Effects of local corticosteroids on acute experimental urticaria

Corticosteroids are often used in the treatment of acute or chronic urticaria. However, their effects on mastocyte activation as well as on the histamine-induced dermal oedema remain poorly investigated. The aim of the present study was to investigate the effects of corticosteroids (CS) on the development of acute experimental urticaria induced by prick-tests with histamine and codeine. This experimental model corresponds to the common form of urticaria. CS were administered at the site of the histamine and codeine prick tests in order to test for a direct effect on the development of acute urticaria. Two types of experiments were performed: 1) after a 48-hour period of topical CS application on the forearm, 7 healthy volunteers were skin prick-tested with histamine and codeine simultaneously in duplicate, one series in the pretreated area and the other in a non-treated area. 2) six other volunteers were prick-tested with histamine and codeine on their forearm, in duplicate. Immediately after testing, intradermal methyprednisolone was injected at the site of the prick-tests in the last series. Skin wheal and flare responses were measured after 20 mns and statistically compared with and without CS treatment. Whereas short-term CS topical application did not appear to modify cutaneous reactivity to histamine and codeine simultaneously in duplicate, one series in the pretreated area and the other in a non-treated area. 2) six other volunteers were prick-tested with histamine and codeine on their forearm, in duplicate. Immediately after testing, intradermal methyprednisolone was injected at the site of the prick-tests in the last series. Skin wheal and flare responses were measured after 20 mns and statistically compared with and without CS treatment. Whereas short-term CS topical application did not appear to modify cutaneous reactivity to histamine and codeine, local CS injection was associated with a significant increase in the flare induced by histamine and codeine (respectively + 18 ± 3% and + 38 ± 3%; \( P = 0.05 \)). The wheal tended to be increased after injected CS. In conclusion, these results show that CS are neither able to prevent nor to improve experimental urticaria, i.e. wheal and flare, and even increase the histamine and codeine-induced erythema. That a similar result could apply to patients with chronic urticaria and with systemic CS remains to be studied.

Key words: corticosteroids, histamine, codeine, urticaria, wheal, flare

Subjects and methods

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Thirteen healthy volunteers (7 women, 6 men average age 32 years, range 22-58 years), not using topical or systemic treatments for at least three months, were included in this study. At inclusion, all patients gave their written informed consent to the protocol. These volunteers were divided into two groups:

Urticaria is a common chronic skin disorder, which corresponds to the activation of dermal mast cells. Once activated, they induce inflammatory reactions by secreting chemical mediators stored in pre-formed granules (essentially histamine, tryptase or chymotrypsin), and by synthesizing leukotrienes, prostaglandins, chemokines and cytokines after activation occurs [1]. The anti-histamines remain the treatment of choice in urticaria ; they act by blocking the effects of histamine on endothelial cells in the superficial dermal blood vessels [2]. Corticosteroids (CS) are sometimes used in the treatment of acute or chronic urticaria, with major differences in prescription practices depending on the medical specialty concerned. Allergologists are thus less likely to prescribe CS than other physicians [3]. However, the efficacy of CS in preventing or improving common forms of urticaria remains debated as the results of clinical studies are often contradictory. The aim of this study was to investigate the effects of CS on the development of experimental urticaria, i.e. urticarial lesions induced by prick-tests with histamine and codeine. The histamine prick-test reflects the vascular reactivity of this mediator with an increase in the endothelial permeability and vasodilation. In contrast, the prick-test with codeine, an opiate inducing mast cell degranulation by a ligand-receptor interaction, illustrates the activation of mast cells and the liberation of histamine and other mediators involved in the urticarial lesion. Codeine seems, moreover, to have a directly relaxing effect on the smooth muscles within the blood vessels. The anti-histamines are capable of preventing urticaria induced by histamine and codeine.

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Volunteers, who formed group I (preventive mode), received a daily application for 2 days of betametasone dipropionate (DIPROSONE® ointment) over one half of the anterior side of the left forearm, the other half remained free of all topical applications. On the third day prick-tests to histamine and codeine were carried out.

Volunteers formed group II (curative mode). Two series of prick-tests with histamine and codeine were undertaken on their left forearm. In one of the two series, an intradermal injection (IDR) of 50 μl of methylprednisolone succinate (SOLUMEDROL®, 20mg/ml) was given a few seconds after, and at the same site as the tests.

Skin tests
One drop of standardized histamine phosphate (10mg/ml) or codeine phosphate (Stallergènes, Antony, France) was placed on the skin which was then pricked with a Staller-point (Stallergènes, Antony, France). A “negative” control at the same time and using the same conditions was systematically carried out with a drop of Glycero-saline in order to exclude any potentially associated dermographism. Reading of the tests took place after twenty minutes, measuring the diameter of any papule and erythema which was induced. Each lesion was then traced onto paper and the longest perpendicular measurements of the diameter of both the papule and the erythema were taken.

Statistical analysis
The results of the measurements of the size of the papules and erythema for groups I and II were expressed as averages ± standard deviation and compared using the student t test. A difference of p<0.05 was considered statistically significant.

Results

Effect of topical corticosteroids
Application of class III (strong) topical CS for 48 hours before carrying out the prick tests had very little effect on the urticarial lesions induced, at the 20 minute reading (Fig. 1). In fact only the erythema (flare) induced by histamine was less intense on treated skin compared to contralateral non-treated skin (24.5 ± 9 vs 19.3 ± 6 mm; p < 0.05). No differences were noted for erythema induced by codeine nor for the papule (wheal) induced by histamine or codeine. Topical corticosteroid treatment had no effect either on the evolution of the induced urticaria : erythema and papules appeared and disappeared at the same time in the treated and non-treated areas.

Effect of systemic corticosteroids
The injection of corticoids immediately after provocation of the urticarial lesion resulted in an increase of the erythema observed with histamine and codeine, in comparison with nontreated skin (Fig. 2). With certain patients, the differences observed in the erythema were pronounced (Fig. 3) and were associated with an increase in the size of the papule. Nevertheless, the overall statistical analysis of all the subjects treated with injected CS failed to detect an effect on urticarial papules. As with topical CS, the time-scale for the appearance and disappearance of skin reactions to histamine and codeine were similar for treated and non-treated skin.

Discussion
Our results show that CS have little effect on histamine- and codeine-induced urticaria. They have no effect on the development of urticarial papules (wheels), which are typically the first lesions in urticaria. On the other hand they have an effect on erythema (flares), which corresponds to a local vasodilatation of small dermal vessels, in response to histamine. Interestingly, the effects of CS on erythema differ with the type of drug administration. Topical CS reduce the size of the wheal, which is one of their classical pharmacological properties [4]. In fact the strong anti-inflammatory properties of topical CS are proportional to their vasoconstriction effects, and are the basis of the McKenzie test, which compares and ranks the efficacy of
different corticoids on human skin [5]. In contrast, corticoids injected intradermally immediately after the urticaria has been triggered induce an increase in erythema. This effect, which may first appear paradoxical, could probably be explained as the result on the dermal vessels of a high local concentration of CS in this model. Our observations can be compared to the known secondary effects of high doses of CS administered in pill form and accompanied by erythema on the face and on the chest. Recent experiments showed that high doses of CS, administered transdermally, result in dermal vasodilation, while moderate doses induced vasoconstriction [6]. Thus, in our model, it is possible that the injected CS add their vasodilating properties to those of histamine, which leads to an increase in the erythema observed after a histamine or codeine prick. Local or systemic treatment with CS is widely used in numerous human diseases, including outbreaks of acute urticaria [4]. Our results do not support the recommendation of corticoids in the treatment of the common form of urticaria as neither topical nor systemic forms reduce the erythema and/or edema. On the other hand clinical experience shows that CS are efficacious in certain forms of systemic urticaria such as those associated with cutaneous vasculitis and auto-immune urticarias (lupus, thyroiditis). These systemic urticarias are very different from the common forms of urticaria on clinical, pathological and therapeutic backgrounds. In these clinical forms the urticarial lesion is due to a polymorphous inflammatory and immune cell infiltrate and not to a simple dermal edema [7, 8]. It is thus logical that CS are effective in these systemic urticarias, due to their anti-inflammatory and immunosuppressive properties.

The interpretation of prick-tests in patients undergoing corticoid therapy has been controversial. Our results show that topical and systemic CS do not prevent prick-tests for histamine and codeine from being positive, even if they modify one of the parameters of the evaluation (erythema). These results confirm other studies showing that topical and systemic CS do not affect the interpretation of tests of immediate hypersensitivity [9, 10], even if they are responsible for modifications in the results. Cole et al. showed that topical CS, applied over three weeks, were responsible for a local reduction in the number of mast cells and level of histamine in the tissues treated while the degranulation functions of the mast cells remained intact [9]. The effects of long term corticosteroid therapy on skin reactivity induced by histamine and codeine have also been studied. [10-12]. While the reaction induced by histamine is not affected, the degranulation of mast cells provoked by codeine was significantly reduced with prolonged cortisone treatment [11]. These effects of long-term CS do not prevent the use of prick-tests as they do not modify the results of skin tests for immediate hypersensitivity [10]. In conclusion, CS have no effect on acute experimental urticaria as they are not able to block the mast cell degranulation induced by codeine or to inhibit histaminic erythema. Thus, skin tests for immediate hypersensitivity can be carried out on patients under topical or systemic corticosteroid treatment.

Whether the present results obtained in healthy volunteers and showing that CS had no effect on experimental urticaria

Figure 2. Effects of injected corticosteroids on histamine- and codeine-induced erythema (flare) and urticarial papule (wheal) (n=6).

Figure 3. Effects of injected corticosteroids (SOLU) on histamine- (H) and codeine- (C) induced urticaria compared without treatment.
can be extended to patients suffering from outbreaks of acute urticaria remains to be studied.

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References