Review

Ichthammol revisited

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Abstract

Scientific research has greatly expanded the therapeutic options for patients with cutaneous disease. This expansion, however, has not been without its drawbacks. While newer medications and procedures not only typically offer better disease control but they are also often associated with increased expense and problematic toxicities. Older medications often relegated to the dustbin of history may provide effective treatment of common dermatologic maladies and deserves reconsideration. Ichthammol, derived from shale oil, has been employed in the therapy of psoriasis, eczematous dermatitis, leg ulcers, seborrheic dermatitis, and furuncles for over a century and remains a useful topical medicament.

Introduction

Ichthammol has been used in dermatology since the nineteenth century for a variety of skin conditions, most notably psoriasis and eczematous dermatitis. It is approved in the United States by the Food and Drug Administration for veterinary use but has not been sanctioned as a human medicament. Regardless, it is available in multiple forms in over the counter preparations from pharmacies, grocery stores, and via the internet. Practitioners of dermatology would do well to remember that in the days before antibiotics, retinoids, chemotherapy, and corticosteroids, ichthammol held a prominent place in the therapeutic armamentarium for cutaneous disease for a simple reason – it worked. The use of ichthammol allows dermatologists an additional ''arrow'' in their quiver of therapeutic options, one which is relatively inexpensive, nontoxic, and often efficacious.

Background

Ichthammol is known by a number of colloquial terms such as drawing salve, black ointment, black drawing grease, bear grease, and herbal clay. Scientific names include ammonium bituminosulfonate, ammonium ichthosulfonate, and sodium shale oil sulfonate. Sulfonated shale oil (SSO) refers to ichthammol proper and ichthyol, typically considered separate entities derived from different methods of production. Organic matter produced by anaerobic bacterial degradation of phytoplankton during the Jura period of the Mesozoic era (208–146 million years ago) and deposited in sedimentary rock is termed sulfur rich oil shale. The dry distillation of this rock while excluding air (low temperature carbonization) at 480 °C results in the production of shale oil.[1] Further distillation removes particulate matter and high molecular weight molecules such as polycyclic aromatic hydrocarbons. Treatment of the distillate with sulfuric acid renders a water-soluble product with detergent-like properties. The use of strong acid produces a thick, reddish brown liquid, miscible in glycerin, water-soluble and termed ichthammol or dark sulfonated shale oil (DSSO).[1] Ichthyol or pale sulfonated shale oil (PSSO) is derived when light acid is employed. Depending on the base used for neutralization, ammonium, calcium, or sodium salts are produced.

Both products have a high hydrogen to carbon ratio and are low in nitrogen. They are comprised of sulfur (10%), ammonium sulfate (5–7%), hydrocarbons, nitrogenous bases, acids, and thiophene derivatives.[2] It is estimated there are more than 10 000 different substances in SSO of which only around 100 have been elucidated including substituted heterocyclic aromatic hydrocarbons containing sulfur and nitrogen.[3] Unlike crude shale oil which is known to be carcinogenic, mutagenic and a photosensitizer, ichthammol, and ichthyol have been found to be safe in short- and long-term topical use as well as when systemically administered.[4,5] Compared with crude coal tar, these agents contain far fewer polycyclic aromatic hydrocarbons reducing concern about their use over extended periods.[6]

Chemical properties

Ichthammol is purported to have antimicrobial, anti-inflammatory, antipruriginous, and analgesic properties.[1,7,8] It is also believed to promote blood flow and act as a decongestant.

Research into SSO's mechanism of action has noted substantive interaction with the body's inflammatory response. Rabe *et al.*[9] evaluated three formulations of SSO on guinea pig peritoneal macrophages. They noted a dose dependant inhibition of leukotriene B4 (LTB4) induced Ca^{2+} mobilization and hydrogen peroxide generation. Superoxide anion production by phorbol ester stimulation was also diminished. The authors concluded that SSO modulates inflammatory responses by impeding inflammatory cell function. Similar effects on LTB4 have been described in chemotactic factor stimulated and unstimulated peripheral human leukocyte cultures.[10] Diminished cell secretion and biologic inhibition of chemotactic factors and LTB4 were noted. Diezel *et al.*[11] reported a reduction of 5-lipoxygenase activity in human polymorphonuclear leukocytes (PMNLs) by noncytotoxic concentrations of PSSO, again with diminished LTB4 release. Croton oil induced inflammation in mice ear skin was reduced following PSSO application. Schewe *et al.*[12] posited that SSO decreases LTB4 production in ionophore stimulated human PMNLs by inhibition of 5-hydroxyeicosatetraenoic acid (5-HETE) production from arachidonic acid. Lipoxygenases from rabbit reticulocytes, soybeans, and prostaglandin endoperoxidase synthetase were also downregulated by the presence of SSO.

In the mid 1980s, Kownatzki *et al.*[13] evaluated the chemotactic properties of ichthyol on human PMNLs with divergent findings. While PSSO acted as a chemotactic factor inducing a concentration dependant migration of granulocytes and promoted cell adherence to synthetic nylon fibers it did not induce neutrophil granule release of glucosaminidase or stimulate oxygen radical production. Moreover, when known chemotactic molecules such as eosinophilic chemotactic factor, chemotactic factor of human serum, or formyl–methionyl–leucyl–phenylalanine were added to cell cultures, PSSO inhibited granulocyte enzyme release, fiber adherence, cell migration, and oxygen radical production. It appears that PSSO is capable of acting both as a chemoattractant and inhibiting inflammatory cell chemotactic factor activity.

Ichthammol compounded in glycerin is used in patients with acute otitis externa. Two studies have evaluated the antimicrobial properties of ichthammol on the bacteria most commonly associated with this condition.[14,15] Both reported an inhibitory effect of ichthammol on gram positive bacteria (*Staphylococcus aureus, S. epidermidis,* and *Streptococcus pyogenes*) but not on gram negative bacteria (*Pseudomonas aeuriginosa, Eschericia coli* and *Proteus mirabilis*). Weak inhibition against *Candida albicans* was also noted. Both DSSO and PSSO were tested in fungal cultures involving yeasts, dermatophytes, and hyphomycetes by Listemann *et al.*[16] PSSO demonstrated greater fungicidal activity than did DSSO.

Dermatologic uses

Sulfonated shale oil is believed to have been employed in wound healing as early as the 1400s although it was not until 1882 that Paul Unna reported its use in the treatment of dermatologic disease.[17] Apparently a strong advocate of the drug's attributes, he published the following paragraph five years later in the British Medical Journal:[18]

> "Internally ichthyol is indicated: (1) in skin disease – acne rosacea: nervous forms of eczema in persons of nervous constitution; eczema from teething; lichen urticatus; erythema multiforme; dermatitis herpetiformis; furunculosis – but it is not indicated in psoriasis; (2) in the following other diseases (I speak after five years' experience) in acute and chronic rheumatism; bronchial asthma; chronic catarrh of the stomach and intestines, together with catarrh of the bile duct (icterus); chlorosis, tuberculosis (especially in children), and scrofula; vascular engorgement of all kinds."

Published scientific data on SSO's efficacy in treating cutaneous disease are surprisingly sparse. Much of the research is European in origin, most notably from Germany, where it continues to enjoy widespread use in the treatment of dermatologic conditions. Almost all treatises on the subject attest to ichthammol's use in psoriasis, seborrheic dermatitis, and eczematous dermatitis, however, only a single report in English describes its benefits in hand eczema.[19] As noted above, Unna did not suggest its use in psoriasis.

Currently, these products are advocated in lay publications and the internet as a "drawing salve" for use in the removal of glass or wood splinters, boils, spider bites, arthropod assaults, and abscesses. Ichthammol is commonly compounded in zinc, paraffin, and beeswax in 5–20% concentration for use on glaborous skin and in glycerin (10%) for use in the external auditory canal. Topical application in the case of furuncles is believed to hasten their "pointing" with more ready expulsion of their contents (i.e. "drawing"). Shampoos containing ichthammol are also available. Nasal tamponades with 24% ichthammol have been advocated for use in patients with chronic sinusitis[12] as have ichthammol containing suppositories for anorectal disorders.[1]

A search of the internet reveals no shortage of websites extolling the virtues of ichthammol preparations and

offering proprietary compounds for sale, many of them for animal use. Two European companies, Ichthyol-Gesellschaft (Hamburg, Germany; http://www.ichthyol.com) and Herbacos-bofarma (Pardubice, Czech Republic; http://www.hpf.cz) advertise numerous preparations including shampoos, lotions, facial masks, creams, shower gel, and bar soap with varying concentrations of ichthyol. Herbaco-bofarma offers a line of pediatric products and Ichthyol-Gesellschaft sells Ichthraletten® a 200 mg tablet containing sodium bituminosulfonate for use in acne, rosacea, and seborrheic dermatitis. Two pharmaceutical companies in the United States, Goldline Laboratories (Miami, FL) and Allan Pharmaceuticals (Huntingdon Valley, PA) manufacture 20% ichthammol ointment. A handful of other, smaller companies worldwide also make and sell similar products, usually advocated as shampoo for seborrheic dermatitis or dandruff or a mask for treatment of acne.

Fluhr *et al.*[20] evaluated 91 patients with papulopustular acne using a preparation containing 1% chloramphenicol and 0.5% PSSO vs. placebo. Patients given the active medication demonstrated a significant improvement compared with controls. A significant reduction in *Propionibacteria* counts were noted along with a sebosuppressive effect believed due to squalene reduction induced by the PSSO. No adverse events or side effects were reported.

A double-blind, placebo-controlled study of 200 mg DSSO tablets in patients with acne rosacea was reported by Koch *et al.*[21] Nineteen women and 11 men were administered two tablets three times daily for 2 weeks followed by one tablet three times daily for 4 weeks. The authors reported significant improvement in the number of papules/pustules, erythema, and scaling at study's end. The treatment was well tolerated without side effects. The administration of ichthammol both orally and intravenously reportedly reduces skin lipids, presumably by inhibiting sebaceous activity.[3]

A patient with Sweet's syndrome mimicking rosacea fulminans treated with prednisone, Vytone® (Dermik Laboratories, Bridgewater, New Jersey, USA) and 3% DSSO in zinc ointment with disease resolution has also been reported.[22]

Impregnated bandages containing 6% zinc oxide and 2% ichthammol (Ichthopaste®, Smith & Nephew, London, UK) have been employed in the therapy of psoriasis, eczema, and stasis dermatitis but are most often used for venous stasis ulcers. Rowe *et al.*[1] described the use of ichthammol 10% in glycerin in their burn unit patients (Royal Perth Hospital, Perth, Australia). This compound is applied to wounds which are slow to heal with excess slough and exudate. PSSO has demonstrated enhanced keratinocyte proliferation and growth factor expression *in vitro* as well as wound healing, quantitated as epithelialization, *in vivo*.[23] A large, multicenter study from Europe reported a significant benefit in patients with venous leg ulcers treated with 10% PSSO gel.[24] One hundred and nineteen men and women randomly received active drug or placebo vehicle daily with nonadherent gauze dressings and compression bandages. A significant reduction in ulcer size was noted at both 6 weeks and at completion of the study (20 weeks). Complete healing was noted in 33.9% of treated patients compared with 22.8% of those receiving placebo. There was no significant difference in adverse events between the groups.

Muller *et al.*[25] cited the superior efficacy of 5% DSSO vs. 5% acyclovir cream in the treatment of herpes labialis. Another group noted that a cream containing 4% but not 2% PSSO was capable of reducing UVB-induced cutaneous erythema.[8] Interestingly, DSSO but not PSSO is capable of inciting UVA induced phototoxicity.[2]

The scarcity of the research on SSO makes it impossible to unequivocally establish its effectiveness in ameliorating skin conditions. Randomized-controlled trials are needed for better evaluation, a scenario which, unfortunately, appears unlikely.

Side effects

As mentioned, the use of SSO is believed to be safe and well tolerated. Unlike coal tar and coal derivatives, SSO has not been demonstrated to be carcinogenic, a reassuring feature when long-term application is desired. The most common side effect is skin irritation.[26] Other deleterious effects of this medication have not been reported although Allan and Tidman[27] noted the flammability of SSO impregnated bandages.

Comment

The greatest drawback to SSO use is its smell and messiness. In its pure form, it has a sulfurous odor not similar to that of coal tar. In addition, its use is associated with staining of skin, clothing, and bedding. Although skin discoloration is temporary, restoration of stained fabric is rarely possible. Use of this medication will require the same precautions as with crude coal tar. Some manufacturers have obviated the odor, often by using PSSO in smaller concentrations.

Sulfonated shale oil is most ideal for treating localized areas such as the hands and feet. Overnight application using gloves and socks is recommended. When larger surface areas are treated, short contact use (1–3 h) followed by bathing works better. Although SSO can be compounded in zinc oxide, petrolatum, and paraffin, it will dissolve in glycerin making application and removal

easier. The author commonly employs 10% DSSO in 95% glycerin and 5% dimethyl sulfoxide (DMSO) allowing for an enhanced penetration of the medication.

Testimonials on the Internet lauding the use of SSO are impossible to critically evaluate as they are decidedly anecdotal in nature. Furuncles, abscesses, and arthropod assaults may indeed benefit from application of this product; however, no scientific support for such use exists and clearly more efficacious therapies are available. It is difficult to envision the pathophysiology of SSO's reputed capacity for removing splinters

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