

A Pilot Study to Compare Inhibitory Effects of Central Nervous System Drugs on Histamine-Induced Itch

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ABSTRACT

Histamine is a classic itch inducer, and itch develops in a high percentage of subjects after a histamine skin prick. In this study we examined the antipruritic effects of ketamine (2 mg), naloxone (0.2 mg) and midazolam (1 mg) on the histamine induced itch in 24 healthy male volunteers. Each drug was administered intravenously at subhypnotic doses before the histamine prick. Saline was intravenously injected as a negative control, and azelastine was orally administered for three days as a positive control. Itch intensity was evaluated subjectively using a rating of 1 to 10 every minute until the sensation of itch disappeared. The drugs did not differ significantly in terms maximal itch intensity, itch duration, or the size of wheal and flare. However, ketamine decreased itch intensity and duration somewhat. Because ketamine is a NMDA (*N*-methyl-D-aspartate) receptor antagonist, our results suggest NMDA might play a role in the central processing of histamine-induced itch. (Jikeikai Med J 2003 ; 50 : 15-8)

Key words : histamine prick, itch, ketamine, naloxone, midazolam, double-blind study

INTRODUCTION

Itch is such a common symptom in dermatologic and allergic conditions. Several peripheral chemical mediators of inflammation are pruritogens. However, little is known about the central itch mechanism except that opioids are mediators and opioid antagonists inhibit itch. For example, intrathecal or epidural administration of morphine and other μ agonists induce itch in humans¹. Naloxone and naltrexone are opioid μ antagonists that inhibit itch associated with cholestasis² and chronic renal failure³ and itch caused by central administration of opioids. In addition, ondansetron, a serotonin 5HT₃ antagonist⁴ and propofol, an intravenous anesthetic⁵, are effective against cholestatic itch.

Naloxone reduces peripheral itch induced by histamine injection⁶, which suggests opioids may play

an important role in the transmission of itch impulse, whether induced peripherally or centrally. On the basis of these previous findings we investigated the inhibitory effects of the central nervous system (CNS) drugs, ketamine, naloxone and midazolam on histamine-induced itch.

MATERIALS AND METHODS

The subjects were 24 healthy male volunteers (median age, 33 years ; range, 26 to 51 years) without a history of pruritic skin diseases. The subjects did not take any other oral antihistamines, antidepressants, or corticosteroids during this study. The protocol was approved by the ethics committee of our university. All subjects gave written informed consent.

Each drug was injected into the right median

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antecubital vein at the following doses; ketamine, 2 mg; naloxone, 0.2 mg; and midazolam, 1 mg. The doses of ketamine and midazolam were 1/30 to 1/10 of those used to induce anesthesia and produced no evident sedative effects. Naloxone was administered at doses that are used to antagonize respiratory inhibition due to opioids. Afterward, one drop of 1% histamine solution was applied to a site 10 centimeters distal to the cubital fossa of the left forearm and a skin prick was done when the blood concentration reached a level at which a central effect was expected, i.e., 2 minutes after intravenous injection with ketamine or midazolam and 10 minutes after intravenous injection of naloxone.

The following variables were then assessed: the area of wheal and flare 15 minutes after histamine prick and the maximal itch intensity and duration. A numerical rating scale was used to assess the intensity of itch (Table 1). The area of wheal and flare (mm²) was obtained by multiplying the maximal diameter by another diameter perpendicular to it. Skin pricks were produced with a prick lancet (PRICK-LANCETTER, Sweden). Histamine prick was done without a control drug before the series of intravenous injection in each subject. Intravenous injection of ketamine, naloxone, midazolam and saline were done in a double-blind method. With saline, histamine prick was done 2 minutes after intravenous injection of 5 ml of saline. The application of histamine was done with care to avoid bleeding, and the drop of 1% histamine solution was wiped off soon after the prick.

After these series of intravenous injection were completed, 2 mg of azelastine was administered orally for three days, after which the prick test was repeated with the same method. Each drug was injected on separate days with an interval of less than 1 week.

Table 1. Evaluation of Itch Intensity

0.....	no itch
1.....	subtle dysesthesia
2~4.....	mild itch (easy to refrain from scratching)
5~7.....	moderate itch (some effort to refrain from scratching)
8~10.....	severe itch (8: upper limit of refraining from scratching, 9: light touch or pinch the surrounding, 10: start scratching)

The room temperature was maintained at approximately 24°C with relative humidity of 40 to 60%.

Statistical analysis was performed with one-way analysis of variance, and Bonferroni's multiple comparison was used for comparing the results between drugs.

RESULTS

Neither ketamine, naloxone, nor midazolam significantly inhibited the histamine-induced wheal or flare responses when compared with saline (Fig. 1). However, flare responses were significantly inhibited by azelastine.

Neither maximal itch intensity nor duration differed significantly among the drugs (Fig. 2). However, the inhibitory effect of ketamine was slightly greater than that of naloxone or midazolam. One subject complained of severe headache lasting 1 hour after injection of naloxone. No other serious side effects were observed.

DISCUSSION

Histamine is a potent pruritogen that is used to induce itch experimentally. A histamine skin prick is traditionally used as a positive control in the immediate allergy test and produces itch in a high percentage of subjects. We have previously found that histamine prick produces greater itch intensity and duration but that intradermal injection of histamine produces a larger wheal and flares (unpublished findings). However, even with histamine skin prick, the sensation of itch lasts about 10 minutes. Because the duration of histamine's effects is short, in the present study we performed skin prick after CNS drugs were injected; otherwise, evaluating the inhibitory effect of the drugs would have been difficult.

Opioids also have pruritogenic effects. Fjellner and Hägermark reported⁷ that an enkephalin analogue, FK 33-824, potentiated histamine-induced itch and flare reactions, even in histamine-depleted skin and after oral pretreatment with indomethacin. Hence, histamine and prostaglandins released by mast cells are unlikely to be the cause of this potentiation.

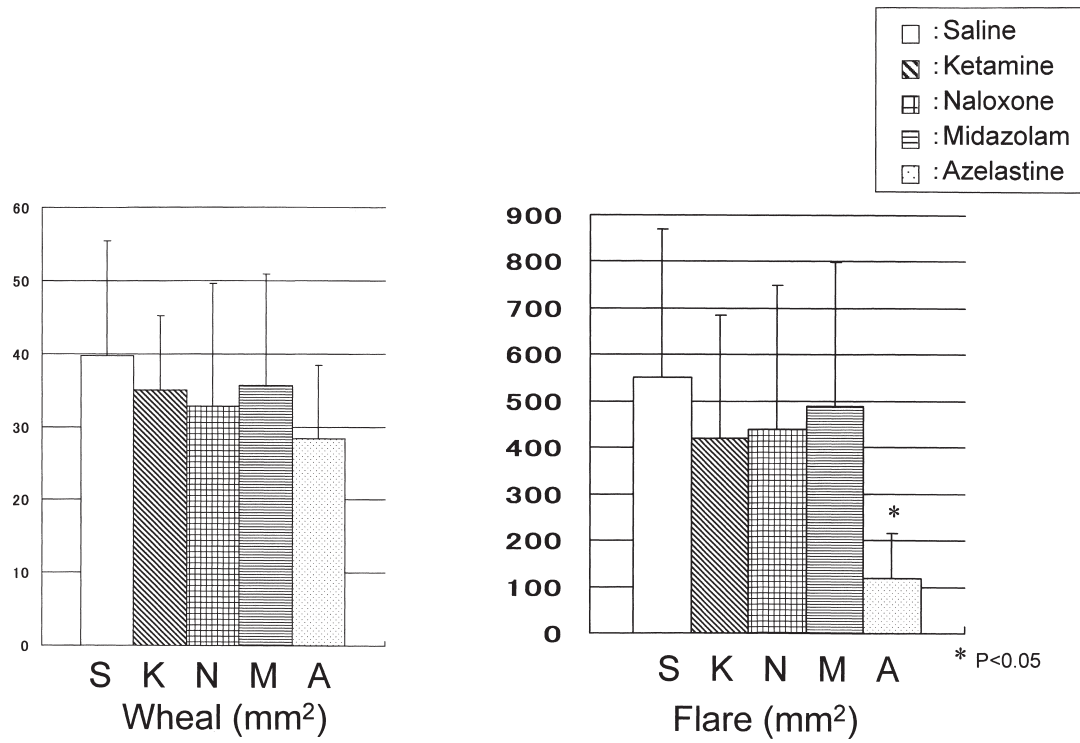


Fig. 1. The area of wheal and flare (mm²)

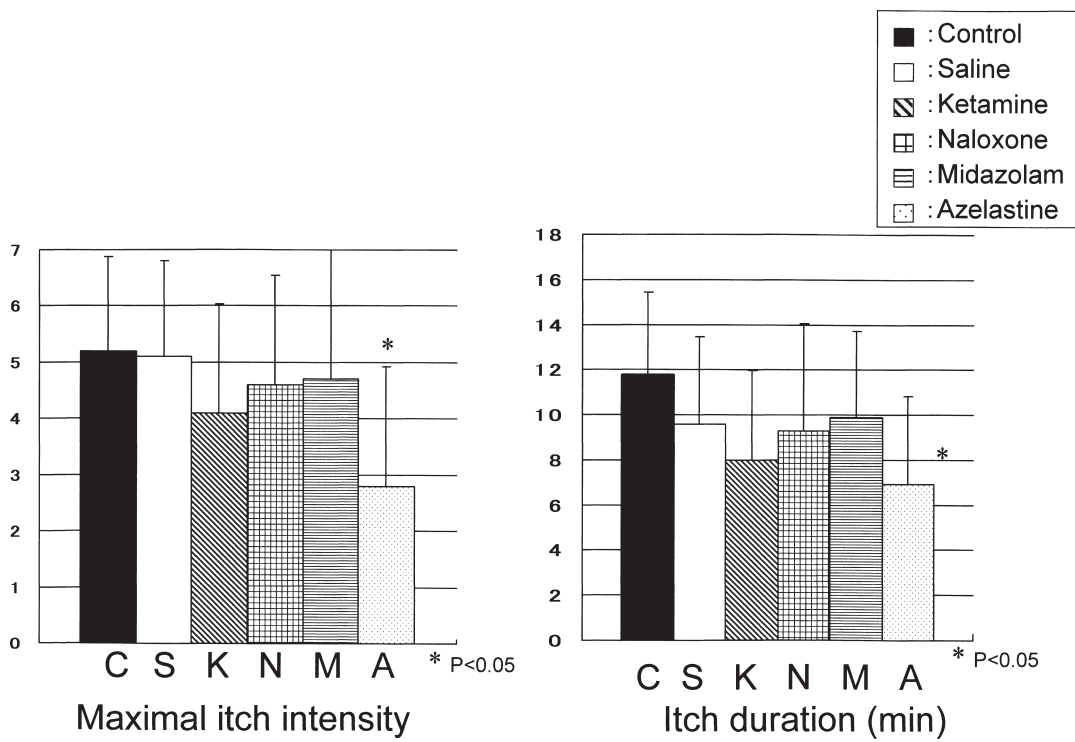


Fig. 2. Maximal itch intensity and itch duration

Because flare reactions were also enhanced in this study, a peripheral opioid action on itch-mediating nerve fibers is an intriguing possible explanation. Naloxone is an opioid μ receptor antagonist that, according to Bernstein et al., also inhibit histamine-induced itch⁶. However, the dose used by Bernstein et al. was four times greater than that used in our experiment. Therefore, the dose used in our present experiment might have been too small.

Ketamine is an intravenous anesthetic that antagonizes the *N*-methyl-D-aspartate (NMDA) receptor and is effective for chronic persistent pruritus in patients with erythroderma⁸. In the present study, we found that ketamine slightly inhibited histamine-induced itch. In some patients ketamine relieved itch without an evident sedative effect, suggesting that ketamine could be used as a treatment for itch if its dosage is studied further. We observed no other side effects of ketamine, such as hallucinations and tachycardia.

Midazolam is a sedative of the benzodiazepine family. Another benzodiazepine sedative, nitrazepam, is reported to have an antipruritic effect⁹. However, nitrazepam is itself a pruritogen, its reported antipruritic effect is probably due to its sedative action. Our previous study found that nitrazepam does not decrease nocturnal scratching of atopic dermatitis¹⁰. In the present study, midazolam inhibited itch in some patients but caused intense itch in others.

We investigated the inhibitory effects of azelastine as a positive control for histamine-induced itch. Azelastine decreased itch intensity and the duration of histamine prick compared with the three other CNS drugs. Our data confirm the potent and antihistamine activity of azelastine.

In conclusion, we performed a preliminary study on the effect of CNS drugs used against histamine-induced peripheral itch. Ketamine seemed to be somewhat effective. Further studies with varying dosages of ketamine will be necessary.

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