For Debate . . .

Mechanism of action of antipruritic drugs

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Abstract

Astemizole and terfenadine, two potent non-sedative H_1 antihistamines, had no effect on itch measured objectively as nocturnal scratching and subjectively on a 10 cm line. Trimeprazine, however, a more sedative but less potent H_1 antihistamine, was antipruritic, as was nitrazepam, a sedative benzodiazepine. We concluded (a) that antipruritic drugs act centrally by a property related to sedation; (b) H_1 receptor antagonists have a peripheral antipruritic action only when itch is due to histamine release, as in the wealing disorders. Thus the new non-sedative H_1 antihistamines have no place in the treatment of itch from other causes.

Introduction

Most drugs used to treat the itch of skin disease are H_1 receptor antagonists, and it is widely thought that their effect is due to peripheral antagonism of histamine action. We have suggested, however, that antipruritic drugs are more likely to act centrally by an action related to sedation.[1 2] Terfenadine and astemizole are the first potent H_1 receptor antagonist drugs without sedative action. Thus we used them to test this hypothesis since they should not be antipruritic. For comparison we measured the response to trimeprazine, a sedative H_1 antagonist used as an antipruritic, and to nitrazepam, a benzodiazepine sedative, using an objective method for measuring itch as nocturnal scratching[3] and a subjective assessment on a linear analogue scale.

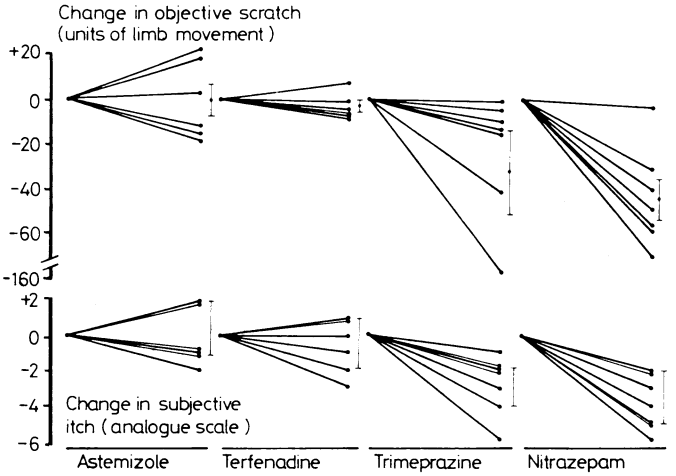
Patients and methods

Twenty three patients of both sexes, aged 16-82, were studied. All had a stable itchy dermatosis that was eczematous in all but two who had psoriasis. None had taken any systemic treatment for at least three days before admission and during the study they were maintained on the same topical treatment used before admission. For the first two nights of the study no drugs were given systemically. For the third and fourth days the patients were given one of the following: terfenadine 60 mg three times a day (six patients); trimeprazine 10 mg three times a day (seven patients); or nitrazepam 10 mg (seven patients) on retiring. On the fifth and sixth days the drugs were discontinued, but the patients continued to use the same topical preparation. Three of the patients given terfenadine were put into the trimeprazine study after three days had elapsed. All other patients were studied once only. There was no patient selection for the different treatment studies and each group of patients was comparable. This regimen of two day study periods was designed for the three short acting drugs studied, but because of the slow onset and prolonged action of astemizole a different experimental design had to be used for it. All six patients to be treated had stable atopic eczema and they were maintained throughout on the same topical treatment. After admission to hospital for two nights for measurement of itch and scratching they were discharged using the same topical treatment plus astemizole 10 mg daily, which they took for 19 to 40 days (mean 28 days) after which they were readmitted for two nights for further measurement of itch and scratching.

Itch was assessed subjectively by recording on a 10 cm analogue scale each morning and scratching was measured as nocturnal limb movement with limb meters (modified self winding watches) as described by Felix and Shuster.[3] This method has been validated using independent measurements of scratching and other body movements,[3 4] which showed that scratching provoked by itch is mostly done by the hands, while leg movement is mostly a measure of restlessness. The method is reproducible and gives measurements that correlate well with subjective itch regardless of cause.[2 5] The results are recorded on the meter as time of movement in hours and are referred to as "units of limb movement."

Results

The results are shown in the figure. The non-sedative but potent H_1 receptor antagonists astemizole and terfenadine had no effect on itch or scratching. By contrast, trimeprazine, a strongly sedative H_1 receptor antagonist, and nitrazepam, a sedative benzodiazepine anxiolytic, both decreased itch and scratching ($p=0{\cdot}05$, Wilcoxon rank sum test for both, and $p<0{\cdot}05$ for nitrazepam using a paired



Mean (SE) changes in nocturnal scratch provoked by itching, measured in units of limb movement (recorded on the meters as time in hours) and mean changes in subjective itch marked on a 10 cm line with median values. The results after stopping treatment are not given, but all patients returned to pretreatment levels.

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t test). When the drugs were stopped itch and scratching remained at their pretreatment levels with the non-sedative H_1 antagonists and had returned to their pretreatment levels in the two days after stopping trimeprazine and nitrazepam (results not shown). The three patients whose itch and scratching failed to respond to terfenadine subsequently responded to trimeprazine.

Discussion

The new non-sedative H_1 receptor antagonists astemizole and terfenadine) in doses that suppress the weal responses to histamine by up to 70%[7 8] had no effect on the itch of eczema assessed subjectively on a linear analogue scale and measured objectively as nocturnal scratching provoked by itch. By contrast the sedative but less potent H_1 receptor antagonist trimeprazine (unpublished results) decreased itch measured both subjectively and objectively. This suggests that sedation is more important than peripheral H_1 blockade in treating the itch of dermatoses such as eczema and psoriasis. In keeping with this nitrazepam, a sedative benzodiazepine, was likewise antipruritic, confirming our findings.[1 2] This study was not designed to compare the antipruritic potencies of trimeprazine and nitrazepam, but preliminary studies suggest that nitrazepam is more potent. The suppression of scratching by nitrazepam and sedative H_1 antihistamines is not simply a depressant effect on body movement because subjective sensation of itch is decreased in parallel and because barbiturates in comparable sedative dose increase scratching provoked by itch.[1 2]

Thus, although sedation is the common property of most antipruritic drugs, inhibition of itch is not a general property of sedatives. Antipruritic activity may be only indirectly related to sedation, and further quantitative studies of the effect on itch and scratching of drugs with different sedative and other central depressant properties may therefore lead to the development of drugs with a greater and more specific antipruritic action. Regardless of the precise nature of the central action of antipruritic drugs our results clearly show that the effect of antipruritic antihistamines is not due to peripheral H_1 blockade but to this central action that is related to sedation. The only exception to this is itch associated with histamine wealing—for example, dermographism, in which the non-sedative H_1 receptor antagonists terfenadine[9] and astemizole profoundly decrease both itch and scratching (in preparation).

Thus the use of H_1 receptor antagonists as antipruritic drugs may now be rationalised as follows: (*a*) they are effective because of peripheral H_1 antagonism where the itch is owing to peripheral release of histamine—for example, weal reactions of urticaria and dermographism; (*b*) they are effective because of properties related to sedation in the pruritus of non-histamine related dermatoses which include most pruritic dermatoses, such as eczema, psoriasis, lichen planus, and for the non-dermatological disorders for which the new non-sedative H_1 antagonists are inappropriate.

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We were always taught that administration of an opiate to patients in a state of shock improved the prognosis and could be life saving. Now we hear that naloxone can be life saving in similar circumstances. Could you clarify this apparent paradox?

Opiates and other analgesics are useful for treating the pain that accompanies many forms of traumatic shock when given in titrated doses together with specific resuscitative measures. They are also used as an adjunct to the specific treatment of acute left ventricular failure after myocardial infarction. Nevertheless, the attending doctor should remember the side effects of such treatment (respiratory depressions, depression of protective reflexes, hypotension, etc). Naloxone has been used with varying degrees of success in several conditions since it was introduced as a specific opiate antagonist. For example, initial enthusiasm for its use in acute alcoholic poisoning has not survived a controlled trial. Its use in shock resulting from septicaemia was suggested by the hypothesis that some of the features of this condition because beta-endorphin, an endogenous opioid, was released. Though results from animal experiments suggest that this may be so[1] it has not been proved in man and no fully documented case studies have been published. Incomplete data have implied that naloxone may have beneficial effects on the circulation as well as on the patient's level of consciousness.[2] Such studies have been criticised because they were based on insufficient details being provided of other treatment and in some instances on whether the patient's symptoms were in part due to treatment with opiates.[3] Possibly some of the beneficial cardiocirculatory effects reported were secondary to an arousal effect of naloxone. Also, in the high doses recommended, naloxone may have pharmacological effects other than opioid antagonism.[2] Thus a satisfactory answer to this part of the question cannot be given until a more comprehensive study has been published.—J C STODDART, consultant anaesthetist, Newcastle upon Tyne.

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Do manic depressive patients commonly develop megalomania? Is there any genetic basis for the latter condition?

Yes, to both questions. The term megalomania is today a term used more by the layman than by the psychiatrist to indicate grandiose ideas, or having an unreasonable belief in one's own greatness or power. Manic depressive patients are subject to periods of illness, often lasting months, when they may be depressed. At other times they may have periods of weeks or months when they are overactive, often overtalkative, and sometimes believe that, for example, they can successfully launch some multimillion pound venture, invent some new theory of memory for worldwide attention, or purchase two new and expensive cars instead of one second hand car. If one member of a twin pair suffers from manic depressive illness, the other twin is much more likely to do so if they are monozygotic twins than if they are dizygotic, and there is a stronger familial tendency to recurrent manic illness than to recurrent illness of a solely depressive type.[1 2]—IAN OSWALD, professor of psychiatry, Edinburgh.

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