

MEDICINES AND WOUND  
HEALING:  
What's the word?

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# What is the word about drugs?



- How do drugs affect wound healing?
  - ▣ Direct actions (intended and adverse effects)
  - ▣ Method of delivery of drugs
- What does this all mean for the wound clinician?

# Overview



- Identify some key issues about medicines and wound healing
  - ▣ Understand potential impacts of medicines
  - ▣ Consider therapy approaches
- Describe key considerations for concurrent medicines use during wound healing
- Briefly explore specific issues for antibiotics and antiseptics

# What does this mean?



- Drugs are external chemical compounds (maybe synthetic, maybe natural)
- Given in a number of ways
- May affect wound healing
  - ▣ Stimulate
  - ▣ Retard
  - ▣ Complicate
  - ▣ Facilitate

# How do they do this?



- Molecular/biochemical modifications
- Changes in cell function or structure
- Exogenous toxins
- Delivery vehicle effects

# Molecular/biochemical modifications



- Changes behaviour at molecular level
  - ▣ Receptor effects
    - Cell action
    - Other chemical release (eg enzymes, etc)
  - ▣ Chemotactic effects

# Corticosteroids (-ve effects)



- Drugs in this class include prednisolone, prednisone, hydrocortisone, etc
  - ▣ Inhibit nearly every aspect of wound healing!
- Inhibit acute wound healing only when given prior to or immediately after injury
  - ▣ Due to inhibition of inflammatory phase
  - ▣ Inhibit initial increase in vascular permeability and vasodilation (normal post trauma) due to inhibition of prostaglandin synthesis

# Corticosteroids (cont)

- Chronic wounds
  - ▣ During inflam phase - ↓ macrophages
    - Affects chemotaxis and proliferation of fibroblasts
    - ↓ collagen production, inhibition of angiogenesis
  - ▣ Reduce wound contraction during proliferative phase due to effects on fibroblasts
  - ▣ Inhibit epithelial migration, poor quality tissue
  - ▣ Decreased tensile strength of healed tissue in maturation phase
  - ▣ Effects on immune system

# Corticosteroids (cont)

- Chronic wounds - Immune system effects (immunosuppressive)
  - ▣ ↑ susceptibility to infection
  - ▣ ↓ chemotaxis and proliferation of T lymphocytes
  - ▣ ↓ protein synthesis (modulation of gene transcription) - ↓ TGF- $\beta$  (cytokine involved with broad range of wound repair activities)
  - ▣ Complex and detailed events – more details in: Roberts, A. and Sporn, M. 'Transforming Growth Factor-  $\beta$ ' in Clark, R. (Ed), The Molecular and Cellular Biology of Wound Repair, (2nd edition), Plenum Press, New York, 1996

# Nicotine (-ve effects)

- Nicotine - smoking or therapeutic
  - ▣ Vasoconstrictor
    - peripheral vasoconstriction decreases blood supply to wound
  - ▣ Increased platelet aggregation
  - ▣ Impaired collagen synthesis
  - ▣ Hypothesis - interferes with reepithelialisation by release of catecholamines, co-factors for chalone formation (wound hormones that inhibit epithelialisation)
  - ▣  $\alpha$ -adrenergic blockade (eg Prazosin) used to overcome peripheral vasoconstriction in recalcitrant smokers for wound healing

# Sex hormones (+ve effects)

- Oestrogen
  - ▣ Menopausal ↓ dermal collagen & thickness
  - ▣ ↑ TGF-β1 with HRT in menopausal women
  - ▣ High levels TGF-β1 in younger women
  - ▣ Suggested hormone modulation of TGF-β1 levels
  - ▣ Research suggests ↓ circulating reproductive hormones with age principal factor in delay of age related healing
- Androgens (testosterone)
  - ▣ Anticatabolic effects
  - ▣ Anabolic effects

# Retinoids (+ve effects)

- Isotretinoin (Roaccutane®) approved for cystic acne
  - ▣ Associated with reversal of steroid induced inhibition of healing and improvement in epithelialising wounds
  - ▣ Regulate expression of growth factors
  - ▣ ↑ secreted TGF- $\beta$  (up to 50x) in certain cells
    - Activation of latent TGF- $\beta$
    - Induction of growth factor
  - ▣ Inhibit all negative effects of steroids except effects on wound contraction
  - ▣ Clinical use – only case reports so far
  - ▣ Care with use – risk of hypervitaminosis A

# Antibiotics (+ve effects)



- Doxycycline
  - ▣ Tetracycline class antibiotic
  - ▣ Animal research shows effects on matrix metalloproteinase activity
  - ▣ Studies on humans in WA
  - ▣ Retards collagen degradation
  - ▣ Stimulates angiogenesis
  - ▣ Other similar chemicals with similar activity in animal models

# Anti-neoplastic drugs (-ve effects)



- General points about antineoplastics
  - ▣ Cytotoxic - not cancer cell-specific
  - ▣ Range of classes and pharmacological actions – generally exert effect on rapidly replicating cells i.e. cancer cells
  - ▣ Wound cells may be replicating more rapidly than normal cells and so at risk
  - ▣ Risk of extravasation injury
  - ▣ Haematological changes may affect healing

# Antineoplastic drugs (cont)

- Hydroxyurea (Hydrea®)
  - ▣ Non-nucleoside anti-metabolite
  - ▣ Associated with causation of ulcers, esp malleolar, with long term use or high doses
  - ▣ Lichenoid eruptions called hydroxyurea dermopathy after long periods of therapy
  - ▣ Number of effects leading to ulceration
    - Damage basal keratinocytes leading to dermal atrophy
    - Platelet mediated inflammatory response leading to micro-thrombi formation
  - ▣ Ulcer treatment
    - Cessation of therapy
    - Erythropoietin and Pentoxifylline may facilitate healing

# Haemorrheologics (+ve effects)

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- Pentoxifylline/Oxpentifylline (Trental®)
  - Effectively change flow characteristics of blood
    - Reduce platelet aggregation
    - Reduce leukocyte adhesion
    - Increase RBC membrane flexibility
      - RBC 8-9µm & capillary 4-5 µm

# Haemorrhheologics (cont)

- Pentoxifylline/Oxpentifylline (Trental®)
  - Used to treat PVD
    - ↑ blood flow to ischaemic tissue
    - Inhibit TNF- $\alpha$
    - Vasodilator effects
    - Reduce effects of build up of anaerobic metabolites in ischaemic tissue which have effect on tissue as well as RBC cell wall rigidity

# Haemorrhheologics (cont)

- Cochrane review
- Pentoxifylline appears to be an effective adjunct to compression bandaging for treating venous ulcers. There was no cost effectiveness data available and health care commissioners may therefore conclude that it not be considered a routine adjunct. Pentoxifylline in the absence of compression may be effective for treating venous ulcers in the absence of compression, although the evidence should be cautiously interpreted. The majority of adverse effects are likely to be tolerated by patients, and gastrointestinal disturbances are the most frequent adverse effect

# Antibiotics (+ve effects)



- Infection will delay or deter healing
  - ▣ Extent depends on type and number of infective organisms and patient factors
- Antibiotic treatment
  - ▣ Initially using guidelines (eg Antibiotic guidelines)
  - ▣ based on culture and sensitivity results from swab or biopsy
    - Swab may not identify tissue infective organism

# Exogenous chemical effects



- Toxins

# Smoking (-ve effects)




- As well as nicotine effects
- Hydrogen Cyanide interferes with cellular function through enzyme inhibition (hypothesised)
- Tissue oxygenation and perfusion
  - CO effect on oxygen carrying capacity of haemoglobin
  - Smoking for 10 minutes decreases oxygen tension for one hour

# Formulation and wound healing



- It is not just the drug that may affect the wound, but how it is delivered – eg enteral, parenteral, topical, etc
- Main concern is for topical treatments
  - ▣ Dermal products designed to penetrate skin layers – cross several layers
  - ▣ Facilitate transdermal drug delivery
  - ▣ May have local actions
  - ▣ Not designed to be used on exposed tissue

# Antibiotics (-ve effects)



- Topical antibiotics
  - ▣ Don't penetrate tissue
  - ▣ Decompose in contact with tissue
  - ▣ Diluted by exudate and decomposition
  - ▣ Inhibition of contraction
  - ▣ Delay re-epithelialisation
  - ▣ Mostly formulated to be applied to skin (or elsewhere) and act locally, not for exposed tissue
  - ▣ Risk of resistance

# Need to consider...



- Why drugs being used?
  - ▣ To treat, manage or prevent disease
    - Includes wound healing
- Should be indication for drug use
- May be necessary therapy
- Consider priorities of other clinicians for other disease states
- Consider priority for wound healing

# Drug therapy decision making



- What influences choices?
  - ▣ Patient outcomes?
  - ▣ Evidence?
    - Treatment guidelines, etc
  - ▣ Access?
  - ▣ Desperation?

# What does it mean in practice?



- Methodical approach
  - ▣ Indications
  - ▣ Approved uses
  - ▣ Pharmacological actions
  - ▣ Interactions
  - ▣ Adverse effects
  - ▣ Risk/benefit analysis

# Evidence based wound care



- Evidence based practice
  - ▣ Plausible mechanism of action
  - ▣ Published evidence to support use
  - ▣ Evaluations of use

# Preventing and managing infection



- Antibiotics
  - ▣ What are they?
  - ▣ Best practice use
- Antiseptics
  - ▣ What are they?
  - ▣ Best practice use

# Antimicrobials

- Antibiotics show selectivity only for specific micro-organisms
- Antiseptics are generally non-selective  
→ potentially damage **ALL** cells on contact

*Need to carefully evaluate the use of all chemical agents used in wound management*

*Fleming 1917*

# Indications for use

- Overt contamination and infection risk
  - ▣ Acute wounds
  - ▣ Chronic wounds containing devitalised tissue (slough) and exudate
  - ▣ Increased risk of infection – eg diabetes
- Chronic wound
  - ▣ Odour control
  - ▣ If all apparent factors evaluated and addressed and wound healing impaired may be high levels of bacterial colonisation
    - critical colonisation
    - Inhibits healing process
  - ▣ Need to reduce bacterial load for healing
- Complement systemic antibiotic therapy

# Infection and chronic wounds

- Infection depends on exposure
- Clinical signs require systemic management
  - ▣ Empirical therapy initially
    - See Antibiotic guidelines
  - ▣ Identification by bacteriology
    - Identify specific antibiotic sensitivities
- Chronic wounds will be colonised – this does not mean that they are infected
- Chronic wounds do not require antibiotics or antiseptics as a matter of course

# Antibiotics



- Chemical compounds that either kill or inhibit growth of bacteria
  - ▣ not viruses or fungi
- Show selectivity only for certain bacteria
  - ▣ Spectrum of action varies from compound to compound

# What are systemic antibiotics?



- Delivered systemically (vs topically)
  - ▣ Usual routes of administration
    - Parenteral (various routes)
    - Oral
  - ▣ Route of administration determined by
    - Urgency
    - Absorption
    - Cost
    - Patient factors

# How do they work?

- Bactericidal or bacteriostatic
- Mechanisms
  - ▣ Inhibit cell wall synthesis
    - Penicillins, cephalosporins, vancomycin
  - ▣ Inhibit protein synthesis
    - Aminoglycosides (b/cidal), chloramphenicol, macrolides, clindamycin, tetracyclines (b/static)
  - ▣ Antimetabolites
    - Sulfonamides, trimethoprim
  - ▣ Inhibit bacterial DNA synthesis
    - Quinolones
  - ▣ Affect on membrane permeability
    - Polymixin B, Colistin

# Common sense antibiotic use

- Is infection present?
- Are systemic antibiotics necessary?
- Therapy selection
  - What antibiotic or combination of antibiotics should be used?  
Including the role of
    - Standard treatment guidelines
    - Diagnostic testing
  - Should treatment be enteral or parenteral?
  - What should be the duration of therapy?
  - What special circumstances are present (i.e., concomitant illnesses, potential drug–drug interactions) that can impact therapy?
- Complementary use/role of antibacterial dressings

# Using topical antiseptics



- Infection risk or colonisation as indicator for use?
- Is systemic therapy necessary?
- Therapy selection based on:
  - ▣ Risk
  - ▣ Therapeutic goal
  - ▣ Understanding of chemical properties
  - ▣ Delivery vehicle
- Antibacterial dressings

# Antiseptic actions



- Can be bactericidal or bacteriostatic
  - ▣ Inhibit reproduction
  - ▣ Inhibit metabolic activity
  - ▣ Change pH
  - ▣ Liberate oxygen – mechanical effects
- Organic and inorganic compounds
- In open wound – some risk of systemic absorption

# Delivery of antiseptics

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- Vehicle or base – carries antiseptic to site of action
- May create sensitivity (eg wool alcohols, lanolin)
- If insoluble - foreign matter in wound
- Ointments may be occlusive
- Issues of solubility
  - Aqueous or lipid

# Common antiseptics



- ❑ Acetic acid
- ❑ Chlorhexidine (+/- Cetrimide)
- ❑ Hydrogen Peroxide
- ❑ Hypochlorites
- ❑ Iodine (inc Povidone-Iodine)
- ❑ Mercurochrome
- ❑ Pot Permangante
- ❑ Silver (various salts and metallic)
- ❑ Triclosan (& other phenolic compounds)

# Essential oils with some antimicrobial effect

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- Oregano
- Tea Tree
- Mint
- Sandalwood
- Clove
- Nigella Sativa
- Onion
- Lavender
- Lemon
- Eucalyptus
- Peppermint
- Cinnamon
- Clove
- Thyme

# Tea-tree oil components

## **MELALEUCA ALTERNIFOLIA** Cheel (Myrtaceae) "Tea-Tree"

1,4-CINEOLE Leaf 0.001 ppm 1,8-CINEOLE Leaf 260 - 16,000 ppm  
ALLOAROMADENDRENE Leaf 45 - 112 ppm ALLYL-HEXANOATE Leaf 0.001  
ppm ALPHA-BULNESENE? Leaf 36 ppm ALPHA-CADININE Leaf 143 - 358  
ppm ALPHA-COPAENE Leaf 10 - 25 ppm ALPHA-CUBEBENE Leaf 4 - 11 ppm  
ALPHA-GURJUNENE Leaf 23 - 58 ppm ALPHA-MUUROLENE Leaf 0.001 - 30  
ppm ALPHA-P-DIMETHYLSTYRENE Leaf 7 - 18 ppm ALPHA-  
PHELLANDRENE Leaf 10 - 50 ppm ALPHA-PINENE Leaf 200 - 700 ppm  
ALPHA-TERPINENE Leaf 190 - 4,375 ppm ALPHA-TERPINEOL Leaf 180 -  
902 ppm ALPHA-TERPINOLENE Leaf 364 ppm ALPHA-THUJENE Leaf 76  
ppm AROMADENDRENE Leaf 235 - 675 ppm BETA-ELEMENE Leaf 0.001  
ppm BETA-PHELLANDRENE Leaf 75 ppm BETA-PINENE Leaf 59 - 950 ppm  
CALAMENENE Leaf 10 - 25 ppm CAMPHENE Leaf 0.001 ppm  
CARYOPHYLLENE Leaf 0.001 - 154 ppm CYMENENE Leaf 12 ppm EO Leaf  
10,000 - 25,000 ppm GAMMA-TERPINENE Leaf 1,154 - 3,000 ppm HEXANOL  
Leaf 0.001 ppm HUMULENE Leaf 0.001 - 12 ppm LIMONENE Leaf 100 - 250  
ppm LINALOL Leaf 10 - 25 ppm MENTHATRIENES Leaf 0.001 ppm  
MYRCENE Leaf 52 - 130 ppm NEROL Leaf 0.001 ppm P-CYMEN-8-OL Leaf  
13 - 32 ppm P-CYMENE Leaf 300 - 2,855 ppm PIPERITOL Leaf 7 - 18 ppm  
PIPERITONE Leaf 8 - 20 ppm SABINENE Leaf 12 - 30 ppm TERPINEN-1-OL  
Leaf 40 - 100 ppm TERPINEN-4-OL Leaf 2,941 - 11,225 ppm TERPINOLENE  
Leaf 236 - 6,125 ppm VIRIDIFLORENE Leaf 103 - 257 ppm

# Risk reduction



- IF antiseptic indicated, wash off after 3-5 minutes
  - ▣ Expose bacteria only to high concentrations
  - ▣ Reduce risk of resistance
  - ▣ Reduce impact on tissue from prolonged exposure

# Practice Points



- Balance benefits of disinfection against risk of harm on wound
- Do not use antiseptic agents in clean wounds
- Consider options (wound cleansing, antibacterial dressing, etc)

# The antiseptic dictum



“I challenge each and every one of you to take the agents you are currently using in your wound management procedures and put them in your eye”

Rodeheaver

# Important resources

- **National standard treatment guidelines**
  - ▣ Australian Therapeutic Guidelines
    - Antibiotic Guidelines
- **National Formulary**
  - ▣ Australian Medicines Handbook
- **Pharmacotherapy: A Pathophysiologic Approach** – Dipiro et al
  - ▣ How drugs affect people, not just cells
- Reading
  - ▣ “The use of systemic antibiotics in the treatment of chronic wounds” R. Hernandez, Dermatologic Therapy, 19, 2006, 326-337