Editorial

Phenytoin beyond epilepsy

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Heinrich blitz German chemist synthesized diphenylhydantoin in 1908. Tracy Putnam and H. Houston Merritt discovered its first clinical use in epilepsy in 1937. The basis of its use was found to be its action directly on the sodium channel to slow the rate of channel recovery from the inactived state to the closed state. By slowing the rate of recovery from the inactivated state to the closed state phenytoin increases the threshold for the action potential and prevent repetitive firing. [1] FDA approved it as antiseizure in 1953. Since then it has been in use in various forms of generalized and partial seizures except pure absence seizure. Till date it is one of the major antiepileptic in spite of introduction of newer ones.

Phenytoin results in various adverse effects like ataxia, nystagmus, incordination, confusion, gingivial hyperplasia, megaloblastic anaemia, hirsutism, facial coarsening and skin rash. The growth of collagen in the connective tissue of gums due to inhibition of collagenase enzyme by Phenytoin lead to speculation that it may have the ability to promote wound healing.

Various studies have shown beneficial effect of topical Phenytoin in decubitus ulcer, venous stasis ulcers, traumatic wound burns, leprosy trophic ulcers and diabetic ulcers. The wound healing enhancing property of phenytoin has been shown due to increase in the platelet derived growth factor –B and its mRNA from macrophages. Inducing fibroblast proliferation, decreasing collegenase activity, enhancing the formation of granulation tissue, inhibition of glucocorticoid activity, direct or indirect antibacterial activity by affecting inflammatory cells and upregulation of angiogenesis are the other mechanisms helping the wound healing. Relief to the localized pain has also been observed which may be due to its membrane stabilizing and anti-inflammatory effect. [2,3,4,5] It has also been reported by various studies that it decreases the bacterial load and facilitate nerve regeneration in the wound. It has been proved that topical phenytoin helps in faster wound healing and can be the superior option when compared to conventional wound dressing. When used systemically, Phenytoin has shown to increase the thickness and density of calvarial and maxillary bones in human. Preclinical studies in rabbits, rats and mice have shown to promote fracture healing and neovascularisation in the healing tendons. [6]

In recent study the scientists at the York University have discovered that phenytoin has the potential to reduce the growth and spread of breast cancer tumour cells. Phenytoin acts through sodium channels, known as VGSCs (Voltage gated Na^+ channels) which exist in the membranes of excitable cells, such as neurons and are involved in transmission of electrical impulses. These channels are also present in breast cancer cells where they are thought to help the spread of tumours. The

researchers found that phenytoin significantly reduced tumour growth in a preclinical model when used in doses equivalent to those used to treat epilepsy (60mg/kg; daily) It also reduced cancer cell proliferation in vivo and invasion into surrounding mammary tissue. [7]

It took years to establish its therapeutic effects in epilepsy, cardiac arrhythmia, digoxin toxicity and neuropathic pain. It has shown beneficial effect in wound healing. Phenytoin being a wonder drug, re-purposing may prove it as a potential novel therapy for cancer in future.

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