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USE OF ANALGESICS IN RHEUMATOLOGY

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- **Pain is the commonest symptom in rheumatology and still presents a major therapeutic challenge**
- **Pain processing is complex; clinical exploitation of this complexity is only just beginning**
- **The type of pain and patients' concomitant conditions should guide the choice of analgesic**
- **Combination therapy allows minimisation of dosage and unwanted effects**

INTRODUCTION

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.

International Association for the Study of Pain
(cited in Mannion and Wolf¹)

Pain can be regarded as nociceptive or pathologic.¹ **Nociceptive pain** results from high intensity nerve fibre stimulation during acute injury. It functions to prevent further injury and allow healing. **Pathologic pain** is a maladaptive response to an initial painful stimulus. It can also occur spontaneously, as neuropathic pain. It represents a hypersensitivity to painful and non-painful stimuli. Both aspects of pain contribute to many musculoskeletal problems.

Pain processing is complex and dynamic. Information about a noxious stimulus is initially sent via peripheral A δ and C-fibres. Second-order neurones in the spinal cord are then activated and transmit the stimulus to the brain, where information undergoes modulation by the central neuronal network, including descending inhibitory pathways from the hypothalamus.

Following injury, two amplifying phenomena occur. In **allodynia**, non-painful stimuli are perceived as painful or enhanced. In **hyperalgesia**, the painful sensation from a high-intensity stimulus is exaggerated or prolonged. Primary hyperalgesia (in the area of injury) results from local sensitisation of nerve fibres by agents such as inflammatory cytokines and prostaglandins, lowering depolarisation thresholds. Allodynia and hyperalgesia outside the area of injury (secondary hyperalgesia) result from 'central sensitisation' of dorsal horn neurones. Prolonged activation of dorsal horn neurones leads to changes in N-methyl-D-aspartate (NMDA) receptors, facilitating activation and release of neuropeptides such as substance P and calcitonin gene-related peptide. Structural changes within the dorsal laminae occur, with sprouting of A δ -fibre neurones and new synaptic connections. New treatment strategies targeting the dorsal horn are being

developed. In current practice, however, we are limited to more conventional agents.

In each rheumatological condition, effective management depends on assessment of the features and, if possible, the cause of pain. Inflammatory pain, as in rheumatoid arthritis (RA), can be targeted via blockade of chemical mediators, which sensitise peripheral nerve fibres, with agents ranging from non-steroidal anti-inflammatory drugs (NSAIDs) to inhibitors of tumour necrosis factor alpha (TNF α). Where pain is mechanically induced, as in osteoarthritis (OA), management may rely on basic analgesia, such as paracetamol, and centrally acting agents, which exert their effect on the central nervous system, although NSAIDs also have a role. Neuropathic pain, which may have no external nociceptive input, requires neuromodulatory drugs, such as anticonvulsants and antidepressants. Chronic pain with complex psychosocial aspects may be helped by cautious use of antidepressants, although analgesia is only a part of a multidisciplinary approach.

Although there is a great choice of analgesics available, we are still far from finding an ideal one: effective in all types of pain and potent enough to control severe pain without unwanted effects or risk of dependence. We can, however, offer patients better pain relief by the appropriate use of what is available in the correct form, doses and combinations.

PARACETAMOL (ACETAMINOPHEN)

Paracetamol is both analgesic and antipyretic and, in doses up to 4 g daily, rarely causes unwanted effects. Skin rashes are commonest, but blood disorders and acute pancreatitis have been reported following prolonged use. Paracetamol overdose can lead to hepatic failure and it is a common practice to use a maximum of 2 g/day in patients with liver disease. Drug interactions are few but the anticoagulant effect of warfarin may be enhanced. Paracetamol is a first choice in symptomatic treatment of OA and a common adjunctive analgesic in inflammatory conditions. Although safe, paracetamol is less effective than NSAIDs in patients with OA, RA and fibromyalgia.²

NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

NSAIDs inhibit cyclooxygenase, which catalyses conversion of arachidonic acid into prostanoids such as PGE₂ and PGI₂. Prostaglandins produce vasodilatation and increased vascular permeability, enhancing the action of histamine and bradykinin. They indirectly sensitise peripheral nerve fibres and enhance pain sensation locally. Main properties of NSAIDs are listed in Table 1.

TABLE 1. Properties of non-steroidal anti-inflammatory drugs.

Antipyresis	Inhibition of PG production in the hypothalamus
Analgesia	Reduction in peripheral sensitisation of the nociceptors and central COX-independent effect mediated via κ opioid receptors (ketorolac) or nitric oxide system (paracetamol)
Anti-inflammatory	Reduction in PG production effect reduces vasodilatation and oedema

COX cyclooxygenase; PG prostaglandin

Low back pain

The Cochrane systematic review of 51 randomised controlled trials (RCT) found that NSAIDs have a positive effect on short-term global improvement in patients with acute back pain; however the data on analgesic effect were inconclusive.³ The heterogeneity of studies included in the analysis made it difficult to assess whether NSAIDs are more effective than paracetamol, opioids, myorelaxants or other non-drug therapies. There were no conclusions drawn about differences between various NSAIDs. A recently published review of 50 clinical trials of pharmacological interventions in acute and chronic low back pain has found, however, that non-selective NSAIDs are effective in reducing pain intensity and facilitate functional recovery.⁴

Osteoarthritis

Paracetamol has been shown to be effective in reducing pain in patients with hip, knee and generalised OA⁵ and has been recommended as the first-line treatment.⁶ However, in a survey of patients with OA, only a third found paracetamol effective. Over 60% of patients responded better to NSAIDs.² 89% of the RCT reported that NSAIDs both reduce pain and improve range of knee motion and functional status when compared with placebo.⁷ Data from RCTs of NSAIDs in hip OA are too heterogeneous to assess efficacy. It seems, however, that low doses of ibuprofen (<1600 mg/day) and naproxen (<750 mg/day) are probably less effective. Indometacin was most often identified as effective but was associated with higher toxicity.⁸ NSAIDs should be avoided in patients over 65 years old and in those at high risk of gastrointestinal complications.

Rheumatoid arthritis

NSAIDs are used in RA alongside disease-modifying agents to reduce joint pain, tenderness, and early morning stiffness.⁶ NSAID doses are usually higher than those used in non-inflammatory arthritis and treatment is long-term. It may be necessary to try more than one agent as responses to individual drugs vary. The selection of

the appropriate drug should be guided by its safety profile and cost in addition to concomitant conditions and treatment. Efficacy and unwanted effects should be reviewed regularly.

Tendinitis

NSAIDs are commonly prescribed in tendinitis and soft tissue lesions, but data from RCTs are limited. NSAIDs seem to relieve pain but an effect on healing remains unproven.⁹

Prostaglandins play an important role in maintaining gastrointestinal mucosal integrity, renal perfusion and haemostasis via platelet activation. NSAIDs, therefore, demonstrate a spectrum of corresponding unwanted effects (see Table 2). Gastrointestinal effects are most common, with dyspepsia affecting between 10–20% of patients.¹⁰ Serious complications such as gastrointesti-

nal bleeding and perforation are less common, affecting 2–4% of patients.¹¹ Mucosal damage distal to the duodenum is also well recognised in patients on prolonged NSAID therapy. NSAIDs enteropathy can be difficult to diagnose but should always be considered in the presence of anaemia and hypoalbuminaemia.¹² The risk of renal impairment is also significant, as many patients with chronic musculoskeletal pain are elderly, with co-existing cardiac or renal failure.

In patients at risk of gastrointestinal complications the following measures have been recommended:¹³

- prescribing a lower dose of NSAID in combination with paracetamol or a mild opiate
- adding misoprostol 800 mcg/day
- adding a double dose of H₂ receptor antagonist
- adding a proton pump inhibitor (combination therapy with H₂ receptor antagonist may be

TABLE 2. Side-effects of non-steroidal anti-inflammatory drugs.

Side-effect		Mechanism
Gastrointestinal	Dyspepsia, nausea, diarrhoea	
	Peptic ulcer Gastrointestinal bleeding Gastrointestinal perforation	<ul style="list-style-type: none"> • COX-1 inhibition • PG synthesis inhibition leads to impaired mucus production • Direct effect on mucosa from rapid absorption and hydrogen ion trapping in mucosal wall • Impaired production of gastric fluid and bicarbonate
	Protein-losing and blood-losing gastroenteropathy	<ul style="list-style-type: none"> • ? Direct vascular injury • Inhibition of PG synthesis
Skin reactions	Mild rashes, urticarial, photosensitivity Stevens–Johnson syndrome	Hypersensitivity reaction
Renal	Analgesic nephropathy and renal papillary necrosis	Due to chronic consumption of excessive doses of NSAIDs
	Reduced GFR	Inhibition of the PGE ₂ -mediated vasodilatation of the renal arteries in response to NA or angiotensin II
	Allergic-type interstitial nephritis	Hypersensitivity reaction
	Oedema and sodium retention	<ul style="list-style-type: none"> • Inhibition of ADH effect on the distal renal tubules • Impaired sodium and chloride reabsorption from the loop of Henle
Cardiovascular	Exacerbation of congestive heart failure and destabilisation of blood pressure control reported with COX-2 inhibitors Increased risk of MI and stroke associated with rofecoxib	
Haemostatic	Antiplatelet effect (COX-1 specific)	Inhibition of thromboxane A ₂ synthesis
Other rare side-effects	Bone marrow suppression	
	Abnormal liver function tests (diclofenac)	
	Infertility	COX-2 is induced by LH in pre-ovulatory follicle and has been implicated in the precise timing of the ovulation
	Bronchospasm	In susceptible individuals, e.g. aspirin-induced asthma

ADH antidiuretic hormone; COX cyclooxygenase; GFR glomerular filtration rate; LH luteinising hormone; MI myocardial infarction; NA noradrenaline; NSAID non-steroidal anti-inflammatory drug; PG prostaglandin

necessary in some patients to achieve full suppression of acid production)

- avoiding NSAIDs associated with a high risk of gastrointestinal toxicity such as azapropazone and indometacin.

CYCLOOXYGENASE 2 (COX-2) INHIBITORS

In 1989 two isoforms of the cyclooxygenase (COX) enzymes were identified.¹⁴ COX-1, constitutively expressed in most tissues, plays an important role in gastrointestinal mucosal protection. COX-2, an inducible isoform, is found at the site of inflammation, i.e. synovial tissue in patients with RA and OA. COX-2 has also been identified in some normal tissues, in particular brain, bone, female reproductive organs and kidney. COX-2 is not expressed in the normal gastric mucosa. As a result COX-2 inhibitors cause significantly less gastrointestinal complications than conventional NSAIDs. COX-2 is not expressed on platelets, and platelet aggregation is often used to assess selectivity of different agents against two COX isoforms.

In the last 5 years we have witnessed a rapid development of COX-2 inhibitors. Rofecoxib (Vioxx) and celecoxib (Celebrex) were introduced in 1999 for use in RA and OA, having been shown to have significantly reduced gastrointestinal toxicity with an efficacy equivalent to traditional NSAIDs. A second generation of coxibs characterised by higher COX-2 selectivity has been subsequently developed: valdecoxib (Bextra), etoricoxib (Arcoxia), parecoxib (Dynastat) and lumiracoxib (Prexige). It is estimated that 1.4 million people in the UK are prescribed COX-2 inhibitors.

Vioxx was withdrawn on 30 September 2004 following reports of an increased risk of cardiovascular events in rofecoxib-treated patients. The initial data came from the VIGOR (Vioxx Gastrointestinal Outcomes Research) study, which compared rofecoxib with naproxen and demonstrated a relative risk (RR) of cardiovascular events of 2.38 in the rofecoxib-treated group. This was followed by early cessation of the APPROVe (Adenomatous Polyp Prevention On Vioxx) study, which demonstrated a 3.9-fold increase in thromboembolic events.¹⁵ Warning about the increased incidence of cerebrovascular events and myocardial infarction was also suggested by data from trials of valdecoxib for postoperative analgesia in patients undergoing coronary artery bypass grafting surgery.¹⁶ The safety concerns regarding COX-2 inhibitors are being investigated by the European Medicines Evaluation Agency (EMA).

TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

Topical NSAIDs have been designed to maximise local anti-inflammatory effect and minimise systemic toxicity. They must penetrate the epidermis and a variety of preparations have been developed to facilitate this: creams, gels, foams, sprays, patches/plasters and drops. Experimental models of drug penetration indicate that micro-emulsions are most effective. Gels and sprays penetrate skin better than creams.¹⁷

There is good evidence that topical NSAIDs reduce pain and can accelerate recovery in soft-tissue injuries at 7–14 days. Comparison of different NSAIDs concludes that ketoprofen is the most effective, followed by ibuprofen, felbinac and piroxicam. There is insufficient evidence for long-term use of topical NSAIDs in chronic musculoskeletal pain, i.e. OA.

Topical NSAIDs are generally well tolerated but patients need to be warned about the risk of cutaneous reactions, in particular photodermatoses. A systematic literature review has not shown increased risk of gastrointestinal complications or renal failure in topical NSAID users.¹⁷ Caution should however be exercised with regard to prolonged use, and concomitant self-medication with oral NSAIDs should be avoided.

TOPICAL CAPSAICIN

Capsaicin, the active ingredient of chilli peppers, is analgesic in conditions such as OA and neuropathic pain. Prolonged or repeated capsaicin application results in local desensitisation and reduced nerve responses to subsequent doses. With higher concentrations of capsaicin functional desensitisation is achieved, when nerve fibres stop responding not only to repeated doses of capsaicin but also to other noxious stimuli.¹⁸ Capsaicin cream 0.025% applied four times daily is available for the symptomatic treatment of knee OA, while higher concentrations (0.075%) have been shown to reduce pain in peripheral neuropathy. It is important to warn the patient about the initial irritant effect of capsaicin application (burning and warmth) and explain that several weeks of treatment may be needed before the full effect is achieved.

OPIOIDS

Opioid analgesics are substances with opioid-like pharmacological effects. Endogenous opiates such as β -endorphin are found in large quantities in the central nervous system. A range of exogenous opioids is available for use in acute and chronic pain, from morphine derivatives to synthetic compounds. Three types of receptor mediate

the pharmacological effect of opioids: μ (responsible for most of the analgesic properties), δ and κ . Specificity for particular receptors determines properties of different opioid analgesics.

Opioids target the brain, as well as stimulating the inhibitory spinal pathways. They also inhibit the discharge of peripheral nociceptors, especially in inflamed tissue. Table 3 lists the pharmacological properties of opioid analgesics.

TABLE 3. Pharmacological properties of opioid analgesics.

Analgesia
Respiratory depression
Pupil constriction
Reduced gastrointestinal motility
Depression of cough reflex
Nausea and vomiting
Euphoria, reduction of anxiety and agitation
Dysphoria
Sedation
Tolerance (need to increase the dose to maintain analgesic effect)
Dependence

Weak opioids (Table 4) such as codeine phosphate, dihydrocodeine, dextropropoxyphene and oxycodone are used frequently in chronic rheumatic conditions, often in combination with paracetamol. A survey of patients with rheumatic diseases (the majority with RA, spondyloarthropathies and connective tissue diseases) found that codeine phosphate and oxycodone had significant analgesic effect.¹⁹ The commonest unwanted effects were nausea, constipation and sedation. Caution is required when prescribing opioids for disabled and elderly patients as they do increase the risk of falls. It is also crucial to review concomitant medications as combinations of opioids and benzodiazepines, psychotropic drugs or anticonvulsants exacerbate sedation and cognitive impairment.

Perceptions about risks of dependence and tolerance have limited the use of opioids in rheumatic conditions. Evidence is growing that these risks have been overstated, particularly for weak opioids.¹⁵ Codeine phosphate, with

TABLE 4. Common opioid analgesics.

Weak opioids (mild to moderate pain)	Powerful opioids (severe pain)
Codeine phosphate	Morphine
Dihydrocodeine	Fentanyl
Dextropropoxyphene	Methadone
Oxycodone	Buprenorphine
	Pentazocine
	Hydromorphone

a low affinity for opioid receptors, carries minimal risk of physical dependence. Studies of morphine use in cancer patients demonstrate that continuous nociceptive input prevents development of dependence, and dose reduction is necessary if pain intensity decreases, as following nerve blockade. Experience shows that opioid tolerance and dependence are rare in patients with rheumatic conditions and that if dose escalation occurs it is usually justified by exacerbation of the disease, trauma or surgery.

A decision to introduce potent opioids has to be made carefully and agreed with a patient. Slow-release preparations are convenient to take, with an efficacy equivalent to short-acting forms.²⁰ Slow-dose titration is recommended, aiming at maximum pain reduction with minimal adverse effects over a 3–4 month trial period. Prophylaxis against constipation should be started early on. It is mandatory that treatment with opioids is monitored for side-effects, analgesic effect and functional status.²¹

TRAMADOL HYDROCHLORIDE

Tramadol hydrochloride is a synthetic analgesic with a modest affinity for the μ receptor and a weak effect on δ and κ receptors. Its additional effect on the descending inhibitory pathways relies on inhibition of serotonin and norepinephrine re-uptake. Tramadol has been shown in a large RCT to control pain in patients with knee OA.²² Moreover, in patients who responded to naproxen, the addition of tramadol allowed the naproxen dose to be reduced in 78% of patients. Tramadol has been demonstrated to relieve neuropathic pain, although no sufficient data exist about its efficacy in comparison with opioids.²³ Tramadol produces nausea, vomiting and dizziness in 15–20% of patients but is less likely to cause dependence and tolerance, respiratory depression and constipation than opioids. The risk of unwanted effects can be reduced by slow-dose titration. Tramadol has been reported to increase a risk of seizures and should be avoided in combination with tricyclic antidepressants and neuroleptics as well as in patients with a history of epilepsy. Smaller doses should be used in the elderly.

CANNABINOIDS

While the political debate on legalisation of cannabis goes on, a number of patients with chronic pain continue to use it for its analgesic and euphoria-inducing effect. Animal experiments show that administration of a cannabinoid agonist reduces allodynia and hyperalgesia in carrageenan-induced skin inflammation.²⁴ Therapeutic use of cannabinoids is also supported by a discovery of endogenous cannabinoids as well as cannabinoid receptors. Cannabinoid receptor CB1 is found predominantly in brain tissue and CB2 in peripheral tissues. Animal

studies indicate that these receptors are involved in pain modulation, particularly at the level of dorsal horn cells.²⁵ Clinical evidence has also been encouraging. A systematic review of RCTs of cannabis in chronic pain identified trials of three oral and one intramuscular cannabinoid in different types of pain.²⁶ The analgesic effect was equivalent to single-dose codeine 60 mg. Adverse effects – mainly sedation, dizziness, and memory impairment – were commonly associated with higher dosages. A recent study of dronabinol, a synthetic cannabinoid, in patients with central neuropathic pain in multiple sclerosis again demonstrated a significant analgesic effect.²⁷

ANTIDEPRESSANTS

Antidepressants are now recognised to have an analgesic effect in chronic pain independent of their antidepressant properties. They have been used successfully in neuropathic pain, as in diabetic neuropathy or post-herpetic neuralgia. They may be of benefit in other conditions, such as chronic low back pain, OA, RA and fibromyalgia.²⁸ RCTs of antidepressants in these conditions demonstrate higher efficacy of traditional serotonergic-noradrenergic antidepressants over newer selective serotonin uptake inhibitors. Amitriptyline in an initial dose of 10 mg/day and titrated up to 50 mg/day remains the first choice of treatment in fibromyalgia, improving pain, sleep pattern, morning stiffness and fatigue.²⁹ A placebo-controlled study of dothiepin in patients with RA and depression/anxiety showed significant reduction in pain in some patients, correlating with reduced depression scores.³⁰

Tricyclic antidepressants are, however, associated with significant problems: sedation, confusion, motor incoordination, dry mouth and blurred vision can be troublesome, especially in the elderly. Potential cardiotoxicity and drug interactions (e.g. with NSAIDs) create additional problems. There is a trend towards the use of serotonergic antidepressants. Combination therapy should be considered in patients not responding to monotherapy. A study of patients with fibromyalgia demonstrated the superior efficacy of a combination of low-dose amitriptyline and fluoxetine in comparison with either drug alone.³¹

ANTICONVULSANTS

Neuropathic pain presents a great therapeutic challenge for a rheumatologist. Peripheral neuropathy is a recognised complication of many autoimmune rheumatic diseases such as systemic lupus erythematosus, RA, Sjögren's syndrome and vasculitis. It can result from metabolic disturbances, as for example in diabetes mellitus, drug toxicity and alcohol abuse. Neuropathic mechanisms play an important role in the pathogenesis of chronic regional pain syndromes such as repetitive strain injury and reflex sympathetic dystrophy. Anticonvulsants

have a major role in treating painful neuropathies. They exhibit various mechanisms of action. Phenytoin and carbamazepine target voltage-dependent sodium channels blocking spontaneous firing of the neurones. Both are effective in treating diabetic neuropathy and post-herpetic neuralgia.³² Their use is limited however by side-effects such as sedation, dizziness, nausea and hepatotoxicity. Carbamazepine also causes myelotoxicity. Gabapentin has several mechanisms of action: it affects synthesis and release of γ -aminobutyric acid (GABA) in the brain, inhibits sodium channels, and alters monoamino-oxidase release. A review of RCTs of gabapentin for neuropathic pain demonstrated its efficacy in relieving allodynia, burning and shooting pain and hyperaesthesia.³³ Dose titration is required. The commonest limiting side-effects of gabapentin are somnolence, dizziness and leg oedema. Lamotrigine inhibits sodium channels and glutamate release. It is effective in painful diabetic neuropathy, human immunodeficiency virus (HIV)-associated neuropathy and trigeminal neuralgia. It tends to be less sedative than other anticonvulsants but can cause severe skin rashes and Stevens–Johnson syndrome. Oxcarbazepine can be an alternative in patients not responding to carbamazepine.³⁴

NEW DEVELOPMENTS

Research into effective and safe anti-inflammatory agents continues. Licoferone, an inhibitor of 5-lipoxygenase and COX-1 and 2, is being developed for the treatment of OA. The initial data are encouraging, demonstrating efficacy comparable with traditional NSAIDs with no increase in gastrointestinal toxicity.³⁵ Nitric oxide-NSAIDs, which comprise a nitric oxide releasing moiety attached to a classical molecule of NSAID, have been shown to have reduced gastric toxicity in an endoscopic study of healthy volunteers.³⁶ As our understanding of pain processing improves, new analgesic agents are being developed aiming at the central nervous system and in particular central sensitisation such as NK1-positive neurones in the spinal dorsal horns. It is therefore conceivable that future analgesics will target a specific step of the pain processing pathway, bringing us closer to the development of more effective and better-tolerated therapeutic agents.

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