National Council for NCOR Osteopathic Research

Pharmacological Pain Management – a snapshot summary report (December 2013)

- **Key messages**
- Many osteopathic patients also take medication to help relieve their symptoms; understanding how these drugs work and the effects they have on our patients is important.
- Developing and testing drugs is a lengthy and rigorous process that involves a number of phases; these are outlined in this summary.
- Many prescription drugs have two names: a brand name and a generic name. Examples are given in a table in this summary.
- This summary contains an overview of the following drugs:
- Non-steroidal anti-inflammatory drugs
- Rubefacients and other topical anti-rheumatics
- Opioid analgesics
- Skeletal muscle relaxants
- Anti-convulsant drugs
- Hypnotics, anxiolytics and antidepressants
- Tricyclic antidepressants
- Compound preparations

Introduction

Many patients who seek osteopathic treatment also take medication to help relieve their symptoms e.g. pain, whether prior to treatment or during a course of treatment. It is important to understand how these drugs work and the effects they may have on our patients. This can help us to understand the nature of their pain; identify adverse reactions to drugs which require referral back to their GP and communicate more effectively with patients about pharmacological approaches to their symptom management. It is not within our remit, unless

we have specific training, to prescribe or review patients' medicines. The aim of this article is to provide some background on clinical drug development and an overview of the types of drugs used for analgesia.

Clinical drug development – background information

Developing and testing drugs is a lengthy and rigorous process, not only do the drugs have to be tested for effectiveness but also for safety. The role of clinical trials is well established in the pharmaceutical world, but there are a number of steps involved before drug trials can begin.

Drug development begins (pre-clinical phase) with the identification of new clinical entities (NCEs) targeted at a specific patient population or area of disease; they are examined for their physicochemical properties and developed into a form for administration e.g. tablets or capsules. The NCEs then go through a number of testing phases: phase I normally involves small groups of healthy volunteers to determine the safety and dosage; phase II investigates safety and dosage further to allow a much larger population to be studied in phase III. Phase III may also involve the comparison of the new drug with existing treatments for the condition of interest. Once these phases have been completed the drug can be licensed for marketing purposes. Phase IV then allows data relating to efficacy and side-effects to be collected from a much larger population, which is particularly important for identifying rare side-effects[1].

The clinical drug development process is subject to a strict regulatory process. The MHRA is responsible for regulating all medicines and medical devices in the UK by ensuring they work and are acceptably safe[2].

Drugs used in pain management

There are a number of pharmacological approaches to alleviating pain; different drugs act on different pain mechanisms within the body. Table 1 gives an overview of the types of drugs commonly used for analgesia along with some examples of drugs, their generic and brand names.

Many prescription drugs have two names:

- the **brand name** given by the pharmaceutical company who develop the preparation;
- the **generic, or scientific name**, which is the name of the active ingredient of the drug and is decided upon by an expert committee[3].

GPs will normally prescribe the generic version of a drug whenever possible as it helps to avoid confusion and is often cheaper for the NHS[4].

Overview of drugs

Non steroidal anti-inflammatories (NSAIDs)

These drugs have analgesic, anti-inflammatory and anti-pyretic actions, depending on the drug; they are widely prescribed and bought over the counter (OTC). Aspirin (acetylsalicylic acid) is classed as an NSAID and has an analgesic effect lasting about 4 hours, it is mainly used for mild to moderate pain and is not effective for visceral pain.

Paracetamol, although classed as an NSAID by some, has weak anti-inflammatory effects, but it is widely used as an analgesic when pain has no inflammatory component.

NSAIDs work by inhibiting the fatty acid cyclooxygenase (COX) enzyme, which inhibits the production of prostaglandins and thromboxanes[5]. Prostaglandins sensitise nociceptors to inflammatory mediators. Inhibiting prostaglandin production is one of the ways in which NSAIDs have an analgesic effect[6]. There is also a central action, possibly in the spinal cord, because prostaglandin release causes facilitation of transmission from afferent pain fibres to relay neurons in the dorsal horn[6], allowing pain messages to reach the brain.

Adverse events are common with these drugs because they are often taken at high doses over long periods. They can cause gastrointestinal problems (ulceration of the mucosal tissues) and kidney dysfunction. Other adverse effects include bronchospasm, especially in asthmatics, and skin allergies.

Rubefacients and other topical anti-rheumatics

Topical NSAIDs can be used to treat musculoskeletal pain as well as oral NSAIDs. They work by locally inhibiting the production of COX enzymes once they have been absorbed by the skin[5]. Using topical NSAIDs is more appealing to many patients due to their reduced association with serious systemic adverse events[7]. Cochrane Reviews found that topical NSAIDS provide good pain relief in acute and chronic musculoskeletal pain, with fewer gastrointestinal side effects [5,7]. Furthermore a diclofenac solution was demonstrated to be as effective as oral NSAIDs for pain relief in hand and knee osteoarthritis[5]. The use of topical ibuprofen was also found to be equally effective as oral NSAIDs in a randomised controlled trial of chronic knee pain in older people[8]. Topical rubefacients work by irritating the skin; as well as acting as a 'counter-irritant', i.e. off-setting the pain from muscles and joints, they also provide a feeling of warmth due to dilation of blood vessels in the area of irritated skin[9]. However, their indication for use is not as well supported by evidence as topical NSAIDs[9].

Opioid analgesics

The term opioid is used to describe a synthetic or endogenous substance that produces morphine-like effects. They produce analgesia, respiratory depression, euphoria and sedation effects. They often cause nausea and vomiting and antiemetics (anti-sickness) may be required. Continuous treatment with opioids can result in tolerance and dependence. Opioid analgesics are normally prescribed for moderate to severe pain, particularly of visceral origin[10]. Although they can be effective for most types of acute and chronic pain, they are not as effective for neuropathic pain[6]. Opioids can induce a sense of euphoria, which is an important part of its pain relieving effect as it can reduce feelings of agitation and anxiety associated with some painful illnesses[6]. Opioids are blocked by antagonists such as naloxone[6].

Skeletal muscle relaxants

These drugs inhibit neural transmission at the spinal cord; they inhibit monosynaptic and polysynaptic activation of motor neurons[6,11]. For example, Dantrolene sodium diminishes actin-myosin interaction, which results in muscle relaxation; this drug is used for chronic severe spacticity[11]. Baclofen is also used in cases of severe muscle spasm, for example in Multiple Sclerosis[6]. Diazepam's analgesic effect is non-specific and may be partly derived from its sedative effects; it may also have a suppressive effect on nociceptive output[11]. Quinine is used for the treatment of nocturnal cramp[6].

Anti-convulsant drugs

Anti-convulsant drugs, such as gabapentin, are generally used for the relief of neuropathic pain, rather than nociceptive pain[12]. Gabapentin and pregablin both inhibit voltage-gated calcium channel function, which in turn inhibits glutamate release and therefore reduces neuronal hyperexcitability[13].

Hypnotics, anxiolytics and anti-depressants

Hypnotics are generally used in the treatment of sleep disorders which are not uncommon in those with chronic pain. Anxiolytics are primary used to reduce anxiety levels.

Hypnotic drugs can be divided into subgroups:

- Benzodiazepines (anxiolytic and hypnotic)
- Buspirone (anxiolytic but not very sedative)
- Zolpidem (similar to benzodiazepines but not as anxiolytic)
- Barbiturates (mostly confined to anaesthesia)

Benzodiazepines can be used in painful conditions to help reduce anxiety, induce sleep and reduce muscle tone[6].

Tricyclic anti-depressants

Anti-depressants used at a low dose have been found to have an effect on pain perception.

Tricyclic anti-depressant drugs are effective in reducing neuropathic pain by acting centrally; they inhibit noradrenaline reuptake[6]. The exact mechanism of action on pain is still not well understood[14].

Compound preparations

Compound preparations, such as co-codamol, for pain relief are believed to be helpful because they suppress more than one pain mechanism simultaneously. Utilising favourable additive or synergistic effects of combining drugs may also help to reduce unwanted side effects[15].

In summary, there are a vast number of drugs that can be used in managing painful conditions. Understanding how they work in different conditions can help you when discussing pharamacological pain management with your patients. Although it is not within our remit to advise or prescribe, we can encourage our patients to speak to their GPs about their pain medication if they have any concerns.

Further information can be found at:

www.mims.co.uk and The British National Formulary website: www.bnf.org

Table 1

Class	Generic name	Brand name examples
Non-steroidal anti inflammatory drugs (NSAIDs)	Aspirin	
	Ibuprofen	Brufen, Nurofen
	Naproxen	Naprosyn
	Fenbufen	
	Fenoprofen	Fenopron
	Flurbiprofen	Froben
	Ketoprofen	Ketocid, Ketovail
	Dexketoprofen	Keral
	Tiaprofenic acid	Surgam
	Diclofenac	Voltarol, Motifene, Defanac
	Aceclofenac	Preservex
	Diflunisal	
	Etodolac	Eccoxolac, Etopan XL, Lodine
	Indometacin	Pardelprin
	Mefenamic acid	Ponstan
	Meloxicam	
	Nabumetone	Relifex
	Piroxicam	Brexidol, Feldene
	Etoricoxib	Arcoxia

	Celecoxib	Celebrex
	Paracetamol	Panadol
Rubefacients and other topical anti-rheumatics	Ibuprofen	Ibugel, Fenbid Gel
	Diclofenac	Volterol, Pennsaid
	Capsaicin	Axsain, Balmosa
	Salicylate	Transvasin, Movelat
Skeletal muscle relaxants	Baclofen	
	Dantrolene sodium	Dantrium
	Diazepam	Diazemuls, Stesolid
	Quinine	
Opioids - strong	Morphine	Oramorph, Zomorph
	Diamorphine	
	Phenazocine	
	Pethidine	
	Buprenorphine	BuTrans (patch), Temgesic
	Nalbuphine	
Opioids - weak	Pentazocine	
	Meptazinol	Meptid
	Codeine	
	Dihydrocodeine	
	Dextropropoxyphene	
Hypnotics, anxiolytics and antidepressants	Nitrazepam	
	Flurazepam	
	Diazepam	Valium
	Loprazolam	
	Lormetazepam	
	Temazepam	
	Zaleplon	Sonata
	Zolpidem Tartrate	Stilnoct
	Zopiclone	Zimofane
	Amitriptyline	
	Nortiptyline	
Anti-epileptics	Gabapentin	Neurontin
	Pregablin	Lyrica
Compound preparations	Paracetamol + codeine phosphate	Co-codamol
	Aspirin + codeine phosphate	Co-codaprin
	Paracetamol + buclizine	Migraleve
	Aspirin + metoclopramide	Migramax

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Appendix 1

Pre-clinical

The identification of new clinical entities (NCEs) targeted at a specific patient population or area of disease. The physicochemical properties of the NCE will be examined including its chemical makeup, stability, and solubility. The NCE will be examined further to identify its suitability to be made into particular formats e.g. capsules, tablets, injectable (via intramuscular or subcutaneous routes), or as an intravenous formulation.

Phase I

This phase allows the determination of safety and dosing. It involves the measurement of the pharmacological actions of the NCE, its potency, its pharmacokinetic characteristics (the effect of the body on the NCE), its pharmacodynamics characteristics (the effect of the NCE on the body), toxicity, and side effects.
This phase normally involves healthy volunteers, but in some instances can involve patients e.g. cancer patients.

Phase II

This phase tests whether the new drug has detectable efficacy when tested on small groups of patients. It also allows safety to be explored further, and the establishment of dosage regimes to be used in Phase III trials.

Phase III

This phase involves large numbers of patients and allows researchers to determine safety and efficacy in a much larger population. This phase allows the NCE to be compared with other treatments which are currently available, establish optimal dosage, and determine the incidence of side effects before the drug is licensed for marketing purposes.

Phase IV

This phase involves post-marketing surveillance of the new drug. This will add to the information already gathered concerning efficacy, and will also detect additional side effects which although rare will be detected once the drug is given to much larger populations of patients as part of their clinical management[1]. Patients can report adverse effects of medicines using the Medicines and Healthcare Products Regulatory Agency (MHRA) yellow card system at www.mhra.gov.uk/yellowcard.

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