Calciphylaxis:

Pain management in renal impairment

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1961 Hans Seyle coined term “calciphylaxis” to describe a condition of induced hypersensitivity in which tissues respond to appropriate challenging agents with tissue calcification.

Step 1: sensitization by agents such as parathyroid extract, high dose vitamin D, high phosphorous diet or induction renal failure

Step 2: challenging agent such as local trauma

Result: Subcutaneous calcification (calci-) as an adaptive or protective reaction (phylaxis)


Experimental Calciphylaxis | Human Calciphylaxis
---|---
No small artery/arteriolar calcifications | Calcification, microthrombosis, fibrointimal hyperplasia of small dermal and subcutaneous arteries/arterioles
Animals able to cast off calcified skin molt and replace with new dermis with no features of calciphylaxis | Skin manifestations predominate but can also have vascular calcifications in skeletal muscle, brain, lungs, mesentery
Able to be prevented by administration glucocorticosteroids | No response to steroids

Also known as calcific uraemic arteriolopathy

- Rare
- 1-4% dialysis patients
- Can also occur in nonuraemic, non dialysis patients
- Female 2:1
- Obesity (BMI>30) lesions occur on trunk, thighs, breasts
- Diabetes: no data whether control or duration changes risks

Co-Morbid Conditions

- Auto immune conditions such as SLE, Temporal arteritis, rheumatoid arthritis
- Drugs used in the management of above such as corticosteroids, methotrexate, ultra violet light
- Hypercoagulable conditions such as protein C and protein S deficiencies
- Longer dialysis vintage > 7 years
- Hypoalbuminaemia

Medications increasing risk

- Calcium supplements
- Calcium based phosphate binders
- Warfarin
- Corticosteroids
- Iron therapy
- Trauma associated with subcutaneous insulin/heparin injections
Mortality high, within months of diagnosis
 One year mortality 45-80% in those with ulcerated lesions
 Lower extremity involvement associated with lower mortality (23%) compared trunk and proximal limbs (63%)
 Morbidity related to severe pain, non healing wounds, recurrent hospitalisations
 Death usually secondary to sepsis

Pathogenesis

- Poorly understood
- Hyperparathyroidism may be implicated but not consistent.
- Ca x PO₄ product may be important
- Vitamin D administration in high doses may induce calciphylaxis? Increasing serum phosphate? Direct action on arterioles

What do we see?

- Mottled skin (livedo reticularis)
- Nodules
- Purpuric plaques
- Necrosis skin, subcutaneous fat, muscle

Histological features

- Calcification of medial wall of arterioles
- Intimal proliferation and fibrosis, endovascular thrombosis
- Ischaemic pathology distal to vessels
Diagnosis
- Skin biopsy BUT risk of ulceration, infection, bleeding, induction necrosis, propagation new lesions
- Punch biopsy (4-5mm deep) recommended

Treatment
- Treat calcification
- Treat ulcers
- Treat pain
- SUPPORTIVE

Sodium thiosulphate
- Thought to dissolve calcium deposits by forming soluble complexes
- May act as antioxidant to restore endothelial function and promote vasodilation improving pain
- 30-60 mins towards end dialysis
- 25mg (in 100mls saline) x3 week

Adverse N&V headache hallucinations

Bisphosphonates
- Action inhibits macrophages and proinflammatory cytokines
- Binds to calcified smooth muscle to inhibit further calcification
- Removed by haemodialysis
- Pamidronate 30mg iv x 5 doses
- Adverse: fever, pain at injection site

Hyperbaric Oxygen Therapy
- 25-30 sessions at 2.5 atmospheres
- To promote healing of ulcers
- Limited number of studies

Opioids in Renal Failure and Haemodialysis
- Parent drug
- Metabolites

Renal Failure

Dialysis

GFR approximates excretion of many drugs
**Dialysis**
- Role of clearance of a drug and its metabolites is complex.
- Removal in dialysis depends on molecular weight, water solubility and volume of distribution: protein binding.
- Dialysis process itself may vary e.g. pore filter (area, pore size, geometry of filter technique) flow rate of patients blood and of dialysate fluid.
- Peritoneal vs haemodialysis.

**Morphine**
- Metabolised by liver.
- Morphine-3-glucuronide (55%), Morphine-6-glucuronide (10%), normorphine (4%).
- Parent compound excreted normally in renal failure.
- M-6-G in renal failure (as glucuronide excretion is affected).
- Crosses BBB slowly, CNS effects can be prolonged after discontinuation morphine.
- Dialysis: Low protein binding, moderate water solubility → removed by most procedures BUT glucuronides would accumulate.

**Hydromorphone**
- Metabolized in liver: hydromorphone-3-glucuronide (36.8%), dihydromorphone (0.1%) and other lesser metabolites.
- H-3-G neuroexcitatory and accumulates in renal failure but not clear whether clinically effect.
- No change in dosage recommended.
- Dialysis: low volume distribution, high water solubility, low protein binding → dialyzable.
- Use carefully and monitor patient.

**Oxycodone**
- Excreted as conjugated and free oxycodone (8-14%).
- Oxymorphone only active metabolite, low plasma levels.
- Excretion slowed in renal failure but little known of effect.
- Dialysis: water soluble, 50% protein bound → dialyzable no definitive data.
- Best to avoid in dialysis.

**Methadone**
- Metabolised to a pyrrolidine then to pyrroline both hydroxylated.
- Excreted in urine (20-50%) as methadone or metabolites.
- Excreted in faeces (10-45%) as pyrrolidine metabolite.
- No changes in excretion in renal failure.
- Dialysis: high protein binding and high volume distribution, moderate water solubility → poorly removed.
- No accumulation → safe to use (usual precautions).

**Codeine**
- Metabolised to codeine-6-glucuronide (81%), morphine, morphine3G (2%) and morphine6G (<1%).
- Significant decrease in clearance in renal failure.
- Accumulation of metabolites.
- Significant accumulation in haemodialysis with toxic effects.
- Do not use.
**Gabapentin**
- Renal excretion as unchanged drug
- Clearance reduced in renal impairment and half life increased
- Suggested reduced dosage (at same intervals)
- 3% protein bound, moderate volume of distribution
- Dialysis: recommended supplemental dose after dialysis in addition to usual dosage

**Pregabalin**
- Negligible metabolism
- Renal excretion as parent drug
- Dialysis: not bound to plasma proteins, 50% reduction plasma levels after dialysis
- Supplemental dose following 4 hour haemodialysis

**Case#1**
RI 72 year old male
ESRF diabetic nephropathy on dialysis
Type 11 diabetic on insulin
Ischaemic heart disease
Hypertension
Pulmonary hypertension
Atrial fibrillation
Obesity 114kg

**Continuing pain**
- Worsening ulceration lesions lower limbs
- Hyperbaric oxygen considered
- Contraindicated due to pulmonary hypertension

- Increased analgesic requirements on dialysis
  - Removal by dialysis of opiates
  - Ionisation changes

- PCA fentanyl 10µ increased to 20µ
- Ketamine 8mg hour s/c
- Hydromorphone oral (Jumilata)
- ↑ right leg pain
  - ulceration worsens
• Decision to perform right below knee amputation
• Gabapentin increased
• Ketamine infusion peri-op
• Femoral sheath with local anaesthetic
• Hydromorphone regular with breakthrough
• Left leg amputated 3 weeks later

4 years later still on dialysis
• phantom limb pain controlled with gabapentin

Case#2
• MT 57 male
• ESRF diabetic nephropathy
• Hypertension
• Ischaemic heart disease
• Implantable defibrillator
• Accidentally knocked right calf

• Developed skin lesion
• Not noticed for three weeks
• Necrotic, infected ulcerating lesions
• Commenced hydromorphone q2hourly
• Gabapentin 100mg after dialysis
• Ketamine infusion 10mg/hour
• Sodium thiosulphate 25mg after dialysis

• Septic given antibiotics
• Increasing pain
• Increased doses gabapentin, now regular 300mg bd
• Jurnista increasing doses to 48mg/day
• Breakthrough hydromorphone
• Still in pain

2 Mervyn Dean, Opioids in renal failure and dialysis patients „JPain Symptom Management“ 2004, 28:497-504
3 Peter Santos, J Edward Hartle and L Darryl Quarles, Calciphylaxis 2013UpToDate
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Peripheral Vascular Disease

Pain Management in ESKD

Chronic kidney disease (CKD) is an independent risk factor for generalised atherosclerosis and coronary artery disease.

Lower limb peripheral artery disease is a significant clinical issue in patients with CKD.

Increased number of studies now describe an association between PAD and CKD.

Older age is associated with higher prevalence of known risks such as cardiovascular disease, diabetes, and hypertension.

After adjustment for these possible confounders, CKD is independently associated with an increased prevalence of PAD.

Symptomatic PAD

More prevalent in those with CKD than in the general population.

Intermittent claudication:
- In the general population: 1-5%
- In CKD: 7% (as high as 12% in some studies).

Incidence of lower limb "incident" rates (e.g., need for revascularization, amputation):
- In CKD: 2.7%
- In renal function: 0.6%

Clinical

Similar to patients without CKD but:
- More likely to develop critical limb ischaemia.
- Have higher rates of limb loss after revascularisation.
- Higher mortality.

How do we diagnose?

Ankle-Brachial Index (ABI):
- Measure systolic blood pressure in both arms.
- Measure systolic blood pressure at the ankle of the affected limb.
- Ratio <0.90 indicates PAD.

BUT:
- In CKD, higher rates of vessel calcification leading to abnormal low pressure due to arterial incompressibility.
- >1.3 indicates calcification.
Vascular duplex studies
- Exercise ABI (after treadmill stress)
- CT angiography
- MRA angiography
- Angiography
- Usually reserved if contemplating revascularisation
- (risk dye)

Treatment PAD?
- Few studies have evaluated impact of medical treatment on peripheral artery disease outcomes
- Recommendations for treatment are extrapolated from described or presumed benefit of interventions in reducing cardiovascular events or modifying markers of cardiovascular risks

Risk Factor Modification
- Statin therapy to reduce overall frequency of cardiovascular events
- Antihypertensives to reduce risk cardiovascular events, delay progression of CKD
- Smoking cessation—although not studied in this population smoking is associated with increased risk amputation among patients with claudication

Invasive treatment
- Indications no different to general population
- More likely to undergo amputation
- Higher mortality and lower limb salvage rates
- Revascularisation has lower mortality rates than amputation or no intervention

References
With thanks to the teams at St George Pain Management Unit and the Renal Palliative Care Unit