



USE OF PHENYTOIN IN WOUND HEALING: A REVIEW

Pharmacology

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ABSTRACT

Phenytoin (Dilantin or Diphenhydantoin), a Hydantoin derivative is a highly efficacious and widely prescribed Anticonvulsant agent and an Antiarrhythmic agent in the treatment of Grand mal and Psychomotor epilepsy. In 1937, Phenytoin was introduced into the therapy for effective convulsive disorder with common side effects being Gingival hyperplasia and Coarsening of the facies. In Dermatology, due to its stimulatory effect on the connective tissue Phenytoin is used in the treatment of wound healing in the pathological conditions such as diabetic ulcer which affects approximately 15% of diabetic individuals, Decubitus ulcer which is also known as Bed sore or Pressure ulcer, Epidermolysis bullosa and Chronic leg ulcer. The mechanism of action by which Phenytoin exerts its effect is that it increases gene expression of the platelet-derived growth factor B chain in macrophages and monocytes. Healthy granulation tissue develops earlier. The Common side effects of Phenytoin which occurs due to its long term use are Gingival Hyperplasia, Coarsening of the facies, thickening of the scalp and face and Enlargement of the lips.

KEYWORDS

Phenytoin, Wound healing, Diabetic ulcer, Decubitus ulcer, Epidermolysis bullosa, Chronic leg ulcer.

INTRODUCTION

Phenytoin is a highly efficacious and widely prescribed anticonvulsant agent and an Antiarrhythmic agent in the treatment of Grand mal and psychomotor epilepsy [1]. In dermatology the stimulatory effect of Phenytoin on the connective tissue suggested probability for its use in wound healing [2]. Studies have reported that topical Phenytoin to promote the healing of diabetic ulcer, decubitus ulcer, venous stasis ulcer, traumatic wounds, burns and leprosy trophic ulcer [3-9]. Phenytoin may have the capability to alter the dynamics of wound healing; suggesting a therapeutic effect for the stimulation of chronic wounds [10]. Phenytoin may induce wound healing by a number of mechanisms, such as the stimulation of fibroblast proliferation, facilitation of collagen deposition, antibacterial activity and glucocorticoids antagonism [11-15].

MECHANISM OF ACTION OF PHENYTOIN

Phenytoin exhibits its action by increasing the gene expression of platelet-derived growth factor B chain in macrophages and monocytes [16]. Healthy granulation tissue develops earlier [17]. Phenytoin increases the proliferation of fibroblast b 50-90 % in two fibroblast cell line, but does not have an impact on the Heart, Lung, Kidney and Squamous epithelium [18]. Topical Phenytoin also eradicates Staphylococcus aureus, E. coli, Pseudomonas and Klebsiella from wounds within 7-9 days [19-23]. More significantly Phenytoin clears all the gram negative bacteria compared to gram positive bacteria [24].

PHENYTOIN IN WOUND HEALING

Diabetic Ulcer:

Diabetic foot ulcer is common and is estimated to affect approximately 15% of all the diabetic individuals [25-27]. Treatment of diabetic foot ulcer requires a multisystem strategy [28]. Almost 85% of amputation is preceded by Diabetic foot ulcer [29]. The Department of surgery of El-Minia faculty of medicine conducted a study on 80 patients with diabetic ulcer, where Topical Phenytoin was used on 40 patients and conservative methods were used on other 40 patients. The study reported that the ulcer healed faster in Patients who were treated with topical Phenytoin and there was no reoccurrence of ulcer within 30 months of follow up [30]. In another study conducted by the Patil medical college on 100 patients, the Patients were categorized into 2 groups, one group was subjected to saline treatment for diabetic ulcer and the other group was subjected to Phenytoin treatment. The group which was given Phenytoin treatment reported the faster shrunk and healing of the ulcer compared to the group which was given saline treatment [31]. The Estimated healing time for a diabetic ulcer is 21 days when treated with Phenytoin compared to ulcers which take an estimated time of 45 days, when treated with saline [32].

Decubitus Ulcer:

Decubitus ulcer which is also known as bedsore or pressure ulcer

usually appears as sores on the skin covering the bone and usually occurs in the area where more pressure is applied [33]. A study was conducted by Zayat on Phenytoin compared to chlorhexidine in fifteen patients. In the Phenytoin treated group the healing time took only a period of 1-3 weeks while the other group took a period of 6-8 weeks [18]. Another study which was conducted by the El-Minia medical university reported that the patients treated with Phenytoin had faster healing time compared to the other treatment given [30].

Epidermolysis Bullosa:

Epidermolysis bullosa is one of the groups of genetic conditions that cause the skin to be very fragile and to blister easily. Blisters and areas of skin loss occur as a result of minor injury or friction, such as scratching or rubbing [34]. In Epidermolysis bullosa, the levels of collagenase are elevated [35]. Phenytoin helps to suppress the collagenase in vitro. By suppressing the collagenase activity, Phenytoin has been demonstrated to stabilize collagen fibrils and decrease the blister formation [36-37]. Phenytoin lowers the contraction of recessive dystrophic epidermolysis bullosa fibroblast populated collagen gels [38].

Chronic Leg Ulcer:

Many techniques have been tried over the centuries to heal chronic leg ulcers [39]. Chronic leg ulcer has varying aetiologies such as topical ulcer, post-operative wounds and burn injury, varicose vein, animal bites etc [40]. There is no particular regime treatment for chronic leg ulcer [41]. Topical and Systemic antibiotics have been used to control infection; local antiseptic with copious chemical has been used but was limited due to poor nutritional status and vascular insufficiency [42]. Edinburgh University reported that Phenytoin is a better healing agent compared to slaked lime [43].

SIDE EFFECTS OF PHENYTOIN

The Common side effects of Phenytoin which occurs due to its long term use include Gingival Hyperplasia, Coarsening of the facies, thickening of the scalp and face and Enlargement of the lips [44]. Hirsutism was also reported in about 12% of the children who were receiving Phenytoin; this usually occurs within 3 months of initiating the therapy and generally occurs on the trunk and the face [45]. The Other common side effects of Phenytoin use include Hypersensitivity syndrome, Collagen vascular side effects, Generalised cutaneous eruptions, Pseudo lymphoma and Birth defects [46]. A Transient burning sensation, rash which develops due to Phenytoin and hypertrophic granulation tissue was also reported in some patients who were treated with Phenytoin [47].

CONCLUSION

After 60 years of use, the mechanisms and uses of Phenytoin continue

to be explained. The inhibition of collagenase by Phenytoin provides it an actual role in facilitating the healing of ulcers. The complex effects of Phenytoin on the immune system, in particular the initiation of a Th2-type response, which might underlie its common induction of eruptions and immunologic effects was also reported. It can also be perceived as an antagonist of cortisol and this might strengthen its effects on wound healing and immune dysregulation. Phenytoin is also used in hard-to-treat conditions that involve excessive or dysfunctional production of collagen, like Morphea and Epidermolysis bullosa. Topical Phenytoin reduces bacterial load, initiates healthy granulation tissue and assists in better graft take up than the conventional dressing. Phenytoin succeeded in promising therapies and fertile fields for later investigation.

So, in the developing Countries like India for Diabetic foot, where the treatment option remains amputation leading to disability and for many other chronic non healing and inflammatory ulcers like Decubitus ulcer, Chronic leg ulcer and Epidermolysis bullosa, Phenytoin is a Promising and Cost effective non invasive medical management.

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