The Drugs
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SCHEDULE 1
Substances administered by injection into the foot
• Betamethasone sodium phosphate beta-acetate
• Dexamethasone sodium phosphate
• Hydrocortisone sodium succinate
• Methylprednisolone acetate
• Triamcinolone acetonide
• Denatured alcohol 4% (ethyl alcohol)
• Bupivacaine
• Lidocaine hydrochloride (with or without epinephrine)
• Mepivacaine hydrochloride
• Sterile saline solution
• B12- Cyanocobalamin

Lidocaine
• Lidocaine hydrochloride was synthesised by Löfgren and Lundquist in 1943, and was clinically introduced in 1948
  – It can be administered parenterally for a peripheral nerve block (PNB), intravenously or applied topicaly at strengths of 2-4%
• The addition of epinephrine 1:100,000 to 1:200,000 slows the vascular absorption of lidocaine and prolongs its effects

Prilocaine
• C_{13}H_{20}N_{2}O.HCl
• N-(2-methylphenyl)-2-propylamino-propanamide

Mepivacaine
• Mepivacaine was the second amide local anaesthetic to be clinically introduced
  – Mepivacaine, together with bupivacaine and ropivacaine, were synthesised by Ekenstam in the 1950’s

Bupivacaine
• The most potent of the amide local anaesthetics
  – It is used in concentrations between 0.25% and 0.5% for local infiltrations and PNBs respectively and has a much longer duration of action than many of the other local anaesthetics

Legislation
• In October 2005 the Medicines and Healthcare products Regulatory Agency (MHRA) published a consultation letter about proposals for amending the range of medicines which can be sold, supplied or administered by podiatrists
  – The proposals were successful and from 17th November 2006, two new local anaesthetics (amongst other drugs) have been introduced for use in Podiatry

Legislation
• Statutory Instrument No. 2807: Medicines for Human Use (Administration and Sale or Supply) (Miscellaneous Amendments) Order 2006 (Burnham 2006)
  http://www.opsi.gov.uk/si/si2006/20062807.htm

• These drugs are:
  –levobupivacaine hydrochloride
  –ropivacaine hydrochloride

More Chemistry
Isomerism
Chemistry
• Stereoisomers are molecules with the same chemical formula (and bonds) but a different atomic arrangement
– As a consequence they possess similar chemical and physical properties

**Chemistry**

- Enantiomers are stereoisomers that are *chiral* (non super-imposable mirror images of each other) much as one's left and right hands are the same but opposite

**Chemistry**

- When compounds exist in different isomeric forms, the different molecules can be classified according to:
  - their geometry
    - (R for rectus or S for sinister)
  - the way in which they rotate polarised light:
    - *levo* for anti-clockwise or *dextro* for clockwise

**Chemistry**

- When the equal amounts of enantiomers are mixed they are termed racemic
  - Enantiomers of chiral local anaesthetics, such as ropivacaine and levobupivacaine, have the advantage over racemic mixtures in showing reduced systemic toxicity

**Ropivacaine**

- Ropivacaine was originally synthesised in 1957 but has only been used medically since 1996
  - It was released into clinical practice to address the issue of bupivacaine cardiotoxicity following fatalities in the 1970’s after accidental intravenous (i.v.) injections in obstetric patients

**Ropivacaine**

- Ropivacaine is structurally similar to bupivacaine, having a propyl group instead of the butyl group of bupivacaine
  - It is therefore chemically similar to bupivacaine and has similar pKa and plasma protein binding values, but is less lipophilic

**Ropivacaine**

- It combines the anaesthetic potency and long duration of action of bupivacaine with a toxicity profile between that of lidocaine and bupivacaine
  - The main clinical advantage of ropivacaine is the safety margin between the therapeutic and toxic doses, allowing administration of ropivacaine in greater doses

**Ropivacaine**

- It is theorised that because ropivacaine is less lipophilic it has a greater effect on the non-myelinated pain fibres rather than the myelinated motor fibres

**Naropin®**

- Naropin® is marketed by AstraZeneca in the U.K. as a 2 mg/mL (0.2%), 7.5 mg/mL (0.75%) and 10 mg/mL (1.0%) solution
  - Naropin® is the pure S-enantiomer and is the isomer best suited for clinical use (its R configuration confers greater cardiotoxicity than racemic bupivacaine)

**Naropin®**

- The British National Formulary (BNF) states that doses should be adjusted according to the patient’s physical status and nature of procedure planned but lists the MSDs as:
  - 30–40 mL of a 7.5 mg/mL solution for a major nerve block
    - 300mg
  - 30mL of a 7.5 mg/mL solution for a field block

**Naropin®**

- Cumulative doses up to 800mg for surgery and postoperative analgesia administered over 24 hours are well tolerated in adults

**Levobupivacaine**

- Racemic bupivacaine exists as levobupivacaine and dextrobupivacaine
  - Dextrobupivacaine exhibits a “fast in; slow out” blockade of cardiac sodium channels whereas levobupivacaine demonstrates a “fast in; fast out”

- The two drugs have a similar partial co-efficient but levobupivacaine has a longer duration of action than bupivacaine and produces less vasodilatation
Foster and Markham reviewed preclinical and toxicity data, reporting an advantage of levobupivacaine over bupivacaine.

**Levobupivacaine**

\((S)-1\)-butyl-N-(2,6-dimethylphenyl)piperidine-2-carboxamide

Levobupivacaine chemical structure and formula

- The S-enantiomer (levobupivacaine) has been developed for clinical use
  - Chirocaine® is marketed by Abbott Laboratories Ltd as a 2.5 mg/mL (0.25%), 5 mg/mL (0.5%) and 7.5 mg/mL (0.75%) solution
- The BNF lists the maximum safe dose 1–40 mL of 2.5 mg/mL or 5 mg/mL solution, to a maximum of 150mg, for peripheral nerve blockade (PNB) but emphasises that doses should be adjusted according to patient’s physical status and the nature of the procedure.

**Selection of the Drug**

- Local anaesthetics should be selected based upon their particular characteristics in terms of:
  - Onset time
  - Duration of action
  - Potency
  - Toxicity
  - Motor power loss
  - Effect on the local vascularity

**Conclusion**

- The development of safer, long lasting local anaesthetics for peripheral nerve blockade has helped to make practice safer
  - Presently ropivacaine appears to be the safest long acting local anaesthetic and is particularly useful where high doses of anaesthesia are being used

**The End**

Questions???