Acta Derm Venereol (Stockh) 1989; 69: 185–189

Some Aspects of the Experimental Induction and Measurement of Itch

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Two different rating scales—a visual analogue scale (VAS) connected to a chart-recorder, and Pain-Track®, a micro-computerized system with a 7-step-graded, fixed-point, non-verbal scale (FPNVS)—were evaluated for their capacity to assess experimental, histamine-induced itch continuously in 38 healthy subjects. The consequences for itch perception of using different injection sequences of various histamine concentrations were also investigated. A linear dose–response relationship was shown with random injection order for all subjective variables studied (itch latency and duration, maximal itch intensity, 'total itch index') with the VAS, but only for itch duration and 'total itch index' with the FPNVS. Using the VAS and injecting histamine solutions with increasing concentration, a significant dose–response curve was obtained for maximal itch intensity and 'total itch index', but when the same histamine stimuli were presented in the reverse (i.e. decreasing) order, there was no dose–response relationship. This indicates that central nervous system interaction may be unequally activated, depending on the order of different injected histamine stimuli. The objective variable flare was unaffected by the injection sequence. It is concluded that random injection order should be used in the assessment of itch sensation, in order to avoid systematic errors. The fact that the FPNVS did not discriminate as well as the VAS could indicate that our experimental stimuli were too weak to be properly discriminated with a 7-step-graded scale.

Key words: Injection order; Histamine; Scales; Visual analogue scale (VAS); Pain-Track.

(Accepted December 5, 1988.)

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Itch is a sensation with similarities to as well as differences from pain. Research in the measurement of itch has not shown the same progress as the intensive research in pain assessment during the last few decades (1).

To circumvent the obstacles in assessing clinical pruritus, investigators have induced itching experimentally in humans by intradermal injection of pruritic compounds such as histamine, peptides and proteases (2). This permits the control of the stimulus in a way that is not possible in the clinical situation. In such a psychophysical test on humans the experimental stimuli can be presented in varying order, e.g. with increasing or decreasing strength, or in a random fashion. There has been little investigation of whether the order of injection is of any importance for the outcome of experimental itch.

Most studies of experimental pruritus have recorded the threshold for itch induction (3–6) or the duration of the induced itch (7–9), but only occasionally itch intensity (2, 10, 11). This is in contrast to pain research, where several rating scales, e.g. the visual analogue scale (VAS) (12), have been introduced for quantitative measurement of different aspects of the pain experience. However, in recent years some methods for measuring the intensity of both experimentally induced itch (2, 10, 13) and clinical itch (14) have been published. In the latter study a new microcomputer-based system (Pain-Track®) was used for continuous recording of itch intensity. The patients indicated the intensity on a 7-step-graded fixed-point non-verbal scale (FPNVS) on transportable data-loggers, which stored the information. This system has been evaluated clinically for its capacity to measure itch (14), but not in an experimental itch situation.

The aims of the study were to compare perceived itch, when

1) introducing different doses of histamine *a*) of increasing strength, *b*) of decreasing strength, *c*) in random order;
2) using two different types of rating scale (VAS versus FPNVS), adapted for continuous itch recording.

MATERIAL AND METHODS

Subjects

Thirty-eight healthy volunteers from the hospital staff, 8 men and 30 women, aged 19–46 years (median age 30), participat-

Table I. *Regression coefficients (mean ± SD) obtained by linear regression analysis*

Subjective ratings were performed with VAS (200 mm). Number of subjects = 15. *p*-values indicate significance of linear dose–response relationship between variable and histamine concentration (1.0, 3.0 and 10 μg/ml). IL = Itch Latency, ID = Itch Duration, Imax = peak itch intensity, Tii = 'Total itch index' (area under the curve). NS = not significant

	Injection order of histamine			
	Increasing dose		Decreasing dose	
IL	−0.45 ± 1.22	NS	−0.09 ± 1.58	NS
ID	18.68 ± 13.16	NS	11.44 ± 10.19	NS
Imax	7.49 ± 5.29	$p<0.001$	1.84 ± 3.47	NS
Tii	1 258.74 ± 1 229.44	$p<0.001$	257.47 ± 546.82	NS
Flare	94.75 ± 29.53	$p<0.05$	104.87 ± 20.88	$p<0.025$

ed in the study. Seven of the subjects took part in more than one of the experiments. None was using any drug. The subjects were paid for their participation. The study was approved by the local medical ethics committee at Karolinska Sjukhuset.

Intradermal test procedure

On the lateral aspect of the upper arm 0.01 ml of histamine hydrochloride (ACO Läkemedel AB, Sweden) and buffered physiological saline (control) was injected intradermally by the same investigator under single- or double-blind conditions. The histamine was given in various concentrations (1.0, 3.3 and 10 μg/ml) made by dilution with sterile pyrogen-free physiological saline containing 10% (v/v) Sørensen phosphate buffer ($Na_2HPO_4 + KH_2PO_4$, 67 mM), pH 7.4.

Recording of flare

The axon-reflex mediated skin flare reaction was outlined with a marking pen on the skin 5 min after the injection and traced onto a transparent plastic film from which the area was calculated using a planimeter (model 317, Gebrüder Haff GmbH, Pfronten, W. Germany).

Recording of itch

Itch intensity and duration were monitored continuously with either the Pain-Track® system (Autenta AB, Uppsala, Sweden) or with a potentiometer with a 100- or 200-mm VAS. The time intervals between histamine injection and start and stop of the itch sensation were recorded as well as the continuous assessment of the perceived itch intensity. This allowed the calculation of itch latency (IL, sec), itch duration (ID, sec), peak value of itch (Imax, 0–100 or 200 mm with VAS, 0–6 with FPNVS) and a 'total itch index' (Tii = area under the curve, mm^2 with VAS, arbitrary units with FPNVS).

(a) The Pain-Track system and FPNVS. Pain-Track is a system for the recording of subjective symptoms (14, 15). It consists of portable data-loggers for patients' use, a hardware terminal unit and a software package. The data-logger has a control for rating the intensity of the symptom, in our case itch, from 0 to 6; 0 is no itch and 6 maximal itch intensity. In the instructions to the participants it is stated that the scale steps should be equal and that 3 should represent half the maximal itch intensity. In our study, the scale position of the itch intensity rate knob was automatically recorded by the data-logger every second (time base adjustable from 0.5 s to 1 h). When the recording was completed, the data were transferred from the logger to a personal computer for storage and analysis.

(b) The potentiometer and VAS. The subjects rated their itch intensity using a lever attached to a linear potentiometer controlling the position of a pen on a plotter out of sight of the patient. The potentiometer was equipped with a 100- or 200-mm VAS. The end-points of the scale were defined as no itch (0 mm) and maximal itch intensity (100 or 200 mm).

Experimental protocol

The subjects were randomly assigned to one of the following groups, 15 in each group:

I: Single-blind injections of stepwise increasing histamine concentrations, followed one week later by stepwise decreasing concentrations; recording with a 200-mm VAS.
II: Randomized order, double-blind injection of histamine concentrations; recording with FPNVS (Pain-Track system).
III: As in group II, but recording with a 100-mm VAS.

Statistical methods

To analyse whether the responses obtained from the different histamine concentrations fitted a linear function, linear regression analysis with calculation of slope (regression coefficient, beta-value) was performed for each variable and subject. Student's *t*-test (two-tailed) was performed on the underlying population of beta-values to ascertain whether a significant dose–response relationship existed.

RESULTS

Increasing versus decreasing order of histamine concentrations (VAS)

The results are summarized in Fig. 1 and Table I. Itch duration (ID), peak itch intensity (Imax), 'total itch index' (Tii) and skin flare increased progressively in

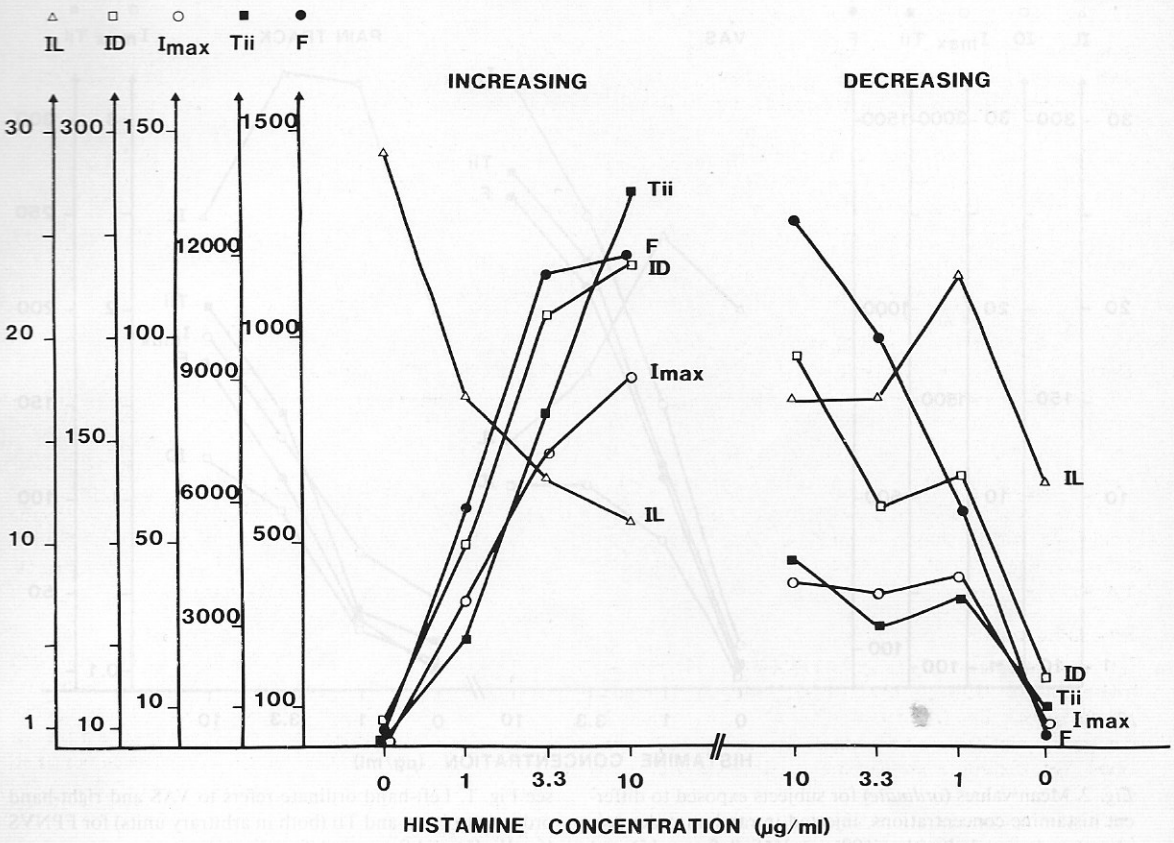

Fig. 1. Mean values for 15 subjects exposed to increasing (*left*) and decreasing (*right*) histamine concentrations. Subjective ratings made by a potentiometer with a 200-mm VAS. IL = Itch Latency (sec); ID = Itch Duration (sec); Imax = maximal itch intensity (mm); Tii = 'Total Itch Index' (mm^2); F = Flare (mm^2).

response to gradual increments in histamine dose. The dose–response relationships were significant for Imax, Tii and flare. An inverse, but non-significant, relationship was seen between latency and histamine concentration. When the injections were given in reverse order, i.e. decreasing concentration, only flare showed a significant linear dose–response curve. The other variables revealed a deviating outline with higher numerical values for 1.0 µg/ml of histamine than for 3.3 µg/ml.

Table II. *Regression coefficients (mean ± SD) obtained by linear regression analysis*

Subjective ratings were performed with VAS (100 mm) or FPNVS. Number of subjects indicated in parentheses. *p*-values indicate significance of linear dose–response relationship between variable and histamine concentrations (1.0, 3.3 and 10 µg/ml). For abbreviations, see Table I

	Scale			
	VAS		FPNVS	
IL	−0.95 ± 1.28 (12)	$p<0.025$	−0.84 ± 1.72 (9)	NS
ID	7.19 ± 8.10 (15)	$p<0.05$	10.44 ± 9.99 (14)	<0.05
Imax	2.54 ± 2.63 (15)	$p<0.025$	0.13 ± 0.09 (14)	NS
Tii	222.55 ± 244.80 (15)	$p<0.025$	18.01 ± 21.83 (14)	$p<0.025$
Flare	109.67 ± 36.89 (15)	$p<0.01$	71.46 ± 34.03 (15)	$p<0.005$

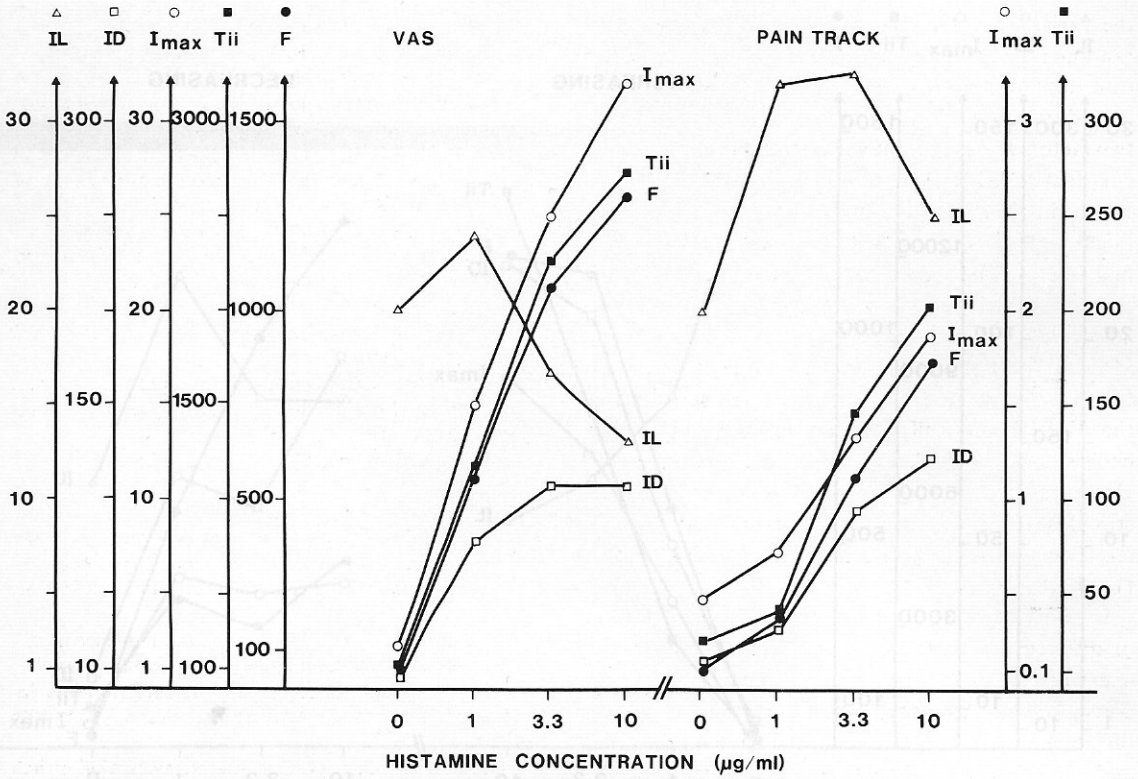

Fig. 2. Mean values (*ordinate*) for subjects exposed to different histamine concentrations, injected in random order (*abscissa*) and recorded with a 100-mm VAS (left; $n=15$) and Pain-Track with FPNVS (right; $n=15$). For abbreviations, see Fig. 1. Left-hand ordinate refers to VAS and right-hand ordinate to Imax and Tii (both in arbitrary units) for FPNVS (for IL, ID and flare, see left ordinate).

VAS versus FPNVS (random injection order)

As shown in Fig. 2, the shape of the curves was similar for the two scales and agreed also with those seen following injection of increasing histamine concentrations. For VAS, significant dose–response relationships were found for all the variables measured, but with FPNVS, this was shown only for ID and Tii (Table II).

DISCUSSION

To check for any systematic errors in the induction and assessment of experimental itch, we investigated the influence of the order in which various histamine concentrations were injected. Our findings strongly indicate a random injection order or, less good, gradually increased doses of the itch-provoking substance. The finding that gradually decreasing doses of histamine gave a non-linear result regarding the subjective itch variables, whereas the flare response was unaffected by the injection order, may be explained, at least partly, by central nervous system (CNS) interactions. It might thus be suggested that an initially higher concentration of histamine triggers the activation of modulatory events in the CNS, leading to a disturbed perception of the following weaker stimuli. This is seen as a flattened dose–response curve reflecting a non-linear relationship. The flare response could in this instance be taken as a 'control', since this variable reflects primarily peripheral effects of histamine on the distal part of the sensory afferent fibres as well as on mast cells and small blood vessels (8).

The measurement of itch intensity is of interest, since it makes it easier to quantify the itch response and to compare different pruritogenic agents or antipruritic treatments. In the present study we have used two different rating scales, the VAS and the FPNVS. The VAS has been validated and used extensively in pain intensity measurements (1, 16). In our work there was a significant dose–response relationship of

the variables measured with the VAS and using the random injection technique. The FPNVS gave significant dose–response curves only for the two variables 'itch duration' and 'total itch index'. Although these two factors are important when studying clinical itch, our data indicate that in studies of experimentally induced, relatively low-amplitude itch, the VAS might be preferable. In the present study the intradermal injection of histamine caused no scratching or intense itching, such as the clinical pruritus in e.g. atopic eczema, and on average, Imax was only about 30% of the highest itch intensity imaginable. The FPNVS as used here only permits seven steps, while the VAS theoretically has an infinite number of choices but is divided in practice into mm-steps. However, opinions differ on how many steps in stimulus strength a subject might be able to differentiate. This is of interest in designing valid rating scales (1, 17, 18, 19).

In conclusion, our data indicate that the sequence of different concentrations of histamine injected in experimentally induced itch is of importance in itch perception, and that subjective rating scales may give differing results. Our study shows that both the VAS and FPNVS can be used to assess pruritus, but for some variables the VAS discriminated better. Thus, it would be of interest to provide the Pain-Track data-logger with a VAS, as the Pain-Track system is of considerable advantage in the continuous assessment of clinical itch (14).

ACKNOWLEDGEMENTS

The skilful technical assistance of Ingrid Vedin is gratefully acknowledged. We thank Elisabet Berg at the Department of Medical Information Processing, Karolinska Institutet, Stockholm, for advice and assistance with the statistical analysis. This investigation was supported by Karolinska Institutet, the Finsen Foundation and the Edvard Welander Foundation.

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