

Wound Pharmacology

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Good news in wound care

*Is sex good for wounds?
.....maybe!*

How is sex good for wounds?

- Lots of studies try and link good health to plenty of sex (researchers predominantly male of course)
- Latest theory being explored:
 - TGF β is an important cytokine involved in wound remodelling
 - TGF β is one of key molecules in semen
 - Can be delivered orally with some anti-cancer effects (stimulates protective mechanism and inflammatory response against some cancers)
 - Topical for wounds?
 - Alternative source is cows milk
 - Some pharmaceutical companies working on freeze dried semen tablets!!!

Food for thought

- How do drugs affect wound healing?
 - Direct actions (intended and adverse effects)
 - Method of delivery of drugs
 - Drug interactions
- Entertainment value (well it would be funny if it weren't true)
 - Irrational rationale's
 - Dodgy combos
- What does this all mean for the wound clinician?

Some drugs with negative effects on wound healing

- Corticosteroids
- Cytotoxic drugs
- Nicotine (and smoking)
- Anti-platelet drugs
- Antibiotics
- Colchicine
- β -blockers

Negative effects - Corticosteroids

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

Negative effects – Antineoplastic drugs

- 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

- Hydroxyurea (Hydrea®)
 - Non-nucleoside anti-metabolite
 - Associated with causation of ulcers, especially malleolar, with long term use or high doses
 - Lichenoid eruptions called hydroxyurea dermatopathy 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

Negative effects – Nicotine

- 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)
 - α -adrenergic blockade (eg Prazosin) used to overcome peripheral vasoconstriction in recalcitrant smokers for wound healing

Nicotine (cont)

- Smoking - 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

Negative effects - Anti-platelet drugs

- Class includes Aspirin and other NSAIDs
 - Most research done with aspirin
- Two main effects at higher doses
 - Inhibition of prostacyclin synthesis (a potent vasodilator) so vasodilation does not occur by this mechanism
 - Inhibits inflammatory response and acid mucopolysaccharide synthesis in wounds
- Impact of COX-II inhibitors not yet known

Negative effects - Antibiotics

- Significant overuse in treatment of acute and chronic wounds
- Suggested no role in uncomplicated venous ulcers
- Need better understanding of wound physiology
 - Normal inflammatory response – heat redness, swelling pain, (?) lack of function or movement
 - Infection – extensive erythema, swelling, fever, pain, change in exudate colour, increase exudate, odour, elevated neutrophils
- 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

Negative effects - Colchicine

- Treatment and prophylaxis for gout
- Number of negative effects on wounds
 - ↓ Granulocyte migration and cytokine release
 - Vasoconstrictive
 - ↓ fibroblast synthesis
 - Interrupted extracellular transport of procollagen
 - ↑ collagenase synthesis - ↑ collagenolysis
 - Inhibit wound contraction

Negative effects - β -blockers

- Potential for effects on wound healing due to known pharmacological effects
 - ↓ heart rate
 - ↓ BP
 - Some more cardio selective (dose-dependent) – β 1
 - β 2 antagonism can lead to ↓ peripheral blood flow due to action on arteriolar smooth muscle
- Not a lot of evidence of effects on wound healing

Drugs with positive effects on wound healing

- Antibiotics
- Haemorrhheologics
 - Pentoxifylline (Trental®)
 - Other Methyl Xanthines
- Sex hormones
- Retinoids
- Anti-platelet drugs
- Immunosuppressants
- Phenytoin

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 - Infection – extensive erythema, swelling, fever, pain, change in exudate colour, increase exudate, odour, elevated neutrophils
- 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
- 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

Positive effects - Haemorrhheologics

- 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
- Pentoxifylline/Oxpentifylline (Trental®)
 - Used to treat PVD
 - ➔ blood flow to ischaemic tissue
 - Inhibit TNF-α
 - 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
- Pentoxifylline/Oxpentifylline (Trental®)
 - Uses in other cerebrovascular disorders
 - Well tolerated – A/Es usual suspects
- Other Methyl Xanthines
 - caffeine, theophylline, theobromine
 - Used in 1920s for intermittent claudication but deemed “too unreliable and feeble as a vasodilator to be of value in the treatment of PVD”
- 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

Positive effects - Sex hormones

- 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

Positive effects - Retinoids

- 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-β (up to 50x) in certain cells
 - Activation of latent TGF-β
 - 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

Positive effects - Anti-platelet drugs

- Aspirin
 - At lower doses platelet aggregation inhibition predominates over anti-inflammatory effect
- Other NSAIDs
 - More anti-inflammatory effect than anti-platelet activity
 - Inhibit both cyclo-oxygenase and lipo-oxygenase transformations of arachidonic acid
- Two main effects of aspirin at lower doses
 - Inhibit platelet aggregation which may lead to thrombus development
 - Inhibit arachidonic acid pathway to inhibit inflammation mediated by arachidonic acid metabolites
- Research
 - one small study with inconclusive positive results

Positive effects - Immunosuppressants

- Drugs other than corticosteroids
- No evidence of significant inhibition of healing
- Facilitate healing in wounds related to auto-immune diseases
- Some evidence (animal models only) of improved tensile strength of tissue

Positive effects - Phenytoin

- Anticonvulsant since 1930s
 - Centrally acting - not related to wound healing
- Gingival hyperplasia common side effect – may be useful for wound healing
- Unsure of mechanism of action for wound healing properties
 - Fibroblast proliferation
 - Facilitation of collagen deposition
 - Glucocorticoid antagonism

How formulation affects wound healing

- It is not just the drug that may affect the wound, but how it is delivered – eg enteral, parenteral, topical, etc
- Formulation affects
 - Administration
 - Absorption
 - Distribution
 - Metabolism
 - Excretion

- Pharmacokinetics
- Pharmacodynamics
- 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

Drug/dressing nightmares

- Why are these dodgy treatment choices used?
 - Mercurochrome mixed with Chloromycetin® eye ointment
 - Kenacomb® ear ointment
 - Ground Flagyl® tablets +/- gel
 - Kaltostat with Silvazine
- What influences choices?
 - Patient outcomes?
 - Evidence?
 - Desperation?

What does it all mean in practice?

- Methodical approach
 - Indications
 - Approved uses
 - Pharmacological actions
 - Interactions
 - Adverse effects
 - Risk/benefit analysis
- Evidence based
 - Plausible mechanism of action
 - Published evidence to support use
 - Evaluations of use

Useful references

- Australian Medicines Handbook
- Cochrane library via www.nicsl.com.au/cochrane/index.asp
- (NICS guide to using the Cochrane Library <http://www.nicsl.com.au/cochrane/guide.asp> and the Wiley Interscience Detailed User Guide for The Cochrane Library: a “zipped” file half way down the page at <http://www3.interscience.wiley.com/cgi-bin/mrwhome/106568753/userguides.html>)
- Primary Intention
- Journal of Wound Care
- Pharmacotherapy: A Pathophysiologic Approach – Dipiro et al