EFFECTS OF CIMETIDINE, RANITIDINE AND PROMETHAZINE ON HISTAMINE—INDUCED DERMAL WEALS AND PRURITUS — A CASE STUDY

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SYNOPSIS

A non-atopic patient with methyltestosterone-induced cholestasis and severe pruritus was given in sequence, oral ranitidine, ranitidine and promethazine, then cimetidine, cimetidine and promethazine. Weals induced by skin-prick testing with histamine and pruritus were assessed after each of the above regimens. Ranitidine or cimetidine combined with promethazine relieved the itch although ranitidine did not when given alone whereas cimetidine did. On doing the histamine skin-prick tests while on ranitidine, pruritus was severely aggravated at the prick sites. Both H-2 receptor antagonists did not diminish weal sizes when administered alone. Ranitidine appears to be a more H-2 selective antagonist compared to cimetidine and both drugs need not be withheld before skin-prick tests are done unlike with H-1 receptor antagonists.

INTRODUCTION

Vascular and itch receptors are present in the skin and histamine is accepted as a mediator causing vasodilation and pruritus (1). There is evidence that both histamine-1 (H-1) and histamine-2 (H-2) receptors are present in the human skin blood vessels (2). In contrast H-2 receptors are thought to play little or no part in histamine-induced itching (3), and the existence of a new subclass of H-2 receptor mediating itch is being sought (4). There are now two widely used H-2 receptor antagonists, cimetidine and ranitidine, of different chemical structures. The effects of these two drugs, with promethazine, were investigated on a patient with severe pruritus from cholestatic hepatitis induced by methyltestosterone.

CASE STUDY

The patient a 23 year-old male Indian was seen in this hospital in August 1982. He presented with vomiting, fever, chills and rigors for three days after returning to Singapore from India where he had gone to get married. He was jaundiced but there was no hepatosplenomegaly. Liver function tests showed the total protein 7.6 gm/dl (normal 6.2 — 8.2 gm/dl), serum albumin 4.5 gm/dl (normal 3.7 — 5.1 gm/dl), serum bilirubin 9.4 mg/dl (normal 0.2 — 1.4 mg/dl), serum alkaline phosphatase 214 U/L (Normal 32-105 U/L) and SGPT (transaminase) 27 U/L (normal 9 — 36 U/L). Urine for bile and bile pigments was positive. His total white cell count was 6000/mm^3, haemoglobin 17.1 gm/dl and serum hepatitis B antigen was negative by reverse passive haemagglutination. The diagnosis was viral hepatitis and he was treated symptomatically.

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One week later he developed intense pruritus, nausea, lethargy and deepening jaundice (his peak serum bilirubin level was 35.5 mg/dl and peak alkaline phosphatase 410 U/L). A percutaneous transhepatic cholangiogram showed a normal biliary tree excluding extrahepatic cholestasis. He then volunteered the information that he had seen a doctor in India for ejaculatory failure and had received injections of methyltesterone. Cholestyramine and topical calmine lotion failed to relieve the itch. Promethazine, ranitidine and cimetidine were then administered. During the period of tests, his serum bilirubin was failling from 29.5 mg/dl to 3.7 mg/dl while the alkadine phosphates was falling from 410 to 193 U/L. However the SGPT was rising from 86 to 140 U/L. His pruritus was very several initally and the same was excoriated by persistent scratching. This precluded skin testing being done earlier.

MATERIAL AND METHOD

1 Atopic status

The patient gave no history of atopic diasthesis and family members were also unaffected by eczema, rhinitis and bronchial asthma. Skin prick testing by the method of Pepys (5) was carried out on the volar aspect of the left forearm. Bencard allergens consisting of a negative control, house dust, house dust mite, mixed feathers, cat fur, dog hair and human hair and a positive control solution containing 1 mg/ml of histamine acid phosphate were used. Details of the method and choice of allergens have been described (6). The patient was tested and proved non-atopic.

2 Histamine skin tests

By the same method of atopic skin prick testing but in place of Bencard allergens, histamine acid phosphate solutions of various strengths were skin prick tested on the volar aspect of his right forearm. The strengths of histamine solution were 1 mg/ml, 3.1 mg/ml, 6.25 mg/ml and 25 mg/ml. The weals produced after 15 minutes of skin prick were circumscribed with ink, transferred onto transparent tape, pasted onto graph paper with one millimetre squares and through a magnifying glass, the area was counted. Total areas for the four weals were expressed in square millimetres.

3 Experimental procedure

The patient was told that he would receive tablets to try and relieve his itching but he was unaware of the exact nature of the tablets. Cimetidine (Tagamet) was given as 400 mg bid, ranitidine (Zantac) as 150 mg bid and promethazine (Phenergan) as 25 mg tid. A minimum of 48 hours was allowed between cimetidine and ranitidine challenge. Skin testing was done 2 hours after the morning dose of drug(s). The patient was asked to estimate the effect the drug(s) had on his pruritus using a visual analogue scale of 1 to 5.

Day 1. This was a control day. He had not taken any antihistamines. The skin tests of atopy and the response to the four concentrations of histamine introduced by skin pricks were assessed. He was then administered ranitidine till day 4.

Day 4. Two hours after the morning dose of ranitidine, histamine skin tests were carried out. Promethazine was added into the ranitidine regime till day 6.

Day 6. Histamine skin tests were done two hours after the last doses of combined ranitidine and promethazine tablets were taken. All drugs were then stopped till day 9.

Day 9. This was another control day with no antihistamines given for the preceding 48 hours. Baseline histamine skin reactions were repeated after which cimetidine was started till day 12.

Day 12. Two hours after the morning dose of cimetidine, skin prick tests were done as previously. Promethazine was added into the cimetidine regime till day 14.

Day 14. Histamine skin tests were done after the last dose of combined cimetidine and promethazine tablets were ingested.

RESULTS

Objectives measurement on the effects of the H-1 and H-2 blocking drugs on the weal sizes showed that both ranitidine and cimetidine failed to diminish weal size. In fact the tendency was to an increased weal size when each was given alone. After each was combined with promethazine, weal size drastically decreased (Table I).

TABLE I: Effect of ranitidine, cimetidine and combined with promethazine on total weal area (square mm) induced by histamine skin prick testing.

CONTROL			
Day 1	46	Day 9	43
H-2 BLOCKADE			
Ranitidine Day 4	48	Cimetidine day 12	53
H-1 and H-2 BLOCKADE			
Ranitidine & Promethazine Day 6	29	Cimetidine & Promethazine Day 14	31

Subjective evaluation by the patient on the effects these drugs had on his pruritus revealed that after ranitidine alone, there was no improvement of the itch. Neither did it worsen. Cimetidine alone alleviated his pruritus. With combined H-1 and either H-2 blocking drugs, pruritus improved. While performing the histamine skin test on day 4, the patient complained bitterly that the introduced histamine gave intense pruritus at the test sites. This increased itch during skin testing did not occur on any of the other days.

DISCUSSION

Cimetidine and ranitidine are classified as H-2 receptor antagonists which block gastric acid secretion resistant to conventional antihistaminic drugs (H-1 receptor blockers). Cimetidine has been found to exert many effects not attributable to H-2 receptor antagonism but to the properties of the cimetidine molecule itself and these have not been found to apply to ranitidine where the furan ring replaces the imidazole nucleus (7).

H-1 and H-2 blockers have been tried on various dermatological conditions. Matthews et al (8) and Kaur, Greaves & Eftekhari (9) found that combined chlorpheniramine and

cimetidine gave a greater reduction in the weal and flare response to graded dermographic stimuli than chlorpheniramine alone. Similar synergistic effects on alcohol-induced flushing (10) and carcinoid flushing (11) have also been demonstrated. This present study showed that with either H-2 antagonist blockade alone, weal sizes did not decrease but with combined H-1 and H-2 blockade, they did. Whether the increase in weal size on ciemtidine blockade alone is significant is unknown. Harvey and Schocket (12) demonstrated that cimetidine potentiated the block effect of H-1 antihistamines on histamine-induced (intradermal method) cutaneous weals although cimetidine alone had no significant effect. But a more recent paper (13) showed that the suppression produced by combined chlorpheniramine and cimetidine did not significantly differ from that produced by chlorpheniramine alone in asthmatic patients. Further these authors also found that on cimetidine, the weal areas induced by intradermal histamine were also increased but did not reach statistical significance. Thus it would appear that for skin prick testing, only H-1 receptor antagonists are contraindicated as these diminish the reaction while H-2 receptor antagonists do not appear to invalidate the results of skin prick testing.

The evaluation of pruritus must remain subjective and this patient's itch was unchanged on ranitidine alone but improved on cimetidine. Less itch occurred when either H-2 antagonist was combined with promethazine. Of greater significance was the fact that while on ranitidine alone, the introduction of histamine by skin prick gave intense pruritus. Cimetidine has been used for the treatment of pruritus associated with cholestasis, two patients responded dramatically to cimetidine (14) but after a small controlled trial with six patients, the efficacy of cimetidine was in doubt. Whether any added advantage is present for combined H-1 and H-2 (cimetidine) antihistamines as against H-1 antagonist alone is also not clear. As shown in this study, ranitidine, a newer and more potent H-2 receptor antagonist did not improve the patient's pruritus thus supporting a study that showed that H-2 receptors play little or no part in histamine-induced itching (3). However when the H-2 receptors were already blocked by ranitidine and histamine was introduced by skin prick, the enhanced pruritus may be the result of histamine action solely on H-1 itch receptors. That this did not occur with cimetidine when given alone could be because ciemtidine is not as pure or selective a H-2 receptor blocking drug as ranitidine is and therefore also blocks some H-1 itch receptors. Partial block of H-1 itch receptors by cimetidine could account for the improvement in the patient's pruritus. That ranitidine is a more potent H-2 receptor antagonist is supported by cimetidine-resistant gastric hypersecretion in patients responding to ranitidine treatment (15).

The airways of asthmatic subjects have been shown to possess both H-1 and H-2 receptor sites (13, 16), which appear to mediate opposite effects when stimulated or blocked. H-1 receptor blockade with chlorpheniramine raised the threshold to inhaled histamine bronchoconstriction while cimetidine (H-2 receptor blockade) had the reverse effect. In the skin of normal subjects H-2 blockade may cause an increase in the size of histamine-induced weals whereas H-1 blockade is known to cause a decrease. But in asthmatics, H-2 receptor effect on histamine-induced skin weals appears deficient and this is in contrast to normals (13). Only H-1 receptors appear relevant in pruritus and the increased itch evoked by histamine prick on ranitidine-blocked skin histamine receptors may be explanined without considering the existence of H-2 receptor subtypes. Should the larger weals obtained after cimetidine but not rainitidine block be consistently shown in further studies, then perhaps H-2 receptor subtypes may be involved.

REFERENCES

1. Davies MG, Greaves MW: The current status of histamine receptors in human skin: therapeutic implications. Br J Dermatol 1981; 104: 601-6.
2. Robertson I, Greaves MW: Responses of human skin blood vessels to synthetic histamine analogues. Br J Clin Pharmacol 1978; 5: 319-21.
3. Hagermark O, Strandberg K, Gronneburg R: Effects of histamine receptor antagonists on histamine-induced responses in human skin. Acta dermatovenereologica 1979; 59: 297-300.
4. Eyre P, Chand N: Preliminary evidence for two subclasses of histamine H2 receptors. Agents Actions 1979; 9: 1-3.
5. Pepys J: Laboratory methods in clinical allergy. Proc Roy Soc Med 1972; 65: 271-4.
6. Chee YC: Skin prick tests for atopy in asthmatic adults in Singapore. ASEAN J Clin Sci 1982; 3: 259-64.
7. Editorial. Cimetidine and ranitidine. Lancet 1982; 1: 601-2.
8. Matthews CNA, Boss JM, Warin RP, Storari F: The effect of H1 and H2 histamine antagonists on symptomatic dermographism. Br J Dermatol 1979; 101: 57-61.
9. Kaur S, Greaves MW, Eftekhari N: Factitious urticaria (dermographism): treatment of cimetidine and chlorpheniramine in a randomized double-blind study. Br J Dermatol 1981; 104: 185-90.
10. Tan OT, Gaylarde PM, Sarkany I: Blocking of alcohol-induced flush with a combination of H1 and H2 histamine antagonists. Lancet 1979; 11: 365.
11. Roberts LJ, Marney SR, Oates JA: Blockade of flush associated with metastatic gastric carcinoid by combined histamine H1 and H2 receptor antagonists. N Engl J Med 1979; 300: 236-8.
12. Harvey RP, Schocket AL: The effect of H1 and H2 blockade in cutaneous histamine response in man. J Allergy Clin Immunol 1979; 63: 108-9.
13. Nathan RA, Segall N, Schocket AL: A comparison of the actions of H1 and H2 antihistamines on histamine-induced bronchoconstriction and cutaneous wheal response in asthmatic patients. J Allergy Clin Immunol 1981; 67: 171-7.
14. Harrison AA, Littenbery G, Goldstein L, Kaplowitz N: Pruritus, cimetidine and polycythemia. N Engl J Med 1979; 300: 433.
15. Danilewitz M, Tim LO, Hirschowitz B: Ranitidine suppression of gastric hypersecretion resistant to cimetidine. N Engl J Med 1982; 306: 20-2.
16. Nathan RA, Segall N, Glover GC, Schocket AL: The effects of H1 and H2 antihistamines on histamine inhalation challenges in asthmatic patients. Am Rev Resp Dis 1979; 120: 1251-8.