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INVESTIGATIVE REPORT

Comparison of Perceived Itch Induced by Skin Prick-tests with Histamine and Codeine

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The role of personal factors makes it difficult to correlate subjective data, such as those obtained with the use of a visual analogue scale, and objective data, such as a quantity of injected histamine. In this study, prick tests with histamine and codeine on the forearms allowed a coherent variation in itch scores to be obtained over time, with highly significant differences from controls and with a peak at 4 minutes. These tests are therefore valuable for screening anti-pruritic agents. A significant difference between initial scores and scores for new prick tests after 7 days suggest that tachyphylaxis persists.

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The measurement of itch (1, 2) is difficult because itch or pruritus is a subjective sensation defined by its association with a need to scratch. Nonetheless, it is necessary to measure itch for the follow-up of some patients and in clinical studies. Itch can be measured through complex recording of scratch movements or, more simply, through the use of scales. Recently, a very fine scale was defined (3) and validated (4): the Itch Severity Scale (ISS). Yet, the most frequently used itch scale is the traditional visual analogue scale (VAS).

To assess the clinical efficacy of anti-pruritic components, there is a need for experimental induction of itch, through electrical or mechanical stimulation or primarily by the intradermal injection of itch inducers (2). Among them, histamine is the most widely used.

The measurement of itch after its induction in humans is difficult to assess because perceived itch is related to both peripheral (injection of histamine) and central factors. Indeed, the role of personal, emotional and psychological factors and the activation of motor areas (need to scratch) are very important in the central integration of itch in the brain. These allow us to define itch as "a sensation accompanied by the contralateral activation of the anterior cortex and the predominantly ipsilateral activation of the supplementary motor areas and the inferior parietal lobule; scratching may follow" (5), reflecting the fact that "it is the brain that itches, not the skin"(6).

Hence, it could be difficult to correlate subjective data, such as those obtained with the use of a VAS (from 0 to 10) with objective data, such as a quantity of injected histamine. This is why authors have preferred to search for a correlation with skin blood flow (7, 8) or, more recently, with functional magnetic resonance imaging data (9, 10), without a measured level of intensity, or both (11). To our knowledge, there was no validated protocol that uses prick-tests and VAS allowing further clinical trials. In this work, we have measured itch intensity at different times following prick-tests with histamine and codeine in a randomized double-blinded study.

SUBJECTS AND METHODS

This study was approved by the ethics committee of Brest. Thirty-six men, age range 18–30 years, with phototypes I, II or III, were included in the study. They did not use any cosmetics on the studied areas from one week prior to the initiation of tests nor any anti-inflammatory drug within one week, any anti-histamines within three weeks, any topical or systemic steroids 2 months prior to the study or psychopharmacological drugs 2 years prior to the study. They had no antecedents of atopic, allergic or neurological disease and had no skin lesions or scars on their forearms.

A screening visit was organized one week before the first tests. It was required that participants wash their skin in the evening prior to testing. At their second visit, prick-tests were performed on each forearm. Two areas of 1 cm^2 were marked 10 cm apart on each volar aspect. Four prick tests were performed with a polymethacrylate lancet (Stallerpoint®, Antony, France) in the middle of these areas: one without any product, one with NaCl (1 µl, 0.9%), one with histamine chloride (1 µl, 10 mg/ml, Stallergènes, Antony, France) and one with codeine phosphate (1 µl, 9%, Stallergènes). The order of prick tests was randomized. The diameter of induced papules was measured to ensure that tests were performed accurately: greater than 4 mm 20 min after histamine or codeine prick tests, and smaller than 3 mm after NaCl prick tests. Subjects evaluated itch intensity (from 0 to 10) by using the classic VAS after 1 min (T1), 2 min (T2), 4 min (T3), 10 min (T4), 20 min (T5) and 30 min (T6). Scratching was forbidden. At the third visit, 7 days later, the same prick tests were repeated with VAS assessment times being recorded as T11, T12, T13, T14, T15 and T16, respectively.

Descriptive, intra-group (comparing results from the second and third visits) and inter-group (comparing areas) analyses were carried out. Statistical analysis was made by analysis of variance, Bonferroni, Tukey, Student's *t*-test and Wilcoxon tests.

RESULTS

Thirty-six men were enrolled in the study (average age 24.5 years), with one subject who missed the third visit.

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Prick-tests were correctly performed in all subjects: diameters of papules were greater than 4 mm 20 min after histamine or codeine prick tests, and less than 3 mm after NaCl prick tests with no papules observed in areas where a prick test was performed without product.

VAS results were variable according to each patient. Intra- and inter-group comparisons showed significant differences ($p < 0.05$). After prick tests with histamine chloride or codeine phosphate, VAS scores were better than 0 at all times, at the second visit (day 0) and the third visit (day 7). There was no itch in the untreated area, but a weak increase 1, 2 and 4 min after application of NaCl.

In comparison with the untreated area, histamine chloride induced a significant itch at all measurement times and codeine phosphate inducing a significant itch from 1 to 20 min, whereas there was no significant difference with NaCl. In comparison with NaCl, prick tests with histamine chloride induced a significant difference at all times measured and those with codeine phosphate induced a significant difference from 2 to 20 min. A significant difference between histamine and codeine salts was noted only at 1 min.

At days 0 and 7, mean values of the VAS scores increased from T0 to 4 min then decreased (Fig. 1 A and B). A similar change in these scores was noted in the 3 cases, but VAS scores remained near 0 without the addition of a product. Statistical analysis showed significant decreases in VAS scores between the second and third visits for histamine ($p < 0.005$), codeine ($p < 0.01$) and NaCl ($p < 0.005$), whereas there was no modification in non-injected areas (Table I). No significant differences were found in the diameters of papules.

Table I. *Comparisons between VAS scores at days 0 and 7 (n = 34).*

Differences from day 0 to day 7					
Product	Time (min)	Mean	SD	Minimum	Maximum
Histamine	1	–0.49	1.22	–4.40	1.20
	2	–0.66	1.14	–2.90	2.60
	4	–0.95	1.08	–4.00	0.70
	10	–0.83	1.52	–4.20	3.30
	20	–0.20	1.04	–3.20	1.60
	30	–0.03	0.45	–1.40	1.70
Codeine	1	–0.67	1.59	–5.10	2.00
	2	–0.81	1.94	–7.70	2.60
	4	–0.91	1.74	–6.20	1.70
	10	–0.68	1.67	–4.90	3.50
	20	–0.31	0.91	–2.60	1.30
	30	–0.02	0.53	–1.50	2.00
NaCl	1	–0.26	0.55	–2.00	0.10
	2	–0.33	0.57	–1.90	0.40
	4	–0.29	0.61	–2.30	0.50
	10	–0.10	0.29	–1.40	0.00
	20	–0.01	0.04	–0.20	0.00
	30	–0.01	0.03	–0.20	0.00
Control	1	0.05	0.37	–0.50	2.10
	2	0.03	0.11	0.00	0.60
	4	0.01	0.03	0.00	0.20
	10	–0.01	0.03	–0.10	0.00
	20	–0.00	0.02	–0.10	0.00
	30	0.00	0.02	–0.10	0.10

SD: standard deviation; VAS: visual analogue scale.

DISCUSSION

The aim of this study was to validate a reproducible model of itch induction for further pharmacological studies. Prick tests with histamine chloride and codeine phosphate on the forearms of healthy test subjects show significant and coherent variations of VAS scores with time and very significant differences with controls. A similar study also used the prick tests to compare the effects of loratadine and montelukast. The authors found similar results 10 or 15 min after the application of histamine and codeine (12).

However, differences between days 0 and 7 suggest that these tests are not reproducible in the same subjects over this time span. This could be due to the memory of induced itch that subjects acquired, which may diminish certain emotional factors, such as anxiety in comparison with the first prick tests. In the future, studies for screening anti-pruritic agents with this model should be made with only one visit or by using a ratio of scores if there are 2 visits. The main parameter for evaluating efficacy of an anti-pruritic agent should be the intensity of itch perceived 4 min after itch induction.

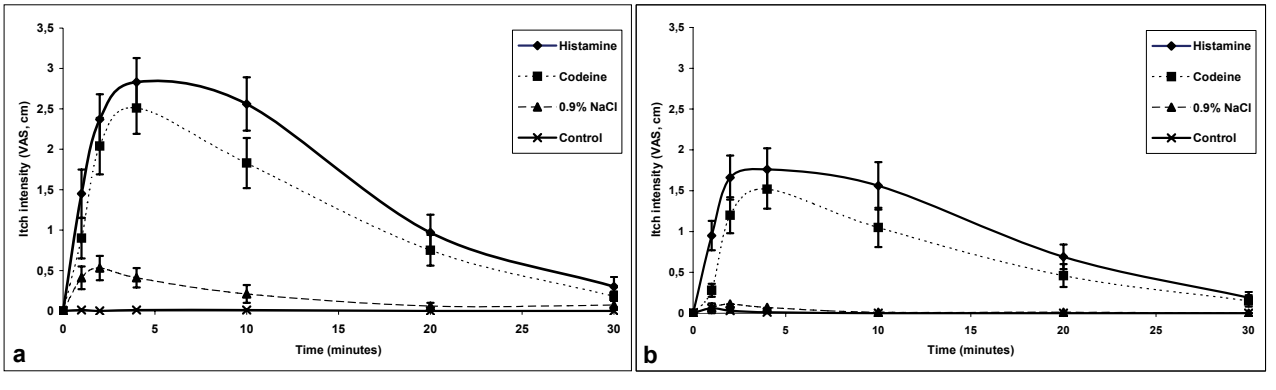

Fig. 1. Visual analogue score (VAS) scores at (a) day 0 ($n = 36$) and (b) day 7 ($n = 35$) (mean ± standard error, $n = 36$).

The development of histamine tachyphylaxis was demonstrated previously in healthy human skin and in uraemic patients (13). After repeated histamine injections at intervals of 90 min, both itch and flare responses decreased rapidly. A similar decline in histamine reactivity occurred when the interval between injections was extended to 24 h. Our study suggests that tachyphylaxis could be observed after 7 days.

Prick tests with histamine and codeine are usually positive controls for the induction of wheal and flare in allergic tests (14). Prick tests with histamine produce more itch than iontophoresis, which induce rather transient itch sensations (15). Flare reactions are correlated with itch VAS scores, but wheal is not, which suggests that this is an independent phenomenon (15). Intersubject variations of wheal size are lower with histamine than with codeine (16). However, we did not find such results with our tests. It is notable that all tested subjects were young adults. A new study with different age groups could be interesting.

Codeine induces release of histamine and tryptase by activating mast cells, as confirmed by microdialysis (17), but naloxone does not attenuate these effects. It is unlikely that μ-opioid receptors are involved in this mast cell activation. Analogies between cough and pruritus suggest that this effect could be due to δ-opioid receptors (18, 19). Whatever the mechanism, codeine-induced itch is secondary to the release of histamine. However, this phenomenon is probably very fast because we did not find a delayed effect of codeine by comparison with histamine in our work.

Although skin prick tests with histamine and codeine are very useful to evaluate IgE-mediated allergic disorders, many variations of the techniques are described and there is a need to validate procedures and very recent studies on this topic (20). Concerning itch evaluation, we did not find such studies, with the exception of Van Neste (7), who performed a similar study with histamine (but not codeine) and did not study reproducibility.

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