Pharmacology

Anticholinergics

Indications
- Detrusor instability
- Incontinence
- Urgency
- Catheter induced bladder spasm

Mechanism of action
- Blockage of muscarinic acetylcholine receptors to inhibit unstable detrusor contraction

Side effects
- Dry mouth
- Constipation
- Sweating
- Blurred vision
- Tachycardia
- Urinary retention

NHS Available Drugs
- Classic antimuscarinics (propantheline, glycopyrrolate, atropine, etc)
  - Non-selective M antagonists
  - Poor side effect profiles
Bladder pharmacology

- **Oxybutynin**
  - Some selectivity for M1 and M3 receptor subtypes
  - Additional direct smooth muscle relaxant, probably via calcium channel blockade
  - Potent antimuscarinic but weak direct smooth muscle relaxant (500x less)
  - Extensive first pass metabolism. Metabolite (desethoxybutynin) more potent but more side effects
  - Multiple randomised trials have confirmed efficacy but at expense of compliance rates due to side effect profiles
  - OxybutyninXL comparable efficacy to immediate release but improved tolerability in multi-centre trial (Andersson 1999)

- **Tolterodine**
  - Not receptor specific but greater affinity for bladder vs. salivary gland
  - Most commonly prescribed drug in US
  - Efficacy of immediate release tolterodine vs. oxybutynin similar but tolterodine has improves side effect profile (Chapple 2000)
  - Comparison of TolterodineXL (4mg od) vs immediate release (2mg bd) resulted in 18% reduction in urge incontinence and 23% lower side effects (Van Kerrebroek 2001)

- **Trospium**
  - Non-selective M antagonist with some anti-nicotinic effects in vitro
  - Similar efficacy to oxybutynin but more favourable side-effect profile
  - Further studies required

- **Flavoxate**
  - Initially thought to be weak anticholinergic but in fact acts as calcium channel blocker and PDE inhibitor
  - Good quality side-effect profile but questionable efficacy in DI and hyperreflexia

- **Darifenacin (Non-NHS)**
  - Highly selective M3 receptor antagonist
  - Animal studies indicate predilection for bladder vs. salivary gland
  - Too few studies at present to recommend routine usage
  - Unlicensed at present

- **Solifenacin (Vesicare)**
  - M3 receptor antagonist
  - STAR trial Chris Chapple – need to review

**Beta-Agonists**

- Animal studies show strong dose-related effect of β2 agonists on bladder body, but not on bladder base or urethra.
- Direct stimulation of β receptors induces adenylyl cyclase mediated smooth muscle relaxation
- No effect reported on normal human bladder but terbutaline reported to be efficacious in small case series in patients with DI and urge incontinence.
Bladder pharmacology

- Troublesome tachycardia, palpitations, and tremor
- Currently not recommended

**Alpha-Blockers**
- Whilst alpha-adrenergic responses not present in normal detrusor, they appear to develop in bladder dysfunction due to spinal injury and bladder outflow obstruction.
- Spinal injury/ bladder denervation associated with urethral supersensitivity to α-adrenergic stimulation, increased outflow resistance and decreased compliance.
- A reduction in bladder compliance, contraction, and filling pressures, can be achieved with alpha-blockers.
- Alpha-blockers well-recognised to reduce irritative symptoms in BOO, but quality randomised trials in DI/ detrusor hyperreflexia lacking. Not currently licensed for this indication.

**Calcium Channel Blockers**
- Antagonise muscarinic-mediated calcium channel opening and intracellular calcium release
- Known to be a potent mechanism for detrusor smooth muscle relaxation
- Calcium channels not bladder specific however
- Side-effects
  - hypotension, facial flushing, headache, dizziness, abdominal discomfort, constipation, nausea, rash, weakness, and palpitations
- Available information at suggests that **oral administration of calcium channel blockers ineffective for treatment of DI.** There may be a role for intravesical therapy or synergistically with anticholinergics
- Terodiline has combined anticholinergic and calcium channel blocking properties, and confirmed efficacy, but withdrawn due to unacceptable cardiotoxicity in elderly and with antidepressants/antipsychotics.

**Tricyclic Antidepressants**
- Extensively studied in CNS – findings extrapolated to LUT
- Mechanisms of action
  - Central and peripheral anticholinergic effects
  - Serotonin and noradrenaline reuptake inhibitors
  - Sedatives
- Significant side-effect profiles
  - Predominantly anticholinergic
  - Allergic – rash, abnormal LFTs, agranulocytosis
  - CNS – weakness, fatigue, parkinsonism, UL tremor, mania, psychosis
  - Other – Impotence, postural hypotension, arrythmias
- Imipramine
  - Weak antimuscarinic effects on bladder BUT strong direct inhibitory effects on bladder smooth muscle. ? mechanism – not cholinergic or adrenergic ? Serotonergic
Bladder pharmacology

- Clinical trials in 1970s + 1980s confirm efficacy but use declined.
- Well known efficacy in childhood enureisis. ? mechanism

Other Drugs
- Duloxetine
  - Selective serotonin and noradrenaline re-uptake inhibitor
  - In animal models acts to depress bladder contractility (serotonergic) and increase EUS tone (serotonergic and adrenergic)
  - Recent multi-centre RCT (n = 450) reports good efficacy for 40mg bd of duloxetine in reducing SUI frequency. Main side-effect = mild nausea 17% (Millard BJUI 2004)
- Baclofen
  - GABAb agonist
  - Depresses motoneurones and interneurones in spinal cord
  - Appears to work in DSD by relaxing EUS but also reported to reduce frequency and incontinence in idiopathic DI
  - Few quality randomised trials however (nothing since 1993)
- No evidence for Potassium channel openers or Prostaglandin inhibitors in bladder instability

Intravesical Agents
- Reduction in afferent inputs decrease likelihood of abnormal micturition reflex
- Capsaicin
  - Acts on vaniloid receptor subtype 1 found on polymodal nociceptors
  - Receptor activation opens calcium/sodium channels – depolarisation of c-fibres
  - Repeat stimulation desensitises and inactivates sensory neurones after primary ‘flare’
  - 1-2mM single installation clinically effective in small study groups with neuropathic bladders
  - Problematic side-effects, including burning, bleed, and autonomic dysreflexia. Pain abolished with LA pre-treatment
  - DeRidder (2000) reported 84% improvement in meta-analysis of 115 patients
- Resiniferatoxin
  - Vaniloid from Euphorbia resinifera
  - 1000x more potent than capsaicin without ‘flare’
  - Highly promising. Study of 27 patients with MS showed mean bladder capacity increase of 259ml after 1 month.
- DMSO effective in interstitial cystitis but not in DI/ DH