system and in cases having organic loss of bladder function. Recent studies have demonstrated that Mentat improves passive avoidance acquisition and retention in naïve as well as amnesic mice. Studies on elevated plus-maze have shown anxiogenic and nootropic actions of Mentat. Since dementia and cognitive dysfunctions are known to occur in narcotic addicts, in the present study an attempt has been made to demonstrate, if any, the effectiveness of this herbal preparation in prevention of development of tolerance and dependence to morphine in mice.

MATERIALS AND METHODS
Animals - Balb'C strain, albino mice of either sex bred in Central Animal House facility of the University, weighing 20-25 gm, were used. The animals were housed under standard light/dark
cycle with food and water provided *ad libitum*. The experiments were performed between 09.00 and 17.00 hrs.

*Analgesia* - Analgesic response was assessed by tail-flick latency to radiant heat as described by D'Armour and Smith and as modified by Kulkarni. Baseline latencies to tail-flick withdrawal from the radiant source (3-4 sec) were established. A cut-off time of 10 sec was observed to prevent any injury to the tail. A minimum of three trials were recorded for each animal.

*Drugs* - The drugs used were Mentat (Himalaya), morphine (Government Analytical Laboratory, Chandigarh) and naloxone (Endo, New York).

Mentat powder was suspended uniformly in de-ionized water and administration orally, while the remaining drugs were given s.c., as aqueous solutions, in a constant volume of 1 ml/100 g body weight.

*Treatment schedule* - In acute studies, the animals received saline or Mentat (20-500 mg/kg), followed 30 min later by saline or morphine (10 mg/kg). The analgesic response to morphine was assessed by the tail-flick test 60 min after the second injection.

For induction of tolerance to morphine, animals received the opiate injection twice daily (09.00 and 16.00 hrs), for 9 days. On days 1, 3 and 9, the analgesic response was assessed by the tail-flick test 60 min after morphine injection. Various treatment groups (pre-treatment: treatment) included (i) saline: saline; (ii) saline: morphine (10 mg/kg); (iii) Mentat (20-500 mg/kg): saline; and (iv) Mentat (20-500 mg/kg): morphine (10 mg/kg). On the 10th day, the treatments were reversed so that the animals that had received Mentat followed by morphine on days 1 through 9 were challenged with saline followed by morphine. In addition, the animals that had been treated with Mentat followed by saline were challenged with Mentat followed by morphine. Immediately after the tail-flick test on day 10, the animals were injected with naloxone (2 mg/kg) to precipitate withdrawal. The withdrawal syndrome was assessed by placing each mouse in a 45 cm high plexiglass box and the incidence of escape jumps was recorded for 15 min.

*Statistical analysis* - The data, expressed as mean ± SE, were analyzed by one-way analysis of variance (ANOVA) followed by Dunett's 't' test. Probability levels of less than 5% were considered significant.

**RESULTS**

*Effect of chronic administration of morphine on analgesic response* - Animals receiving chronic treatment with morphine (10 mg/kg) displayed maximal analgesia on days 1 and 3 (Fig.1). In saline-treated mice, the analgesic response to morphine displayed rapid development of tolerance, reaching baseline latencies by days 9 and 10.
Effect of chronic concomitant treatment with Mentat and morphine on development of tolerance to morphine - The animals treated repeatedly with Mentat (20-500 mg/kg) showed significant analgesic response on days 1 and 3 of morphine (10 mg/kg) treatment (Fig.1). Pretreatment with Mentat prevented the development of tolerance to the analgesic response of morphine on day 9 of testing (Fig.2). The animals that had been treated with Mentat and morphine on days 1 through 9, then given morphine alone on day 10, also displayed considerable analgesia on the 10th day (Fig. 2).

Effect of chronic treatment with Mentat on analgesic response - Chronic administration of Mentat (20-500 mg/kg) followed by saline failed to elicit any analgesic response on days 1 and 3 in mice (Fig.3). Animals treated with Mentat followed by saline displayed tail-flick latencies no greater than saline-pretreated animals on days 1 through 9 (Fig.4). Challenging with Mentat and morphine (10 mg/kg) on day 10 produced significant analgesia; a response comparable to morphine effect on day 1 (Fig.4).
Effect of chronic treatment with Mentat and morphine on naloxone-precipitated withdrawal jumps - Animals that had received repeated administration of saline followed by morphine (10 mg/kg) displayed numerous escape jumps in response to an injection of naloxone (2 mg/kg) on day 10. In contrast, the animals treated with Mentat (20-500 mg/kg) and morphine (10 mg/kg) on days 1 through 9, then with saline and morphine on day 10, displayed significantly fewer jumps after naloxone (2 mg/kg) administration (Fig. 5).

DISCUSSION
Development of physical dependence and tolerance with repeated use is a characteristic feature of all the opioid drugs and entails major limitation in their clinical use. Thus, a decision to relieve any chronic symptom, especially pain, may be shortsighted and can be a disservice to the
patient. In the present study, the potential utility of Mentat, a herbal psychotropic preparation, has been examined against the development of tolerance and dependence to morphine.

Animals treated with morphine (10 mg/kg) displayed maximal analgesia on days 1 and 3 of treatment. In saline-treated animals the analgesic response to morphine displayed rapid development of tolerance on days 9 and 10. In contrast, the animals treated with Mentat showed less tolerance, maintaining an analgesic response throughout the testing period. The increased analgesia seen in the Mentat-treated group was not attributable to an analgesic action of Mentat alone or to an acute analgesic interaction between Mentat and morphine. Animals treated acutely with Mentat (20-500 mg/kg) showed no change in tail-flick latency, demonstrating a lack of effect of Mentat on pain responsiveness. Further, the animals that were treated with Mentat and morphine on days 1 through 9, then challenged with saline and morphine on day 10, showed no greater analgesia than that seen the previous day.
Substitution of saline with morphine on day 10, in the group that had been receiving Mentat, followed by saline on days 1 through 9, produced significant analgesia. This demonstrates that chronic treatment with Mentat does not affect the expression of morphine analgesia. Further, the animals receiving chronic treatment with Mentat and morphine, then morphine alone on day 10, displayed considerable analgesia on day 10, despite the lack of Mentat pretreatment on this day. The results suggest that Mentat need not be present during testing to observe analgesia in chronically Mentat-treated animals. Mentat, therefore, inhibits the development of tolerance to the analgesic effect of morphine.
In addition to interfering with tolerance, Mentat pretreatment inhibited naloxone-precipitated abstinence syndrome. Pretreatment with Mentat (20-500 mg/kg) significantly, and in a dose dependent manner, reduced the number of jumps after naloxone administration in groups chronically treated with morphine. As with the above experiments on tolerance, the effect of Mentat was attributable to the repeated administration of Mentat with morphine. Animals which received saline and morphine on days 1 through 9 displayed numerous jumps after administration of naloxone (2 mg/kg) on day 10 of testing. Animals that had received Mentat and morphine on days 1 through 9 displayed few jumps despite the fact that they did not receive Mentat on day 10 prior to the naloxone-precipitated withdrawal. Thus, Mentat administered during repeated treatment with morphine interferes with the development of tolerance to and dependence on opiates.

In conclusion, Mentat is safe non-analgesic herbal preparation, which can be used in the treatment of opiate addiction.

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REFERENCES


