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Analgesic effect of paracetamol on cancer related pain in concurrent strong opioid therapy. A prospective clinical study

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Abstract

Introduction. In palliative cancer care, when approaching death, swallowing difficulties and the burden of tablet intake frequently makes us reconsider each individual drug prescribed. Through the last two decades the routine of always combining a strong opioid with paracetamol has been widely spread in Sweden. Clinical experience has challenged this routine as many patients seem to manage equally well without paracetamol. To find out whether this might be of clinical importance, we wanted to perform a more systematic registration. *Material and methods.* Thirty-four incurable cancer patients with well controlled pain (NRS <4), treated by specialised palliative home care teams, with ongoing medication with the strong opioid paracetamol combination was recruited to this prospective clinical study. The effect of completely stopping paracetamol medication was evaluated four days later at follow-up. *Results.* At follow-up nine patients (26%) felt more pain compared to when they entered the study, two patients (6%) felt less pain and 23 (68%) felt no difference. When asked about their preference about future paracetamol treatment 18 patients (53%) wanted to stop taking it, six patients (18%) wanted to continue with regular paracetamol medication as before, and ten patients (29%) wanted to take paracetamol as needed. No clinical predictors of paracetamol response could be identified. *Discussion*. The results of this study indicate that a critical evaluation, in every patient, of the subjective additive analgesic effect of paracetamol in concurrent strong opioid therapy is advisable and that stopping paracetamol medication not necessarily implies increased pain. Rather in some patients the cessation of paracetamol medication is experienced as a relief as pain control is maintained with a lesser tablet burden.

In palliative cancer care at the end of life, the prime purpose of all interventions is to optimize quality of life (QoL) [1]. As QoL is a subjective measure [2,3] the autonomous patient is the one with the final say when choosing between two treatment alternatives or deciding whether to continue or stop a specific treatment. As physicians we can only advise the patient to try what we regard as the most efficient treatment. When approaching death these treatment considerations tend to be even more individualized. When approaching death the burden of oral medication is always an issue. Decreased salivation, loss of appetite, and sometimes swallow difficulties add to the need of critical revision of the drug chart. To minimize the burden of numerous tablets it is vital to stop any medication that is not essential to symptom control and to consider other ways of administration of effective oral medications.

In palliative cancer care at the end of life optimal pain treatment is crucial to enable best possible QoL. The WHO analgesic ladder summarizes the recommendations for treatment of cancer related nociceptive pain [4]. Step 3 on the ladder recommends the use of a strong opioid with or without a non-opioid. In Sweden, during the past two decades, the words "or without a non-opioid" has been neglected and paracetamol has been prescribed routinely with strong opioids [5]. As full dose paracetamol, i.e. eight extra tablets of 500 mg per day, sometimes is experienced as a burden to terminally ill cancer patients it is important to critically revise the analgesic effect of the combination (paracetamol+strong opioid) in each patient. Our clinical experience from incurable cancer patients in palliative home care has nurtured our reluctance to routinely prescribe the combination

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in a life-long manner. Numerous patients have stopped paracetamol medication on their own due to terminal swallowing difficulties or tablet burden resulting in surprisingly few pain problems, if any. This prompted us to review the literature and also to perform this study.

There are several studies and reviews exploring the benefits of combining paracetamol and *weak* opioids for post-operative pain and dental pain [6–9]. These conclude that the addition of paracetamol to both codeine, dextropropoxyphene, and tramadol seams to have an extra analgesic effect. Most of the included studies are either single-dose or of short duration. We have found only two randomized controlled studies in the literature [10,11] studying the effect of combining paracetamol with a strong opioid in continuous treatment of cancer related pain. They are almost identical in design and results, but the interpretations diverge. To summarize, the clinical effect of adding paracetamol to the medication of a strong opioid is, at group level, small and many patients do not notice any difference at all. However, to some patients the difference in analgesic effect can be substantial. Further doubt on the benefits of combining paracetamol with strong opioids was recently reported from paediatric oncology [12]. In a prospective evaluation of using the WHO analgesic ladder they found higher pain scores for patients on the combination than for those medicated with strong opioids only. Whether this was a result of or a reason for the different drug regiments was not stated.

The mechanism of action of paracetamol is still not clear. Traditionally it has been regarded as an analgesic with a peripheral action. Its effect on prostaglandins in peripheral tissue is weak and it does not have any anti-inflammatory effect at clinically relevant doses in humans [13]. Recent experimental [14,15] as well as clinical investigations [16] strongly favour the theory that it has a direct action on the central nervous system. Animal studies indicate that the serotonergic 5HT1B receptor is involved [17,18]. If the analgesic action of paracetamol is mediated by receptors located in the central nervous system rather than peripherally, this may explain why the analgesic effect of paracetamol clinically sometimes "drowns" in concurrent strong opioid therapy. To empirically explore whether omitting paracetamol was clinically feasible at all in concurrent strong opioid therapy when treating incurable ill cancer patients in palliative home care, and to get an estimate of the proportion of patients that could benefit from a more individualised prescription of paracetamol, we decided to conduct this clinical trial.

Material and methods

Those considered eligible for our study were incurable cancer patients, medicated with paracetamol (2–4 grams/day) and a concurrent strong opioid, who were being cared for by one of three participating palliative home care teams. Eligible patients should not be imminently dying. Further criteria for selection were that the pain should be well controlled, i.e. NRS (=numeric rating scale) 3 or less on a scale 0 to 10 and that there should have been no change of opioid dose during the last week. Steroid and non steroidal medication should not have been changed during the last fortnight and short term memory should be grossly intact.

At weekly rounds all new patients were assessed and those fulfilling the inclusion criteria were approached. After informed consent basic data was collected and the patients were asked to estimate their present pain intensity on the NRS scale. We recorded the most and least pain experienced through the day and pain at rest and during movement. The patient was then asked to completely stop paracetamol medication immediately. If the pain increased we recommended the participating patients to take an extra dose of a regular strong opioid (1/6 of the 24-hourly dose). If this did not lessen the pain, patients were free to restart paracetamol medication at any time.

Four days later the patients were interviewed. They were asked whether they had restarted paracetamol or not? How the pain intensity had been during the last 24 hours? Whether they had noticed any change in pain intensity compared with the day before starting the study and how they would like to proceed with their paracetamol medication: to stop, to take as needed, or to take the regular dose?

Converting other strong opioids to oral morphine equivalents was calculated as follows: 10 mg of OxyContin = 20 mg of morphine, 25 μg/h of transdermal phentanyl = 60 mg of morphine/24 hours, 10 mg of ketobemidone = 10 mg of morphine.

Main research question was how large a proportion of patients would do as well without paracetamol medication? The second question was if any pattern could be noticed predicting paracetamol response?

Statistics

Comparisons of pain measurements before and after the study period were performed using Wilcoxon's signed rank test. Kruskal-Wallis and χ^2-analyses were used to compare paracetamol responders with non-responders.

Results

During the six month study period 187 patients were admitted to the three participating palliative home care teams. The median survival time (admission to death) of patients treated by these palliative teams were 1.5–2 months. Of these 53 patients were fulfilling the inclusion criteria. Three of the approached patients denied participation and 16 had either already quit taking paracetamol or used a dose less than 2 g per day. Accordingly, 34 patients were both eligible and willing to participate in the study and also managed to complete the four-day study period.

Their median age was 68 (range 48–88 years) and 18 were males (53%) and 16 females. Diagnoses were cancer of the prostate (n = 9), pancreas (n = 5), breast (n = 5), gynaecological sphere (n = 4), bladder (n = 3), lung (n = 2), colorectal (n = 2), and miscellaneous (n = 4). Pain was classified as nociceptive in 19 patients (56%), neuropathic in 5 (15%) and mixed in 10 (29%). The median dose of strong opioids was 90 mg oral morphine equivalents per 24 hour (range 20–880 mg). Medium slow release morphine was used by 18 (53%), slow release oxycodone 7 (21%), fentanyl patch 4, slow release ketobemidon 3, and immediate release morphine 2. Adjuvant analgesics were used as follows: 10 patients used NSAIDs, 18 patients corticosteroids (17 betamethasone), 5 patients antineuropathic drugs (4 amitriptyline, 1 gabapentin), and 4 bisphosphonates.

The average pain measure was 0.7 at rest, 1.9 in movement, 0.5 minimum last 24 hours, 3.1 maximum last 24 hours on a 0–10 numerical rating scale (0 = pain free). At follow-up after 4 days these values had not changed significantly (p = 0.63–0.95).

At follow-up day 4, when comparing the last 24-hour period with the pain situation before study start, 9 patients (26%) felt more pain, 2 patients (6%) felt less pain and 23 (68%) felt no difference. When asked about their preference about future paracetamol treatment 18 patients (53%) wanted to quit, 6 patients (18%) wanted to continue with regular paracetamol medication as before, and 10 patients (29%) wanted to take paracetamol as needed. The indications for paracetamol as needed were fever (n = 4), head ache (n = 3), pains in shoulders or back (n = 4), unspecified sense of unease (n = 3), feeling of security (n = 2). More than one indication was noted for some patients.

We found no significant differences in age, diagnosis, baseline pain, pain type, and opioid consumption between those who got more pain and those who did not notice any difference (Table I). When comparing both pain levels (more, less or no difference) and patient's preferences (quit, continue or as needed) with whether they used different adjuvant analgesics or not there were no significant differences found between any of the groups (Table II). The only trend noticed was that patients with steroid medication tended to be less effected by the cessation of paracetamol (3 of 18 patients got more pain with steroids compared with 6 of 16 without; p = 0.08). Only 4 patients used bisphosphonates which makes statistical calculations invalid.

Discussion

As only 6 patients (18%) wanted to continue with their regular paracetamol medication, a less dogmatic approach towards mandatory paracetamol medication in concurrent strong opioid therapy might be suggested. As available experimental data argues for a central analgesic effect of paracetamol, this may provide an understandable explanation why paracetamol medication sometimes does not add further analgesia to a concurrent medication with strong opioids. The question whether an increased dose of the strong opioid would achieve the same analgesic effect as a maintained paracetamol medication was not evaluated in this study, but would be an interesting research question to address in future studies.

This study supports the hypothesis that a fair number of patients on strong opioids do as well without paracetamol. In this study we could not find any significant prognostic factors to help predict which patients that would respond or not to paracetamol in concurrent strong opioid therapy. Thus,

Table I. Patient characteristics in relation to patient's pain response and choice regarding paracetamol medication after 4 days period without paracetamol. Median values and range. (Kruskal-Wallis test and χ^2-analysis).

	Median (range)	Pain response (more, less, no diff.)	Choice (quit, go on, prn*)
Age	68 (48–88)	n.s. (p = 0.81)	n.s. (p = 0.80)
Baseline pain (NRS 0–10)	0 (0–3)	n.s. (p = 0.28)	n.s. (p = 0.64)
Morphine dose/24 h (mg)	90 (20–880)	n.s. (p = 0.99)	n.s. (p = 0.79)
Diagnosis (GI, breast, uro, lung, misc.)		n.s. (p = 0.90)	n.s. (p = 0.34)
Pain type (nociceptive, neuropathic, mixed)		n.s. (p = 0.92)	n.s. (p = 0.91)

* prn = as required.

Table II. Ongoing adjuvant analgesic medication in relation to patient's pain response and choice regarding paracetamol medication after 4 days period without paracetamol. (χ^2-analysis).

	Pain response (more, less, no diff.)	Choice (quit, go on, prn*)
NSAID (yes/no)	n.s. (p = 0.51)	n.s. (p = 0.66)
Steroids (yes/no)	n.s. (p = 0.08)	n.s. (p = 0.17)
Antineuropathic drugs (yes/no)	n.s. (p = 0.80)	n.s. (p = 0.86)
Bisphosphonates (yes/no)	n.s. (p = 0.09)	n.s (p = 0.21)

*prn = as required.

an individualized test period in which the patient completely stops taking paracetamol may be a good way to identify those patients who do benefit from the paracetamol medication. Noticeably a substantial number of patients approached by the study group had already stopped taking paracetamol on their own initiative. These decisions may partly have been encouraged by the general attitude of the staff involved who are relaxed about allowing the patients to be involved in decisions regarding their care. Accordingly the proportion of incurable cancer patients wanting to continue with continuous paracetamol medication in real life may be less than estimated in this study. On the other hand, we should not forget that 16 patients (47%) in this study wanted to continue taking paracetamol one way or another. Besides the 6 patients who wanted to continue with regular paracetamol, 10 patients appreciated the opportunity to take paracetamol as needed. Being a pharmaceutical substance with few side effects in clinical doses and a drug that most lay men are familiar with, we should definitely not exclude paracetamol from the therapeutic repertoire.

Even though there is plentiful evidence of paracetamol's additional effects to weak opioids in postoperative pain and dental pain these data may not necessarily be extrapolated into the palliative setting with continuous treatment of incurably ill cancer patients with a combination of paracetamol and a strong opioid. In a recent meta-analysis of the use of NSAIDs or paracetamol, alone or combined with opioids, in cancer related pain the authors conclude that their findings do not substantiate the WHO recommendations of adding a weak opioid to the patient's regimen [19]. The two existing randomized studies of the combination of paracetamol and strong opioids [10,11] diverge in their conclusion concerning paracetamol's additive effect on group level. Nevertheless, there is no doubt that some patients experience a clinically important additive analgesic effect of the combination. The question is whether this implies that all patients treated with strong opioids should be treated with paracetamol in a mandatory way even through the terminal phase. The present study rather strengthens the more individualized approach generally preferred within palliative medicine. As in all other instances an individual assessment of the therapeutic effect of each drug prescribed is recommended.

The major limitation of this study is the small number of participating patients. This hampers any attempts to identify specific characteristics of "paracetamol responders" and to draw firm conclusions on paracetamol's analgesic effect in concurrent strong opioid therapy. In spite of the relatively small number of included patients, we still got valuable information in the area of the main research question. The results pointing at that maybe as many as half of the patients previously treated with the combination (paracetamol + strong opioid) can maintain equally good pain control without paracetamol stimulates us to adopt a more individualized treatment approach. It also supports the clinical feasibility of a brief attempt without paracetamol letting the individual response guide decisions regarding future prescription of paracetamol. Any patient that maintains equally good pain control without paracetamol should be offered the benefit of a decreased tablet burden. Any patient with swallowing difficulties but a need for paracetamol medication should be offered the most suitable preparation of paracetamol (suppository, mixture, intravenous).

Some may argue that the patients in this study were too heterogeneous as far as pain types, co-analgesic medication etc. Our impression has been that the patients in this study represent a cross section of incurable cancer patient admitted to the participating three palliative home care teams, where the median patient survives a couple of months after admission. Nevertheless, the results has to be interpreted with care as selection bias was present as the most pain stricken patients were excluded (NRS > 3) and as patients admitted to a palliative home care team probably are more polysymtomatic compared to those not referred.

How should the results of this study influence our daily practise? Until these findings are verified by others, we will not substantially change our previous routines when starting up on strong opioids. We still offer full dose paracetamol initially. Once the pain is well controlled (NRS < 4) we ask the patient to try going without paracetamol for a couple of days– those who do not feel any different then benefit to the extent that they need to take fewer pills per day. Those who do feel a difference go back on their regular dose of paracetamol. Hopefully future studies will either provide selection criteria to enable us to target "paracetamol responders" or to encourage us to achieve the same analgesic effect with an

increased opioid dose when the burden of numerous tablets is the issue.

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