Medicinal and nutritional substrates to assist wound healing: a review

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The flow of blood brings with it the most important elements for successful wound care: growth factors and substrates. Good care may also prevent infection, keep the wound moist and provide support by local physical methods. A wide range of drugs might also be helpful.

Introduction

Some phases of the wound healing process and underlying biochemical pathways are increasingly well understood. This has led to some innovations in wound management, including pharmaco- and nutritional therapy. Although the timeline of wound healing is altered by various local conditions, e.g. inflammation and neuropathy, the most important factors affecting wound care are blood flow and angiogenesis. Nutraceuticals can have short and long-term effects through a variety of mechanisms. The most promising approaches at present are the use of nitric oxide (NO·) mimetics and the supply of growth factors e.g. the vascular endothelial growth factor (VEGF) family derived from autologous platelet lysates. These are used in the first phase of wound healing, i.e. haemostasis and inflammation. In the course of the first and second phase until granulation or epithelialisation they are then combined with local treatment by modern dressings, keeping the wound moist. For at-risk patients, e.g. malnourished or ICU patients, adequate food enriched with zinc, copper, arginine and glutamine should provide essential substrates throughout the healing process.

Modern wound care is complex

A pharmacist's role as a member of a wound care team is more than dispensing dressings. If better use were made of pharmacists' skills in biochemistry and pharmacology, wound healing should be faster, free from complications, e.g. infections, and painless. This should lead to shorter hospital stays, reduced workload for other staff and lower costs compared to traditional wound care. State-of-the-art wound care involves the use of dressings that keep the wound moist and can be left in place for several days. A number of factors can affect wound healing, including the aetiology and underlying pathology (trauma, infection, nutritional status [mainly malnutrition], neuropathy, diabetes, the patient's age and drug treatment). Systemic pharmacotherapy of wounds, such as in the case of venous ulcers, is still largely restricted to the use of anti-infective drugs, painkillers and diuretics; there has been little systematic assessment of the effect of other drugs so far. This mini review points to the mechanisms of action of agents that accelerate wound healing in combination with modern local wound care methods [1-4]. A recent review on burns and infected wounds is also recommended [5].

Objectives and general strategy of wound care

The main phases of wound healing comprise haemostasis and inflammation followed by cell proliferation and matrix deposition (proliferation) afterwards, followed by granulation, epithelialisation and matrix remodelling. The most important processes are angiogenesis and perfusion, which provide substrates at the site of injury. Pharmacotherapy and nutrition support these processes [1]. Although few drugs are officially indicated in first-line wound care, many can be used (off label) as supportive treatment because of their, in this case, positive, 'side effects'. Adverse drug reactions may limit use in wound care despite a suitable mechanism of action, e.g. headache caused by nitrates. The aim of scarless healing is only realistic in the case of foetal skin and oral mucosa. Adult skin will heal with scarring. Prevention and treatment of hypertrophic scarring with keloid formation, as well as the fight against non-healing as the wound becomes chronic are the most challenging aspects of wound care. Anything that is preventing wound healing, e.g. pressure, insufficient tissue perfusion, should be eliminated by relieving the pressure and encouraging angiogenesis. Tissue engineering, vacuum-assisted closure and hyperbaric oxygen provide additional physical support for hard-to-heal chronic wounds [1, 6, 7], Eur J Hosp Pharm Prac. 2008;14(5):57-8.

Wound healing agonists

Drugs with at least a theoretical impact on wound healing can be grouped pharmacologically by their structure or on a physiological basis according to the time of intervention in the wound healing phases (see Table 1). Real effects are often controversial, as is the case for platelet lysate products and vitamins where severe deficiencies are rarely encountered, or convincing evidence is still lacking due to underpowered studies, or standards are not yet defined [8].

Mechanism A: Promotion of haemostasis, tissue reperfusion, inflammation and anti-infection effect

Haemostasis needs substrates such as calcium, coagulation factors, phytomenadione, platelet activators and complement. To improve transportation capacity, drugs for treating anaemia may be applied. In the course of clotting, cyclooxygenase-(COX-2) induction and inflammation occur as the result of macrophage influx and the liberation of oxygen-derived free radicals. These oxygen derivatives arise from a Fenton-like biosynthesis: hydrogen peroxide reacts with metal ions (Me^{n+}) which contain

Table 1: Drugs that may serve as substrates and agonists of wound healing

Drug categories	Examples	Haemostasis	Inflammation and anti-infection	Angiogenesis and vasodilatation	Oxygen and substrate supply	Matrix remodelling and turnover
Drugs affecting the nervous system						
Analgesics	Paracetamol, pethidine, morphine (local, 0.2% hydrogel)		✓			
Psychotropics	Clorazepate, oxazepam, flupentixol, paroxetine			✓		
Hypnotics, antiepileptics	Barbiturates, phenytoin					✓
Agonists and antagonists of neurotransmitters	Clonidine, urapidil, terazosin, tamsulosin, alfuzosin, phenoxybenzamine, guanethidine, buphenine, bamethan, phentolamine, tolazoline, propranolol, labetalol, nikethamide, clenbuterol, papaverine			✓		
Drugs affecting the heart and the vascular system						
NO· donors	Nitroglycerin, isosorbide dinitrate, pentacyanonitrosyl ferrate, amyl nitrite, pentaerythrityl tetranitrate, nicotinic acid, xantinol nicotinate, nicotinyl alcohol			✓		
Cardiac glycosides	Digoxin				✓	
Vasodilators	Minoxidil, buflomedil, diazoxide, dihydralazine, naftidrofuryl, milrinone, triptans (e.g. sumatriptan), molsidomine, nicorandil, dipyridamole, bradykinin, kallikrein, sildenafil			✓	✓	
Calcium antagonists	Dihydropyridines (e.g. nifedipine, nimodipine), diltiazem, verapamil, flunarizine, cinnarizine			✓	✓	
Antihypertensives	ACE inhibitors (e.g. perindopril), sartans (e.g. candesartan), reserpine, prazosin			✓	✓	
Endothelin receptor antagonists	Bosentan			✓	✓	
Drugs affecting the respiratory system						
Drugs used to treat asthma	Beta agonists (e.g. salbutamol, terbutaline), caffeine, theophylline, theobromine, aminophylline, pentoxifylline			✓	✓	
Drugs affecting the kidney						
Diuretics	All substances, mainly indapamide			✓	✓	
Drugs affecting the haemopoietic system, haemostasis and thrombosis						
Haematopoietics	Erythropoietin					
Stable and unstable blood products	Whole blood, microencapsulated haemoglobin, erythrocytes, thrombocytes, platelets, plasma coagulation factors, anticoagulants, heparin, thrombin	✓	✓	✓	✓	
O_2 transport, capacity, dissociation	Perfluoron, efaproxiral			✓		
Drugs and substrates affecting metabolism and the endocrine system						
Nutrients	Compounded: Glamin (parenteral), Abound (enteral), Cubitan (enteral), Oral Impact (enteral), Resource Arginaid (enteral)			✓		
Vitamins	Retinol and retinoids, tocopherols, ascorbic acid, pantothenic acid, Ca pantothenate, dexpanthenol, thiamine, riboflavin, pyridoxal, niacin, biotin, folic acid, phytomenadione	✓	✓	✓	✓	✓
Oligoelements	Iron, copper, zinc, selenium, manganese, iodine		✓	✓	✓	✓
Minerals	Calcium	✓				
Amino acids, proteins, substrates for protein metabolism	Arginine, glutamine, hydroxyproline, α-ketoglutarate, becaplermin, VEGF, PDGF			✓		✓

Table 1: Drugs that may serve as substrates and agonists of wound healing (cont'd)						
Lipids and lipid modulators	Iloprost, epoprostenol, statins (e.g. pravastatin), ω-6- and ω-3-fatty acids			✓		✓
Steroid hormones and anti-hormones	Dutasteride, finasteride, megestrol acetate			✓		✓
Non-steroidal anti-inflammatory drugs	COX-1 and COX-2 inhibitors, acetylsalicylic acid		✓	✓		
Antioxidants/reactive oxygen species scavengers/ phytochemicals	Superoxide dismutase, tirilazad mesylate, flavonoids, anthocyanidins, bromelain		✓	✓		
Anti-infection						
Anti-infective drugs	All substances		✓			
Disinfectants	PVP iodine, H_2O_2, silver, aqua Dalibouri		✓			
Tissue engineering						
Products from tissue engineering	Apligraf, EpiDex, Dermagraft					✓

Drugs that may serve as substrates and agonists of wound healing, grouped by supposed mode of action. See text for explanation [2, modified and adapted].

readily available electrons in their d-orbitals, mainly iron or copper:

$Me^{n+} + H_2O_2 \rightarrow Me^{(n+1)+} + OH\cdot + OH^-\cdot$

The reaction with copper is 60 times faster than with iron. Wounds are rich in copper (around 30 μM). Copper, but not iron, induces VEGF formation [8]. Although infection control improves with greater concentrations of these mediators, excessive inflammation can harm tissues and compromise healing. In this case, non-steroidal anti-inflammatory drugs can be used as radical scavengers. However, oxygen-derived free radicals induce angiogenesis by activation of VEGF expression and upregulation of VEGF receptors. Perfusion is essential to remove debris and toxic products from tissue metabolism and to provide substrates for the following reconstruction. A special option for hard-to-heal wounds is the application of hyperbaric, i.e. radical-enriched oxygen, which is used to induce angiogenesis [6, 7]. Infection control may be achieved by PVP-iodine or silver-impregnated dressings or hydrogels. The low level of iodine released from such complexes (5 ppm) avoids iodine allergy or inhibition of wound healing at the margins compared to traditional iodine formulations [2, 4].

Mechanism B: Promotion of angiogenesis by activation of NO·/VEGF, granulation and epithelialisation

Angiogenesis and vascularisation of injured tissue is induced by hypoxia (ideally alternating with re-oxygenation), hydroxyl radicals (and other oxygen derivatives), nitric oxide, and various platelet-derived growth factors, e.g. PDGF and VEGF. These growth factors are occasionally harvested from autologous platelet lysates by some in-house or external laboratories, unfortunately not in GMP-controlled environments [10, 11]. Growth factors are substrates that bind to a transmembrane receptor tyrosine kinase at the cell surface. Binding is followed by several phosphorylation steps which activate a highly regulated cell-signalling cascade that ends with the induction of protein synthesis [1].

Sufficient perfusion of injured tissue is the *conditio sine qua non* for providing the wound with substrates and building blocks: enzyme co-factors/oligoelements (e.g. iron, copper, zinc, selenium, manganese), vitamins (e.g. ascorbic acid, retinol, alpha-tocopherol, biotin, B vitamins, folic acid and pantothenate), lipids (e.g. omega-3- and omega-6-fatty acids), amino acids and other important substrates for protein metabolism (e.g. glutamine, arginine, hydroxyproline, alpha-ketoglutarate) and proteins (e.g. becaplermin, a recombinant human growth factor, and growth factors liberated from thrombin-activated platelets or harvested from platelet lysates). Mechanisms of action are anti-oxidation, cell signalling, protein synthesis, or a combination. The efficacy of ascorbic acid depends on oxygen, alpha-ketoglutarate and prolyl hydroxylase. Tocopherols seem to be cell-signalling messengers although receptors have not yet been confirmed [12]. Arginine is a source of NO·, known up until 1987 as 'endothelial derived relaxing factor'. NO· is formed within 48 hours of an injury, catalysed by an inducible nitric oxide synthase. This inducible enzyme competes with arginase for the substrate arginine. This competition is why arginine may be essential in some patients. A minimum of 10–12 g per day, enteral route, is required for a positive effect on wound healing [2]. In addition, NO synthase contains a reductase and an oxidase domain which depend on several B vitamins. The need for substrates (deficiencies are currently believed to be rare) is highly dependent on the patient's situation. For ICU patients or for patients suffering from large sacral bedsores glutamine is essential because they would not have enough ATP to synthesise it *de novo*. In general, malnourished patients have an increased need for a rich supply of substrates and energy.

Mechanism C: Matrix remodelling and turnover

Full recovery may take up to several

years and results from an equilibrium between cell apoptosis and regeneration. Restricted perfusion due to ischaemia, arterial, venous, or mixed insufficiency, neuropathy, diabetes, or age-dependent atrophy must be overcome and may require several therapeutic approaches.

Involvement of medicines

In theory, many drugs can have an impact on wound healing (see Table 1), either by their main mechanisms of action or by their side effect(s). Following physical laws, perfusion depends on blood pressure and vascular diameter. It is regulated by the autonomic nervous system according to CO_2 partial pressure and O_2 deficiency. Thus, 'NO· mimetics' may be considered for wound care [2]. In practice, my own retrospective studies of the pharmacotherapy of patients treated by a wound care team has revealed or confirmed short-term stimulation of wound healing by anxiolytics, antidepressants, renin-angiotensin-aldosterone (RAA) inhibitors, beta blockers, paracetamol, acetylsalicylic acid, heparin, oral antidiabetics, and antibiotics. No, or at least no negative, impact has been found with coumarins, proton pump inhibitors or insulin [3, 4]. Mechanisms often include NO· liberation followed by vasodilatation and angiogenesis and the regulated (not excessive) production of reactive oxygen species.

Peripheral vasodilators (indicated for Raynaud's disease, ulcers, eschar, gangrene), positively inotropic cardiac glycosides, sympatholytics, RAA inhibitors and beta blockers improve tissue perfusion by vasodilation due to inhibition of bradykinin degradation. They are therefore suitable for patients with poor blood supply in wounded tissues. Non-selective beta blockers antagonise the contracting action of catecholamines and can increase perfusion without opening arteriovenous shunts. In addition, beta blockers decrease oxygen consumption by tissues. Perindopril acts by stimulating NO synthase, thus increases NO levels and causes vasodilation and angiogenesis via VEGF. Short-term stimulation of wound healing can be induced by pharmacotherapy with anxiolytics and antidepressants, if the patient is anxious. Anxiolytics tend to reduce blood pressure and thus could improve venous insufficiency. Tricyclic antidepressants have anticholinergic actions, and therefore also improve venous insufficiency. Serotonin reuptake inhibitors are also vasodilators that act by formation of NO·.

Paracetamol, acetylsalicylic acid, heparin (improves reperfusion by preventing local hypercoagulability), oral antidiabetic agents and antibiotics also have positive effects on wound healing. Paracetamol and acetylsalicylic acid have a positive effect on wound healing indirectly through their analgesic action and consequent potential reduction of anxiety. Furthermore, paracetamol has an anti-oxidative effect and can scavenge free oxygen- and nitrogen-derived radicals, especially if taken in higher amounts. Oral antidiabetic agents have a positive effect due to their anti-oxidative capacity as well. Insulin does not show this effect. A long-term synergism is supposed for statins and diuretics due to a decrease of local pressure caused by oedema. Other drugs that appear to be associated with improved wound healing include diuretics (long-term effect) and anti-infective agents (mainly with diabetic patients). Finally, products from tissue engineering are available to bridge gaps in the skin surface (Appligraf, Dermagraft, EpiDex) [1].

Conclusion

Proper tissue perfusion is key to wound healing. The application of knowledge of physiology and pharmacology may be helpful in accelerating the wound healing process. However, much is experimental and most applications are off label; there is unfortunately only a small evidence base. So, most applications are based on a hypothesised mechanism of action.

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