Does phenytoin have a role in the treatment of pressure ulcers?

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Abstract

Pressure ulcers (PUs) are common in clinical practice. Apart from causing suffering to patients and at times contributing to their demise, they also result in increased length of hospital stay and increased cost of health care. Although prevention of PUs is the desirable goal, it may not always be possible. Skin, the largest organ of the body, is affected by the ageing process, nutritional deficiencies and systemic illnesses and, like other organs, can fail too. Phenytoin can play a significant role in reducing bacterial growth and improving the rate of healing of PUs. Topical phenytoin is simple to use, safe, inexpensive and readily available. We hope that this article will encourage other wound care specialists to engage in further research in this area.

Introduction

Pressure ulcers (PUs) are a significant health problem worldwide and Australia is no exception. Studies undertaken in a number of hospitals throughout Australia have indicated the prevalence of PUs to be between 4.5-27% [1], estimated that a PU occurs in 60,000 Australians per year [2] and that they were responsible for 54 deaths in 1997 and 47 deaths in 1998 and were a contributing factor in a further 181 deaths in 1997 and 227 deaths in 1998 [1].

Although prevention of PUs is the desirable goal, it may not always be possible. Skin, the largest organ of the body, is affected by the ageing process, nutritional deficiencies and systemic illnesses such as hypertension, diabetes and sepsis and, like other organs, can fail too [3].

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The exact cost of PUs on the healthcare system is difficult to quantify due to the multitude of factors involved in managing them. However, it was estimated that PUs cost the Australian economy $350 million per annum [4], with an average cost of $11,172 per patient annually [5]. In an extreme case in Tasmania, it was reported that one PU case cost the healthcare system $61,230 [6].

Staging of PUs is related to healing time, with ulcers of higher stages taking longer to heal. It has been reported that approximately 75% of Stage II ulcers heal within 8 weeks, 52% of Stage IV ulcers heal within 1 year and only 62% of Stage IV ulcers ever heal [7]. PUs are also at a high risk of infection. This is related to the ischaemia that contributes to their formation. A partial pressure of oxygen (pO_2) level of at least 25mmHg is needed to generate superoxides to kill bacteria [8]. Therefore, wounds with impaired blood flow and reduced tissue oxygenation, such as PUs, have a significantly higher risk of infection and may lead to sepsis [9, 10].

Phenytoin and wound healing

The possibility of using phenytoin for wound healing was first recognised in 1939 when it was observed that patients receiving oral phenytoin had a side-effect of gingival hyperplasia [11]. In 1958, a clinical study demonstrated that phenytoin sodium accelerates gingival wound healing compared with controls [12, 13]. The first double blind, placebo-controlled clinical study involving the use of phenytoin in leg ulcers demonstrated that, when compared with controls, the use of phenytoin promoted wound healing [14].

Since this study, a number of other studies have been conducted that have demonstrated the effectiveness of phenytoin in the treatment of a variety of wounds including diabetic ulcers [15, 16], trophic ulcers in leprosy [17-20], chronic leg ulcers [21, 22], PUs [23], and superficial burn wounds [24]. Recently, Shaw *et al.* [25] published a systematic review identifying, summarising and critically appraising the clinical evidence regarding the effects of phenytoin on wound healing.

The possible mechanism of action by which phenytoin promotes wound healing has been investigated. Various animal *in vitro* and clinical studies have indicated that phenytoin has actions that contribute to:

- An increase in the proliferation of fibroblasts [12, 15, 26-28].
- An increase in the deposition of collagen [15, 26-29].
- Neovascularisation [15, 26, 27].
- An enhanced granulation tissue formation [12, 15, 17-19, 30].
- A decrease in the action of collagenase [28, 29].
- A decrease in bacterial contamination in wounds [12, 15, 31-34].

The precise mechanism of phenytoin decreasing bacterial contamination of wounds is not known. It has been reported that phenytoin has contributed to the removal of *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella* spp, *Pseudomonas* spp [32, 33] and Gram-negative organisms [34] from wounds. It is not known if this effect is due to a primary antibacterial effect of phenytoin or if it is due to a secondary effect of phenytoin, such as neovascularisation and/or collagenisation [32, 33].

Oral phenytoin does have dose-related side effects. The most serious of these is the hypersensitivity syndrome [35]. However, the side effects of oral phenytoin have not been reported in the topical application of phenytoin in wound healing. The most probable reason for this is that the topical application of phenytoin results in minimal systemic absorption of phenytoin compared with oral phenytoin. In fact, only one case has reported any significant level of phenytoin in the serum after topical application [30]. This was in a large PU that required 12.5g of phenytoin per day to cover adequately. Even then, the serum concentration of phenytoin after 1 month was only 4.3mg/L, highlighting the minimal systemic absorption of topical phenytoin.

Side effects of topical phenytoin includes a transient burning sensation when it is first applied to a wound [19, 33] and hypertrophic granulation [15, 31]. The latter was found to be avoidable by ceasing therapy once granulation tissue covers the total wound area [15].

Clinical application

Earlier we conducted a pilot study on patients with chronic venous ulcers and were disappointed by the fact that all of our patients found burning pain on application of phenytoin powder and declined to continue the treatment.

The works of El Zayat in 1989 [32] and Anstead *et al.* in 1996 [30], who reported on the beneficial effects of topical phenytoin in the treatment of PUs as well as on the publication on the efficacy of topical phenytoin in the treatment of trophic ulcers in leprosy [17-20], prompted us to use it in PUs.

Our first patient was a case of traumatic paraplegia with PUs. Later on we used this method in patients with PUs associated with paraplegia and also in patients without neurological injuries and found that the topical application of phenytoin in the later group did not cause the burning pain. We believe that in PU the nociceptive pain is absent or reduced due to destruction of sensory receptors from ischaemia due to pressure. In our wound care practice, both at the clinic and in-patients, we found that, for Stage II PUs, modern available dressings (hydrocolloids, Cadexomer dressings etc) work well. We have only used phenytoin in its powdered form in Stage III and IV PUs. We report here two illustrative cases.

Case studies

Case 1

AD, a male aged 52 with a longstanding paraplegia following a motor vehicle accident was seen at the wound clinic for multiple PUs overlying left sacral tuberosity, right leg, right heel and one PU over the left pre-patellar area due to pressure from the dashboard of his car (which was modified to adapt his disability).

While all the above ulcers continued to heal, the pre-patellar ulcer did not improve, in spite of addressing the off-loading by modifying his car dashboard, and he was advised excision of the patella. At this stage, it was decided to try topical

Figure 1. Case 1: with chronic pre-patellar ulcer (pre-treatment).

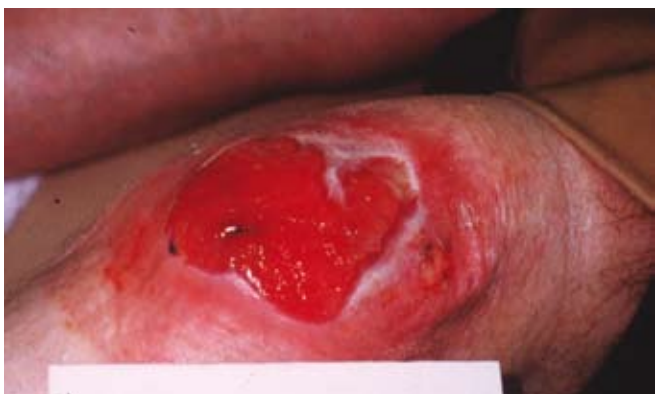
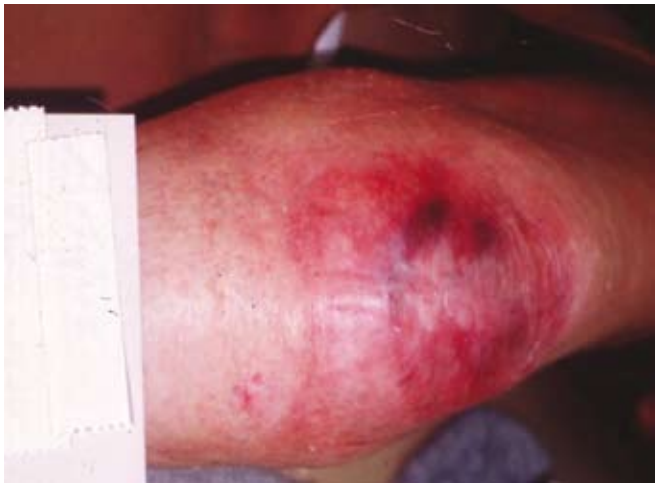


Figure 2. Case 1: healed ulcer 10 weeks after treatment with phenytoin.

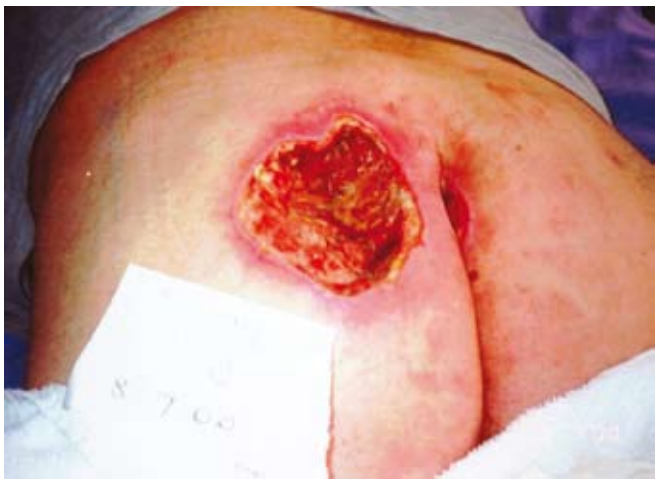


phenytoin powder on this ulcer as a last resort. Dressing with 100mg of phenytoin powder on alternate days resulted in progressive healing and complete healing was achieved in 10 weeks. He was followed up at the clinic subsequently for recurrence of other ulcers, but the pre-patellar one remained healed (Figures 1 & 2).

Case 1

BP, a male aged 49 developed PUs on both buttocks while in the intensive care unit of the local tertiary care hospital. He suffered from acute myocardial infarction followed by cardiac arrest. He was successfully resuscitated, but developed acute renal failure and, a week later it was noted that he had a large Stage IV PU on the left buttock and a smaller one on the right natal cleft.

Figure 3. Case 2: pressure ulcers on the buttocks (pre-treatment).



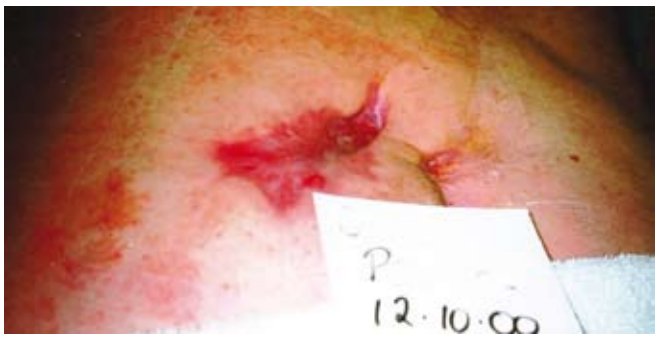
Both ulcers were debrided surgically under local anaesthetic and initially dressed with alginate rope for 3 weeks. Following this his wound was dressed with application of phenytoin powder (400mg) and alginate rope on alternate days. There was progressive rapid improvement in healing and, after 6 weeks, the wound become very shallow and smaller at which time the dressings were changed to alginate only. Complete healing occurred after 14 weeks (Figures 3 & 4).

Discussion

In recent years there has been considerable progress in the understanding of wound healing and a number of new therapeutic approaches are now available e.g., growth factors like PDGF (Regranex™) [36] and negative pressure dressings (VAC™) [37-39]. However, these are expensive and are not always available in all hospitals around Australia.

Earlier we undertook case studies with topical phenytoin on chronic leg ulcers. However, within a short time, we had to abandon this study as patients complained of burning pain soon after application of phenytoin and declined treatment with this. We were surprised that this was not highlighted in several publications, except in two studies [19, 33] and, interestingly, in one study, in which pain actually improved with phenytoin [24].

Figure 4. Case 2: healed ulcers on the buttocks 14 weeks post treatment with phenytoin.



Later on, when we came across to the case of intractable pre-patellar ulcer in case of Mr AD (Case 1) who had paraplegia, we decided to use it as a last resort of conservative treatment. The successful outcome in this case, combined with the experiences from others with regards to diabetic foot ulcers [15, 16] and trophic ulcers in leprosy patients [17-20], led us to its subsequent use in other patients with PUs as in Case 2.

Interestingly, Arinzon *et al.* [40] reported reduction of PUs in long-term bedridden institutionalised patients who received

phenytoin. Also, another study in which two groups of patients with ulcers were treated with only topical phenytoin in one and with both systemic and topical in the other, the only benefit of systemic application was noted to be that those patients receiving both "were calmer and more cooperative" [19]. We have found that application of phenytoin powder in PUs does not provoke any pain and is well tolerated by the patients. We postulate that in PUs the causative factors 'damage' the underlying nociceptive receptors. Whether the loss of nociceptive receptors is the primary event or a secondary event is open to speculation.

The exact mechanism by which phenytoin accelerates wound healing is not well understood and there has been at least one study which refutes its beneficial healing effect [41]. However, this study was conducted *in vitro* which may not replicate the biological milieu of a chronic wound which has multiple interacting cellular, biochemical [42] and immunological factors [43].

We believe that topical phenytoin is particularly useful when used in Stage III and IV PUs after surgical debridement reducing the bioburden of the chronic wound [44]. In our experience, Stage II PUs can be treated effectively with available modern dressing such as hydrocolloid. However, a recent article by Rhodes *et al.* [23] has shown significant reduction in healing time for Stage II PUs treated with phenytoin as opposed to hydrocolloid.

Finally, we would like to emphasis that this treatment must be used in conjunction with the other measures, especially relief of pressure, friction and shearing effects over the affected area, and improving nutrition of the patient.

Conclusion

Prevention of PUs should be the ideal goal in clinical care settings. However, in some critically ill patients, PUs do occur in spite of appropriate preventive measure as part of the multi-organ failure. In patients with Stage III and IV PUs, initial management should be debridement, off loading and improving nutrition. Once a relatively clean wound bed is achieved, topical application of phenytoin powder may improve the rate of healing of PUs. Topical application of phenytoin in such cases is not associated with any serious side effects.

There have been instances throughout the history of medicine where techniques and treatments have been put into widespread use many decades after they were first described [45]; hence we believe that it is important to reconsider the use of phenytoin for the treatment of PUs. In the absence of a controlled study it may be argued that expert care by the wound clinic rather than the effect of phenytoin is responsible for the healing, the so called 'Hawthorne effect' [46]. We therefore plead for other wound care specialists to engage in further clinical trials to validate the role of topical phenytoin, especially in the treatment of PUs.

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