The effect of medicines on wound healing

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Outline

• Principles that medicines can delay the wound healing process
• Pathophysiology of wound healing
• Chronic wound healing
• Medicines affecting wound healing processes
  • Coagulation
  • Inflammation
  • Proliferation
  • Wound closure
• Resources
• Conclusion
Principles that medicines can delay the wound healing process

- Many types of wounds, varying from size, depth, and sterility
  - Medicines may prolong healing time
- Different wound classifications i.e. traumatic, surgical, chronic
  - Different strategies to manage medicines
- During wound healing process
  - Time that factors are produced by cells/cellular activity cf. drug characteristics
  - Drug characteristics i.e. pharmacokinetics/pharmacodynamics
  - Dose, route, frequency, and time that drug is administered
  - Blood supply to wound area
- Medicines may affect more than one stage of the wound healing process
- Important to note why patient on a medicine – to treat a condition!
Pathophysiology of wound healing\textsuperscript{1,2}

- Overlap of four events
  - Coagulation
  - Inflammation
  - Proliferation
  - Matrix remodeling and scar tissue formation i.e. wound closure
- Many growth factors and cytokines involved
  - Regulate cellular function and recruitment
Chronic wound healing\textsuperscript{1,6}

- Classified into venous/arterial ulcers, diabetic ulcers, and pressure ulcers
- Characterised by:
  - ongoing/excessive inflammation
  - incomplete wound closure
  - persistent infection
  - innate inability of epithelial/dermal cells to respond adequately to therapy
- Mediated by underlying pathology e.g. diabetes, poor blood flow (e.g. heart failure)
Medicines affecting wound healing – Coagulation

- Occurs immediately, within 12-24 hours area is clotted
- Mediated by Platelet Derived Growth Factor, Transforming Growth Factor, coagulation factors
- Cytotoxics can directly destroy production of platelets e.g. carboplatin used in breast cancer
- Anticoagulants can inhibit coagulation factor production e.g. heparin, enoxaparin, warfarin, dabigatran
- Antiplatelets can inhibit platelet’s ability to clot e.g. low dose aspirin, clopidogrel, dipyridamole
Coagulation: Putting it into practice

- Management of warfarin is different in traumatic, surgical, and chronic wounds
- Traumatic wounds require reversal of warfarin
- Surgical wounds require peri-operative strategy to balance risk of bleeding and VTE vs ability of wound to coagulate
- Chronic wounds require INR monitoring and management if INR excursion occurs
Medicines affecting wound healing – Inflammation

- Minutes - 12 hours, invasion of inflammatory cells
- Mediated by interleukins, prostaglandins, Tissue Necrosis Factor alpha (TNF-α), and Transforming growth factor
- NSAIDs e.g. ibuprofen, high dose aspirin, indomethacin
  - Inhibit prostaglandin synthesis and recruitment of WBC
- Cytotoxics e.g. docetaxel for ovarian cancer
  - Arrest neutrophil and macrophage in their late stage of replication
- Monoclonal antibody antagonists e.g. infliximab for Rheumatoid Arthritis
  - Bind to and stop the activity of TNF-α which prevents migration of WBC
Inflammation: Putting it into practice

- NSAIDs – the double edged sword!
- In traumatic/surgical wounds the reduction of WBC recruitment can reduce the ability of the wound to be sterile…
  - …so we must balance pain relief and wound sterility!
- In chronic wounds inflammation can be reduced so wound can progress to the next stage of healing!
Medicines affecting wound healing – Proliferation

- Days 3-7, max neutrophil counts; proliferation of epi/endothelial cells/fibroblasts; macrophage remain
- Mediated by Vascular Endothelial Growth Factor, interleukins, Insulin-like Growth Factor
- Aminoglycosides e.g. gentamicin has a direct toxic effect on corneal epithelial cells
- Cytotoxic agent bevacizumab inhibits VEGF that prevents angiogenesis
- Corticosteroids e.g. long term prednisolone reduces Insulin-like Growth Factor via the hypothalmic-pituitary axis
  - Reduces proliferation and differentiation of many cells
Putting it into practice: Proliferation

- Cytotoxics e.g. capecitabine used for colorectal cancer
  - Causes “Hand-Foot Syndrome” or “sloughing-off” of skin
- In any wound, increased risk of HFS
  - Epithelial/endothelial proliferation is suppressed
  - Reduced ability of proper scar tissue formation
  - Leads to easily skin that is easily able to “slough-off”
- Requires input from patient’s oncologist
  - May need to delay treatment or reduce dose
Medicines affecting wound healing – Remodeling

- 1-2 weeks after injury, fibroblasts have transformed into myofibroblasts to maintain matrix, remodeling, and wound contracture
- Mediated by Transforming Growth Factor, Fibroblast Growth Factor, TNF-\(\alpha\)
- Putting it into practice: Immunosuppressants e.g. cyclosporin, tacrolimus
  - Reduces production of interleukins that mediate production of extracellular matrix by myofibroblasts
  - Inability of wound to contract properly leading to gross scarring
Resources

- Your friendly pharmacist 😊
- Medicines Line at the National Prescribing Service
  - Ph 1300 MEDICINE (1300 633 424) Monday to Friday 9am to 5pm
- Australian Medicines Handbook
- MIMs and Product Information
Conclusion

- Medicines can delay/improve the wound healing process
- Affect any stage of the process
- Management of medicines is different for traumatic, surgical, and chronic wounds
- Must balance the risk of delayed wound healing vs treatment of a condition
- Goal is to have complete wound closure with minimal scarring, complications, and impact on patient’s health
References


2. Werner, S and Grose, R. Regulation of wound healing by growth factors and cytokines. Physiol Rev 2003, 83: 835-870


