PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 159, 223-225 (1978)

Salbutamol as a Topical Anti-inflammatory Drug (40319)

ROBERT J. SEELY[1] AND E. MYLES GLENN[2]

The Upjohn Company, Department of Hypersensitivity Diseases Research, Kalamazoo, Michigan 49001

One of the initial events in acute inflammation is the release of histamine from mast cells in response to tissue injury or antigen–antibody complexes. Histamine causes dilation and increased permeability of capillaries. Local reddening and edema appear, followed by secondary characteristics of heat and pain (1). Drugs that inhibit histamine release prevent or reduce tissue inflammation. Inhibition of histamine release is accomplished partly by increasing the cellular level of cyclic adenosine monophosphate (cAMP) (2). Anti-inflammatory steroids stimulate adenyl cyclase to convert adenosine triphosphate to cAMP, and β-adrenergic agonists stimulate adenyl cyclase at the β-adrenergic receptor (3).

Hydrocortisone (17α-hydroxycorticosterone, Cortisol) is used effectively to reduce local inflammation; however, salbutamol may have several distinct advantages. Salbutamol (x-xylene-a,a'-diol,a'-terbutylaminomethyl-4-hydroxy) is a relatively specific β-adrenergic agonist and selectively stimulates β-adrenergic receptors (4). The cardiovascular and central nervous system effects of other sympathomimetic amines are caused in part by actions on the receptors which are prevalent in those tissues.

Here we report the local anti-inflammatory activity of salbutamol when applied topically to inflamed rat ears.

Materials and Methods. This method of creating local inflammation in rat ears by croton oil is essentially that of Tonelli *et al.* (5). A 5% (v/v) croton oil solution in absolute ethanol is applied by micropipet to the outer surface of both ears (0.05 ml each). The ears become edematous in 3 to 6 hr and remain inflammed for up to 48 hr. Inflammation (edema) is measured by cutting off the ears at 5.5 hr and weighing them. Drugs are usually applied simultaneously in the croton oil–ethanol mixture. In some cases, as noted, drugs are applied after the croton oil. Male Sprague–Dawley rats (200–240 g) are used. Untreated control rats provide the weight of normal nonedematous ears. Croton oil-treated rats demonstrate the extent of inflammation in the absence of drugs. Hydrocortisone (1%), serving as a positive control, consistently inhibits inflammation by 80 to 100%. Data are expressed as milligrams of edema of both ears, that is, the increase in weight of both ears over the untreated controls. The weights in each group are averaged and the standard error of the mean is calculated (depicted by vertical line extensions on the graphs).

Results. Local inflammation is inhibited totally by hydrocortisone and salbutamol when they are applied topically to the ears at 1 to 2% (w/v) in the croton oil solution (Fig. 1). Croton oil causes the ears to gain an average of 155 mg in the absence of any anti-inflammatory agent. Drug concentrations of 0.1% reduce the edema by 80%. When drugs are applied to a distant shaven area of the back, anti-inflammatory activity still occurs but higher concentrations are required (Fig. 1B).

Hydrocortisone and salbutamol reduce local edema even when applied after the inflammation reaction is in progress (Fig. 2). In the case of salbutamol, significant reduction of inflammation is obtained when given up to 2 hr after application of the croton oil. Hydrocortisone is not as effective when given this late in the development of acute inflammation.

Salbutamol is found to be inactive orally in our model (Fig. 3). Doses of up to 35 mg/kg body wt, delivered orally by stomach tube, failed to significantly inhibit ear edema.

Propranolol (a β-adrenergic receptor blocking agent) interferes with the ability of salbutamol to inhibit inflammation, but di-

[1] Present address: The Great Western Sugar Company Research and Development Lab, Loveland, Colorado 80537.

[2] To whom reprint requests should be addressed.

0037-9727/78/1592-0223$01.00/0

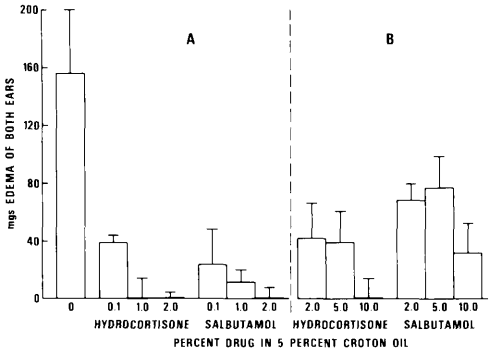

FIG. 1. Local and systemic anti-inflammatory activity of hydrocortisone and salbutamol. The drugs are applied directly to the ears (A) or to a shaven area on the back (B). In both A and B, the croton oil was applied to the ears to induce inflammation. In this and subsequent graphs the averages of five animals per group are presented, and the vertical line extensions represent the standard errors of the mean.

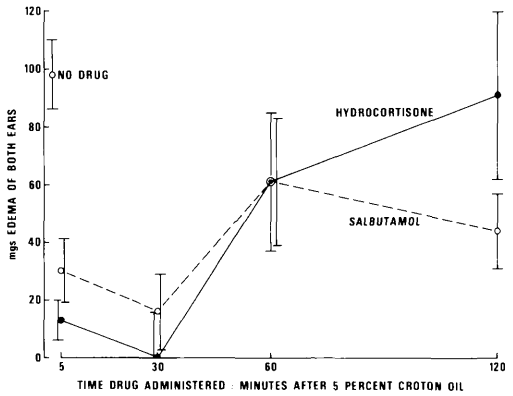

FIG. 2. The effects of salbutamol and hydrocortisone on local inflammation when they are administered during the course of the inflammation reaction. Croton oil was applied to the ears to induce inflammation, while salbutamol (1%) and hydrocortisone (1%) were also applied but at various times after the croton oil.

benamine (an α-adrenergic receptor blocking agent) has no influence (Fig. 4). Neither propranolol nor dibenamine prevents the anti-inflammatory activity of hydrocortisone.

Discussion. The need exists for a locally active anti-inflammatory drug that can be applied directly. Salbutamol (Ventolin, Allen and Hansbury) is used in foreign countries in the management of asthma (6). Green (7) has reported that salbutamol, injected ip, could reduce inflammation both in the mouse peritoneum induced by acetic acid and in the rat hindpaw edema induced by carrageenin. He also demonstrated that the activity is not mediated by release of adrenal corticosteroids.

Salbutamol is very effective in the prevention of local inflammation. Although it is not orally active in our model of inflammation, salbutamol is effective if applied directly at the inflamed site or at a remote site. This suggests that the drug is readily absorbed into the circulatory system; however, larger concentrations are required if the drug is not applied at the site of inflammation.

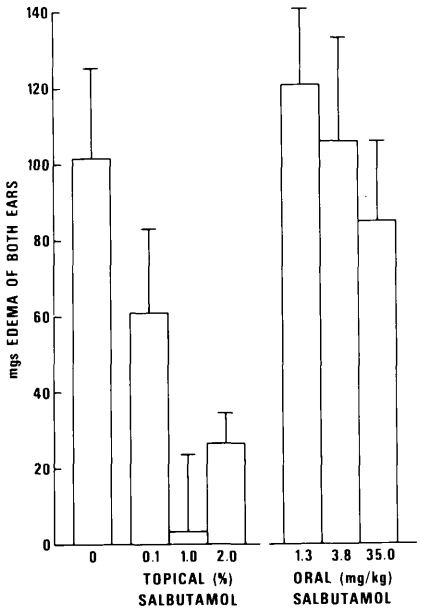

FIG. 3. Topical and oral activity of salbutamol on local inflammation. Salbutamol was applied directly to the ears, or given orally by stomach tube, at various doses, 30 min prior to the croton oil.

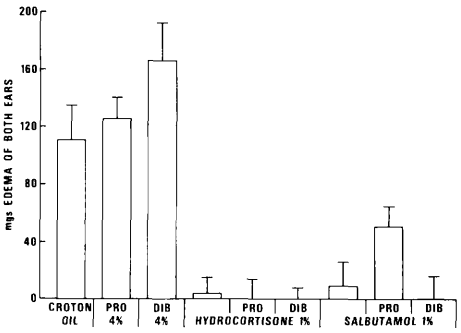

FIG. 4. Effects of 4% propranolol (pro) and 4% dibenamine (dib) on the local anti-inflammatory activity of hydrocortisone and salbutamol. Croton oil, propranolol, and dibenamine were given independently (for controls and in combination with the drugs (simultaneous application, including croton oil).

The action of salbutamol as a bronchodilator in the treatment of asthma is mediated by the β-adrenergic receptors in the bronchus (4). The β-adrenoceptors in the mast cells may be involved in the action of salbutamol in inflammation. The β-blocking agent propranolol interferes with the ability of salbutamol to inhibit inflammation. Dibenamine, an α-blocking agent, has no effect. Hydrocortisone acts in a different manner since neither propranolol nor dibenamine block the effect of the steroid.

Undesirable cardiac side effects are expected to be minimal, because salbutamol is relatively selective for β_2-receptors and has little effect on β_1 receptors which predominate in the heart. The minimal adverse effects of this drug compared with other β-agonists used in the control of asthma are discussed by Brittain (8) and by Dochorn (9). We have found anti-inflammatory activity of other agonists, but salbutamol was pursued because it is the most effective and because of its "selectivity." Morrison and Farebrother (10) have reported a case of salbutamol overdose and describe the physiological and cardiovascular events that occur. Further studies are required, but it appears safe to attempt to treat local inflammatory conditions of the skin with salbutamol.

Summary. Using croton oil-induced rat ear edema, hydrocortisone and salbutamol show anti-inflammatory activity when applied topically. Both drugs act to some extent even when applied after the inflammation reaction is in progress. Both drugs are also active when applied to a shaven area of the back, a site remote from the ear inflammation. Salbutamol acts by a different mechanism than anti-inflammatory steroids. The advantages of salbutamol are discussed and it appears to be a useful adjunct in the treatment of inflammatory dermatoses.

1. Melmon, K. L., and Morrelli, H. F. (eds). Clinical Pharmacology. p. 382. Macmillan (1972).
2. Lichtenstein, L. M., and Margolis, S., Science **161,** 902 (1968).
3. Brittain, R. T., Jack, D., and Ritchie, A. C., Adv. Drug Res. **5,** 197 (1970).
4. Zsoter, T. T., and Epstein, S. W., Chest **64,** 465 (1973).
5. Tonelli, G., Thibault, L., and Ringler, I., Endocrinology **77,** 625 (1965).
6. Rebuck, A. S., Drugs **7,** 344 (1974).
7. Green, K. L., Brit. J. Pharmacol. **45,** 322 (1972).
8. Brittain, R. T., Proc. Roy. Soc. Med. **65,** 759 (1972).
9. Dockhorn, R. J., Ann. Allergy **29,** 539 (1971).
10. Morrison, G. W., and Farebrother, M. J. B., Lancet **2,** 681 (1973).

Received January 11, 1978. P.S.E.B.M. 1978, Vol. 159.