REVIEW

The negative impact of medications on wound healing

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Abstract
Chronic wounds can lead to amputations and significant decreases in quality of life. Many commonly used medications are known to cause ulcers or perpetuate chronic wounds. A variety of medication classes can impair wound healing through affecting cells within the skin, metabolism, immune cell function, angiogenesis and coagulation. This review aims to highlight the main types of drugs which negatively impact wound healing. Cancer treatments, non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulants, immunosuppressants, and some antibiotics are all risk factors for cutaneous adverse effects. Identifying drug-induced impaired wound healing is important to counsel patients and their medical practitioners on weighing up the benefits and risks of these medications.

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Introduction
Medication is an essential part of disease management and plays a vital role in both treatment of acute and chronic diseases. When a patient has an acute or chronic wound, the use of any medication which may impact on or delay wound healing must be considered. It is essential to obtain a full medication history including prescribed, 'over-the-counter' and complementary products being taken by the patient including oral, injected, topical or inhaled formulations. Risks and benefits must be recognised and weighed up by clinicians and patients to make informed decisions about whether to cease or dose-reduce these medications that can delay wound healing.

Impact of medication on wound healing
Medication use in patients for the management of their chronic diseases plays an important role in either the stimulation or inhibition of wound healing. Pharmaceuticals are used both directly and indirectly in wound management practice. Drugs are applied topically and used systemically as part of wound management for infection, pain management and sometimes immunosuppression for autoimmune aetiologies. Medications interfere with specific phases of wound healing and will affect cells, pathways, growth factors, cytokines, and other important components of the wound healing cascade. In addition, some drugs will, as part of their side-effects, reduce blood flow, blood cells and organ functions critical to wound healing.

Antineoplastic drugs
Chemotherapy can have wound healing complications that can lead to devastating consequences including loss of limb function. This risk is particularly concerning when cancer surgery is performed in conjunction with chemotherapy due to potential surgical wound complications. Some intravenous chemotherapy drugs can induce vein irritation which can result in non-healing necrotic ulcers.[1]

There are a variety of mechanisms of impaired wound healing due to chemotherapy, such as inhibiting cellular metabolism, cell division or angiogenesis. Many chemotherapeutics disrupt DNA replication, transcription, and translation. In wounds they impede cell migration, reduce extracellular matrix production, and inhibit fibroblast proliferation.[1-3] Consequences of these mechanisms include apoptosis, cell cycle arrest, senescence, mitotic catastrophe, inflammatory responses and fibrosis.[4] Chemotherapy can severely impair wound healing through profound immunosuppression. As such, wounds may become infected due to decreased neutrophil and macrophage activity delaying removal of dead tissue and foreign bodies from the wound.[5]

Chemotherapy drugs purposefully target rapidly dividing cancer cells; however, they can also affect susceptible proliferating cells involved in skin wound healing. Some conditions such as excessive dry skin from chemotherapeutic agents can be complicated by cracks and open wounds and infections. One serious complication is hand-foot syndrome which is caused by 5-fluorouracil derivatives such as capecitabine. It is characterized by numbness and paraesthesia in the hands and feet that can quickly progress to serious ulceration and blisters.[6]

Chemotherapy causes apoptosis or dysplasia of rapidly dividing cell types which include keratinocytes, hair matrix keratinocytes (which causes alopecia), fibroblasts and melanocytes.[4,7,8] Cyclophosphamide is associated with a higher risk of severe keratinocyte dysplasia.[8] Cyclophosphamide reduces vasodilatation and subsequent neovascularisation during the proliferative phase of wound healing. Furthermore, chemotherapy has been shown to impair multiple stem cell types in skin including mesenchymal stromal stem cells (MSCs), epidermal stem cells (EPSCs), and hair follicle stem cells (HFSCs).[1,9,10]

Vesicants

Some chemotherapy drugs are vesicants which when extravasated can inflict permanent tissue damage. Symptoms of vesicant extravasation include erythema and pain that can progress to blistering, desquamation, necrosis, eschar formation and ulceration. The classes of chemotherapy that are vesicants include DNA-binding drugs (mustard gas derivatives, anthracyclines, dactinomycin), and non-DNA-binding drugs (vinca alkaloids, alkylators and taxanes).[11] The DNA-binding agents remain bound to nucleic acids even after cell death and subsequently, when endocytosed by adjacent cells will lead to a repeating cycle of cell death that enlarges the wound. Non-DNA binding agents are metabolised and do not perpetuate in this way, with less breakdowns in skin integrity.[12] Prompt cessation of the infusion when extravasation is recognised is key to limiting the tissue damage.

Hydroxyurea

Hydroxyurea is a cytostatic agent that inhibits DNA synthesis as a ribonucleotide reductase inhibitor. Hydroxyurea is one of the most widely publicised medications to cause leg ulcers. It is used for treatment of myeloproliferative disorders. Sirieix et al[13] reported a retrospective series of 41 patients who developed leg ulcers during long-term use of hydroxyurea. Most cases (80%) had complete recovery after cessation of hydroxyurea in a mean of 3 months (range of 1–24 months). In the remaining cases, the ulcers had a reduction in size after discontinuation. Many patients had multiple ulcers, and the ulcers were located near the malleoli or on the calf and foot. For 70% of these patients, it was their first episode of leg ulcers. All ulcers were painful and 25% of cases were necrotic. A typical histopathology involves dermal fibrosis, scar tissue and epidermal atrophy. The mechanism for these ulcers is direct cytological damage due to hydroxyurea. Recommencing hydroxyurea is associated with recurrence of ulceration which confirms hydroxyurea as the cause.[14] In the most serious cases of hydroxyurea ulceration, leg amputation may be required.[15]

Chemotherapy affecting growth factors and angiogenesis

Chemotherapy blocks the synthesis of growth factors subsequently causing decreased cell migration, decreased proliferation and reduced angiogenesis.[1]

Capecitabine and oxaliplatin have been shown to cause reduction in measured levels of growth factors including epidermal growth factor (EGF), platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF) and

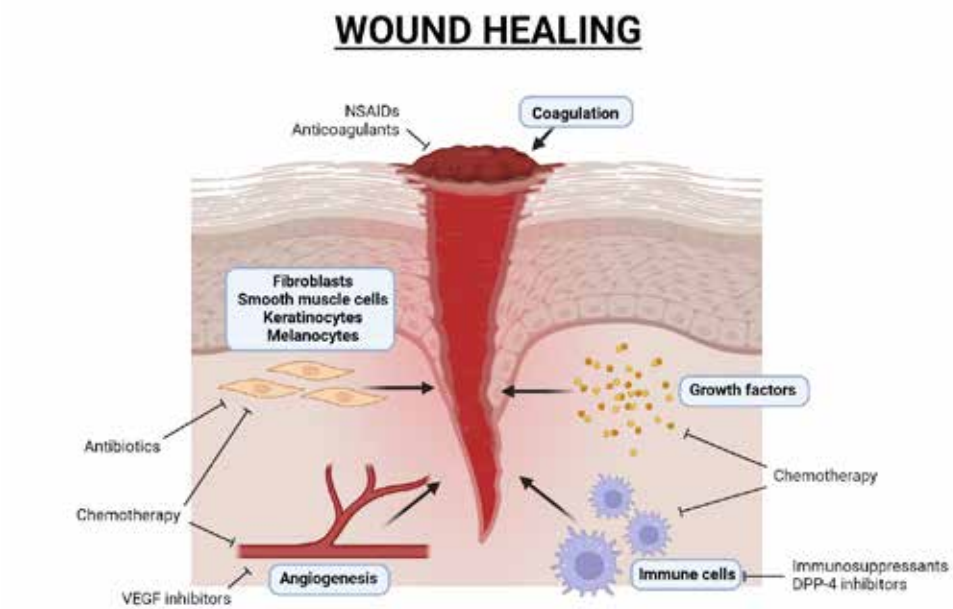

Figure 1. Diagram of wound healing and medications that impair wound healing processes. Created with Biorender.com

hepatocyte growth factor (HGF).[16] These growth factors are important for angiogenesis, hence, the anti-angiogenic properties of chemotherapy may be a key cause for impaired wound healing in these patients.[1]

VEGF plays multiple roles in wound healing: recruitment of monocytes, macrophages, fibroblasts and endothelial cells, increased vascular permeability, and deposition of collagen.[17] The monoclonal antibody VEGF inhibitor bevacizumab works as a treatment for colon cancers by inhibiting new vessel formation, altering vascular function and decreasing tumour blood flow.[18] However, angiogenesis is important for wound healing, and reports of impaired wound healing have occurred in patients on bevacizumab.[19,20] This risk of surgical wound complications can be mitigated by administering bevacizumab 28–60 days after surgery due to its 20 day half-life.[19] Additionally, VEGF inhibitors may be withheld during wound healing. Withholding bevacizumab was implemented to manage a patient with a large necrotic surgical wound and subsequent colostomy dehiscence which developed after bevacizumab and chemotherapy administration.[21]

Targeted cancer treatments

As more directed cancer treatment drugs become more widely available, there have been reports of skin ulcers with targeted cancer treatments as contributing causes. Targeted cancer treatments including tyrosine kinase inhibitors and VEGF inhibitors have been implicated in impaired wound healing.[22,23]

In 2016, there were two case reports of tyrosine kinase inhibitor induced foot wounds with sunitinib and nilotinib, however, the case treated with nilotinib had a confounding factor of premorbid peripheral arterial disease.[24] Tyrosine kinase inhibitor use was independently associated with higher risk of post-operative complications after nephrectomy for stage IV renal cell carcinoma. Complications were broadly defined and included both vascular and wound healing complications.[25] In 2022, Matsuo reported a case of pharyngocutaneous fistula developing after pharyngeal surgery for cancer where imatinib, a platelet-derived growth factor receptor alpha inhibitor was suspected to be implicated as a causative factor.[23]

Non-steroidal anti-inflammatory drugs (NSAIDS)

NSAIDs are members of a therapeutic drug class which reduces pain, decreases inflammation, decreases fever, and prevents blood clotting. There are two general types of NSAIDs available: non-selective, and COX-2 selective. COX-2 selective drugs include celecoxib, etoricoxib, and meloxicam. Most NSAIDs are non-selective and inhibit the activity of both COX-1 and COX-2; examples include naproxen, ibuprofen, diclofenac, indomethacin. These NSAIDs, while reducing inflammation, also inhibit platelet aggregation and increase the risk of gastrointestinal ulcers and bleeds. Their mode of action is to inhibit inflammatory response and acid mucopolysaccharide synthesis in wounds, inhibit inflammatory mediators derived from arachidonic acid metabolism and platelet aggregation. NSAIDs inhibit the production of prostaglandins (PGs), which may be the likely mechanism through which NSAIDs impart their deleterious effects on bone healing. By inhibiting the COX enzymes and the subsequent PG production, NSAIDs not only achieve their desired anti-inflammatory effects but also inhibit the increased production of PGs that is necessary for bone healing to occur. Additionally, the inhibition of COX-1 can increase the local ischemia and hypoxia associated with chronic venous ulcers.[26]

A study found reduced ligament repair and strength in surgically incised medial collateral ligament in 50 rats treated post operatively with a COX-2 inhibitor when compared with the non-treated rats.[27] The inhibition of migration and proliferation of tendon cells by NSAIDs has also been demonstrated by Tsai et al.[28,29] In animals treated with indomethacin or parecoxib, the Achilles tendon has decreased tensile strength compared to the control groups.[30,31]. Timing of NSAID use is important perioperatively, as the use of indomethacin for the first 7 days after surgery has been shown to contribute to the deterioration of healing compared to treatment after 7 days. Indomethacin has also been shown to have negative effects on the proliferation of human tenocyte cultures.[32]

Anticoagulants

Warfarin

Warfarin has a rare but well-known adverse effect of skin necrosis occurring in an estimated 0.01-0.1% of patients with over 300 cases reported.[33,34] Cases of gangrenous skin necrosis attributed to anticoagulant therapy has been described since the 1950s.[35,36] The onset of warfarin-induced skin necrosis (WISN) often occurs between day 1–10, most often between day 3–6.[37] The disease is usually unilateral, however, 30% of cases have bilateral lesions.[34,38–41] The condition has a female predominance, with a 4-fold to 9-fold risk compared to men, and in females the lesions more commonly affect the breast.[33,34,41-43] WISN predominantly affects women treated for acute thromboembolic disease and has not been reported when warfarin is used for atrial fibrillation.[34] The lesions in WISN typically localise in an areas of skin with abundant subcutaneous fat such as the breast, buttock, abdomen or thigh, and has a weak association with obesity.[34,38,41,43,44] They begin as an area of erythema or petechiae that progress to haemorrhagic bullae, and subsequent necrotic eschar. Surgical debridement is required in 50% of cases.[41,42,45] Nalbandian et al[37] proposed that the pathophysiology of WISN begins with a direct toxic effect causing vascular dilatation at the arteriocapillary loop of the dermis, specifically at the junction of precapillary arteriole and capillary. This correlates clinically to the initial erythematous flush. However, lesions are not related to drug dose or duration. Next, damaged capillaries rupturing may correlate to the appearance of petechiae. Ecchymosis results from coalescent haemorrhages, as a consequence

of the anticoagulant effect. The necrotic stage develops after venules thrombose distal to the dermo-vascular loop due to stasis.[37] The pathogenesis appears to involve a combination of changes in haemostasis regulation and local vascular changes. WISN is associated with low levels of protein C, and there have also been reports of WISN in patients with low levels of free protein S. When warfarin is commenced, due to the inhibition of vitamin K-dependent factor production, there is a faster reduction in protein C and factor VII levels due to its shorter half-life compared to the other coagulation factors (factor IX, factor X, protein S and factor II).[43, 44] This leads to a transient hypercoagulability until levels of procoagulant factors sufficiently decrease. Protein C and S deficiencies also cause a hypercoagulable state, therefore, the combination of protein C or S deficiencies with warfarin initiation is theorised to exacerbate thrombosis in microcirculation of the skin leading to skin necrosis.[33,44] Protein C and total and free protein S levels should be measured in patients consistent with hypercoagulable state. Preventing WISN in people with hypercoagulable states may also involve heparin therapy as bridging anticoagulation to counteract the temporary initial hypercoagulable state with warfarin treatment.[39] Ceasing warfarin and changing to a direct oral anticoagulant is the usual management to manage the anticoagulation requirements of these patients, meanwhile, treatment of the skin necrosis often requires surgical intervention.

Heparin

Heparins are polysaccharides that inactivate many coagulation factors and are widely used to treat and prevent thrombotic disorders. Heparin can cause adverse effects related to its anticoagulant effect such as purpura and haematomas either at the site of the injection or elsewhere.[46] Another adverse effect is heparin-induced thrombocytopaenia type II (HIT II) which may lead to arterial and venous thrombosis and subsequent skin necrosis. The mechanism of HIT is the formation of autoantibodies against heparin platelet factor 4 complexes. The onset of HIT II is usually within the first 10–14 days of treatment, and the prevalence is approximately 0.1–2% of patients treated with heparin.[46]

Direct Oral Anticoagulants (DOACs)

DOACs are widely used and there have been reports of rare serious cutaneous side effects.[47] There have been two case reports of dabigatran causing leukocytoclastic vasculitis.[48,49] In 2012, Tsoumpris et al[50] also described a case of toxic epidermal necrolysis (TEN), although the precipitating drug could have been either iron protein succinylate or dabigatran, or an interaction between the two drugs. There has been one case report of rivaroxaban-induced drug reaction with eosinophilia and systemic symptoms (DRESS) and liver injury in 2015.[51] In 2021, Pansuriya[52] described a case report of apixaban causing skin necrosis, which subsequently improved after discontinuing apixaban and changing to low-molecular-weight heparin. It is unknown whether warfarin and heparin related skin toxicities share the same pathophysiology as DOAC-skin toxicities.

Immunosuppressants

Methotrexate

Methotrexate, a folic acid antagonist inhibits DNA synthesis and cell replication by competitive inhibition of dihydrofolate reductase impairing folic acid conversion to folinic acid, providing immunosuppressive and anti-inflammatory actions.[53] Thymidine synthetase activity is reduced resulting in deficient conversion of 2-deoxyuridinylate to thymidine, which subsequently partially blocks DNA and RNA synthesis.[53] Methotrexate inhibits IL-1 and decreases IL-6 synthesis.[53] It is indicated for the treatment of rheumatoid arthritis, ectopic pregnancy, certain cancers and psoriasis. Adverse effects include rare skin reactions, skin ulceration, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Some people receiving high doses of methotrexate experience skin erosions.[54] Biopsies of patients treated with high dose methotrexate show a variety of keratinocyte dystrophies.[54] Leucovorin can be used to minimise risk of adverse effects with methotrexate in cancer patients.

Azathioprine

Azathioprine (AZA) is a purine antimetabolite which is metabolised via 6-mercaptopurine to its active metabolite 6-thioguanine nucleotide (6-TGN). Because AZA suppresses inosinic acid and purine synthesis, it interferes with B and T lymphocyte proliferation, T cell mediated immune reactions (decreased IL-2 secretion) and antibody responses.[55] T lymphocytes play an important role in wound healing especially during the inflammatory phase. AZA is indicated for organ transplant rejection prevention, rheumatoid arthritis, inflammatory bowel disease and systemic lupus erythematosus. Adverse effects include Stevens-Johnson syndrome and toxic epidermal necrolysis.

Leflunomide

Leflunomide inhibits pyrimidine synthesis through selective dihydroorotate dehydrogenase and tyrosine kinase enzyme block-aid.[56] Active metabolite teriflunomide acts on rapidly dividing cells and lymphocytes inhibiting their effects.[57] Leflunomide's toxic effect on epidermal cell lines impairs ulcer healing and arrests the production of epidermal growth factor.[56] Skin ulceration with an incidence rate of 1–3% from post-marketing surveillance is listed in the American Hospital Formulary Service.[56] It exhibits immunosuppressive, immunomodulating and antiproliferative properties. It is indicated for rheumatoid arthritis and psoriatic arthritis. Adverse effects include Stevens-Johnson syndrome and toxic epidermal necrolysis. Teriflunomide has an elimination half-life of approximately 2–4 weeks, therefore, its effects on wound healing can remain post cessation.[58]

Ciclosporin

Ciclosporin is a calcineurin inhibitor, forming a complex with cyclophilin inhibiting calcineurin action in activated T cells.[55] Calcineurin inhibition prevents cytokine gene expression, reducing IL-2, IL-4 and TNF-α production and consequent

T cell proliferation and differentiation.[55] It is indicated for transplant rejection prevention, psoriasis, severe rheumatoid arthritis and nephrotic syndrome.

Mammalian target of rapamycin (mTOR) inhibitors

Sirolimus is a first-generation mTOR inhibitor used for prevention of transplant rejection. Impaired wound healing after surgery has been reported with sirolimus and everolimus. mTOR activation is important for angiogenesis, therefore, it is proposed that sirolimus causes impaired wound healing by inhibiting angiogenesis.[59] The mechanism of sirolimus causing impaired wound healing also involves the inhibition of intraepithelial T cells to proliferate and produce normal levels of growth factors. In a mouse model, normal wound closure could be restored by addition of the skin gammadelta T cell-produced factor, insulin-like growth factor-I.[60]

A prospective randomised trial comparing sirolimus-based immunosuppression versus tacrolimus-based immunosuppression found a significant increase in wound complications in the sirolimus group.[61] Tacrolimus is a calcineurin inhibitor and an alternative to sirolimus. Sirolimus also has additional adverse effects including hyperlipidaemia and leukopenia. Dean et al[61] adjusted for these in their prospective randomised trial by excluding patients with dyslipidaemia and leukopenia prior to randomisation. However, they were unable to control for pre-existing diabetes mellitus as the sirolimus group had significantly more diabetes compared to the tacrolimus group. In the sirolimus group, 47% (30 of 64) developed wound complications ($p<0.0001$) compared to 8% of the tacrolimus group (5 of 59). Most wound complications were superficial wound infections, peri-graft fluid collections, and incisional herniae. The sirolimus group had more surgeries and readmissions for wound-related conditions.[61]

Everolimus is another mTOR inhibitor which reduces wound strength when given at time of surgery. This effect is prevented by delaying administration to 2–4 days after colon surgery in rats.[62]

Corticosteroids

Corticosteroids are regularly used for their immunosuppressant and anti-inflammatory properties. They include prednisolone, prednisone and dexamethasone and are indicated for the treatment of auto-immune and inflammatory conditions including rheumatoid arthritis, ulcerative colitis, Crohn's disease, acute asthma and COPD exacerbations and acute gout. Corticosteroids impair wound healing and repair by inhibition of gene expression, anti-inflammatory actions and suppression of multiple cellular wound responses.[63] Corticosteroids delay fibroblast proliferation, collagen synthesis, fibroplasia, vascular proliferation and epithelisation.[63,64] Their immunosuppressive affects increase wound infection risk which also impedes healing. Corticosteroids used in the inflammatory phase of healing impair leucocyte migration including macrophages into wounds leading to diminished neovascularisation and fibroplasia. Dexamethasone decreases cytokine expression including TNF, PDGF, and IL–1 in damaged wound tissue.[64]

Colchicine

Colchicine is indicated in acute gout attacks, gout prophylaxis and familial mediterranean fever (FMF). New acute gout guidelines endorse low dose treatment with a reduced adverse risk profile to be as effective as previous high dose treatment; with 1mg taken at the first sign of attack, followed by 500mcg, one hour later.[65] Daily prophylactic dosing is once or twice daily and similarly in FMF with daily life-long dosing. Colchicine reduces inflammation, following raised urate crystal levels which commonly deposit in joints and surrounding tissue, providing pain relief.[66] Colchicine, an alkaloid, is extracted from plants in the Genus Colchicum.[67] Colchicine binds to tubulins with high affinity blocking microtubule assembly and polymerisation.[67] Microtubules form complexes used in mitosis, vesicular trafficking and cell motility.[68] Successful wound healing requires cell migration into a wound.[68] Impaired microtubule assembly and polymerisation impairs cytokine and chemokine secretion, inhibits optimal cell shape maintenance, impairs cell migration and blocks mitotic cell division.[67] Colchicine also acts on the immune system inhibiting neutrophil chemotaxis and phagocytosis and adhesion in inflamed tissue.[69] Decreased granulocyte migration, decreased fibroblast activity, decreased blood supply due to vasoconstriction and increased collagenase synthesis resulting in a decreased wound breaking strength are all associated with colchicine.[53]

Antibiotics

Antibiotics treat bacterial infection supporting wound healing in infected wounds. Antibiotics do not heal wounds explicitly as not all wounds are infected, and their indiscriminate use can be harmful.[70,71] Correctly identifying infection is key. All open wounds are contaminated with micro-organisms and colonisation occurs when bacteria are replicating without tissue invasion, cellular injury, or wound breakdown.[70] Colonised wounds do not require antibiotics.[70] Antibiotics treat infection, however they can reduce the tensile strength of wounds, and can affect collagen cross-linking.[72]

Surprisingly, wound healing is supported in 'colonised' wounds by bacteria stimulating neutrophil chemotaxis.[71] Proteolytic enzymes from bacteria including hyaluronidases support autolytic debridement and protease release from neutrophils.[71]

Macrolide antibiotics include erythromycin, clarithromycin and roxithromycin and have diverse biological actions including extensive inflammation modulation and immunomodulatory actions.[73] Their use outside their antimicrobial activity in treatment of inflammatory conditions is evolving. Macrolides accumulate within cells and act on receptors that modulate immune cell activities.[73] Erythromycin decreases

proinflammatory cytokine production, including IL-8 which is a potent neutrophil chemoattractant.[73]

Tetracycline antibiotics include doxycycline, tetracycline and minocycline. Tetracyclines reduce inflammation by the inhibition of leucocyte chemotaxis and by decreasing pro-inflammatory mediators including TNF and IL-1.[74] Tetracyclines inhibit matrix metalloproteinases (MMP) which support wound matrix modification, cell migration and tissue remodelling.[75]

An exception is doxycycline which has demonstrated positive impacts in the chronic wound environment. Doxycycline inhibits MMP-mediated degradation of a host defense protein (a-1 antitrypsin) which inhibits leucocyte elastase. This reduction in leucocyte elastase indirectly prevents the degradation of connective tissue.[76] Nitric oxide (NO) a pro-inflammatory free radical is cytotoxic to the micro-wound environment and overexpressed in chronic wounds. Doxycycline reduces cytokine-induced NO synthesis by inhibition of NO synthase expression reducing excessive tissue breakdown and chronic inflammation.[76]

Gentamicin is an aminoglycoside which acts to inhibit protein synthesis causing cell membrane damage. It also delays re-epithelialisation in the maturation phase.[77]

In most wounds topical antibiotic use is not recommended.[72] Current 2022 International Wound Infection Institute[78] guidelines state, as topical preparations are typically low dose they support resistance and their use should only be employed in critically infected wounds under specialist clinicians.

Dipeptidyl peptidase-4 inhibitors

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors) used in the treatment of type 2 diabetes mellitus have been associated with cutaneous adverse effects. DPP-4 inhibition increases GLP-1 and GIP concentration increasing insulin secretion and inhibits glucagon release to maintain euglycemia.[79] DPP-4 inhibitors include alogliptin, linagliptin, sitagliptin, sitagliptin and vildagliptin. DPP-4 is involved in wound healing and immune pathways.[80] DPP-4 inhibitors are implicated in the development of cutaneous disease, including Bullous Pemphigoid (BP), mucous membrane pemphigoid and Stevens-Johnson syndrome.[81] The average time to BP occurrence is 8-27 months with interpatient variability.[81] Rates of BP are higher with vildagliptin, followed by linagliptin.[79,81,82] DPP-4 is expressed on immune cell surfaces, including T cells, B cells, macrophages and natural killer cells, endorsing varied immunomodulating affects.[82,83] DPP-4 activation on T cells promotes activation and migration, inflammation and autoactivation.[80] DPP-4 interacts with other signal transduction pathways (CD3) as a co-stimulator of T cells with activation promoting T cell response to foreign antigens, cytokine secretion, cell proliferation and cellular mobility.[84] Fibroblast activation by DPP-4 increases the expression of profibrotic gene expression. Consequently, DPP-4 inhibition inhibits T cell proliferation and helper cell presentation, inhibits keratinocyte DNA synthesis and migration, and suppresses fibroblast survival and proliferation.[81]

Discussion

Medications are used to improve patient health outcomes by treating disease and symptoms, and sometimes to prolong life in life-threatening conditions. Unfortunately, adverse effects of many medications involve impaired wound healing which can be complicated by necrosis or infection requiring surgery or amputation. Taking a holistic approach to patient management by looking at the patient global wellbeing allows prescribers to treat the condition at hand while remaining cognisant of other current issues which may potentially be negatively affected by the treatment prescribed.

Prior to the prescribing of medication and formulation of a wound management plan, it is essential that a full and complete medication history is taken. Knowledge about medications with potential to cause wounds or delay wound healing aids in reducing these adverse effects from occurring. Medications with long half-lives may still exert their effects when patients are no longer taking them. Identifying previously administered medications can help to mitigate potential negative consequences. For example, perioperative wound complication risk can be reduced by delaying surgery after administration of mTOR inhibitors or VEGF inhibitors or withholding NSAIDs perioperatively. Regular reviews of medications ensures medications with potential negative wound healing impacts are not continued where no longer indicated. Medication dosage and treatment duration also affects the risk of impaired wound healing. Treating an acute gout flare with colchicine for a short duration will have a smaller impact compared to chronic daily dosing for gout prevention.

A pharmacist is the ideal professional to consult prior to prescribing a new medication, especially for patients with wounds. Hospital pharmacies have a dedicated drug information service which can be utilised to support patient-centred prescribing.

Determining the risks and benefits associated with medication use is critical. In some cases, medication use is essential and life-saving and potential associated negative impacts may be accepted, such as in cancer or anticoagulation therapy. Where there are no alternative options available, the choice to use a medication that may impede wound healing may be accepted, but wound prevention and management must be prioritised.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

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