Tamoxifen Citrate – A Potential Therapy for the Treatment of Keloids

For a topical, aim for a concentration that will inhibit keloids, with minimal side effects.

Keloid scar formation is a significant problem that affects millions of patients yearly. The presence of a keloid, or hypertrophic scar, is frequently cosmetically unacceptable to the affected individual. In addition, it may be painful or pruritic and may restrict range of motion. Physicians have attempted to improve the appearance of scars by both physical and chemical means for many years. Various methods of manipulation have been enlisted to normalize their topography as well as to eliminate erythema and dyspigmentation. Because the treatment of scars is often undertaken, at least in part, for cosmetic concerns, it must be free of adverse sequelae in addition to being effective. Proposed management or prevention of keloids includes three distinctly different therapeutic approaches: correction of abnormal collagen metabolism when the equilibrium between collagen synthesis and degradation has been destroyed, alteration of the immune/inflammatory response and manipulation of the mechanical properties of wound repair. There currently is no universally accepted treatment modality resulting in permanent keloid scar ablation.

Pathology of Keloids

The complex interplay of events that occurs following injury to the skin does not always eventuate in a normal, smooth skin surface. Rather, the skin often responds to injury with a proliferation of fibrous tissue. When tissue response to injury is overzealous, the result is a hypertrophic scar or keloid. The substance of the majority of keloid and hypertrophic scars consists of extracellular matrix, which is primarily collagen. By definition, hypertrophic scars remain within the boundaries of the original wound, whereas keloids extend beyond the original area of skin injury. The time between cutaneous injury and the onset of hypertrophic scar or keloid formation may vary from weeks to years; hypertrophic scars differ from keloids in their tendency to regress spontaneously over time, while keloids remain elevated.

The pathological repair process underlying keloid formation may be mediated in part by the biological activity of transforming growth factor beta (TGF-β) during wound healing. Transforming growth factor beta exerts protean effects during wound healing, including increased production of collagen, increased expression of integrins, decreased expression of metalloproteinases and increased expression of metalloproteinase inhibitors. Collectively, these effects of TGF-β occurring in excess could result in the abnormal accumulation of extracellular matrix, along with fibrosis and scar formation. Thus, the biology of TGF-β makes this family of peptide growth factors a potential culprit in the pathophysiology of keloid formation.

The effect of TGF-β on the rate of collagen synthesis in keloid fibroblasts, hypertrophic scar fibroblasts and normal skin fibroblasts has been studied. Keloid fibroblasts display a marked sensitivity to TGF-β, which is abundant during the proliferative phase of wound healing. Keloid fibroblasts produced up to 12 times more collagen than normal skin fibroblasts, and up to four times more than hypertrophic scar fibroblasts in response to TGF-β. Although keloid fibroblasts increased their rate of collagen production by up to 2.7 times in response to TGF-β, hypertrophic scar fibroblasts and normal skin fibroblasts did not (p<0.065). This finding represents another very important difference between keloids and hypertrophic scars.

Tamoxifen Citrate

Efficacy

The most important study to date about the potential of tamoxifen citrate to treat keloids was done by Mancoll and colleagues. In this study, supported by a grant from the Plastic Surgery Education Foundation, tamoxifen citrate concentrations greater than 20 μM (corresponding to a tamoxifen citrate concentration of about 0.01%), were shown to have a deadly effect on keloid cells. At 48 hours, tamoxifen citrate concentrations between 8 and 12 μM demonstrated significant inhibition of fibroblast cells (p<0.01). Collagen production assays also demonstrated a reduction in collagen at 12 μM and 16 μM. The study results demonstrate tamoxifen citrate's ability to inhibit keloid fibroblast production in a dose-dependent manner and to decrease collagen production.

Description

Tamoxifen citrate is a triphenylethylene-derivative, nonsteroidal antiestrogen that is structurally related to clomiphene. Tamoxifen citrate occurs as a fine, white crystalline powder and has a solubility of 0.5 mg/mL in water at 37°C and is very slightly soluble in alcohol. The drug has a pKa of 8.85. Following oral administration, peak serum tamoxifen concentrations average about 17 ng/mL (which is equal to 0.017%), after a single 10-mg dose. Common adverse reactions to oral doses of tamoxifen citrate include flushing, skin rash, nausea, vomiting, weight gain, myelosuppression, hepatotoxicity and neuromuscular pain. Therefore, a topical application of tamoxifen citrate at a concentration...
Formula for Tamoxifen Citrate Cream 0.1% (100 g)

Tamoxifen citrate 100 mg
Propylene glycol to wet
Water-washable cream base qs 100 g

Place the tamoxifen citrate in a mortar and grind to a fine powder. Slowly wet with propylene glycol and bring to weight with cream base.

would produce limited side effects, if any. The effectiveness and safety of tamoxifen citrate topical creams have yet to be determined in long-term studies and its use should be based upon a strong, well-informed patient-physician-pharmacist relationship. Tamoxifen citrate, however, does represent an exciting new option for the treatment of keloids.

References