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Pain Treatment in Multimorbid Patients, the Older Population and Other High-Risk Groups

The Clinical Challenge of Reducing Toxicity

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Summary

The prevalence of pain is high in multimorbid patients and they can experience a multitude of painful conditions. The changes in physiology and homeostasis associated with multimorbidity and increasing age and the immature metabolism of neonates all increase the risk of toxicity from analgesics. Altered pharmacokinetics and metabolism influence drug pharmacodynamics and therapeutic windows. Imbalances in local homeostatic mechanisms increase local toxicity. The gastrointestinal organs and the kidney have a major role in the absorption, metabolism and excretion of analgesics and changes in their function predispose in-

dividuals to adverse effects. Knowledge of such compromise should influence the choice of analgesic, the administration regimen and the mode of application.

The mainstay of chronic pain treatment are 3 classes of drugs: nonsteroidal anti-inflammatory drugs (NSAIDs), opioids and a host of so-called adjuvant drugs, which are used to enhance the analgesic action of the classic analgesics. In each class a wide range of drugs are available, that differ in pharmacokinetic and pharmacodynamic characteristics. These differences can be exploited to either increase analgesic efficacy and reduce toxicity, or to minimise the interference of pain therapy with daily life.

Clinically important differences in analgesic and toxic effects between drugs in each analgesic class will be discussed in this article from the perspective of reducing adverse effects. New knowledge concerning the mechanism of action of analgesics and their metabolites is making the specific selection of NSAIDs and opioids to reduce adverse effects in multimorbid, chronic pain patients possible.

The awareness of the necessity for adequate pain control has increased over the last few decades, both in the acute postoperative setting and in patients with chronic pain. Substantial improvements are evident in the treatment of severe pain in patients with cancer or a terminal disease, and similar efforts must be made in the sphere of chronic nonmalignancy-associated pain. These advances can be attributed to improved general acceptance and enlightenment, but also to a more profound knowledge of the pharmacological characteristics of the drugs employed in pain control. Putting the emphasis on basic principles, such as regular analgesic administration for pain prophylaxis and the pre-emption of adverse effects, has been a valuable milestone that we owe to such pioneers as Dr Robert Twycross and Dr John Bonica.

Despite improvements, failure to reduce pain to adequate levels remains common.[1] The terms 'failure of analgesia' and 'inadequate analgesia' are ambiguous and unquantifiable, but in a general sense they imply that either the pain or the analgesic interferes with the individual's normal way of life. This can be caused by several major factors: insufficient analgesic efficacy of medication, toxicity of pain medication or interference of mode of application of analgesic with the patient's activities.

These factors apply to pain control in patients with normal organ function and to multimorbid or geriatric patients. Because the latter 2 patient groups have important changes in compensatory and metabolic mechanisms, caused by compromised organ function, they are more prone to toxicity and to aberrant pharmacodynamic responses. In the following article we will discuss the possible underlying causes for suboptimal pain relief in these at-risk patient groups, and additional references relevant to paediatric pain treatment will be made. The necessity of preventing pain in neonates and infants is becoming increasingly recognised, with the demonstration of developmental, psychological and neuroanatomical changes associated with inadequate analgesia during painful procedures.

Detailed discussions of the pharmacokinetics of the many analgesics available, and of the medications used adjuvantly for analgesia, are outside the scope of this clinically oriented article, but references to appropriate reviews will be made.

1. Common Causes of Suboptimal Pain Relief in Multimorbid or Elderly Patients

1.1 Drug Unsuitable for Type of Pain

Experience has shown that certain classes of analgesics are unsuitable for specific types of pain, because of their inadequate efficacy or their profile of adverse effects. It is accepted that neuropathic pain caused by nerve damage is poorly responsive

to opioid treatment, although some response can be obtained at higher doses.[2,3] Specific examples of inappropriate indications for analgesics are: (i) the use of opioids for crampy or constipation-induced pain; (ii) nonsteroidal anti-inflammatory drugs (NSAIDs) for peptic ulcer pain or for pain in patients with a history of peptic ulceration; (iii) monotherapy with sedatives for severe chronic or acute pain; and (iv) analgesics for psychological or spiritual pain.[4] Conversely, some types of pain are generally very responsive to certain classes of analgesics. Pain caused by osseous metastases or arthritis should be treated primarily with NSAIDs, although bisphosphonates are also useful in the former condition. Antidepressants and anticonvulsants are the drugs of choice in neuropathic and complex regional pain syndromes. It appears that α_2-agonists, such as clonidine, may also be useful for these types of pain. Antispasmodic drugs are indicated in crampy intestinal pain and discomfort. It follows that the causal diagnosis of pain is clearly of great importance to ensure efficacy and minimal toxicity.

1.2 Low-Potency/Efficacy Drug with Ceiling Effect

Partial agonist-antagonist opioids, and probably most NSAIDs, display a maximum effect within the clinical dosage range, with no additional effect at higher dosages. This implies that, in the case of insufficient pain relief, the analgesic should either be replaced or combined with another analgesic with a different mode of action.

1.3 Toxicity

The toxicity and potency of drugs may be increased in elderly or multimorbid patients because of changes in local and systemic protective and homeostatic mechanisms. Examples are: decreased respiratory drive and compensation, resulting in increased respiratory complications with opioids and decreased production of mucosal protective factors predisposing to gastrointestinal damage from NSAIDs. Other common problems are the cumulation of metabolites of analgesics because of hepatic and/or renal compromise [e.g. pethidine (meperidine), morphine, indomethacin and ketorolac], changes in bioavailability because of gastrointestinal dysmotility, absorption, protein binding, metabolism or volume of distribution [e.g. methadone and paracetamol (acetaminophen)], and interactions with other drugs because of polypharmacy (e.g. monoamine oxidase inhibitors, enzyme induction, synergism or antagonism).[5-8] Reduced efficacy in poor metabolisers of certain analgesics classified as prodrugs can be postulated (e.g. possibly codeine and nabumetone).[9,10] There are multiple pharmacokinetic and pharmacodynamic changes associated with organ failure and aging, which cannot be detailed in this overview. There are changes in perfusion, production of defensive factors and regulatory reflexes, amongst others. For in-depth discussions of these changes see Inturrisi,[5] O'Malley,[11] and Bodenham et al.[12]

The pharmacology of analgesics is very different in neonates compared with adults; neonates have a smaller volume of distribution and often slower elimination of analgesics, especially opioids.[13-15] However, by the first year of life many metabolic parameters are similar to, or even higher than, those of adults, and dosage requirements are often higher. Infants and children do not appear to have greater sensitivity to the effects of opioids than adults.

1.4 Patient Compliance

Changes in cognitive and cortical function will influence patient compliance. Amnesia, a reduction in concentration skills and confusion may lead to over- or underadministration. Exaggerated fears of adverse effects and addiction often lead to inadequate analgesia. Impractical modes of application of analgesics encourage poor compliance.

2. Guidelines to Reduce Adverse Effects

General clinical guidelines for the reduction of adverse effects of pain control therapy in 'at-risk' patients are outlined in table I.

Table I. General guidelines for reducing analgesic toxicity in elderly patients and those with compromised organ function

1. Diagnose type and origin of pain
2. Ascertain type and degree of organ dysfunction
3. Choose drug least likely to cause toxicity either by direct damage or by accumulation
4. Consider shorter-acting drugs (3-4 hours, e.g. codeine, morphine, hydromorphone) with minimal toxic metabolites and low interaction potential with commonly prescribed drugs
5. Generally begin with lower dosages and longer administration intervals, titrate doses individually
6. To increase compliance inform patient, relatives and responsible staff of expected efficacy and toxicity. Consider prophylactic medication for adverse effects
7. Choose route of drug administration and formulation least restrictive to patient
8. Monitor organ function and toxicity regularly, more frequently during initial dose titration

These general guidelines can be translated into practice by exploiting clinically relevant differences in pharmacokinetics and dynamics between the analgesics available. The 2 classes of analgesic drugs most commonly used are NSAIDs and opioids. The clinically relevant differences in the potential for toxicity and the influence of organ compromise on drug action and practical suggestions for the prevention of adverse effects for each class of drug will be discussed in the following sections.

3. Pain Assessment

Pain assessment in multimorbid, elderly or confused patients and in infants is a considerable challenge, and is the first major step towards an effective pain treatment. Many of the these patients cannot adequately verbalise or document their pain using the commonly used assessment tools, such as verbal rating or visual analogue scales. Depending on the degree of consciousness and mental and physical incapacitation, other mainly observer-rated pain assessments are necessary. Validated methods are now becoming available for rating pain behaviour in both geriatric and paediatric populations. Detailed discussions are provided in several recent reviews.[16-23] Behavioural pain scores, comprising ratings of facial expression, defensive movements, breathing patterns, state of arousal and vocalisations, are being standardised. In critical care patients, physiological indicators of pain seem to be of additional value.[24] In young children, several self-rating scales have been validated, including a scale of facial expressions and colours of different intensities. Even children in the 5 to 7 year range can describe pain in effective, qualitative and intensity terms.[25] Pain assessments are used to rate pain before and after analgesic interventions to allow dose titration for each individual.

4. Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs, including paracetamol and salicylates, are the most commonly used analgesics, and the most commonly prescribed drugs, worldwide.[26] They represent the first step in the WHO cancer pain treatment ladder and are used daily by some 13 million Americans, which amounts to 70 million prescriptions that cost well over $US1 billion each year.[27] Annually, over 1 million prescriptions are dispensed in the UK for osteoarthritis alone[28] and 26% of elderly patients in the US regularly take NSAID medication.[29] This implies that NSAIDs are generally effective and well tolerated. However, NSAID-associated gastrointestinal disorders are the most prevalent serious drug toxicity in the US. NSAID-associated gastrointestinal disorders are estimated to result in 2600 to 7600 and 1000 to 3000 excess deaths annually in the US and UK, respectively, and in 24 000 hospitalisations annually in patients in the US with rheumatoid arthritis.[26,30] 25% of all reported adverse drug events in the UK are NSAID-related.[31] The annual rate of hospitalisation for gastrointestinal-related disease for patients with rheumatoid arthritis is 1.6% for patients taking NSAIDs, compared with 0.3% for patients not taking NSAIDs.[32]

By far the most common adverse effect of NSAIDs are upper gastrointestinal lesions, although with longer-acting NSAIDs, the incidence of small and large bowel lesions is increasing noticeably.[33] Bleeding oesophageal ulcers have also been increasingly described during NSAID use.[34]

4.1 Gastrointestinal Toxicity

The incidence of upper gastrointestinal ulcers, both asymptomatic and symptomatic, is estimated to be approximately 10 to 25% in patients receiving NSAIDs; the incidence of gastrointestinal pathology requiring hospitalisation is around 3 to 4% and major gastrointestinal complications – predominantly gastrointestinal haemorrhage and perforations – occur in 0.5% of NSAID users.[32,35,36] Many studies have examined risk factors for NSAID-induced gastrointestinal lesions. The consensus is that age >60 years (odds ratio 5.5), a history of peptic disease (odds ratio 2.1), disability (odds ratio 1.9), greater dosages, type of NSAID, and anticoagulant or corticosteroid comedication are all risk factors for NSAID-associated gastrointestinal adverse effects.[30-32,35-39] In a recent large cohort study of over 78 000 patients who had been newly prescribed NSAIDs, the estimated risk ratio for upper gastrointestinal bleeding and perforation was 2.48 compared with matched controls.[40] The age, gender and race adjusted risks for upper and lower gastrointestinal bleeding associated with NSAID use were 3.2 and 2.6. The risk associated for bleeding from diverticular disease was high at 3.4.[41]

The changes in physiology in the elderly patient that predispose the patient to increased NSAID-induced gastrointestinal and renal damage were summarised in a recent review by Soloman and Gurwitz.[42] According to these authors there is clear evidence of an inverse relationship between age and gastrointestinal prostaglandin levels and there are findings that suggest that renal prostaglandin excretion changes with age.[42] Soloman and Gurwitz[42] stipulated, however, that the increased risk of gastrointestinal and renal toxicity was caused by elevated background risks of these toxicities secondary to comorbidity and the increased use of NSAIDs in the elderly population. This issue clearly requires further elucidation, but it confirms the substantially higher risk of adverse effects associated with NSAIDs in geriatric and multimorbid patients. Besides changes in physiology, there are important changes in the clinical presentation of adverse effects in the elderly.[43]

Can these risks for gastrointestinal toxicity with NSAIDs be reduced in elderly patients and those with compromised renal function? Age and disability are two factors that cannot be changed. However, if other analgesics or loco-regional forms of analgesia can be used, these should be preferred. If this is impractical, several steps to minimise gastrointestinal damage can be helpful. Suggestions for reducing the risk of NSAID-induced gastrointestinal toxicity are outlined in table II.

Table II. Reducing the risk of nonsteroidal anti-inflammatory drug (NSAID)–induced gastrointestinal toxicity in elderly patients and those patients with compromised organ function

1. NSAIDs should be avoided whenever possible in patients who are: over 60 years of age; who are disabled; who have a history of peptic disease; or who are taking corticosteroids or anticoagulants. If avoidance is not feasible, see points 2 and/or 3
2. Choose an NSAID with lower risk of gastroduodenal toxicity (see section 4.1.1)
3. Co-administer misoprostol or an antisecretory agent (histamine H_2 receptor antagonist or proton pump inhibitor) to patients with 2 or more risk factors (see point 1)
4. Investigate early in the case of symptoms and be aware of lower intestinal tract lesions with long-acting NSAIDs

4.1.1 Appropriate Choice of NSAID

Some NSAIDs are more mucosally aggressive than others: indomethacin, uncoated or unbuffered aspirin (acetylsalicylic acid), tolmetin, meclofenamate, ketoprofen and piroxicam are mostly likely to induce gastrointestinal adverse effects, whereas coated or buffered aspirin, ibuprofen and naproxen seem better tolerated.[35,44-47] Overall, the risk of gastrointestinal complications is approximately 3.5% with older NSAIDs.[31] Co-administration of several NSAIDs increases the risk of gastroduodenal lesions.[35]

Dipyrone (metamizole) is an useful NSAID that is associated with a low risk of ulcers, has a unique antispasmodic effect, is available in a parenteral formulation and, despite earlier reports, is associated with a low incidence of agranulocytosis (1 per million weeks of use).[47,48] Ketorolac has gained widespread acceptance for use perioperatively, but the intravenous formulation is associated with an increased risk of gastroduodenal lesions and an in-

creased risk of gastrointestinal bleeding, especially when the agent is used either for more than 5 days or in patients over 75 years of age.[49,50]

Several newer NSAIDs show some cyclooxygenase (COX) 2 selectivity and therefore do not inhibit the production of gastroprotective prostaglandins (COX 1). They cause less gastrointestinal damage than older NSAIDs, with a gastrointestinal complication rate of approximately 1 to 2% and are often prodrugs or do not undergo enterohepatic circulation.[51-53] Nabumetone is a non-acidic NSAID prodrug and a postmarketing analysis of data from approximately 45 000 patients, who had received the agent for 3 weeks to 8 months, revealed a gastrointestinal complication rate of less than 1%.[35,54] It has also been shown that etodolac does not inhibit gastric prostaglandin and this agent is associated with a similarly low rate of gastrointestinal toxicity.[35,55] Nimesulide, with a similar claimed mode of action (i.e. is COX 2 selective), has been shown in short term volunteer studies to induce no more gastrointestinal damage than placebo.[56] However, long term studies in patients have shown similar erosive toxicity compared with comparator NSAIDs.[57] Oxaprozin is a potent inhibitor of prostaglandin synthesis with once daily administration, but has demonstrated a very low incidence of gastrointestinal damage in animal models and clinical studies.[35,58] A dissociation of anti-inflammatory from other NSAID properties will be considered in section 4.4.3. The development of nitric oxide–releasing NSAIDs is an exciting perspective, as agents they appear to be have a very low ulcerogenic potential and may even heal ulcers.[59,60]

Instead of changing to newer, less gastrointestinal-toxic NSAIDs, it is also possible to protect the gastrointestinal mucosa by co-administering gastroprotective agents in patients at high risk of toxicity. Sucralfate appears to have no consistent protective effect.[61] Histamine H_2 receptor antagonists and proton pump inhibitors have been shown to prevent gastroduodenal erosions and ulcers.[62-67] Omeprazole 20mg given once or twice daily for 8 weeks healed NSAID-related peptic lesions in approximately 80% of patients and relapse was prevented in the subsequent 6 months in approximately 60% of patients.[66] Overall, the healing rates with omeprazole were superior to ranitidine 150mg twice daily and similar to misoprostol 200μg 4 times daily. Misoprostol, a prostaglandin E_1 analogue, protects gastric mucosa against NSAID-induced damage by enhancing a multiplicity of local factors, and by a slight antisecretory effect.[68,64] The recommended dosage for the gastric effect is 200μg 4 times daily. Higher dosages are required to effectively prevent duodenal lesions.[64,69] Misoprostol causes diarrhoea and abdominal pain in approximately 25% and 15% of patients, respectively; both adverse effects are usually transient.[64] Other adverse effects include uterine contractions or bleeding. Recently a fixed-dose combination of diclofenac sodium 50mg and misoprostol 200μg, Arthrotec®, has become available. In several large, double-blind comparisons with other NSAIDs, Arthrotec® given twice daily or thrice daily reduced the incidence of gastroduodenal lesions significantly (by at least 50% in most studies), while showing equivalent joint anti-inflammatory efficacy.[70,71] The incidence of diarrhoea and abdominal pain are slightly increased with Arthrotec®, but normally abate spontaneously with continued administration.

The relationship between *Helicobacter pylori* infection, NSAID use and gastrointestinal ulceration and haemorrhage is currently a subject of intense research, but no firm conclusions can yet be reached. There is emerging conflicting evidence concerning the risk for ulceration in patients with *H. pylori* infection taking NSAIDs.[72-75] Studies evaluating the effect of *H. pylori* eradication on the incidence of gastrointestinal ulceration and bleeding in patients taking continuous NSAID treatment will provide a definitive answer. The first recently published study indicates that eradication of *H. pylori* does reduce the occurrence of NSAID-induced peptic ulcers, but further large studies must be performed to allow a definitive verdict.[76] *H. pylori* eradication by triple therapy in *H. pylori* positive patients with bleeding ulcers very significantly re-

duces subsequent ulcer recurrence and rebleeding.[77,78] It is consequently recommended that *H. pylori* positive patients with peptic ulcers receive triple therapy including a proton pump inhibitor, metronidazole or tinidazole, amoxycillin or tetracycline or clarithromycin and bismuth, according to the different standard regimens (see Hopkins[79] for recommended regimens).

NSAID-induced symptoms and lesions have not been thoroughly investigated in paediatric patients, but appear to be considerably less common than in adults.[80] However, NSAID suppositories may cause proctitis.

4.2 Renal Toxicity

The most frequent renal changes associated with NSAID use are acute ischaemic renal failure, acute interstitial nephritis, electrolyte changes (changes in sodium and potassium levels), fluid retention and papillary necrosis.[81,82] Most NSAIDs have a pressor effect, which is strongest for indomethacin, naproxen and piroxicam, and the antagonism of β-blockers and also probably for other antihypertensive agents can exacerbate renal impairment.[83] The renal effects of prostaglandins include maintenance of renal blood flow rate, modulation of renin release and tubular ion transport and excretion of water.[82,84] The association between NSAID use and renal toxicity is ambiguous and is mainly based on case control and cohort studies.[36,81] In the largest study, that involved over 40 000 patients, the relative risk of renal toxicity associated with NSAIDs was found to be 0.9. Other case control studies have shown relative risks of between 0.9 and 2.1, with an increased risk for elderly patients.

Table III. Reducing the risk of nonsteroidal anti-inflammatory drug (NSAID)–induced renal toxicity in elderly patients and those patients with compromised organ function

1. Avoid use of NSAIDs (especially those with delayed renal excretion, see text) in patients with compromised renal function or perfusion and the elderly whenever possible
2. Avoid co-administration of NSAIDs and loop diuretics
3. Frequently monitor renal function, discontinue in the case of toxicity. Most effects are reversible

It has clearly emerged, however, that NSAID use in healthy individuals at therapeutic dosages is associated with a low incidence of renal toxicity (less than 1%).[36,81,84,85] In contrast, patients with previously compromised renal function or perfusion (age >60 years, hypovolaemia, arteriosclerosis, congestive heart failure, cirrhosis), or patients taking loop diuretics have an increased risk of reversible renal failure.[36,81,84] Additionally, in patients with renal insufficiency, the excretion of some NSAIDs will be delayed (e.g. alclofenac, indomethacin, ketorolac, ketoprofen, oxaprozin), possibly predisposing to renal toxicity. Interstitial nephritis usually occurs after 2 to 18 months of use and there is an increased risk of this adverse renal effect with fenoprofen. The increasingly rare analgesic-associated nephropathy secondary to papillary necrosis is seen after very prolonged exposure to high dosages of combination analgesics, typically containing aspirin, phenacetin and caffeine. Sulindac has been promoted as having less nephrotoxicity than other NSAIDs, but there are conflicting data on this point.

In paediatric patients the risk factors for renal toxicity are similar to those for adults, but toxicity appears to be less common.[86]

General guidelines for the reduction of the adverse renal effects of NSAIDs in the elderly and patients with compromised organ function are outlined in table III.

4.3. Other Adverse Effects

4.3.1 Hepatic

Four very large case control and cohort studies showed a minimally increased risk for liver toxicity (relative risks 1.2 to 1.7) with long term NSAID therapy.[36] Case reports have described a wide variety of hepatopathies and mild elevations in aminotransferase levels can occur with almost all NSAIDs.[87] Hepatocellular necrosis is very rare, but has been associated with diclofenac and very high doses of paracetamol.[36,87] The potentially serious hepatotoxicity that can result when adult doses of paracetamol are given to children has recently been highlighted.[88,89] Salicylates fre-

Table IV. Reducing the risk of nonsteroidal anti-inflammatory drug (NSAID)–induced hepatic toxicity in elderly patients and those patients with compromised organ function

1. Most toxicity occurs in the first few months of administration, therefore monitor monthly during this time
2. Mild elevations in aminotransferase levels occur with most NSAIDs. Discontinue or change to other class of NSAID if other indications of liver damage (e.g. elevated bilirubin levels) occur
3. Avoid salicylates in children (because of the risk of Reye's syndrome) and adult doses of paracetamol (acetaminophen)

quently lead to raised aminotransferases levels and rarely to hepatocellular necrosis, which is normally reversible on drug discontinuation.[87]

Reye's syndrome can be seen after salicylate treatment in children following viral syndromes and is characterised by fulminant liver failure and encephalopathy with cerebral oedema. This is the commonest cause of hepatic mortality in children in the US.[80] In neonates, toxic paracetamol metabolites can accumulate because of immature hepatic enzymatic capacity and cause liver damage.

General guidelines for the reduction of the adverse hepatic effects of NSAIDs in the elderly and patients with compromised organ function are outlined in table IV.

4.3.2 Haematological

Haematological adverse effects with NSAIDs are very rare. Agranulocytosis and aplastic anaemia have been reported with butazones, dipyrone (at a frequency of less than 1 case per million weeks of use) and indomethacin.[36,48]

Numerous other rare adverse effects have been described in association with NSAIDs. For example, hypersensitivity reactions are more common in patients exposed to NSAIDs than in unexposed patients (relative risk 2.0).[36] The risk of hypersensitivity appears to be elevated with salicylates and relatively low with nimesulide in children.[90] The link between NSAID use and necrotising fasciitis remains unclear.[91]

4.4 Recent Developments in NSAID Therapy

4.4.1 Modes of Action

The modes of action of NSAIDs are being more clearly defined. It is now accepted that NSAIDs have both peripheral and central actions.[92-94] Besides the inhibition of anti-inflammatory, peripheral prostaglandin synthesis, NSAIDs have central actions which are either prostaglandin-dependent, monoaminergic or occur by other nonprostaglandin mechanisms.

4.4.2 Dose-Response Effects

A dose-response relationship for NSAIDs appears to exist, although increasingly an analgesic ceiling effect is being confirmed in meta-analyses.[95,96]

4.4.3 Dissociation Between Anti-Inflammatory and Analgesic Properties

The anti-inflammatory and analgesic or antinociceptive components of NSAIDs appear to be independent of each other.[97,98] This dissociation is apparent for paracetamol, but McCormack and Brune[97] have demonstrated that this distinction is true for other NSAIDs as well. For example, azapropazone, naproxen and tolmetin are strong analgesics, but weak prostaglandin synthesis inhibitors. The opposite is true for fenbufen or nabumetone. Dissociation of the anti-inflammatory and antinociceptive effects has also been shown with stereoisomers of NSAIDs, which are usually used clinically as racemic mixtures (i.e. *R* and *S* enantiomers are present in equal proportions). Recent work with ibuprofen, ketoprofen and flurbiprofen has shown the anti-inflammatory and analgesic properties to differ markedly between the 2 enantiomers of each of these agents.[98,99] In the case of flurbiprofen, the *R* isomer had little anti-inflammatory activity, but substantial antinociceptive properties and caused no gastrointestinal lesions in rats. The *S* isomer was both anti-inflammatory and analgesic. These differences may be of clinical benefit in the future.

4.4.4. Nitric Oxide-Releasing NSAIDs

Preliminary studies have shown that nitric oxide–releasing NSAIDs protect against gastrointestinal damage (see section 4.1.1).[59,60]

5. Opioids

Most patients with cancer-related pain will require treatment with opioids at some time, and there is an increasing trend towards using opioids in severe nonmalignant pain. Pain is relieved inadequately in approximately 70% of the estimated 9 million cancer patients who have pain.[100] The judicious use of opioids and other analgesics may help relieve up to 90% of this pain, according to figures from the hospice setting.[100] However, opioids are still viewed with suspicion and unease by medical staff and patients. It is not the within the scope of this review to deal with the prejudices related to opioids, but I hope to minimise the justifiable fears of toxicity related to opioid use in multimorbid patients and patients with compromised renal function. All opioids can and do cause adverse effects, even in patients with normal organ function. In patients with chronic pain these adverse effects can severely compromise daily functioning and can lead to discontinuation of medications. Multi-organ failure potentially increases the risk of opioid toxicity by modulating metabolism, excretion and end-organ sensitivity. The choice of opioid to minimise interference and toxicity is consequently of great relevance. In the following sections, clinically relevant differences between the opioids will be highlighted with the aim of reducing the potential for adverse effects in patients with specific organ dysfunction.

Opioids can be classed as so-called low-potency or weak opioids and high-potency or strong opioids. In the WHO pain treatment ladder, these agents constitute steps 2 and 3.[101] The rationale behind this grading seems to be the presupposition of a lower incidence of adverse effects with a weak opioid compared to low doses of a strong opioid, and better efficacy compared with NSAIDs, although these hypotheses have, to date, not been validated.[95] Besides differences in potency, there are other pharmacokinetic and metabolic distinctions of significance between the opioids. The number of available opioids is constantly increasing, although most of the newer opioids are designed for anaesthetic use. These include remifentanil, sufentanil, alfentanil and fentanyl. Because of their short duration of analgesia they are impractical in the treatment of chronic pain, unless given by infusion or as sustained-release formulations. Currently, there is much discussion concerning the role of opioids in chronic nonmalignant pain. The balance between undoubted efficacy in many pain syndromes and possible morbidity, both pharmacological and functional, must be carefully weighed. An excellent and comprehensive review of this indication has recently been published.[102]

5.1 Opioid Receptor-Related Effects

The receptor affinities of the opioids and their metabolites determine their clinical characteristics. The main classes of opioid receptor are μ, κ and δ (see Reisine and Pasternak[103] for information on the different receptor types). The σ-receptor appears to be a phencyclidine receptor and hence probably not a true opioid receptor.

The most commonly used opioid analgesics exert their predominant action by binding to the μ-receptor. An agonist action at the receptor site results in analgesia, as well as adverse effects such as constipation, sedation and respiratory depression. The partial agonists, such as buprenorphine (also a κ-receptor antagonist) may precipitate abstinence syndromes when used immediately after full agonists, and some patients have a ceiling effect for analgesia as well as for adverse effects. κ-Receptor agonists also induce analgesia, and can mediate respiratory depression, however they appear not to have the antipropulsive gastrointestinal effects of μ-receptor agonists.[104,105] Because of the preponderance of κ-receptors on visceral nerve afferents, several peripheral κ-receptor agonists are being clinically tested in the treatment of visceral pain syndromes.[106] Some opioids have excitatory adverse effects, such as dysphoria, tachycardia, hypertension, excitation, hyperalgesia, the mechanism of which is unclear but may be related to non-opioid or κ-receptors.[103,107]

Receptor differentiation is not complete at birth, but develops rapidly, and receptors are expressed at different sites in neonates than they are in

adults.[13-15] This may be one of the explanations for the reduced analgesia but increased respiratory depression caused by opioids in neonates.

5.2 Adverse Effects

The most common adverse effects of opioids affect the gastrointestinal tract (nausea, vomiting and constipation) and CNS (sedation, dizziness, respiratory depression and hypotension).[103] There are many other possible adverse effects, such as pruritus and urinary retention. These adverse effects are mainly μ-receptor effects and clinical observation suggests that most of these effects, except constipation, ameliorate with long term administration. General guidelines for reducing the incidence of adverse effects in the patient with compromised organ function are shown in table V.

5.3 Relevance of Opioid Metabolites

Several of the commonly used opioids have active metabolites with analgesic and other pharmacological effects. The major metabolites of morphine are morphine glucuronides. The significance of the morphine-6- and 3-glucuronides remains unclear. A large proportion of the analgesic and toxic effects of morphine have been attributed to morphine-6-glucuronide which, on the basis of uncontrolled trials, is considered a potent analgesic.[5,7,108] However, a recent double-blind, short term intravenous infusion study was unable to confirm any analgesic effect of this metabolite.[109]

Morphine-3-glucuronide is a major non-opioid metabolite postulated to antagonise morphine analgesia and to exert excitatory actions.[5,7,110,111] The half-lives of both glucuronides are considerably longer than that of the parent compound, and these metabolites can thus accumulate in the plasma and CSF with repeated administration.[5] Pethidine and propoxyphene have neurotoxic or cardiotoxic nor-metabolites.[5,103] Codeine and dihydrocodeine are metabolised to morphine and dihydromorphine, respectively. Tramadol has an active metabolite, *O*-demethyltramadol, the exact analgesic significance of which is still somewhat unclear.[112]

Table V. Reducing the risk of toxicity during opioid treatment in elderly patients and those patients with compromised organ function.

1. Choose an opioid least likely to cause toxicity. Avoid opioids with common idiosyncratic adverse effects such as pethidine (meperidine) and propoxyphene
2. Choose an opioid with the most practical form of application for each individual patient
3. Initially titrate doses according to pain intensity and adverse effects with shorter-acting opioids (3-4 hour analgesic action, e.g. codeine, morphine, hydromorphone, tramadol) using frequent pain intensity and pain relief assessments. Because of increased sensitivity and accumulation of metabolites in patients with compromised organ function and elderly patients, initially lower doses and increased administration intervals compared with normal practice are recommended. This is especially necessary in renally compromised patients where pethidine and propoxyphene should be avoided
4. In patients with liver cirrhosis, begin dose titration with reduced doses of opioids that undergo extensive first-pass elimination, avoid pethidine, propoxyphene and pentazocine. Methadone is not affected by cirrhosis

5.4 Idiosyncratic Effects of Opioids

Some of the opioids have idiosyncratic effects and attention to these effects can spare patients with organ dysfunction considerable discomfort. Some clinically relevant properties are as follows. Morphine is known to cause substantial histamine release when given rapidly intravenously, which can precipitate or exacerbate hypersensitivity reactions, such as asthma.[113] It may also raise intracranial pressure, and can cause myoclonus and other excitatory reactions.[103,107,114] The bioavailabilty and half-life of morphine is increased by some tricyclic antidepressants.[5] Pethidine has local anaesthetic properties, it interacts with monoamine oxidase inhibitors, potentially resulting in seizures and hyperexcitability.[5] Some studies suggest that pethidine has a minor spasmogenic effect on smooth muscle compared with other opioids.[115]

Tramadol has recently been shown to exhibit approximately half of its analgesic action by serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine) reuptake blockade.[112,116] Its other mode of action is μ-receptor agonism. Each of these modes of action predominates in 1 of

the 2 tramadol enantiomers. The presence of 2 modes of action in 1 drug are exciting, as we know that α_2-agonists (e.g. clonidine), via a spinal monoaminergic mechanism to potentiate opioid analgesia, can reverse opioid tolerance and show good effects on neuropathic pain syndromes. Clinically, tramadol is distinguished from other opioids by having a low psychological dependence potential (it does not fall under opioid restrictions after over 20 years of monitored clinical use), much reduced respiratory or cardiovascular depression, a minimal effect on smooth muscle tone and on upper and lower gastrointestinal motility.[112,117-119] With long term administration, nausea and vomiting appear uncommon.[112,117] Co-administration with monoamine oxidase inhibitors should be avoided because of possible monoaminergic interactions resulting in excitatory adverse effects (such as myoclonus) at high doses.

The effects of buprenorphine can only be reversed slowly by naloxone because of tight receptor binding. Buprenorphine causes less sedation, constipation or respiratory depression when given sublingually than morphine, but may reach a ceiling effect, at higher doses, in some patients.[103,120,121] Methadone has the advantage of little metabolic changes with renal or hepatic compromise. However, dose titration and adaptation is complicated by its considerably longer plasma half-life than duration of analgesic effect.

Overall, morphine remains the favoured drug for chronic pain treatment. Newer opioids are more useful in the perioperative setting.

Multimorbid and geriatric patients are at an increased risk of adverse effects from opioids secondary to organ failure. When prescribing opioids the considerable distinctions in normal pharmacokinetics, including half-life, distribution, binding and lipophilicity must be appreciated. Additionally, pharmacokinetics are changed because of shifts in protein binding, tissue composition, volumes of distribution and other physiological variables. It has been shown that patients over the age of 50 years have an increased sensitivity to opioids and experience a longer duration of pain relief compared with younger patients.[5,6,122,123] Renal and hepatic compromise are the most important predictors of toxicity.

5.5 Influence of Renal Failure

Renal failure leads to decreased clearance of active and/or toxic metabolites. This can increase the analgesic and adverse effects of morphine and possibly codeine, dihydrocodeine and tramadol.[7,124-127] The toxic compounds norpethidine (normeperidine) and norpropoxyphene can accumulate, especially as they have a considerably longer half-life than the parent drugs, pethidine and propoxyphene.[5,128] Methadone kinetics are probably largely unchanged by renal insufficiency.[129]

Compared with adults, neonates have decreased elimination and hence increased accumulation of opioids and decreased opioid protein binding, allowing greater blood-brain barrier opioid penetration. Elimination half-lives in young children are similar to, or even more rapid than in adults.[13,130,131]

5.6 Influence of Cirrhosis

Cirrhosis can cause shunting from portal to systemic circulation. When this occurs there is an increase in systemic bioavailability and a decrease in systemic clearance because of decreased first-pass elimination. These effects are known to lead to increased availability and decreased elimination of pethidine, propoxyphene and pentazocine, with substantial risk of toxic accumulation of the parent substance and metabolites.[5,132,133] Because of its extensive hepatic transformation, tramadol can also be expected to accumulate in patients with severe hepatic failure. Morphine disposition does not appear to be affected by moderate cirrhosis, but in severe liver cirrhosis, both oral bioavailability and elimination half-life are increased. Glucuronidation pathways appear to be conserved until late in the course of liver failure, and extrahepatic metabolism of morphine (probably renal) can be enhanced.[134-137] Methadone kinetics are not significantly changed by cirrhosis.[138]

Because of genetic polymorphism of the cytochrome P450 isoenzyme CYP2D6, *O*-demethyla-

tion of some analgesics is significantly reduced in approximately 7% of Caucasians and in a higher percentage of Asians.[139] These poor metabolisers produce fewer active metabolites of some opioids, such as codeine or dihydrocodeine (the active metabolites of which are morphine and dihydromorphine, respectively) and have consequently been postulated to derive a reduced analgesic benefit compared with normal metabolisers.[140-142] However, this hypothesis currently remains unproven.[143]

It should be noted that hepatic glucuronidation and conjugation is immature and diminished in neonates, but matures quickly, reaching adult levels in the first months of life.[131]

5.7 Method of Opioid Administration

Different methods of opioid administration are possible, depending on the patient's circumstances and preferences. An important factor in the choice of method is the patient's compliance. Sustained-action drugs or fentanyl patches can increase compliance in forgetful patients. Subcutaneous infusions are popular in the palliative setting, but not all opioids should be given in this way. Pentazocine and pethidine can be locally irritating. More potent drugs can be applied in smaller volumes, reducing the need for pump refills. If patients have difficulty swallowing, sublingual application of buprenorphine or buccal application of morphine or fentanyl may be useful.

6. Conclusion

To maximise the analgesic efficacy-to-toxicity relationship in multimorbid and elderly patients the degree of renal and hepatic malfunction must be assessed and an effective medication with the least likelihood of toxicity must be chosen. Individual dose-titration is always necessary and prophylaxis for adverse effects is possible. Regular monitoring of effects helps prevent toxicity. Analgesic drugs with new and more specific modes of action are in development. These include analogues of neurotransmitters, immunomodifiers and novel anti-inflammatory agents. The increasing implementation of disease management programmes and information technology for the creation of integrative patient databases should in future allow better characterisation of therapeutic effect and adverse effect profiles of drugs and more specific and individual choices of drugs for patients. This will especially benefit elderly patients and those with organ dysfunction.

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