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Sertaconazole nitrate mediates its antiitch activity by inducing PDG2 via the p38 MAPK pathway

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Sertaconazole nitrate (STZ), a broad-spectrum antifungal agent, has recently been shown to exhibit antiitch activity; however, the signaling pathways that mediate this action are unknown. Therefore, to elucidate the cellular mechanism behind this activity, the effects of sertaconazole nitrate were examined in vitro and in vivo. We used compound 48/80, an agent known to induce itch and promote the release of histamine, in RBL-2H3 mast cells to mimic a pruritic response, and observed that sertaconazole nitrate induced PGD2 production. PGD2 is known to have antipruritic activity by suppressing histamine release. Similar results were obtained in the macrophage cell line, RAW-264.7, when lipopolysaccharide (LPS)-stimulated PGD2 levels were further enhanced by sertaconazole. In order to dissect the pathway involved in PGD2 production, an inhibitor of p38 MAPK, SB203580, was used along with the aforementioned secretagogues. Blocking the p38 MAPK pathway eliminated PGD2 induction in both cell lines. Furthermore, using a murine model of pruritus we showed that compound 48/80-induced scratching was successfully reduced by the topical application of sertaconazole nitrate. This effect was reversed by the addition of ibuprofen or a PGD2 receptor antagonist, confirming that sertaconazole-induced PGD2 production was responsible for inhibiting the itch response. Thus, the antipruritic activity of sertaconazole nitrate is mediated by the induction of PGD2 through the p38 MAPK pathway.

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Novel follicular-targeted nanoemulsions for acne

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Background: Acne vulgaris is a common condition caused by the blockage of pilosebaceous units with proliferation of *P acnes* bacteria leading to unsightly, inflamed lesions primarily on the face, neck, and back. The effectiveness of acne treatments have been limited by the ability to permeate into the pilosebaceous unit. A novel antibacterial nanoemulsion (NB-003) composed of nanometer-sized droplets that physically disrupt *P acnes* was investigated in the hamster ear model for its ability to permeate the pilosebaceous unit.

Methods: In vitro skin permeation studies with several different NB-003 formulations (eg, lotions and gels) were performed using hamster ear as the skin model. Nanoemulsions with entrapped fluorescein or green fluorescent protein were assayed at various time points (4, 24, and 48 hours) under varying dosing conditions (QD vs BID). Residual test article was removed by rinsing and swabbing. Hamster ear skin was cryosectioned to 7-μm sections and viewed under a fluorescent microscope. The permeation of NB-003 was assessed by measurement of a chemical marker for the emulsion droplets, cetylpyridinium chloride (CPC), by HPLC following dissection of sebaceous glands from hamster ears. The levels of NB-003 were analyzed in surrounding tissues (eg, epidermis dermis, dorsal ear) by measurement of CPC content.

Results: Fluorescence micrographs showed permeation of NB-003 into the entire pilosebaceous unit. All pilosebaceous units in the examined fields showed evidence of NB-003 uptake. There was an increase in the delivery of CPC to the sebaceous glands with increasing concentrations of NB-003 at 24 hours that appeared to plateau at the 0.5% NB-003 concentration.

Conclusions: These data suggest that NB-003 specifically targets the pilosebaceous unit achieving high concentrations where acne begins. The concentrations of NB-003 are well above the MBC for *P acnes*, providing a potential acne therapy. NB-003 is currently being studied in a phase I clinical trial to measure the reduction of facial *P acnes*.

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Understanding sunscreens: The proposed FDA rule on UVA assessment and labeling will drive US sunscreens towards a uniform UVB/UVA protection profile

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Prevention of sunburn, photoaging, and eventually skin cancer is practiced in most cultures by avoiding the sun and covering up (ie, solar radiation is reduced uniformly without preference for either UVB or UVA). Consequently, the spectrum of solar radiation to which the human skin has adapted to is essentially maintained. Yet with the introduction of topical UV-sunscreens and more so with the sunburn protection factor (SPF) relating mainly to UVB, this protection became biased towards UVB This imbalance fostered ideas that extensive use of sunscreens may rather promote than prevent skin cancer. As early as 1991, Diffey advocated for uniform UV protection as the ideal sunscreen—this at a time when the importance of UVA in photoaging and skin cancer was not yet of general consideration. In the meantime, the damaging effect of UVA radiation has become generally accepted. In parallel, specific procedures for UVA assessment are becoming international recognition. Nonetheless, only few sunscreens provide uniform UV protection. The FDA Proposed Rule, published in the Federal Register, 27 Aug 2007 would require US sunscreen manufacturers to declare, in addition to the SPF, the degree of UVA protection expressed in five categories; no, low, medium, high, and highest UVA protection. Sunscreen fulfilling the "highest" UVA category (4 stars) is very close to a uniform sun protection profile. Calculations of the sunscreen performance on the skin (in silico) show that a four-star sunscreen transmits 10 times less UVA-I radiation than a 1-star sunscreen. In silico simulations of typical US sunscreen compositions show which UV filter combinations provide broad-spectrum UV protection. To date it is mainly the content of the UVA filter avobenzone up to the maximum allowed concentration 3 % that determines the degree of UVA protection of a US sunscreen. Moreover simulations show that uniform sun protection cannot be achieved, at high SPF, the highest UVA category with an in vitro ratio UVA-I/UV > 0.95 cannot be achieved with the UV filters available to date. In contrast modern European sunscreens that can contain avobenzone (up to 5%) and broad-spectrum UV filters such as bisoctrizole or bemotrizinol (both allowed up to 10%). If such sunscreens fulfill the highest Boots UVA star rating criteria of 5 stars with a UVA/UVB ratio > 0.9 that is used in Great Britain, they will putatively comply with the US highest (4 stars) criterion. The rirst in vitro applications of the proposed FDA UVA method are in line with our silico results.

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Muscle contractility reduction via the application of low temperatures

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Background: A novel, minimally invasive, percutaneous technology has been developed to reduce muscle contractility with potential application in the reduction of dynamic facial wrinkles. The device (MyoScience, Redwood City, CA) reduces muscle activity by applying controlled low temperatures to targeted muscle groups via needle-like probes. The thermal algorithm is designed to reduce the muscle fiber count and weaken the muscle temporarily, without causing long-term chronic changes in the tissue. Optimal treatment efficacy depends on the total volume of affected tissue, which is determined by the temperature dosage delivered through the device. These studies were undertaken to establish correlations between treatment temperature and physiologic and histologic outcomes in a murine model.

Methods: Preclinical studies were conducted in Swiss-Webster white mice which underwent treatment to the gastrocnemius muscle. Animals survived for up to 6 weeks posttreatment. Muscle function was assessed daily using the Digit Abduction Scoring (DAS) assay, and tissue specimens were explanted for histologic evaluation at weekly intervals.

Results: Treatment with the test device produced effective muscle weakening in the murine model for approximately 3 weeks with gradual return to normal muscle function. Adjustment to colder temperatures yielded an increase in efficacy and duration of effect. Probe temperatures of -10 °C, -20 °C, and -30 °C created progressively larger regions of affected tissue, and correlated to progressively more profound muscle weakening (higher DAS scores) and a slower return to baseline function. Myofiber regeneration leading to complete restoration of normal muscle fiber size and density occurred within 5 to 6 weeks posttreatment for all temperatures studied. No systemic effects were observed at any point in any of the animals.

Conclusions: These preclinical data demonstrate that the device is able to temporarily reduce muscle contractility by application of mild low temperatures, with an inverse correlation between treatment temperature and degree and duration of effect. Recovery of normal muscle function and morphology and the absence of any systemic effects were observed for all temperatures studied.

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