The Role of Substance P and its Receptor NK1R in Chronic Prurigo: Results from a Randomized, Proof-of-Concept, Controlled Trial with Topical Aprepitant

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BACKGROUND **Chronic prurigo (CPG) is a debilitating disease characterized by pruritus with chronic and persistent lesions, papules and/or hyperkeratotic nodules. The underlying pathophysiological mechanisms of CPG remain unknown, but Substance P (SP) and its receptor neurokinin 1 (NK1R) are held to be involved in the pathogenesis of chronic prurigo.**

OBJECTIVE **To characterize serum levels of Substance P, cutaneous expression of NK1R, and the effects of topical aprepitant, an NK1R antagonist, in patients with chronic prurigo.**

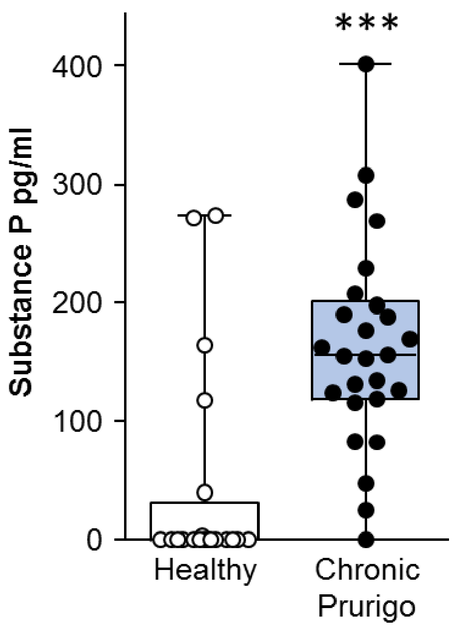
PATIENTS AND METHODS **26 CPG patients and 20 healthy individuals were assessed for serum levels of SP. 19 CPG patients were assessed for cutaneous NK1R expression and were included in the clinical trial. These patients had CPG with symmetrical prurigo lesions at upper or lower extremities and therapy-resistant pruritus with a visual analogue scale (VAS, 0-10) of 6 or higher.**

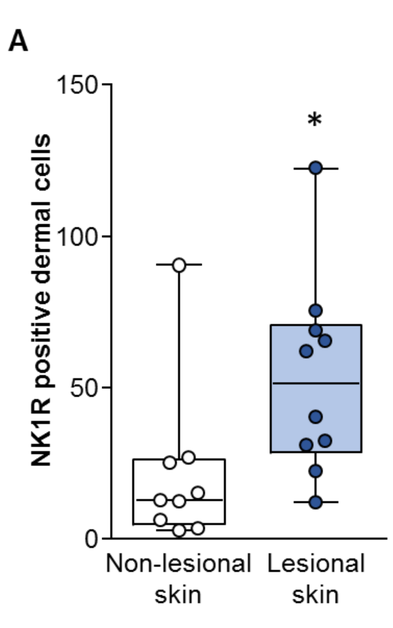
The study was a single-centre, prospective, randomized, placebo-controlled, double-blind, left/right split-side comparison, phase IIa, trial to evaluate the effects of topical aprepitant in 19 patients with therapy-refractory CPG.

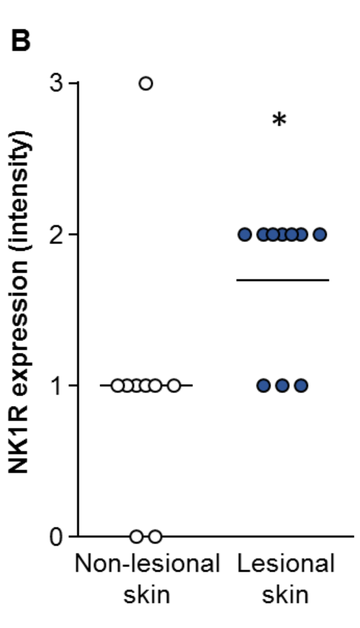
Patients received aprepitant gel (10 mg/g gel) on one side of the body and placebo vehicle (gel) on the other side of the body, applied twice daily for 28 days. Pruritus and other parameters were assessed and efficacy of aprepitant was compared to gel after 28 days of treatment.

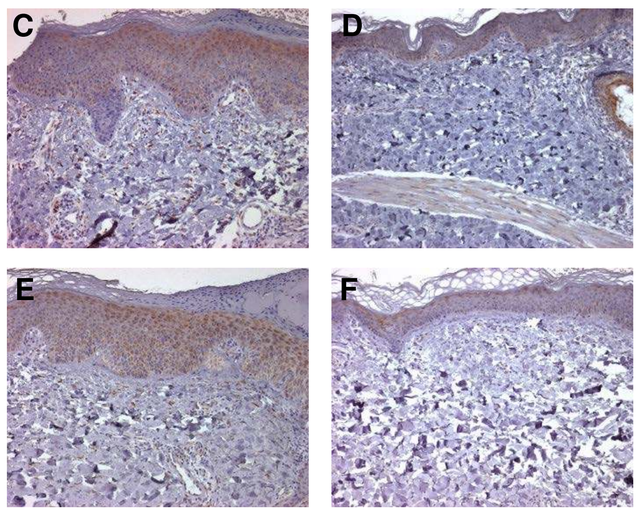
RESULTS

Serum Levels of Substance P are Elevated in Patients with Chronic Prurigo. Substance P was measured by enzyme-linked immunosorbent assay in the serum of chronic prurigo patients (n=26), and age and sex matched healthy controls (n=20). Boxes represent 25th and 75th percentiles, horizontal lines the median and whiskers show minimum to maximum values with the dots representing individual subjects, ***P<0.001 (unpaired t test).

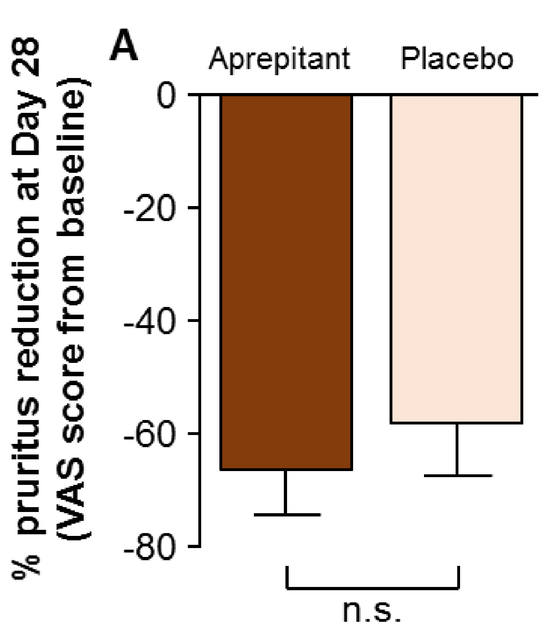


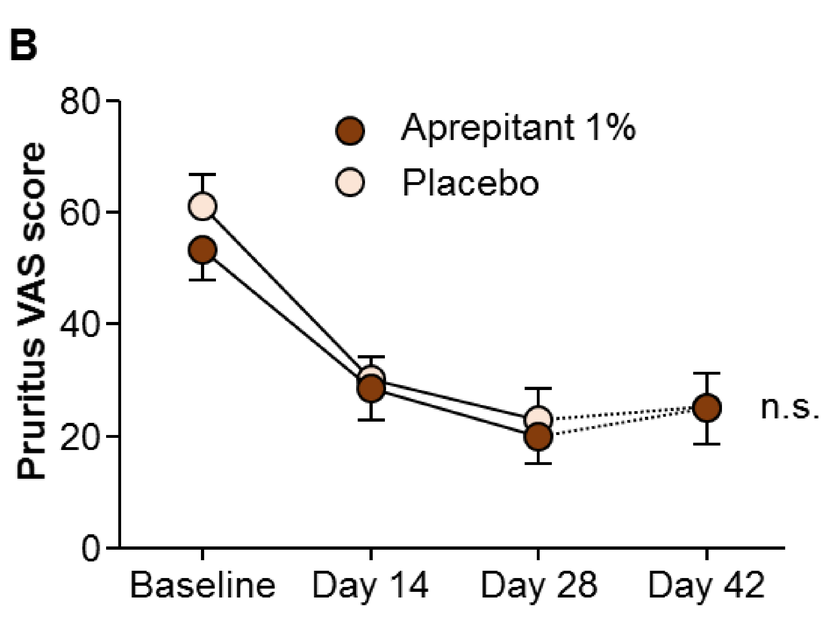


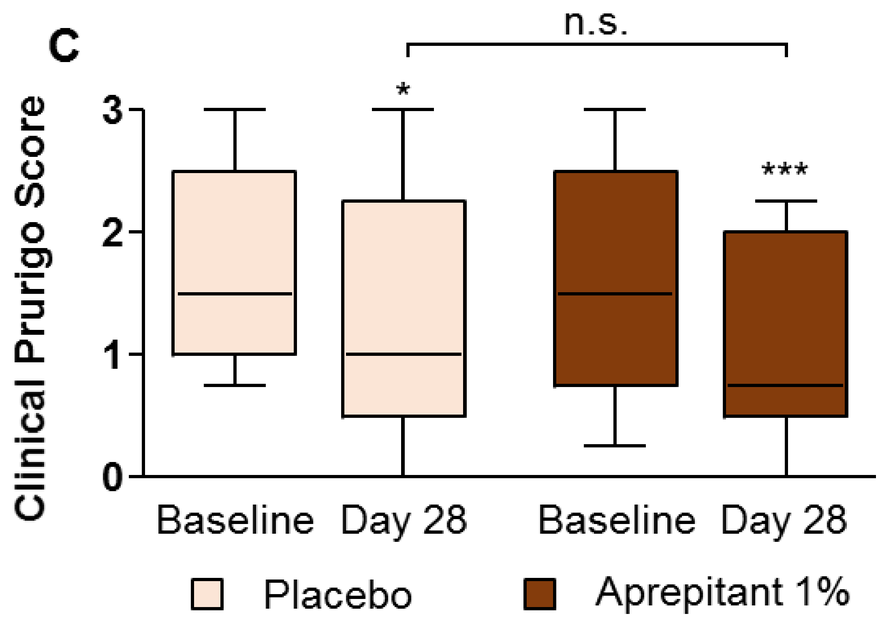




Expression of Neurokinin 1-Receptor is Increased in the Lesional Skin of Patients with Chronic Prurigo. (A) and (B). Paraffin embedded skin sections were stained with a polyclonal rabbit antibody against the 2nd extracellular domain of human Neurokinin 1 receptor and blind counted by an investigator. Sections were evaluated at 100x magnification and staining intensity was rated between 0 and +++. Boxes represent 25th and 75th percentiles, horizontal lines the median and whiskers show minimum to maximum values with the dots representing individual sections, * *P*<0.05 (paired t test). (C-F). Examples at 100x magnification of samples from two individual patients. C and E is lesional skin, D and F is non-lesional skin.







Treatment with both topical aprepitant and placebo vehicle reduces pruritus intensity and improves prurigo lesions. Topical aprepitant 1% on one extremity, and placebo on the other was applied twice daily for 28 days and pruritus intensity on each arm was assessed by patients using a visual analogue scale, ranging from 0 (no pruritus at all) to 100 (maximum pruritus imaginable). (A). Pruritus reduction from baseline to the end of the application period after 28 days. (B). Pruritus intensity over time. (C). Clinical prurigo score is a 4-point score ranging from 0–3, assessed by an investigator using the average from a score of 0 (non-existent) to 3 (severe) for erythema, crusts, scratch artefacts and infiltration. Data is presented as mean ± SEM (A,B), in C, Boxes represent 25th and 75th percentiles, horizontal lines represent the median and whiskers show minimum to maximum values *P<0.05, ***P<0.001, n.s.=not significant, using unpaired t test (A), 2-way ANOVA (B), and paired t test (C).

SUMMARY & DISCUSSION

High levels of SP were found in patients with prurigo compared with healthy individuals and NK1R is upregulated in lesional skin of prurigo patients
Both, topical aprepitant 1% gel and placebo vehicle showed a large improvement in pruritus intensity with an over 50% reduction, as measured by VAS
Treatment with topical aprepitant 1% gel did not result in a significantly more effective treatment for pruritus vs. placebo vehicle
The aprepitant gel was well tolerated overall with pain and irritation at the site of administration being the most commonly experienced AE.