The Influence of the Opiate Antagonist Naloxone on Experimental Pruritus

BO FJELLNER and ÖSTEN HÄGERMARK

Department of Dermatology, Karolinska sjukhuset, Stockholm, Sweden

Fjellner B, Hägermark Ö. The influence of the opiate antagonist naloxone on experimental pruritus. Acta Derm Venereol (Stockh) 1984; 64: 73–75.

The antipruritic effect of naloxone hydrochloride was evaluated in a double-blind, cross-over design. Systemic pretreatment with the opiate antagonist did not interfere with the cutaneous itch and flare responses evoked by morphine or histamine, nor did it inhibit the morphine-produced potentiation of the histamine-elicited skin reactions. *Key words: Histamine; Morphine.* (Received March 15, 1983.)

B. Fjellner, Department of Dermatology, Karolinska sjukhuset, S-104 01 Stockholm 60, Sweden.

There is much evidence to indicate that opioid receptors in the CNS are involved in the mechanism of pruritus. Thus, epidural or intrathecal injection of morphine is known to elicit itch in humans (1, 2, 3, 4) and heroin addicts often show signs of pruritus (5). Violent scratching appears in animals after intracisternal administration of morphine (6). Furthermore, the opiate antagonist naloxone, reported to relieve intractable itch in patients with hepatic pruritus (7), prevents itching induced by intrathecal injection of morphine (1, 2, 4).

Morphine also has peripheral pruritogenic effects which have been ascribed to its histamine-releasing properties. Thus, it is well known that intradermal injection of morphine induces release of histamine causing itch at the injection site (for ref., see (8), p. 16). However, morphine and endogenous opioid peptides also act as local modulators and potentiate experimentally induced itching by a mechanism independent of histamine release (9). In our hands this enhancing effect was not inhibited by local injection of naloxone, nor did naloxone influence itch induced by morphine or histamine injected alone. Hence, we concluded that ordinary opioid receptors did not seem to be involved at a peripheral level (9). However, Bernstein et al. (10) reported that systemically administered naloxone inhibits itching experimentally induced by histamine. In the present paper we therefore extended our experiments by studying the effects of naloxone administered systemically on peripherally evoked pruritus. However, we could still find no inhibition by naloxone of experimental itch induced by morphine or histamine, or of that enhanced by morphine.

MATERIAL AND METHODS

Fifteen female healthy volunteers, aged 26 to 62 years, took part in the investigation. Each subject was pretreated with 2 ml of either naloxone hydrochloride (Endo Lab. Inc., Garden City, N.Y. USA),

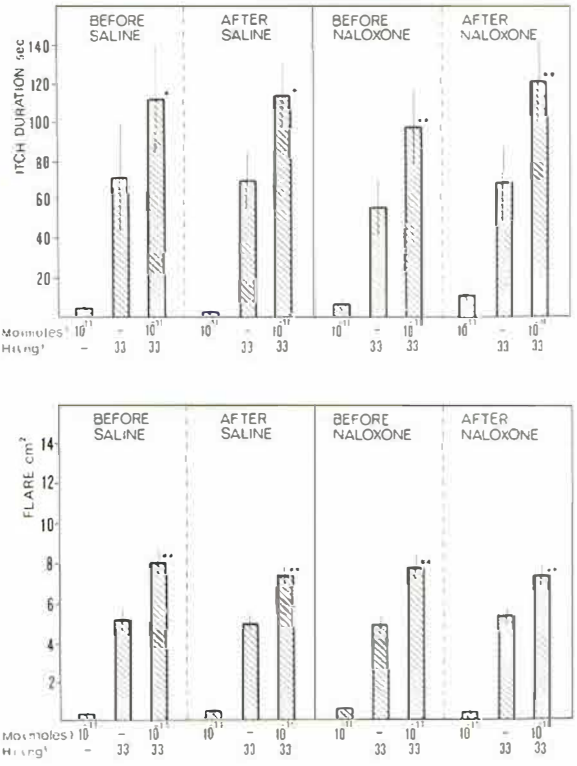

Fig. 1. Itch and flare responses induced by histamine (Hi) and morphine (Mo) injected intradermally alone and in combination, before and after systemic treatment with saline and naloxone (mean ± SE, $n=15$). The histamine responses were significantly potentiated by morphine: ** $p<0.01$, * $p<0.05$. None of the responses was significantly influenced by the pretreatment procedures.

0.8 mg, or physiological saline according to a predetermined randomization schedule. The solutions were administered subcutaneously in the thigh 10 min prior to the intradermal test procedure. The experiment was performed according to a double-blind, cross-over scheme carried out on two different days.

In the intradermal test procedure, small volumes, 0.01 ml, of histamine hydrochloride and morphine hydrochloride (ACO, Solna, Sweden), were injected intradermally under single-blind conditions. The solutions were injected as such or in a mixture on the lateral aspect of the upper arms. The duration of the itch response was recorded as well as the flare size 5 min after the injection. The technique has previously been described in detail (8).

RESULTS

The results are presented in Fig. 1. All of the 15 subjects experienced itching after intradermal injections of histamine (33 ng), whereas the itch response to morphine (10^{-11} moles) was noticed by only 3 of the 15 subjects. A flare reaction was observed concomitantly with the itch response for both substances. Systemic pretreatment with naloxone or saline did not influence the cutaneous responses evoked by histamine and morphine. In a mixture, morphine potentiated the histamine-evoked itch ($p<0.05$–0.01) and flare ($p<0.01$) reactions. This synergism was influenced by neither naloxone nor saline pretreatment procedures. Statistical analysis was performed with Wilcoxon's matched-pairs signed-ranks test.

DISCUSSION

Opiates may be involved in pruritus both at a central and at a peripheral level. At the peripheral level, opiates may initiate or aggravate itching. Their itch-eliciting capacity may

be due to release of histamine from dermal mast cells, while the mechanism responsible for their potentiating effect is obscure and independent of endogenous histamine liberation (for ref. see 8). As mentioned in the introduction the central effects are inhibited by naloxone, whereas somewhat contradictory findings are reported regarding the influence of naloxone in the periphery. The present study confirms our previous findings (9) that neither the itching induced by 'direct' stimulation, nor that enhanced by opioids is influenced by naloxone. The discrepancy between our results and those of Bernstein et al. (10) who found that systemically administered naloxone inhibits histamine-evoked itching might be explained by our different techniques. Bernstein et al. induced itching with increasing concentrations of histamine solutions, thus studying the sensory *threshold* for itch, whereas we studied the *duration* of the itch response induced by histamine and morphine, given alone or in a mixture. With our method however, opioids seem to have a peripheral, itch-potentiating effect not involving ordinary opioid receptors.

ACKNOWLEDGEMENTS

The skilful technical assistance of Mrs Halla Bornstein is gratefully acknowledged. This study was supported by grants from the Edvard Welander Foundation, the Finsen Foundation, the Karolinska Institute, the Swedish Society for Medical Research and the Swedish Medical Association.

REFERENCES

1. Baraka A, Noueihid R, Hajj S. Intrathecal injection of morphine for obstetric analgesia. Anesthesiology 1981; 54: 136–140.
2. Bonnardot JP, Maillet M, Colau JC, Millot F. Réversibilité du prurit induit par l'administration intrathécale de morphine au cours de l'accouchement. Nouv Presse Med 1982; 11: 673–674.
3. Rawal N, Sjöstrand U, Dahlström B. Postoperative pain relief by epidural morphine. Anesth Analg (Paris) 1981; 60: 726–731.
4. Scott PV, Fischer HBJ. Intraspinal opiates and itching: a new reflex? Br Med J 1982; 284: 1015–1016.
5. Rathod NH, Alarcón R de, Thomson IG. Signs of heroin usage detected by drug users and their parents. Lancet 1967; ii; 1411–1414.
6. Méhes J. Experimentelle Untersuchungen über den Juckreflex am Tier. Arch Exp Pathol Pharmakol 1938; 188: 650–656.
7. Bernstein JE, Swift RM. Relief of intractable pruritus with nalaxone. Arch Dermatol 1979; 115: 1366–1367.
8. Fjellner B. Experimental and clinical pruritus. Studies on some putative peripheral mediators. The influence of ultraviolet light and transcutaneous nerve stimulation. Acta Derm Venereol (Stockh) 1981; 97. Suppl. 97.
9. Fjellner B, Hägermark Ö. Potentiation of histamine-induced itch and flare responses in human skin by the enkephalin analogue FK 33-824, β-endorphin and morphine. Arch Dermatol Res 1982; 274: 29–37.
10. Bernstein JE, Swift RM, Soltani K, Lorincz AL. Antipruritic effect of an opiate antagonist, nalaxone hydrochloride. J Invest Dermatol 1982; 78: 82–83.