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Role of Paracetamol in Acute Pain Management

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Abstract

Paracetamol (acetaminophen) has been shown to be an effective analgesic for the treatment of moderate pain where it is chiefly indicated, as shown in placebo-controlled studies in the perioperative setting, and in other acute pain states. In addition, an opioid-sparing effect has been demonstrated. No clinically relevant adverse effects are usually apparent with recommended doses. Paracetamol is an effective component in 'multimodal analgesia' in combination with morphine, weak opioids and nonsteroidal anti-inflammatory drugs (NSAIDs). Although most studies involve the perioperative setting, similar results have been obtained in other acute pain states, such as acute musculoskeletal pain, migraine, etc. In conclusion, paracetamol has a favourable efficacy-tolerability profile and is therefore recommended as a basic, first-line analgesic in acute pain states and as a valuable component in multimodal analgesia.

1. Introduction

The aim in the treatment of acute (postoperative) pain is primarily to alleviate discomfort, but in addition to serve as a rational basis for early rehabilitation and, potentially, to improve outcome. Despite great progress in our understanding of the physiology of acute pain, the drugs and techniques available remain essentially unchanged and only modest improvement in pain relief has been obtained. Thus several surveys continue to emphasise the inadequacies in acute pain treatment.[1] At the same time, government agencies and, more recently, the Joint Commission of Accreditation of Healthcare Organisations have provided guidelines for the treatment of acute pain, underlining the patient's right to adequate assessment and treatment of pain.[2]

The choice of analgesic for acute pain treatment depends on efficacy, side effects, compliance, pharmacokinetics, costs and effects on outcome. Furthermore, it must be emphasised that acute pain cannot be considered as a single entity, as it may vary in characteristics and intensity depending on the type of injury. Accordingly, treatment strategies should be individualised and the choice of analgesic based on the clinical circumstances and the severity of pain, in addition to the patient's co-morbidities and co-medication. Unfortunately, no existing drug can be considered to be ideal on the basis of these criteria. Therefore, the principle of 'multimodal analgesia' or 'balanced analgesia' has been advocated in order to improve analgesia and to reduce side effects by combining different analgesics.[3,4]

Paracetamol is one of the oldest analgesics available and fulfils several of the above criteria, thanks to its virtually non-existent side effects when dosage recommendations are followed, its low cost and good compliance because of the alternative available routes of administration, the lack of interactions and very few contraindications.

This review updates and summarises data on the efficacy of paracetamol (oral and injectable formulations) in the treatment of acute pain, with a primary focus on postoperative pain, and on the role of paracetamol in multimodal analgesia. On the basis of these data, recommendations are provided for the use of paracetamol in acute pain states.

2. Analgesic Efficacy

Analgesic efficacy is often presented as the number of patients needed to treat (NNT) for one patient to achieve at least 50% pain relief compared with placebo or active comparator over a given period.[5,6] Although NNT values are of importance for selection of an analgesic, they should be interpreted with caution.[6] Thus they have often been derived from patients undergoing minor (dental) surgery and these results may not be applicable to major procedures. Also, differences in dosing and administration regimens may limit interpretation. Furthermore, valid estimates often demand data from more than 500 patients,[6] which is not always the case. Finally, the duration of assessment may influence the NNT value. Nevertheless, NNT estimates are an important instrument for assessing the efficacy of analgesics (and other treatment modalities).

2.1 Monotherapy

In various systematic reviews, oral paracetamol is indicated to have an NNT value of around 4 with administration of a single dose of 1 000mg. A dose of 600–650mg has a greater NNT value (5.4 [95% CI 4.2 to 7.4]),[6] whereas values for ibuprofen 400mg vary from 2.7 to 3.1 and those for tramadol 100mg from 4.8 to 5. Table I presents a complete list of analgesics assessed for NNT.[5-12]

In the above-mentioned efficacy analyses, NNT values were assessed in different acute pain settings, predominantly in studies of dental surgical pain.[5-9] However, we cannot be certain whether these findings reflect real differences in efficacy between or within drugs, as there may be specific drug-related differences in sensitivity between different surgical models. Thus, in a qualitative review of direct comparative studies between paracetamol and NSAIDs in various acute pain (postoperative) states, NSAIDs were consistently found to be about 20–30% more efficacious than paracetamol in minor (dental pain) surgery, in line with previous data, whereas there were no substantial differences between the efficacy of NSAIDs and that of paracetamol in major and orthopaedic surgery.[13] This conclusion is supported by an analysis of NNT values for paracetamol and tramadol, where the lowest NNT

Table I. Number needed to treat (NNT) values (95% CI) for paracetamol and other analgesics commonly used to treat postoperative pain: data from systematic reviews of randomised, placebo-controlled studies

	NNT	Reference
Paracetamol 975–1 000mg	4.6 (3.9 to 5.4)	McQuay & Moore[5]
	3.7 (3.3 to 4.3)	McQuay et al.[6]
	3.6 (3.0 to 4.4)	Moore et al.[7]
	4.6 (3.8 to 5.4)	Moore et al.[8]
Ibuprofen 400mg	2.7 (2.5 to 3.0)	McQuay & Moore[5]
	2.7 (2.5 to 3.0)	Collins et al.[10]
Ketorolac 30mg IM	3.4 (2.5 to 4.9)	Smith et al.[11]
Tramadol 100mg	4.8 (3.4 to 8.2)	McQuay & Moore[5]
	4.4 (2.8 to 10)	Edwards et al.[9]
Morphine 10mg IM	2.9 (2.6 to 3.6)	McQuay et al.[12]
Meperidine 100mg IM	2.9 (2.3 to 3.9)	Smith et al.[11]

IM = intramuscular.

values were found with dental surgery pain as compared with other types of postoperative pain.[9] Therefore, interpretation of NNT values should consider the surgical operation for which the data have been collected, and the results may not always be extrapolated to other types of acute pain. In addition, almost all data come from single-dose studies, which differ from the clinical situation, in which repeated dosing is warranted. Presently, the NNT data do not allow conclusions for repeated dosing of paracetamol. Nevertheless, analgesic efficacy of paracetamol has been proven in different acute pain settings in many randomised, placebo-controlled studies (table I, figure 1).[14-22]

A further consideration is that the injectable formulation of paracetamol may be more effective than the equivalent oral dose of paracetamol. Thus preliminary data show that injectable paracetamol has a faster onset of action, is more efficacious and has a longer analgesic effect.[23] There are also studies to suggest that, when used alone, injectable paracetamol has an efficacy similar to that of intravenous ketorolac 30mg or intravenous metamizol 2.5g in major procedures,[17,24] in agreement with other observations comparing paracetamol and NSAIDs in major procedures.[13]

2.2 Combination Therapy

The combination of paracetamol with other analgesics has been assessed in several randomised comparative studies (table II).

2.2.1 Combination Therapy with Oral or Injectable Paracetamol and Opioids

Combination studies have shown that injectable paracetamol has opioid-sparing properties and can reduce the total morphine requirement by 24–46%,[14,21,25,26] leading to better overall patient satisfaction with their analgesic therapy.[21]

Studies using oral paracetamol have also shown an opioid-sparing effect ranging from 20 to 30%.

2.2.2 Combination Therapy with Oral Paracetamol and Weak Opioids

The combination of paracetamol 600mg with codeine had an NNT value between 7.7 and 9.1, compared with paracetamol 600 mg alone.[7,8]

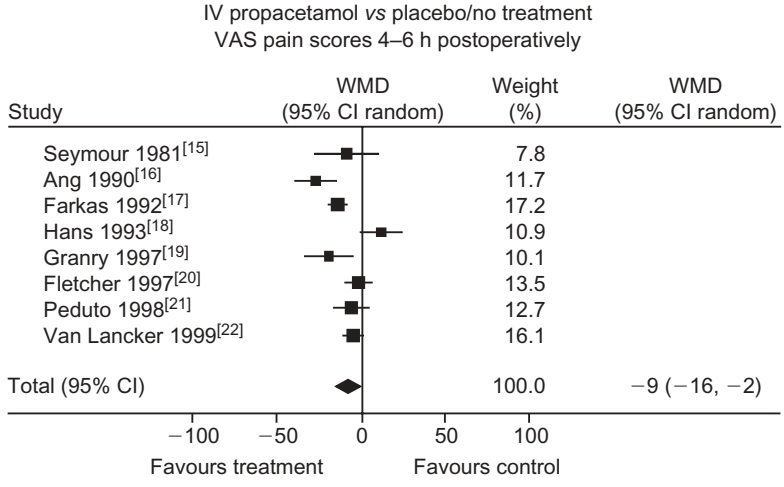

Fig. 1. Weighted mean differences (WMD) and 95% CIs (horizontal lines) in visual analog scale (VAS) scores between parenteral paracetamol groups and placebo groups 4–6 hours after surgery. **Total** = results of pooling all the trials; **Weight** = weight of the individual trial in the analysis, taking into account study size and SD of VAS scores. (Modified with permission from Rømsing J, et al.[14])

Table II. Number needed to treat (NNT) values (95% CI) for paracetamol combined with other analgesics. Data from systematic reviews of randomised studies

	NNT, or effect not assessed in NNT value	Reference
Paracetamol 600/650mg + codeine 60mg vs paracetamol 600/650mg Pain reduction over 4–6 hours	9.1 (5.8 to 24) 7.7 (5.1 to 17)	Moore et al.[7] Moore et al.[8]
Paracetamol 650mg + tramadol 75mg vs placebo Pain reduction over 8 hours	2.9 (2.5 to 3.5)	Edwards et al.[9]
Paracetamol + NSAID vs paracetamol alone	Improved analgesia in six of nine studies	Rømsing et al.[14] Hyllested et al.[13]
Paracetamol + NSAID vs NSAID alone	Improved analgesia in two of six studies	Rømsing et al.[14] Hyllested et al.[13]

Although side effects from the addition of codeine (sedation, nausea, constipation) may be limited according to data from single-dose trials, multiple-dose studies have demonstrated a slightly greater proportion of side effects with the paracetamol–codeine preparations than with paracetamol alone.[27]

The combination of paracetamol (650 or 975mg) with the weak opioid, tramadol (75 or 112.5mg), has been assessed in a systematic review of randomised clinical trials in dental and postoperative pain (table II).[9] Treatment with the combination of paracetamol and tramadol was associated with significantly lower NNT values compared with those for either component alone, and comparable to those for ibuprofen 400mg. However, once again, most of these efficacy data came from studies in dental surgery, which may hinder interpretation and extrapolation of efficacy to other more severe acute pain states. This precaution was supported by the findings of the systematic review,[9] but limited data from major procedures hinder final interpretation. In single-dose studies, adverse effects of sedation and nausea occurred with tramadol alone, but the incidence did not increase with the combination including paracetamol.[9]

2.2.3 Combination Therapy with Oral Paracetamol and NSAIDs

The combination of paracetamol with NSAIDs may also seem rational, because they have different sites of action. Qualitative and quantitative systematic reviews of the combination of paracetamol and NSAIDs compared with paracetamol alone have relatively consistently demonstrated improved analgesia (table II).[13,14] Limited data also suggest that, compared with NSAIDs alone, paracetamol may enhance analgesia when added to an NSAID.[13,14] Further studies are required to allow valid conclusions as to whether a clinically relevant improvement is obtained by combining paracetamol with NSAIDs, compared with monotreatment with NSAIDs. Such studies should be conducted in both minor and major procedures.[9,13] As for adverse effects, these have, to date, not been observed to increase as a result of the combination of paracetamol and NSAIDs but, again, too few scientific data are available to allow final conclusions to be reached. However, it has been common clinical practice for many years to combine these two analgesics, with no reports of increased adverse effects.

A more relevant comparison for multimodal analgesia may be the combination of paracetamol with the new selective cyclo-oxygenase (COX)-2 inhibitors, which may have an improved safety profile compared with conventional NSAIDs,[28] although more data are clearly needed in the acute pain setting. The data so far available with COX-2 inhibitor–paracetamol combinations compared with other combinations do not allow relevant conclusions to be drawn.[29,30]

In conclusion, a combination of paracetamol with other analgesics may improve analgesia, without any apparent increase in adverse effects.

3. Adverse Effects

The choice of analgesic for the treatment of acute pain may often depend on the side-effect profile, including the risk of interactions. This may be of particular importance in surgery, where many patients are at high risk as a result of co-morbidity and concomitant drug therapy.

Side effects of paracetamol in the postoperative setting are probably minimal, because of the favourable safety profile (see paper by Graham et al. in this supplement). However, according to data from randomised controlled studies, the assessment of harm from analgesics used for acute pain treatment is hampered by insufficient data on side effects, except for the most severe ones. Also, in previous trials there has often been insufficient reporting of patient inclusion criteria, exclusion criteria, type of anaesthetic and other concurrent pharmacological treatments used. Despite these strictly scientific inadequacies and criticisms, clinical experience from an extensive use of paracetamol for treatment of acute pain indicates a very low incidence of severe side effects, provided that recommended dosages are followed. In addition, more recent data from well-performed studies with propacetamol (an intravenous prodrug of paracetamol) do not suggest any relevant side effects (see paper by Bannwarth et al. in this supplement).

In summary, therefore, paracetamol is an analgesic with a very favourable safety profile compared with other analgesics, thereby allowing a wider indication, including even high-risk patients.

4. Effects of Paracetamol on Postoperative Outcome

It has been widely assumed that, the better the pain relief, the better the postoperative outcome and rehabilitation after surgery and other acute pain states, both because mobilisation and physiotherapy are made easier and because there is a potential reduction in surgical stress responses and subsequent organ dysfunctions. To date, however, such positive effects on outcome have been very difficult to demonstrate for common analgesics including paracetamol and NSAIDs, possibly because these agents have very limited, if any, effects on surgical stress responses.[31] The potential beneficial outcome effects may therefore be related to the well-documented opioid-sparing effect of paracetamol.[14] Unfortunately, no clinically relevant conclusions can be given at present, because opioid-sparing may not easily translate into an improved outcome,[31] and the anticipated improvements in opioid-related symptoms such as nausea and vomiting, sedation, urinary retention and paralytic ileus have been demonstrated in only about 20% of the studies.[32] The most probable explanation is that many of the opioid-related side effects may also be reinforced by neural reflexes as components of surgical stress (i.e. nausea, vomiting, ileus). Such side effects by the surgical injury *per se* may therefore override the expected positive effects of opioid-sparing. An additional explanation may be that a 30–50% opioid-sparing may not be enough to translate into a positive outcome regarding reduction of opioid-related side effects. As an example, a reduction of morphine use from 24mg to 16mg over 24 hours represents a 33% opioid-sparing effect, but it remains to be demonstrated whether sparing of 8mg of morphine may provide clinical outcome effects. Further studies are therefore required to quantify the clinical consequences of paracetamol-related opioid-sparing, and positive effects may mostly be expected in relatively minor (ambulatory) procedures.

In summary, research into the positive outcome effects of paracetamol and the opioid-sparing effect obtained has so far been limited, and further studies are required. However, one recent study did show that opioid-related adverse events increase both the duration of hospital stay and the total hospital costs; the authors therefore concluded that research into opioid-sparing strategies must be pursued.[33]

5. Effects of Paracetamol in Other Acute Pain States

Although most data on analgesic efficacy and

safety come from surgical procedures, these findings may easily be extrapolated to other acute pain states such as migraine[34] and acute musculoskeletal pain.[35] However, with the exception of low back pain, quantitative systematic reviews of analgesia in other acute pain states are not available.[35]

6. Conclusions and Recommendations

It appears from the available data from clinical, randomised, placebo-controlled studies that paracetamol is an efficacious analgesic, has intermediate potency and is mostly effective in relatively minor to moderate-sized surgical procedures if administered alone. It has also been demonstrated that improved efficacy, without an increase in drug-related side effects, can be obtained by a combination of paracetamol with NSAIDs and weak opioids such as codeine and tramadol; however, more data are needed with the new selective COX-2 inhibitors. Although the available systematic reviews came from surgical studies, the consistent findings may allow similar applications of paracetamol to other acute pain states, such as strains, acute low back pain, headache, etc.

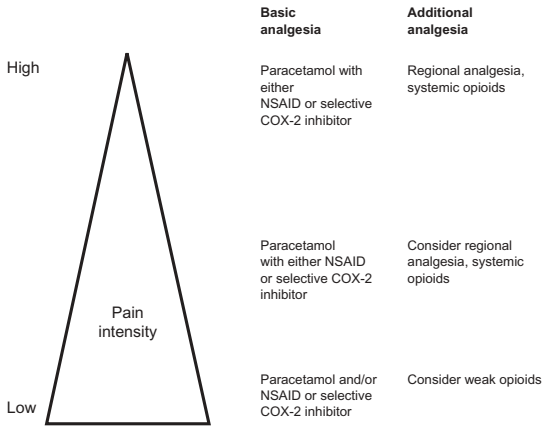

Fig. 2. Suggested algorithm for use of paracetamol in acute postoperative pain states. Note: The recommendation of combined paracetamol and NSAID or COX-2 inhibitor with regional analgesia in moderate-to-severe pain is empirical and not based on data from randomised studies.

These efficacy data, combined with the low cost of paracetamol, the high compliance as a result of the several routes of administration that are available, and a safety profile with virtually no clinically relevant side effects when recommended dosage regimens are followed, suggest that paracetamol should be used as a first-line, basic analgesic. However, additional analgesic treatment with other analgesics may be necessary, depending on the intensity of the acute pain state. Again, paracetamol may be an ideal component for multimodal analgesia in such more severe pain states. Figure 2 shows a guideline proposal for use of paracetamol in acute postoperative pain. Future studies should focus on multimodal analgesia regimens, including paracetamol with three or four (or more) drugs, and in addition should ascertain the safety profile of such multimodal regimens.

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