The use of ichthammol glycerin in burn wound care: a literature review

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Introduction

The current concept in the clinical management of patients focuses on evidence-based quality use of medicines. In the area of wound management it has been purported that evidence-based practice has not kept pace with the numerous wound care products that are now available on the market [1]. So, are wound care products that have been tested for efficacy by randomised controlled clinical trials the only ones that should be used in clinical practice? Is there still a place for those traditional 'tried and true' products in the management of wounds? One such product is ichthammol glycerin APF [Australian Pharmaceutical Formulary and Handbook], for which the question remains: Is its current use based on clinically supported evidence?

Ichthammol is derived from marine sediments in Mesozoic era rock formations. It has a high hydrogen/carbon ratio and is low in nitrogen. This is opposite to a tar with which it is often confused. Ichthammol is generated from low temperature carbonisation of shale oil [2, 3]. It is obtained by distillation from certain bituminous schists, sulphonation of the distillate and neutralisation of the product with ammonia to pharmacopeial specifications after which it is available for medical use [British Pharmacopoeia grade (BP)]. Ichthammol is also referred to as ammonium bituminosulphate, sulfonated shale oil and ichthyol although the latter usually refers to the pale version. Dark ichthammol is a result of strong acid treatment and pale ichthammol is the result of light acid treatment [4]. Dark ichthammol is a dense, blackish-brown liquid which is miscible with glycerol (BP). Glycerol, a clear liquid possessing humectant and moisturising actions, therefore serves as a suitable vehicle for topical preparations containing ichthammol, and the resultant preparation is called ichthammol glycerin.

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Believed to have been used in wound healing as early as the 1400s, with documented use in dermatology since the late 1880s, ichthammol has also been combined with a number of other ingredients, including mercury [5]. Ichthammol is purported to have antibacterial, antiphlogistine, anti-inflammatory, antiseborrhoic, antieczematous, antimycetic, antiprurinous and blood flow stimulating effects. The literature claims that shale oils inhibit sebaceous secretion, migration of leucocytes and release of chemotactic factors by granulocytes [3]. There are four anecdotal case reports [15, 16, 17, 18] of success in its clinical application, one clinical study [19] supporting claims about its efficacy and one randomised control trial (RCT) [6] identified through the Cochrane database. Ichthammol glycerin has been described as being used in combination but not in burn wounds [16, 17, 18]. However, despite the paucity of information on both the mode of action and the antibacterial properties of these agents, they continue to be used in clinical practice in dermatology, vascular medicine and, the subject of this paper, burn wounds.

Burn wounds

A burn injury stimulates the release of inflammatory mediators which are responsible for the increased vessel permeability leading to burn oedema. Cytokines and growth factors produced cause vasodilation and chemo attraction of other inflammatory cells. Neutrophils are activated and this further increases vessel permeability. Neutrophils invade burn wounds at four–five days post injury followed by macrophages. There is documented evidence regarding neutrophil activity in the burn wound and their involvement in the production of oxygen radicals. Oxygen radicals are generated as part of the inflammatory cascade of events following a burn injury and inhibition of these would likely have an anti-inflammatory effect [3, 4, 7, 8].

Mediators released into a burn wound stimulate phagocytosis. Any non-viable cells remaining delay healing and prolong inflammation. Slough, a yellow fibrous tissue accumulates in the slow to heal wound. The presence of slough allows bacterial colonisation that can increase bacterial burden. In the presence of slough, keratinocytes must overcome the physical barrier to migrate across the surface releasing enzymes to debride and find a viable surface. In this kind of wound, excess exudate is often present as well. Both these factors delay wound contraction and epithelialisation. When debris builds up there is a delay in fibroblast formation as well as a formation of a friable matrix. When a wound does not follow what is considered the normal pathway for healing, there is an increased infiltration of mast cells, which release histamine

and in combination with the continued release of growth factors by macrophages and polymorphonuclear leukocytes (PMNLs) continue the inflammation phase. Disturbance of the normal cascade of events triggered by a burn injury leads to the development of chronic wounds, the management of which can frustrate both patient and staff, and can lead to hypertrophic scarring [9, 10]. Preparing the wound bed for healing requires removing the eschar, slough, non-viable tissue and the excess exudate as well. There is some literature to support the recommendation that chronic wounds need to be converted to acute wounds in order to heal [10, 11].

In acute burn wound care, healing can occur either with conservative treatment or by surgical intervention. When there is a delay in healing, graft breakdown or inadequate debridement there is a role for tailored conservative wound care.

The type of wound in which ichthammol glycerin APF is mostly used is the slow to heal, sloughy, inflamed wound that often has excess exudate. Generally, other wound care products have already been used with no success in managing the wound; in effect, what would be considered a 'stubborn' wound.

Ichthammol glycerin, as extemporaneously prepared and used at Royal Perth Hospital, is the product 'ichthammol 10% in glycerol' of the *Australian Pharmaceutical Formulary and Handbook 14th Edition* [12]. The ichthammol used is of BP grade, ensuring a consistency in the quality of the product. The final product has a strong odour, not unlike a tar and is black and viscous in consistency.

The search

Databases including PubMed®, MEDLINE®, CINAHL®, EMBASE, AUSTHealth, National Guidelines Clearinghouse and the Cochrane Library were searched for publications on the use of ichthammol in wound care. The Cochrane Collaboration is an independent organisation which promotes evidence-based practice and disseminates systematic reviews of health care. Reviews are stored in the Cochrane Library [27]. Along with these, TRIP (Turning Research Into Practice), HSTAT (Health Services/Technology Assessment Texts) through the National Library of Medicine, Joanna Briggs Institute and ERIC (Education Resources Information Centre) were searched. Google™, Ask Jeeves, and VitalSeek search engines were also utilised. Key words were: 'ichthammol'; 'ichthyol'; 'ammonium bituminosulphate'; 'dark sulfonated shale oils'; 'wound'; 'burns' etc. PubMed® returned approximately sixty-nine responses to the key word 'ichthammol'. However, many of the publications were not available in English or were pre-1950s. Another difficulty encountered was that it was often not differentiated from a tar and details on the specifications of the amount of ichthammol tested were not provided, making direct comparisons difficult.

Wound care websites were reviewed and email enquiries were sent out to manufacturers of products containing ichthammol as well as senior nurses in burn units and nursing wound care specialists in England, Australia and United States. Additional citations were obtained from references in retrieved papers. This returned limited results.

The literature

Anti-inflammatory effect

The pharmacological effects of sulfonated shale oils have been recorded in both animal and human studies in vitro and in vivo. Rabe et al [13] conducted an in vitro investigation on the effect of sulfonated shale oil fractions on the oxidative burst and the mobilisation of intracellular calcium in purified guinea pig peritoneal macrophages. Their study demonstrated that sulfonated shale oil fractions are capable of modulating inflammatory responses. While the study did not provide enough detail on the specifications of the sulfonated shale oil fractions to draw direct comparisons to the ichthammol used in ichthammol glycerin APF, the study results did provide a possible mechanism for the pharmacological effect of ichthammol and therefore some basis for the efficacy of the product [13].

Kownatzki et al [4] studied the effect of sulfonated shale oil extract, ichthyol, on the migration of human neutrophilic granulocytes by the Boyden chamber technique. Based on their study results, the authors proposed that "various substances contained in Ichthyol interacted with either the chemotactic factors or the cell membrane or both and thus blocked cell stimulation". This was thought to serve as an explanation for the cell accumulation and abscess formation observed with the use of ichthyol in inflammatory skin lesions and the resultant anti-inflammatory properties of the compound [4].

Czarnetzki [14] also found that sulfonated shale oils inhibit chemotactic response of neutrophils and cell migration. Ichthammol had no effect on the release of inflammatory mediators in cells in normal condition [14]. Another study states that ichthammol speeds up the maturation of an abscess giving the patient faster relief [15].

Antibacterial properties

Ahmed et al [16] tested the antibacterial effect of ichthammol glycerin on common bacteria that cause otitis externa using agar dilution. Their results showed an inhibitory effect against the gram positive bacteria *Staphylococcus aureus, Staph. epidermidis* and *Streptococcus pyogenes*. There was less inhibition of the gram negative organisms *Pseudomonas aeruginosa* and *Escherichia coli*. They also found weak inhibition of *Candida albicans*. The antibacterial effects were more pronounced with the use of ichthammol alone, which lead the authors to conclude that the main antibacterial substance in ichthammol glycerin is in fact ichthammol [16].

In this study, the swelling and oedema of the ear canal also decreased in those patients who had ichthammol glycerin,

possibly due to the moisturising action of glycerol and the anti-inflammatory action of ichthammol. Though this study was looking exclusively at otitis externa, it provided some clinical support for the use of ichthammol glycerin in burn wounds, primarily because it actually looked at the combined use of ichthammol with glycerol. It also provided some supportive evidence for the likely efficacy of the product, against bacteria commonly seen in burn wounds [16].

Similar results were found in a later study by Nilssen et al [17]. Ear swabs from a three-year period were reviewed to ascertain common organisms. The organisms studied were similar to those in the study by Ahmed et al [16]. Glycerol on its own had no antibacterial effect and ichthammol alone was more effective than ichthammol glycerin, suggesting a dilutional effect of the glycerol [17]. Maw reported management of otitis externa using repeated applications of ichthammol glycerin with good effect [18].

A clinical investigation identified through Cochrane database involved comparison of a topical formulation containing 5% dark sulfonated shale oil with a proprietary cream containing acyclovir 5% in the treatment of herpes simplex. A decrease in the time to response was observed in each of the groups treated with dark sulfonated shale oil. The investigators recorded a statistically significant superiority regarding the assessment of efficacy (P=0.0030 for group one, those 24 patients in the early infection stage and P=0.0253 in group two, those 22 patients from the vesicular stage onwards). While this study demonstrated a possible efficacy of dark sulfonated shale oil against herpes simplex, it provided little applicability to the use of ichthammol in the burn wounds scenario [6].

In a double blind, randomised, placebo-controlled clinical study, dark sulfonated shale oil was compared to placebo for the systemic treatment of rosacea. Thirty patients were randomised to receive either coated tablets containing 200 mg sodium salt of ichthammol or placebo tablets. The duration of treatment was six weeks and the dosage was decreased after two weeks. The investigators observed that the clinical signs of rosacea decreased markedly in the ichthammol group. The study reported a statistically significant difference between the outcomes from the two groups ($p < 0.0001$). Again this study has little relevance to the management of burn injuries, in that the ichthammol was ingested, but it did identify a reduction in the erythema associated with rosacea, which may once again support an anti-inflammatory effect of ichthammol [19].

Ichthammol has a long history of use in veterinary medicine as a black ointment (drawing salve). It is used for abscesses, furuncles and other inflammatory conditions [20, 21]. Sulfonated shale oils are also used in therapy of dandruff, psoriasis capitis as well as topical therapy of yeast infections and in suppositories for anorectal disorders. It is often combined with zinc in medicated bandages for wet eczema [22].

Cases reporting the inclusion of ichthammol in zinc cream in a present-day regimen for the treatment of vulval dermatitis, illustrated that the treatment dramatically cleared the problem [23].

Risks and side effects

A safety study found dark ichthammol to be well tolerated whether applied for a long or short period of time. It was found that there were no carcinogenic, teratogenic or mutagenic effects when administered topically or orally. There are few side effects reported in the literature, the most common being minor skin reactions. It is considered safer than tar preparations for long term treatments due to its purity [2, 24]. However, it has been reported as being flammable in proprietary dressings [25].

International approved indications for use

Ichthammol is listed as a banned substance in the US for reasons of unproven effectiveness and safety [26]. A reply to a recent email enquiry to the United States regarding the use of ichthammol, stated that the drug is "not Federal Drug Authority (FDA) approved as a wound medicament only as a veterinary product". The wool fat in it is not an FDA approved ingredient (Stone, pers. comm.). In Germany, ichthammol 20% ointment is an approved treatment for abscesses [16]. In comparison, ichthammol glycerin is a registered product for use in humans in Australia [29], although no specific indication is documented for its use (Therapeutic Goods Administration, pers. comm.)

Discussion

Whilst ichthammol has been reported to have antibacterial and anti-inflammatory properties, and studies do support observed clinical response to its use, it would appear that the evidence supporting the definitive clinical efficacy of ichthammol is lacking. The combined antibacterial, anti-inflammatory and antimycotic actions offer an exciting possibility for its application in wound care, including the management of burn wounds. However, given that none of these published trials were conducted on burn wounds, their findings would not necessarily be suitable for extrapolation. There were two studies, a clinical investigation and a randomised control trial identified from the Cochrane database, but these did not provide enough detail on the specifications of the sulfonated shale oil fractions to draw direct comparisons to the ichthammol used in ichthammol glycerin APF. The remaining literature evidence reviewed was rated low level based on the National Health and Medical Research Council guidelines for hierarchy of evidence [28].

Many clinical decisions made regarding wound care may often be influenced by tradition and the experiences of the practitioner. In addition, personal preferences as well as the availability of more expensive and seemingly superior wound care dressing products, which in some settings is not within budgetary constraints, may influence the management strategies employed.

So, are wound care products that have been tested for efficacy by randomised controlled clinical trials the only ones that should be used in clinical practice? Or should the choice of treatment in difficult-to-treat wounds include alternative remedies, including those lacking trial evidence, based on careful assessment and identification of what the aim of treatment is in relation to particular stages of the healing process? Has evidence based practice in wound care kept up with the large number of products marketed?

Given the current paucity of information, further investigation of ichthammol glycerin in wound care is required. Wound care and the selection and utilisation of a particular dressing product follows a comprehensive assessment of the wound and the patient as a whole. Variation in the individual ability and experience of nursing staff in relation to wound management suggests that the development and implementation of appropriate guidelines on the subject are necessary to ensure that patients receive quality of care in the management of their wounds.

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