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The use of oral analgesics in primary care

Pain is a common complaint in general practice. Analgesics account for about 12% of all UK prescriptions and include many compound preparations.[1]

This *Bulletin* discusses the use of oral analgesics for the relief of mild to moderate pain in primary care. Attention is given to some combination agents and the evidence for their use. It does not cover palliative care or neuropathic pain, which involve the use of 'strong' opioids or co-analgesics (adjuvants). Detailed discussions of pain assessment and non-drug treatments are also not included.

Assessment

Inadequate assessment is a barrier to effective pain relief. However, assessment may be difficult as the experience of pain is subjective and tolerance varies between individuals. Tissue damage or disease is only one of many factors which contribute to the pain experience. Others include behavioural, psychosocial and psychological influences. **The patient's report is the most accurate measure of pain.[2]**

Assessment should include a thorough history and physical examination, considering the location, intensity and nature of the pain, as well as any identifiable cause. The 'success' or 'failure' of analgesics that have been tried before may indicate the type of pain present. Patients should be asked about the dosage and duration of any 'failed' treatment to ensure that they had an adequate trial. Scales and questionnaires may help to determine the intensity, location and type of pain.

SUMMARY

* Analgesics should be prescribed in a logical stepwise manner, with drug choice and dosage tailored to the individual and based on the severity and type of pain and supporting evidence. It is important to titrate doses to the response and review patients regularly.
* At present, most evidence on analgesics is based only on single-dose studies in acute pain, mainly post-surgical. Until further evidence is published, extrapolation of these results to chronic or regular use may be inappropriate.
* There is little evidence that **combinations containing low doses of opioid** (e.g. 8mg of codeine or 10mg of dihydrocodeine per tablet) with aspirin or paracetamol are more effective than aspirin or paracetamol alone. In addition, the doses used may still be enough to cause opioid side-effects, particularly constipation.
* When addition of an opioid to paracetamol is necessary to improve analgesia, a **full dose of opioid** (e.g. 60mg of codeine) may be more effective, as single dose studies have found that it provides additional analgesia. However, patients are more likely to experience opioid-induced side-effects.
* **Co-proxamol** is no more effective than paracetamol when given in single-doses for acute pain. Since it is also particularly dangerous in overdose and may accumulate with chronic use, it should not be prescribed routinely.
* If a combination containing a full dose of opioid is considered necessary, initial prescription of the separate constituents will allow individual dosage titration of each component. An equivalent fixed analgesic combination should only be used once pain control has been well established.

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Limitations of the evidence

There is little clinically useful evidence in many areas of analgesic use. Most trials are in only a few specific pain types (mainly post-surgical), and it cannot be assumed that the response will be the same in other situations. Interpretation of the evidence is difficult because trials show a high but variable placebo response, with few published direct comparisons of analgesics over the range of doses used. **Most evidence on analgesics is based only on single-dose studies. Extrapolation to chronic or regular use may be inappropriate.**

Despite the limitations of analgesic trials, some valuable evidence has been published in systematic reviews. They describe the response in terms of the Sum Pain Intensity Difference (SPID) or the Total Pain Relief (TOTPAR).[3] SPID is the sum of the differences in pain intensity relative to the period before taking the drug. TOTPAR is the summed pain relief over a period of time. A more clinically relevant measure, the proportion of patients reporting moderate to excellent pain relief is sometimes used.

General treatment approach

Treatment of underlying disease causing the pain may reduce the need for analgesics. The approach to analgesic use depends on the type of pain present, considered in the context of patient factors and supporting evidence. The World Health Organisation (WHO) three-step analgesic ladder for cancer pain[4] (see **figure 1**) is also used for non-malignant chronic or acute nociceptive pain (i.e. due to tissue inflammation or damage). Analgesics should be started at the 'step' most appropriate to the patient's level of pain.

An approach that addresses only one aspect of the pain experience is likely to fail. Therefore, non-drug treatments should also be maximised, particularly in chronic pain where psychological and psychosocial factors are important.[5] Realistic treatment goals should be discussed with patients, since their expectations influence analgesic response.[6]

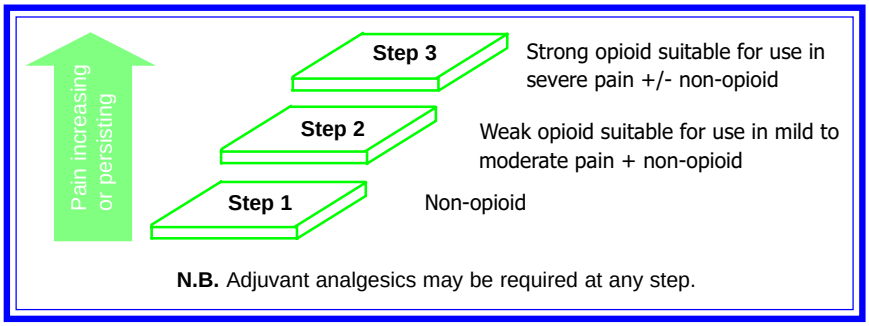

Figure 1. The World Health Organisation (WHO) three-step analgesic ladder[4]

If left untreated, acute pain can become chronic, making pain control more difficult.[7] An important goal is to prevent this with prompt, effective pain relief, while avoiding adverse effects. It is not always possible to eradicate chronic pain completely. Hence, the aim is to control pain and rehabilitate the patient so they can function as well as possible.[5]

Step 1 - Non-opioid analgesics

Paracetamol is a suitable first choice simple analgesic for most patients with mild to moderate pain as, in normal therapeutic doses, it is generally well tolerated, effective[8] and inexpensive. It has antipyretic properties and appears to act centrally, with no anti-inflammatory effects. Therefore, it may not be as effective for pain which has an inflammatory component, such as in rheumatoid arthritis. For patients with chronic pain, a trial of up to 4g/day for at least a week may be required.[9] Although paracetamol is relatively safe in normal doses, overdose can lead to fatal hepatotoxicity.

Aspirin or another **non-steroidal anti-inflammatory drug** (NSAID) may be more suitable for bone pain, or pain with an inflammatory component (e.g. dysmenorrhoea,[10] dental[11] or musculoskeletal pain). However, paracetamol is the first choice analgesic for osteoarthritis as there is no good evidence to suggest that NSAIDs are more effective.[12] NSAIDs block local formation of prostaglandins by inhibiting the enzyme cyclo-oxygenase (COX). A response occurs about 30 mins to 4 hrs after the first dose and full analgesic effects should be seen within a week.[13] Although published evidence seems to be limited, it has been suggested that regular dosing for up to three weeks may be required for a full anti-inflammatory effect.[13] Where appropriate, NSAIDs are used as adjuvants at any stage of the analgesic ladder.

There appears to be variability in individual patient response to different NSAIDs. If the first drug tried is ineffective, it may be worth changing to a different NSAID. When taken regularly at high doses, aspirin has anti-inflammatory effects similar to other NSAIDs, but may be less well tolerated.[13] All agents have antipyretic properties, but only aspirin (in adults) and ibuprofen (in children) are licensed for pyrexia.

NSAID use is limited by their side-effects, particularly upper gastrointestinal (GI) toxicity. Risk factors include use of steroids or anticoagulants, old age, cardiovascular disease or a history of peptic ulcer.[14,15] In 'at-risk' patients other drugs should be considered first. All patients taking NSAIDs should be warned about GI toxicity and started on the lowest dose of a low-risk agent, used for the shortest time.[13] Low dose ibuprofen has been associated with the least GI risk.[16] A previous *MeReC Bulletin* (Vol. 7 No. 12) considered the relative GI toxicity of individual agents. If NSAIDs are deemed essential, use of a gastroprotective agent may be appropriate in 'at-risk' patients.

NSAIDs may cause fluid retention which can exacerbate heart failure.[13] Also, renal function may worsen[13] and should be checked regularly during chronic therapy.

Rofecoxib▼ (*Vioxx*, Merck Sharp & Dohme) and **Celecoxib**▼ (*Celebrex*, Searle/Pfizer) are selective inhibitors of COX-2 which have recently been licensed. Evidence to date suggests

that they may be associated with less severe GI toxicity than other NSAIDs.[17,18] However, as with all new drugs, the long-term safety of selective COX-2 inhibitors are not established. Guidance on these agents from the National Institute for Clinical Excellence (NICE) is awaited.

Step 2 - Opioid analgesics

Patients who have an inadequate response to 'step 1' analgesics may require the addition of a weak opioid such as **codeine** or **dihydrocodeine**. A response should be seen within one or two hours of a single dose. However, certain pain e.g. dysmenorrhoea, dental, bone and rheumatic pain may be less sensitive to opioids than to drugs such as NSAIDs.

Although dihydrocodeine and codeine may be prescribed alone, there is little evidence that they are more effective than paracetamol when given in single-doses for acute pain. Both drugs are often prescribed in combination with paracetamol (see **insert**).

Opioids cause nausea, vomiting, constipation and drowsiness. However, adverse effects, particularly respiratory depression, are less likely to be a problem with therapeutic doses of codeine and dihydrocodeine than with strong opioids. Nevertheless, patients taking these drugs long-term may need regular laxatives.

Dextropropoxyphene is usually prescribed in combination with only 325mg of paracetamol per tablet as **co-proxamol** (see **insert**). Unfortunately, accumulation of the active metabolite may occur with chronic use, causing delayed side-effects such as drowsiness and nausea.[19] Co-proxamol interacts with certain drugs (e.g. warfarin and alcohol) and overdose may cause death within hours (especially after taking alcohol).[13]

Tramadol is licensed for moderate to severe pain, but may not be as effective as strong opioids in severe pain.[13] There is little evidence to show that tramadol is any more effective, or better tolerated, than other 'step 2' analgesics. As it is also expensive, it should not be a first choice agent.

Which combination analgesics are effective?

Compound analgesics containing a **low dose of opioid** (e.g. 8mg of codeine or 10mg of dihydrocodeine per tablet) with paracetamol or aspirin are commonly prescribed. **However, as well as being more expensive (see insert), there is little evidence that they have any benefits over aspirin or paracetamol alone.** Furthermore, the low dose may still be enough to cause opioid side-effects, particularly constipation.[13]

When addition of an opioid to paracetamol is necessary to improve analgesia, a **full dose of opioid** (e.g. 60mg of codeine) may be more effective. However, patients are more likely to experience opioid-induced side-effects.[13]

Evidence for adding **60mg** of **codeine** to **paracetamol** comes from a Cochrane review, which analysed the results of 51single-dose trials.[8] This included 12 head to head comparisons in 794 patients with post-surgical pain, mainly from oral surgery. It was found that, in single oral doses, the addition of codeine 60mg to paracetamol produces additional pain relief, but increases drowsiness and dizziness. Addition of dihydrocodeine to paracetamol has not been studied as widely.

Co-proxamol is no more effective than paracetamol, when given in single-doses for acute pain. This was demonstrated in a systematic review of 26 trials in 2,231 patients with postpartum, musculoskeletal, orthopaedic or post-surgical pain (oral surgery, episiotomy, caesarean and tooth extraction).[20] Four to six hours after a single dose, there was no significant difference between 65/100mg dextropropoxyphene with 650mg paracetamol and 650mg paracetamol alone, in the SPID or the proportion of patients who had moderate to excellent pain relief. **Since co-proxamol is also less safe than paracetamol and is more expensive, it should not be prescribed routinely.**

In single doses, **codeine 60mg** may add to the analgesic effect of **aspirin 650mg**, but the effect is modest and unlikely to be clinically significant. A meta-analysis of 110 trials found the combination to be more effective than aspirin alone but only in the TOTPAR in indirect comparisons. Patients had orthopaedic, post-partum, or postoperative pain (mainly tooth extraction, episiotomy and oral surgery).[3]

Another meta-analysis of similar design (55 reports of trials) found an 8% increase in pain relief (TOTPAR) when **codeine 60mg** was added to **ibuprofen 400mg** after episiotomy, dental or other surgery.[21] However, this was only significant in the six head to head comparisons and it is not clear whether more patients had moderate to excellent pain relief. The only fixed combination of these drugs contains ibuprofen 300mg modified-release with codeine 20mg (see **insert**). There is no good quality evidence showing a consistent benefit over ibuprofen or codeine alone and side-effects are likely to be increased.

Considerations of chronic use

Whilst the above studies provide information on the relative efficacy of analgesics in acute pain, the situation for chronic use is less clear. Certain drugs may be more effective on repeated dosing. Large multiple-dose comparative trials are required to fully understand the place of each drug.

A lack of adverse effects in single-dose studies does not imply that a drug will be safe for regular use over long periods. The possibility of accumulation should be considered before prescribing any drug regularly, particularly in patients with reduced renal or hepatic function, or those on interacting drugs including alcohol.

Headaches are associated with chronic regular use of analgesics, particularly combinations. Where possible, patients with a previous history of headaches should not take analgesics every day.[22] Nephropathy has also been reported.[23]

The long-term use of opioid analgesics in non-malignant pain is controversial.[24] However, although physical dependence is common, the risk of psychological dependence in patients with opioid-sensitive pain and no history of

drug dependence is low.[25] Fear of dependence does not justify the failure to relieve pain. Tolerance may develop but it is not usually a clinically significant problem.[25] Nevertheless, opioids should only be used long-term if other drugs have failed and it is clear that the pain is opioid responsive.[26] For certain patients, advice from a pain specialist may be necessary.

Titrating and individualising treatment

The analgesic regimen should be tailored to the individual. Patients with continuous pain usually need regular analgesics,[24] whereas 'as required' dosing is suitable for intermittent pain. Dosages should be titrated to the response and side-effects. 'As required' dosing may be needed initially to establish the most suitable regimen. Patients should be involved in treatment decisions.

If pain control is inadequate, despite titrating up to the maximum dose of a non-opioid, the 'analgesic ladder' (see **figure 1**) suggests that a weak opioid e.g. codeine should *also* be given.[4] It is thought that by using two drugs with different mechanisms of action, a greater efficacy will be achieved than with either constituent alone.[27] This depends on the combination being used. Another argument for combinations is to allow lower doses of each agent to be used, producing fewer adverse effects than an equi-analgesic dose of either single constituent.[24]

Whilst the severity of adverse effects may be reduced, the range of possible effects is increased by using more than one drug. Therefore, in some patients, it may be preferable to try an opioid alone at 'step 2' before a combination, despite the lack of evidence in terms of efficacy.

When a patient requires combination therapy containing a full dose of opioid, prescription of the constituents separately will allow individual dosage titration of each component. An equivalent fixed combination preparation should only be used once pain control has been well established. Modified-release preparations may be useful for patients requiring frequent dosing which is incompatible with their lifestyle or those with 'breakthrough pain' towards the end of the dosage interval. However, they may be expensive and are more likely to accumulate when used regularly. They should not be used on an 'as required' basis for intermittent pain.

All patients should be reviewed frequently to ensure treatment is effective, free from adverse effects and still required. Stepping-down the analgesic ladder is often necessary as healing occurs. Where pain control is difficult, referral to a specialist pain clinic is advisable.

Patients taking paracetamol should be reminded not to exceed the recommended dosage and to avoid other products containing paracetamol, particularly over the counter (OTC) preparations. Similar advice, tailored to the specific drug, should be given with all analgesic prescriptions (check with the community pharmacist).

Analgesic use in the elderly

Elderly patients have an increased risk of adverse effects from drugs and many have some degree of renal impairment. Therefore, a 'start low, go slow' approach should be adopted when prescribing for this group, particularly with opioids as increased analgesic sensitivity also occurs. NSAIDs should be used cautiously and long term use of high doses avoided.[2] Paracetamol is the drug of choice for mild to moderate musculoskeletal pain.[2] In order to reduce the risk of falls, co-proxamol should be avoided. Compliance may be particularly problematic in these patients.

Conclusion

Analgesics should be prescribed in a logical stepwise manner, based on the severity and type of pain, supporting evidence and patient factors. Regimens should be individualised and reviewed regularly. The potential toxicity of each prescription must be balanced carefully against the patient's analgesic requirements. Further study is needed to fully understand the position of each drug in the management of mild to moderate pain, particularly in the chronic dosing situation.

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