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Computerized Recording of Itch in Patients on Maintenance Hemodialysis

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Itch was assessed both continuously using a computerized method, Pain-Track, and retrospectively using visual analogue scales (VAS) by 28 patients undergoing maintenance hemodialysis and suffering from uremic pruritus. Measurements were performed during 7 consecutive days including three dialysis sessions. Pain-Track recordings showed that itch intensity was greater during dialysis than on days following dialysis ($p < 0.05$). Possible explanations are that pruritogenic substances might be released during treatment or that removal of such substances during dialysis leads to amelioration of symptoms after treatment. Alternatively, lowering of the sensory threshold due to general discomfort in association with dialysis may exacerbate the itch intensity. There was no consistent difference between daytime and bedtime itch scores over the week, except on the second day without treatment, when bedtime itch ratings significantly exceeded those during the day ($p < 0.05$), suggesting that factors other than inactivity are essential for this peak in itch intensity. Thus, after 2 days without treatment, when patients become increasingly metabolically deranged, they reported maximal itch, implying that the accumulation of pruritogenic substances is of major importance in the pathogenesis of uremic pruritus. There was a positive correlation between Pain-Track and VAS data, although significant fluctuations in itching could be detected only with Pain-Track. ***Key words: Pruritus; Chronic renal failure.***

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Itching is one of the most disabling symptoms of chronic renal failure. It affects 65–80% of patients in this category (1, 2). The etiology is unknown and although various explanations such as xerosis of the skin, secondary hyperparathyroidism, mast cell hyperplasia, etc., have been proposed (3–6), the pathogenesis remains to be clarified. Before the introduction of dialysis, the prevalence of pruritus was estimated to less than 20% (7). Whether the increased frequency in today's patients represents the natural metabolic history of renal insufficiency due to prolonged survival or reflects a side-effect of dialysis treatment is unknown. Gilchrest et al. reported that the majority of patients suffering from pruritus experienced their symptoms only or mostly during dialysis sessions (1). However, in our study based on interviews with 29 patients on maintenance hemodialysis, we were unable to discern any consistent pattern of pruritus (2).

The subjective and capricious nature of itching makes its assessment extremely difficult and, especially if assessment is performed retrospectively, its reliability may be limited. The evaluation of pruritus and antipruritic therapy is therefore an intricate task for clinical investigators. Recently, Pain-Track, a portable data-logger, has been shown sensitive enough to distinguish the effect of a known antipruritic treatment in patients with atopic eczema (8). The aim of the present investigation was to study uremic pruritus by means of the Pain-Track and to follow fluctuations in itch intensity over various days with special reference to dialysis sessions.

PATIENTS, MATERIAL AND METHODS

Patients

All patients were being treated with maintenance hemodialysis at the Division of Nephrology, Department of Medicine, Karolinska Sjukhuset or Södersjukhuset. At the time of the investigation, 46 patients (67%) were suffering from uremic pruritus. Ten patients were excluded due to serious illness or impairment of eyesight and/or hearing, and another 8 did not wish to take part in the study. The age range of the remaining 28 patients, 15 men and 13 women, was 30–77 (mean 59) years. The underlying renal diseases are listed in Table I. The duration of dialysis prior to the investigation ranged from 1 to 120 (mean 35) months and the duration of pruritus from

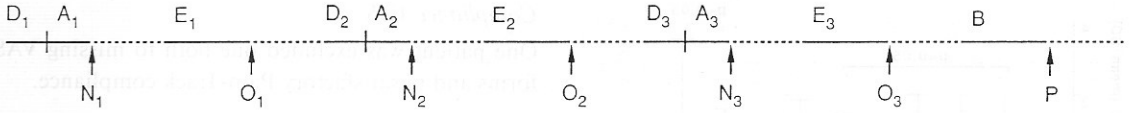

Fig. 1. Flow chart showing 7 consecutive days comprising three dialysis sessions; D_1, D_2 and D_3. A_1, A_2 and A_3=after dialysis sessions, the same day. E_1, E_2 and E_3=days following dialysis. B=2 days after dialysis. N_1, N_2 and N_3=bedtime, dialysis days. O_1, O_2 and O_3=bedtime, days following dialysis days. P=bedtime, 2 days after dialysis. ——=day, – – –=night.

0.5 to 106 (mean 19) months. All patients were dialysed for 3–4 h three times weekly.

Experimental procedure

Pruritus was assessed continuously using a computerized system (Pain-Track) and retrospectively using visual analogue scales (VAS) on diary cards. The investigation spanned 7 consecutive days including three dialysis sessions (Fig. 1). Thus, periods of measurements were divided into different categories shown in Fig. 1 (D, A, N, E, O, B, P). Bedtime ratings (N, O, P) refer to the itch intensity scored by the patients before going to sleep. No antipruritic therapy or sedatives were allowed during the study. No ultraviolet irradiation was given for one month before the investigation.

Pain-Track

Pain-Track® (Autenta AB, Uppsala, Sweden) is a system for self-recording of subjective symptoms. It was originally developed to measure epigastric pain (9). Pain-Track consists of data-loggers for patients' use, a terminal unit and a software package for storage, analysis and presentation of data. The portable, microcomputer-based data-logger (size 160×100×25 mm; weight 350 g) is designed to be simple enough for use by individuals without training in electronics.

The data-logger has three controls: a knob for rating the intensity of itch according to a fixed-point non-verbal scale from 0 to 6, a switch to indicate sleep/awake, and a marker button to indicate the patient's presence. To save battery and memory capacity, the data-logger reads the setting of the intensity knob at intervals of 10 min, which allows nearly 8 weeks' continuous recording.

When the switch is in the 'awake' position a buzz every 60 min instructs the patient to mark his presence by pressing the marker button and to rate the intensity of itch at that very moment, i.e. *not* over the preceding hour. The scale is operationally defined, with zero as no itch and 6 as the worst itch imaginable. The patient is told that position 3 on the scale should be half the maximal itch and that the intervals between the steps should be equal.

When the patient intends to go to sleep, the switch is turned to the 'sleep' position. This turns off the hourly buzz, but it is still possible to adjust the intensity rate. However, since there was no surveillance of compliance, night recordings were not included in the final evaluation of data.

Visual Analogue Scale

Every morning, evening and at the end of each dialysis session, the patients also rated the itch intensity of the preceding period on separate 100-mm VAS forms (10). The boundaries of the scale were defined as the extremes of itch intensity, i.e. 0=no itch, and 100 mm=the worst itch imaginable. The VAS markings were converted to scores between 0 and 100 by reading off each mark against a millimetre grid.

Compliance

Pain-Track compliance was calculated as the percentage of patient responses to the buzzer. As no hourly signals were given during sleep, the compliance could not be assessed for the night recordings. As an arbitrary choice, days with a compliance less than 70% were excluded.

Statistical analysis

Based on the assumption of variables being approximately interval-scaled, parametric statistics was used (8). Differences between day-time itch ratings (periods D, A, E, B) were calculated according to a two-factor analysis of variance with the factors: patients and category of period (11). Differences between daytime and bedtime itch scores (periods A, N, E, O, B, P) were tested according to a three-factor analysis of variance with the factors: patients, day-time/bed-time, and category of period (11). In both analyses, the patient was the random factor, that was repeatedly investigated during the different periods of measurement. Results are expressed as mean ± SD. Correlation between Pain-Track data and VAS recordings was determined using Pearson's product moment correlation coefficient.

Table I. *Underlying renal dieases*

Diagnosis	No.
Chronic glomerulonephritis	11
Renal hypertensive disease	4
Chronic pyelonephritis	3
Diabetic nephropathy	2
Polycystic kidney disease	2
Interstitial nephritis	1
Renal dysplasia	1
Bilateral nephrectomy	1
Uremia, etiology unknown	3
Total	28

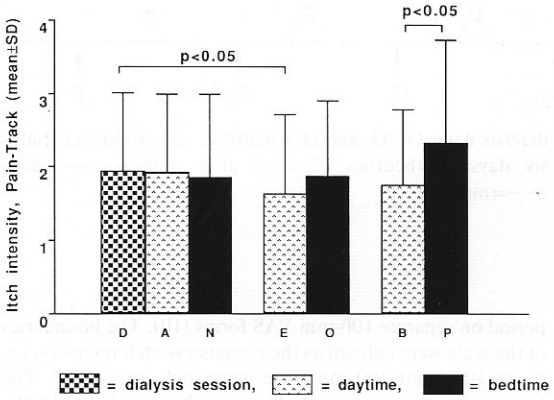

Fig. 2. Intensity of itch measured by Pain-Track in 19 patients. For symbols, see Fig. 1. $D=(D_1+D_2+D_3)/3$. $A=(A_1+A_2+A_3)/3$. $E=(E_1+E_2+E_3)/3$. $N=(N_1+N_2+N_3)/3$. $O=(O_1+O_2+O_3)/3$. $D>E$ ($p<0.05$). $P>B$ ($p<0.05$).

RESULTS

Data from patient interviews

In 9 patients, pruritus had appeared before, and in another 9 at the initiation of dialysis treatment. Ten patients developed itching some time after commencing dialysis. Four patients felt better during the summer, 13 patients denied any influence of season and 11 patients could not decide. Nineteen patients (61%) stated that their itch intensity was unrelated to dialysis sessions, whereas 6 patients (20%) experienced increased, and one patient diminished itching during or immediately after dialysis treatment, and 2 patients were uncertain. Seven patients were most bothered in the evening, while the rest were not conscious of any consistent fluctuations over the day.

Twenty-two patients had tried antihistamines with poor or no relief. Four patients had been treated with ultraviolet light (UVB), with temporary improvement. Topical corticosteroid ointments efficiently suppressed localized eczematous changes in 8 patients.

Compliance Pain-Track

Seventeen of the 28 patients showed at least 70% compliance for all 7 days. In another 7 patients the compliance on individual days, not included in the study, was less than 70%. Four patients had an overall compliance below 70% and were excluded altogether. Altogether 41 of 196 (21%) recorded days were excluded due to non-compliance.

Compliance VAS

One patient was excluded due both to missing VAS forms and unsatisfactory Pain-Track compliance.

Results Pain-Track

Itch scores on dialysis days seemed higher than scores on days without treatment (Fig. 2), although only the difference between ratings during the dialysis sessions (D) and the ratings on the days following dialysis (E) were statistically significant ($p<0.05$). There was no consistent difference between daytime and bedtime itch scores except on 2 days after dialysis, when bedtime ratings (P) were significantly higher ($p<0.05$) than daytime ratings (B) (Fig. 2). Also, there was a tendency for the itch intensity to be higher at bedtime after 2 days without treatment (P) than on other evenings (N, O).

Results VAS

There was good correlation between Pain-Track and VAS-data (Fig. 3), although VAS data disclosed no statistically significant fluctuations in itch intensity over different days.

Clinical data vs Pain-Track and VAS recordings

There was generally poor correlation between patients' statements of diurnal itch fluctuations and the itch intensity measured by Pain-Track and VAS. Only 2 of the patients who reported most itching during dialysis sessions scored maximal itch during treatment as measured by Pain-Track and VAS. The patient reporting least symptoms during dialysis had in

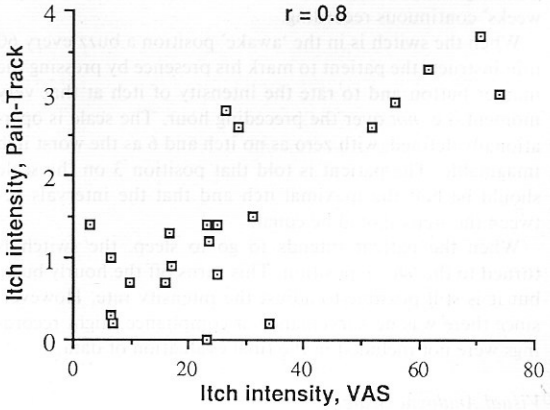

Fig. 3. Correlation between Pain-Track and VAS recordings during days following dialysis (E) in 22 patients.

fact the highest ratings during treatment. Of the 7 patients most bothered at night, 5 showed relatively high bedtime values, especially after 2 days without treatment, but so did patients who were unaware of any consistent fluctuations over the day or who reported most itching during dialysis sessions.

DISCUSSION

Both Pain-Track and VAS are subjective methods for measuring symptoms such as pain and itch. A previous investigation (8), as well as the present one, showed a close correlation between the two methods, although in this study the sensitivity of VAS recordings was too low to detect any significant fluctuations in itch intensity. The major advantage of the Pain-Track seems to be surveillance of the authenticity of itch estimations, whereas VAS forms could be completed retrospectively several days later from memory. Also, VAS ratings might reflect more the intensity of itch experienced by the patient immediately before filling in the form than the average intensity of the whole period. However, many patients found the Pain-Track-logger bothersome to handle, restricting the duration of the study and sometimes resulting in insufficient compliance. In addition, the low buzzer tone, which was difficult for some patients to hear, proved to be a drawback. Patients' own history regarding the pattern of pruritus was not confirmed by the present recordings, which further stresses the difficulties of retrospective assessment of itch.

Fluctuations in itch intensity in relation to dialysis sessions could theoretically be due either to the release of pruritogens or to the removal of such substances during treatment. Besides the biochemical alterations occurring during dialysis, psychological factors are likely to influence the perception of itching.

The present investigation suggests that itch intensity is accentuated on dialysis days compared with days without treatment, which could imply activation of pruritus due to treatment. It is conceivable that the process of extracorporeal circulation would induce the release of inflammatory and potentially pruritogenic substances.

Recently the 'interleukin hypothesis' has been put forward to explain various complications affecting patients undergoing dialysis treatment (12, 13). It has been proposed that monocytes produce interleukin-1 (IL-1) in response to 1) C5a generated via C5 following contact of plasma with dialysis membranes, and 2) endotoxin fragments from contaminated dialysate fluid (12). There is experimental evidence that IL-1 induces acute-phase responses such as fever, headache, lassitude etc. (14) and although IL-1 is not pruritogenic upon intracutaneous injection, the substance is pro-inflammatory in human skin (15). However, the clinical significance of the IL-1 release needs verification, and future studies on the biocompatibility of various dialysis methods are warranted.

Stockenhuber et al. have reported high plasma histamine levels in dialysis patients (16) and proposed that these would trigger itching. Still, if histamine (or other short-acting inflammatory mediators) released during dialysis were the primary cause of uremic pruritus, the itch intensity could be expected to abate rather quickly after termination of dialysis, whereas in our patients it persisted at about the same level all day long.

In association with dialysis sessions, many patients experience increased discomfort, which is liable to depress their sensory threshold for nociceptive stimuli such as pruritus, and may account for the exacerbation of symptoms during treatment. The lowest itch ratings were recorded during the days following dialysis days, when patients usually feel relatively well, which may support this conclusion.

There was no consistent difference between daytime and bedtime itch scores over the week, except after 2 days without treatment when itch intensity at night significantly exceeded that perceived during the day ($P > B$). Thus, inactivity and loss of distraction are not sufficient to explain this peak in itch intensity. If pruritus increases with increasing metabolic derangement of patients, this would suggest that the accumulation of pruritogens, rather than their release during treatment, is of importance in the pathogenesis of uremic itching. Apart from reflecting the relative well-being of patients, the decrease in itch intensity during days following dialysis treatment could be due to the removal of pruritogenic substances during dialysis sessions.

We have earlier found that uremic patients suffering from pruritus experience increased itching after intradermally injected histamine, and have concluded that they might have an augmented susceptibility to itch stimuli in general (17). Even though the basic mechanism underlying uremic pruritus is unknown, this increased reactivity would allow various influences, such as those discussed above, to aggravate the uremic itching and lead to the fluctuations in itch intensity recorded in the present investigation.

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