PAIN

Median effective dose (ED$_{50}$) of paracetamol and morphine for postoperative pain: a study of interaction

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**Editor’s key points**

- This study aimed at defining the median effective analgesic dose (ED$_{50}$) of paracetamol, morphine, and the combination of both.
- The ED$_{50}$s of paracetamol, morphine, and the combination were 2.1 g, 5 mg, and 1.3 g and 2.7 mg, respectively.
- The isobolographic analysis showed that paracetamol and morphine interact in an additive way.
- The ED$_{50}$ of paracetamol is too high and should not be given alone to treat postoperative pain.

**Background.** Paracetamol is widely used to treat postoperative pain and is well known for its morphine-sparing effect. Therefore, the effect of morphine–paracetamol combination can be synergistic, additive, or infra-additive. The primary aim of our study is to define the median effective analgesic doses (ED$_{50}$s) of paracetamol, morphine, and the combination of both. Also, the nature of the interaction for postoperative pain after moderately painful surgery using an up-and-down method and isobolographic analysis was determined.

**Methods.** Ninety patients, undergoing moderately painful surgery, were included in one of the three groups. Determination of the median ED$_{50}$S was performed by the Dixon and Mood up-and-down method. Initial doses were 1.5 g and 5 mg, with dose adjustment intervals of 0.5 g and 1 mg, in the paracetamol and morphine groups, respectively. The initial doses of paracetamol and morphine were 1.5 g and 3 mg, in the paracetamol–morphine combination group with dose adjustment intervals of 0.25 g for paracetamol and 0.5 mg for morphine. Analgesic efficacy was defined as a reduction to or $\leq$ 3 on a 0–10 numeric rating scale, 45 min after the beginning of drug administration. Isobolographic analysis was used to define the nature of their interaction.

**Results.** The median ED$_{50}$s of paracetamol and morphine were 2.1 g and 5 mg, respectively. The median ED$_{50}$ of the combination was 1.3 g for paracetamol and 2.7 mg for morphine.

**Conclusions.** Our study showed that the combination of the paracetamol and morphine produces an additive analgesic effect.

**Clinical trial registration.** NCT01366313.

**Keywords:** median effective dose; morphine; pain; paracetamol; postoperative

Accepted for publication: 20 June 2013

Paracetamol (acetaminophen) is often used alone or in combination with traditional analgesics to treat mild and moderate postoperative pain. Its primary site of action remains unclear. Several studies postulated that paracetamol acts centrally in the brain rather than peripherally (at the nerve endings). The central effect is assumed to be mediated by activation of the descending serotonergic pathways through the inhibition of cyclooxygenase (COX). Recent findings suggest that it is highly selective for COX-2 and possibly for COX-3 and COX-4. Other central mechanisms suggested include the inhibition of the l-arginine-nitric oxide (NO) pathways via N-methyl-D-aspartate (NMDA) and substance P or the effect of the active paracetamol metabolite (p-aminophenol) over cannabinoid receptors. Its peripheral effect can be explained by a reduction in prostacyclin synthesis.

Morphine binds to the opioid receptors of neurons in the brain, spinal cord, and the gastrointestinal tract. These receptors mediate the analgesics and side-effects. It has been shown that the analgesic effect of morphine is mediated through a direct inhibition of the ascending transmission from the dorsal horn of the spinal cord and from the interaction with opioid receptors. This results in hyperpolarization of...
Methods

Research and Ethical Committee approval were obtained from Procare Riaya Hospital (ClinicalTrials.gov identifier: NCT01366313). Written informed consent was obtained from 90 patients (ASA physical status I or II) who enrolled in the study. Patients were undergoing surgery that was considered moderately painful (such as inguinal hernia, appendectomy, varicocelectomy, anal fistulotomy, breast lump, or minor orthopaedic surgery). Exclusion criteria were: (i) any contraindication to the use of paracetamol or morphine, (ii) pregnancy, (iii) age younger than 18 yr, (iv) weight <65 kg, (v) intraoperative use of regional anaesthesia, (vi) intraoperative pain management, consists of the administration of two analgesic agents that act via different mechanisms through a single or multiple routes to provide superior analgesic efficacy with equivalent or reduced adverse effects. Several studies showed that combining morphine with certain analgesics could produce different effects. Synergy between morphine and non-steroidal anti-inflammatory drugs (NSAIDs) has been demonstrated in animals, while interaction between morphine and either nefopam or tramadol has been shown to be infra-additive. On the other hand, clinical studies have described a significant morphine-sparing effect with paracetamol. However, it is difficult to recognize the nature of the interaction since these studies used fixed doses of paracetamol.

The ED$_{50}$ of postoperative paracetamol alone or in combination with morphine has not been defined. In addition, there is no study describing the nature of the interaction between paracetamol and morphine. Accordingly, the aim of the current study was to define the median effective analgesic doses (ED$_{50}$s) of paracetamol, morphine, and their combination and to evaluate the nature of their interaction using the Dixon and Mood up-and-down method and isobolographic analysis.

The median effective dose (ED$_{50}$) of paracetamol and morphine

inter-neurones and depression of the release of transmitters associated with pain transmission. In addition, morphine can interact with the opioid receptors located in the supra-spinal structures and activate the supra-spinal system.

Multimodal (or balanced) analgesia, used in acute postoperative pain management, consists of the administration of two analgesic agents that act via different mechanisms through a single or multiple routes to provide superior analgesic efficacy with equivalent or reduced adverse effects. Several studies showed that combining morphine with certain analgesics could produce different effects. Synergy between morphine and non-steroidal anti-inflammatory drugs (NSAIDs) has been demonstrated in animals, while interaction between morphine and either nefopam or tramadol has been shown to be infra-additive. On the other hand, clinical studies have described a significant morphine-sparing effect with paracetamol. However, it is difficult to recognize the nature of the interaction since these studies used fixed doses of paracetamol.

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Methods

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In the operating theatre, routine monitoring was used and a standard BIS$^\text{®}$ monitor sensor (BIS sensor$^\text{®}$; Aspect Medical Systems Inc., Norwood, MA, USA) was placed on the forehead before induction of general anaesthesia in all patients. The patient received i.v. midazolam (2–3 mg), glycopyrrolate (0.2 mg), and pre-oxygenation at a rate of 10 litre min$^{-1}$ through a semi-closed circle absorber system. Once maximal pre-oxygenation was achieved (end-tidal oxygen >90%), general anaesthesia was performed using propofol (2 mg kg$^{-1}$) and cisatracurium (0.2 mg kg$^{-1}$). A single dose of fentanyl (2 µg kg$^{-1}$) was administered before the surgical incision. Tracheal intubation was performed using a 7.0–7.5 (ID) tube. Mechanical ventilation was started to maintain normocapnia during the operation. Anaesthesia was maintained by an infusion of propofol (50–150 µg kg$^{-1}$ min$^{-1}$) and sevoflurane (0.5–2.5%) in oxygen/air mixture to maintain haemodynamic variation within 25% of the preoperative value and BIS score between 40% and 50%.

Immediately after arriving in the PACU, the pain intensity was assessed using NRS. Thereafter, the pain assessment was performed every 5 min or when the patient complained. As soon as the pain score reached >3/10 (defined as ‘T$_0$’), the patients received analgesia as defined by the protocol after being randomized prospectively to one of the three groups using a computer-generated table and concealed envelopes. Blinding was ensured using blinded syringes and bags freshly prepared by an anaesthetist not involved in the study. Pain assessment was done by an investigator not aware of the drugs given.

Morphine (Morphine sulfate$^\text{®}$; 10 mg ml$^{-1}$; Fresenius PF, South Africa) was given as a bolus (diluted to 1 mg ml$^{-1}$) and paracetamol (Perfalgan$^\text{®}$; 1 g; 100 ml; Bristol-Myers Squibb, Anagni, Italy) was given as a slow infusion (diluted in 250 ml of saline solution when needed). At T$_0$, patients in the paracetamol group (Group P) received paracetamol in a 250 ml bag as a continuous i.v. saline infusion over 15 min and 10 ml saline i.v. as a bolus. Patients in the morphine group (Group M) received morphine i.v. as a bolus in a 10 ml syringe and saline in a 250 ml bag as a continuous i.v. infusion over 15 min. Patients in the paracetamol–morphine group (Group P + M) received paracetamol in a 250 ml bag as a continuous i.v. infusion over 15 min and morphine i.v. as a bolus in a 10 ml syringe. The dose of paracetamol, morphine, or both received by a particular patient was determined by the response of the previous patient within the same group, using an up-and-down sequential allocation technique. In Group P, the first patient received 1.5 g and the dose adjustment interval was 0.5 g with a maximum dose of 2.5 g. In Group M, the first patient received 5 mg. The dose adjustment interval was 1 mg. In Group P + M, the first patient received paracetamol 1.5 g and 3 mg morphine. The dose adjustment interval was 0.25 g for paracetamol and 0.5 mg for morphine. The efficacy of the drug was assessed using the NRS, 45 min after drug administration. Two outcomes were considered:

- Effective: NRS of 3 or lower out of 10 at T$_{45}$. A result value of reduction: 0.5 g paracetamol in Group P; 1 mg morphine in Group M, and 0.25 g paracetamol; and 0.5 mg morphine in Group P + M, for the next patient.
- Ineffective: NRS of >3 out of 10 at T$_{45}$. A result value of increase with the same intervals as above for the next patient.

At 45 min, participants who reported ineffective analgesia were given rescue analgesia and morphine titration was started according to our PACU protocol. Furthermore, the first 24 h of postoperative analgesia protocol did not include any additional paracetamol doses.
In addition to NRS measurement, heart rate, arterial pressure, oxygen saturation, measured by pulse oximetry ($S_{pO_2}$), and adverse effects of paracetamol (e.g. skin rash, malaise, decreased arterial pressure) and the adverse effects of morphine: urinary retention, nausea, vomiting, pruritus, dizziness, sedation (using a simplified four-point scale, according to our hospital policy, where 0, patient awake, 1, respond only to verbal stimuli, 2, respond only to physical stimulation, 3, not arousable), thoracic rigidity (defined by difficulty in breathing normally on visual observation, and $S_{pO_2} < 90\%$) were collected at 15, 30, 45, and 60 min after the beginning of the infusion and every 30 min after, until discharge from the PACU.

**Statistical analysis**

The number of subjects needed according to the method of Dixon and Mood and to the recommendations of the National Institute of Environmental Health Sciences was calculated.\(^{21, 22}\) The theoretical number of patients/group was increased to 30 because the starting point may have been far from the ED\(_{50}\).\(^{9 - 14}\) We first calculated the median and 95% confidence interval (CI) ED\(_{50}\), the analgesic efficacy in 50% of patients, for paracetamol, morphine and the combination of paracetamol and morphine using the Dixon and Mood up-and-down technique.\(^{21}\) Briefly, a first dose is given to the first patient and the next dose is given according to the following rule: if the subject responds positively (NRS ≤ 3), the dose is decreased one step for the next subject, and conversely, if the subject responds negatively (NRS > 3), the dose is increased one step.

Because of the potential toxicity of paracetamol, we limited the maximum dosing to 2.5 g. As some patients experienced insufficient analgesia with 2.5 g of paracetamol (failure), we calculated the median value considering the higher of the ED\(_{50}\) calculated based on successes and on failures and by considering the wider of two CIs as follows: (i) a first boundary was calculated based on the observed success; (ii) the second boundary was calculated by setting a dose increment of 0.5 to each failure above 2 g, then considering the worst possible case scenario. For example, the next dose to a failed 2.5 g dose was considered as 3 g, followed by a 3.5 g dose, until success was obtained. All these doses were considered as failure. We then used an isobolographic representation to determine the interaction between morphine and paracetamol.\(^{21}\) Isobolographic analysis is a graphical method that allows the determination if the two drugs used in combination are additive, infra-additive, or synergistic on the graph, the line joining the ED\(_{50}\) of each drug determines additivity. Ninety-five per cent confidence contours joining the 95% CIs of each axis of the isobologram are also drawn. The association of the two drugs is considered additive if these contours overlap, and synergistic or infra-additive otherwise.

The three groups were compared for patient characteristic data using the $\chi^2$ test or analysis of variance as appropriate. The occurrence of adverse events or side-effects was compared between groups using the $\chi^2$ test (with the Bonferroni correction). ED\(_{50}\)S were presented with their 95% CIs.

**Results**

All patients recruited completed the study. The patient characteristic data (age, sex ratio, body weight, type, and duration of surgery) of the three groups were similar (Table 1). The ED\(_{50}\) of morphine was 5 (3.5 – 6.5) mg (Fig. 1). The ED\(_{50}\) of paracetamol was 2.1 (1.7 – 2.7) g. The two ED\(_{50}\)S (95% CI) of the combination were 2.7 (2.2 – 3.2) mg for morphine and 1.35 (1.1 – 1.6) g for paracetamol. The association was additive (Fig. 2). The study did not show any significant difference between the three groups regarding the side-effects, except for a dry mouth that was observed more frequently in the morphine group. Nausea and vomiting were observed in two patients in Group M and four patients in Group P + M. One patient experienced respiratory depression in Group M and was managed easily and appropriately.

**Discussion**

The current investigation is the first that defines the ED\(_{50}\) of paracetamol alone and in combination with morphine to treat postoperative pain. The median effective analgesic dose of paracetamol was 2.1 g, whereas morphine had an ED\(_{50}\) of 5 mg and paracetamol–morphine combination ED\(_{50}\) was found to be 1.3 g and 2.7 mg, respectively. Our isobolographic analysis demonstrated that paracetamol and morphine are additive when administered in combination.

The limited dose of paracetamol was due to its toxicity. We were obliged to give no more than 2.5 g. Thus, we modified the up-and-down technique that led to an estimate of ED\(_{50}\) bounded by two limits. The upper limit was calculated considering the worse-case scenario (all doses were considered unsuccessful until the first 2.5 g effective dose).

The onset time of i.v. paracetamol and morphine has been questioned; however, it has been shown that morphine and i.v. paracetamol have a similar delayed onset time to peak effect.\(^{23, 24}\) The hydrophobic nature of both molecules may explain why the maximum effect occurs 30 – 60 min after injection. Consequently, we made the choice of 45 min as the testing interval time. On the other hand, while paracetamol is less potent than morphine for postoperative pain, this does not imply that there is a ceiling effect as the endpoint is a reduction in NRS ≤ 3 (as shown in our study). Thus, both paracetamol and morphine showed a similar full effect (both drugs are able to reduce the pain score of NRS < 3).

Previous studies have shown that the ED\(_{50}\) of morphine is ~ 5 mg,\(^{19, 20}\) which is consistent with our findings. A dose of 1 g paracetamol has been recommended for postoperative acute pain management. It has been shown to be effective in reducing acute pain, delaying the time for rescue analgesia and lowering the analgesics’ consumption in the 4–6 h post-surgery.\(^{25, 26}\) Also, it has been demonstrated that the analgesic efficacy of higher doses, 2 and 3 g as a starting dose of i.v. paracetamol, were superior to the recommended dose of 1 g.\(^{27, 28}\) Our study found that the ED\(_{50}\) of paracetamol was 2.1 g, which is higher than the 1 g recommended dose for postoperative moderately painful surgery. However, we do not recommend this ED\(_{50}\) as clinical dose; however, it is reported for
comparison with morphine in the attempt to draw an isobolo-
graphic analysis. Based on our observations, we have to con-
clude that paracetamol should not be given alone to ensure
postoperative analgesia in most patients. Indeed, the values
given here are ED50s, and the ED95 are therefore much higher.

Many studies showed that combining paracetamol with
opioid analgesia in postoperative pain management results
in improvement of analgesia with significant opioid-sparing
effect. A meta-analysis of seven prospective studies included
265 patients of patient-controlled analgesia (PCA) morphine
plus acetaminophen, and 226 patients with PCA morphine
alone revealed a morphine-sparing effect of 20% during the
first 24 h after operation.29 Another report showed more sig-
nificant sparing effect, up to 40%.30 These studies used para-
cetamol with fixed doses, and since the sparing effect does
not mean necessarily synergy, it was difficult to determine
the nature of the interaction of combining paracetamol and
morphine. The current investigation showed that the combin-
ation of paracetamol and morphine was additive. Additivity

<table>
<thead>
<tr>
<th>Group</th>
<th>Paracetamol</th>
<th>Morphine</th>
<th>Paracetamol + morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>35 (18–57)</td>
<td>34 (21–56)</td>
<td>35 (24–54)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76 (7) (65–90)</td>
<td>78 (9) (65–90)</td>
<td>78 (10) (65–95)</td>
</tr>
<tr>
<td>Gender (F/M)</td>
<td>14/16</td>
<td>14/16</td>
<td>14/16</td>
</tr>
<tr>
<td>Surgery types</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General surgery (abdominal, rectal, and chest)</td>
<td>20 (67%)</td>
<td>14 (47%)</td>
<td>17 (57%)</td>
</tr>
<tr>
<td>Urogenital</td>
<td>2 (7%)</td>
<td>4 (13%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Gynaecology</td>
<td>4 (13%)</td>
<td>2 (7%)</td>
<td>3 (10%)</td>
</tr>
<tr>
<td>Orthopaedic</td>
<td>6 (20%)</td>
<td>4 (13%)</td>
<td>10 (33%)</td>
</tr>
<tr>
<td>Ear–nose–throat</td>
<td>1 (3%)</td>
<td>0 (0%)</td>
<td>2 (7%)</td>
</tr>
</tbody>
</table>

Fig 2 Isobolographic representation of the combination of morphine and paracetamol. On each axis are represented the ED50s and 95% CIs for the corresponding drug. There are two ED50s for paracetamol corresponding to the lower and upper (worse possibility) boundaries (see the Methods section). The thick lines (dotted for the line joining the morphine ED50 and the upper paracetamol ED50 and solid for the line joining the morphine ED50 and the lower paracetamol ED50) are the lines of additivity. The dashed thin lines are the global 95% confidence boundaries. Clearly, the combination of morphine and paracetamol are at best additive.
was observed previously when pro-paracetamol (the pro-drug of paracetamol) was associated with morphine in an animal study.\textsuperscript{31} However, our study is the first that calculated the ED\textsubscript{50}s of paracetamol, morphine, and their combination and evaluated the nature of their combination.

The main advantage of the additive interaction is to decrease the untoward side-effect for both drugs when used in combination. Therefore, combining paracetamol with morphine is expected to decrease the well-known morphine side-effects. Several studies have failed to show a reduction in opioid-related adverse effects when combining morphine and paracetamol. Similarly, our study did not show any significant difference between the three groups, except for the dry mouth that was observed more frequently in the morphine group. However, as our assessment was only limited to recovery room period, after analgesics administration, a significant reduction in side-effect cannot be excluded after PACU discharge. It is possible that using our well-defined ED\textsubscript{50}s of paracetamol in combination with morphine may decrease such side-effects. Additional studies are needed to test this hypothesis. In contrast, Marret and colleagues\textsuperscript{28} showed in their meta-analysis that combining NSAIDs with morphine PCA reduced postoperative nausea, vomiting, and sedation by 30\% approximately.

In our study, we limited the maximum dose of paracetamol to 2.5 g as an initial loading dose. However, the optimal maximum safe daily dose is not well defined. It was postulated to 2.5 g as an initial loading dose. However, the optimal

\[ \text{NSAIDs with morphine PCA reduced postoperative nausea,}\]

and the ED\textsubscript{95} are therefore much higher.

In our study, we limited the maximum dose of paracetamol to 2.5 g as an initial loading dose. However, the optimal maximum safe daily dose is not well defined. It was postulated to 2.5 g as an initial loading dose. Hence, previous studies used higher doses than the one recommended without significant adverse effect. Silvanto and colleagues\textsuperscript{28} studied the effect and safety of paracetamol by using 3 g as starting dose for postoperative analgesia. Only one patient out of 107 patients showed transient liver enzymes elevation. However, in our study, we did not monitor the level of liver enzymes; however, our patients did not experience any clinical evidence of hepatotoxicity. Regarding our calculated value of ED\textsubscript{50}, our study would recommend that paracetamol should not be given alone to ensure postoperative analgesia. Indeed, the values given here are ED\textsubscript{50}s, and the ED\textsubscript{95} are therefore much higher.

In conclusion, the current study showed that the median ED\textsubscript{50}s of paracetamol and morphine were 2.1 g and 5 mg, respectively. The median ED\textsubscript{50} of the combination was 1.3 g for paracetamol and 2.7 mg for morphine. The isobolographic analysis showed that the nature of interaction of paracetamol combined with morphine was additive.

**Authors’ contributions**

A.Z.: This author helped to design and conduct the study, analyse the data, and write the manuscript and he is the author primarily responsible for the study. J.X.M.: This author helped to design the study, analyse the data, and was responsible for the statistics section. M.A.A.: This author helped to conduct the study. H.M.: This author helped to design and write the manuscript. TH.G.: This author helped to design and conduct the study. A.S.: This author helped to conduct the study.

**Acknowledgements**

The authors would like to thank Dr Kamal Abdulkhalek, MD, FRCP (Assistant Professor, Chair, Department of Internal Medicine) and Mrs Tessy Sibi, CRNA for their skilled technical assistance.

**Declaration of interest**

None declared.

**Funding**

Only institutional funding supported this work.

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Handling editor: M. M. R. F. Struys