Polidocanol inhibits cowhage - but not histamine-induced itch in humans

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Abstract: Polidocanol is a local anesthetic and antipruritic compound that is used in the treatment of itching skin conditions such as eczema. Its mechanisms of action are largely ill defined. This study has compared the antipruritic efficacy of topical polidocanol in histamine-induced itch and a histamine-independent, cowhage-induced model of pruritus. Polidocanol (3%) or vehicle was applied topically under occlusion for 1 h to the forearms of 45 healthy volunteers before itch was provoked by rubbing in 40–45 spicules of cowhage or skin prick testing with 10 mg/ml histamine. Itch was recorded at 1-min intervals for 30 min on a 100-mm visual analogue scale. Polidocanol significantly reduced the area under the curve for cowhage-induced itch by 58% (P < 0.05), but had no significant effect on histamine-induced itch. This result underlines the importance of histamine-independent itch models in the development of topical antipruritic agents.

Key words: antipruritics – atopic dermatitis – mucuna – polidocanol – pruritus

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Background

While histamine is the major pruritogen in mast cell-mediated diseases, it is thought to play at most a minor role in other conditions where alternative pruritogens, such as gastrin-releasing peptide, activators of protease-activated receptor-2 (PAR-2) or transient receptor potential vanilloid 1 (TRPV1), have been proposed (1–3).

Mucuna pruriens (cowhage) spicules contain the cysteine protease mucunain, which activates PAR-2 and PAR-4 (4) which are expressed on dermal neurons and have been implicated in pruritus associated with atopic dermatitis (AD) (5,6). Further, H₁,-antihistamines are ineffective in itch produced by cowhage (7,8).

Polidocanol (laureth-9) is the polyethylene glycol ether of lauryl alcohol used as an antipruritic agent in galenic formulations and cosmetic products (9). Although preclinical animal experiments and a postmarketing drug survey have suggested local anesthetic properties (9,10), this has not been supported by human studies, including histamine-induced itch and heat sensitivity testing (11–13).

Questions addressed

This study, firstly, compared the characteristics of histamine- and cowhage-induced skin responses and, secondly, tested the hypothesis that polidocanol would reduce cowhage-induced itch but not that induced by histamine.

Experimental design

The effects of polidocanol on cowhage- and histamine-induced dermal responses were studied in a double-blind manner in 45 healthy volunteers (31 females, 14 males, age range 20–49 years).

The study was approved by the Ethics Committee of the Charité – Universitätsmedizin Berlin (Approval number: EA4/063/12).

Three 7 cm² circular areas on the volar surface of one forearm were pretreated with 1 ml of a 3% polidocanol formulation (polidocanol Laureth 9; 3% polidocanol 5% pentylene glycol, 92% pure water; Nikko Company, Tokyo, Japan). The opposite arm received vehicle (placebo) pretreatment. Both areas were covered for 1 h with Tegaderm film (3M Company, St. Paul, MN, USA). After removal of the occlusion, the skin was wiped free from liquid and two sites were provoked with cowhage or histamine and the third site remained unprovoked to serve as vehicle control. For cowhage-induced pruritus, 40–45 spicules of cowhage were counted under a magnifying lens, picked up by micro-tweezers, applied to a 4 cm² area of the volar surface of one forearm and gently rubbed in with a nitrile-butadiene rubber gloved finger for 45 s, as described previously (14). Histamine skin prick testing was performed with 10 mg/ml of histamine dihydrochloride (ALK-Abello, Hørsholm, Denmark).

Itch was assessed every 1 min for 30 min after provocation using a 100-mm visual analogue scale (VAS), and the area under the curve (AUC) was calculated and used as the primary output variable. Maximum VAS score and itch duration were also calculated for each patient. Wheal and flare area was calculated from the mean of the largest diameter and the diameter at right angles to this diameter measured at 15 min. Wheal volume was assessed at 20 min after provocation by three-dimensional (3D) pictures of the tested areas (PRIMOS; GF Messtechnik GmbH, Teltow/Berlin, Germany) (15).

As data were normally distributed, results are shown as means ± SEM. Differences between treatments were compared using Student’s t-test for paired data.

Results

At the placebo-treated sites, provocation of the skin with histamine gave a characteristic wheal and flare response in all subjects. No whealing resulted from rubbing cowhage spicules into the skin.

Both cowhage and histamine resulted in rapidly developing itch responses that reached a maximum within 2–3 min of provocation. With cowhage, the maximum intensity of itch was 41.2 ± 5.4 mm VAS and its duration 11.9 ± 1.2 min. With histamine, the maximum intensity of itch was 28.8 ± 2.6 mm and its duration...
Polidocanol significantly reduced the maximum intensity of cowhage-induced itch by 31% ($P < 0.05$) and its duration by 37% ($P < 0.05$) for cowhage-induced itch. Furthermore, polidocanol did not reduce histamine-induced wheal volume or flare area, the values being 3.80 ± 0.38 vs 3.30 ± 0.42 mm$^2$ for wheal volume and 575 ± 75 vs 425 ± 49 mm$^2$ for flare area after polidocanol and placebo, respectively.

**Discussion**

Dermal responses to histamine and cowhage are quite different. While both produce itch, the response to histamine is accompanied by a characteristic wheal and flare while that to cowhage is not. Polidocanol significantly reduced cowhage-induced itch but not that induced by histamine.

H$_1$-antihistamines appear to be ineffective in many pruritic skin conditions and alternative therapies are inadequate (16). Enhanced PAR-2/PAR-4 signalling, the purported mechanism of cowhage-dependent itch (4), has been suggested as being involved in AD (6). However, the role of this pathway in different conditions remains to be elucidated.

Conduction velocity and discharge rates in neurons activated by cowhage are higher as compared to histamine-responsive neurons (17) and thereby might be inhibited by lower concentrations of a local anaesthetic (18,19). Furthermore, the limited dermal absorption of polidocanol (13) may exacerbate this differential nerve blockade. This may explain the observed clinical efficacy of polidocanol in AD and eczema where PAR-2 dependent itch pathways rather than histamine pathways are thought to be involved (9).

In conclusion, different pathways of pruritus may respond differently to topical antipruritic therapies, such as polidocanol, and underline importance of using histamine-independent itch models in the testing of antipruritic agents.

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**Author contributions**

TH, JWF, VM, DR and MMe designed the study; TH and MMe performed the research; VM and DR contributed essential reagents; TH, JWF, MKC and MMe contributed significantly to analysis and acquisition of data; TH, MKC and MMe wrote the paper; all authors contributed in drafting the paper or revising it critically; all authors approved the submitted and final version.

**Conflict of interests**

VM and DR are employees of Pierre Fabre; JWF received honoraria as an advisor for Pierre Fabre. None of the other authors have potential conflict of interests to declare.

**References**


