EJP
European Journal of Pain

ORIGINAL ARTICLE

Analgesic interaction between ondansetron and acetaminophen after tonsillectomy in children: The Paratron randomized, controlled trial

L. Ramirez[1], J. Cros[1], B. Marin[2], P. Boulogne[1], A. Bergeron[2], G.E. de Lafont[2], F. Renon-Carron[3], M-A. de Vinzelles[3], V. Guigonis[4], N. Nathan[1], P. Beaulieu[1]

1 Department of Anaesthesia, CHU Limoges, France
2 Unité Fonctionnelle de Recherche Clinique et de Biostatistique, CHU Limoges, France
3 Pharmacy and Clinical Trial Unit, CHU Limoges, France
4 Department of Paediatrics, CHU Limoges, France

Correspondence
Pierre Beaulieu
E-mail: pierre.beaulieu@umontreal.ca

Funding sources
This work was supported by the CHU de Limoges, France.

Conflicts of interest
None declared.

Accepted for publication
7 July 2014

doi:10.1002/ejp.587

Abstract

Background: The mechanism of action of acetaminophen remains unclear. One hypothesis involves an interaction with the serotoninergic system. Antagonists to serotonin $(5\text{-HT})_3$ receptors (setrons) have antiemetic properties. Therefore, co-administration of acetaminophen and a setron could lead to a decrease or a loss of acetaminophen analgesic effects. The aim of this study was to demonstrate such an interaction.
Methods: *Paratron* is a prospective, randomized, controlled, double-blind, parallel group trial. All children aged 2–7 years ($n = 69$) scheduled for a tonsillectomy ± adenoidectomy received intraoperative acetaminophen with ondansetron or droperidol. Pain scores [Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)], morphine consumption and the incidence of post-operative nausea and vomiting (PONV) were measured for 24 h following surgery.
Results: Pain scores were not different at all times between the groups but median morphine consumption (μg) in recovery was 322.5 [interquartile range (IQR) 0.0–500.0] and 0 (IQR 0-0) in the ondansetron ($n = 35$) and droperidol ($n = 34$) groups, respectively ($p = 0.004$). The percentages of patients who received morphine titration were 57.1% and 20.6% in the ondansetron and droperidol groups, respectively ($p = 0.008$). No significant difference was found for PONV.
Conclusions: An interaction between acetaminophen and ondansetron is suggested, with children receiving three times more morphine during pain titration in the recovery room. More studies are necessary to evaluate whether this finding is clinically relevant enough to preclude the simultaneous perioperative administration of both drugs in the future.

1. Introduction

Tonsillectomy is one of the most common surgical procedures; e.g., in the United States, more than 530,000 operations are performed annually in children younger than 15 years (Baugh et al., 2011). The main causes of morbidity after tonsillectomy are oropharyngeal pain and post-operative nausea and vomiting (PONV) (Hanasono et al., 2004), the later occurring in more than 70% of children who do not receive prophylactic antiemetics (Litman et al., 1994; Ved et al., 1996). Consequently, several national guidelines have recommended the systematic use of acetaminophen and dexamethasone for the treatment

What's already known about this topic?
- Co-administration of acetaminophen and a setron leads to a loss of acetaminophen analgesic effects.
- This analgesic interaction has been reported in animal and human volunteer studies.

What does this study add?
- This human report shows that the administration of acetaminophen with a setron is associated with less analgesic effect than the administration of acetaminophen with another antiemetic.

of pain and the prevention of PONV. The use of a setron [a selective serotonin $(5\text{-HT})_3$ receptor antagonist] together with steroids has also been advocated for the prevention of nausea and vomiting (Société Française d'Anesthésie-Réanimation, 2005).

The mechanism of action of acetaminophen has not been fully elucidated, but several systems have been shown to be involved, including the serotoninergic, cyclo-oxygenase, opioid, vanilloid and endocannabinoid systems (Mallet and Eschalier, 2010). The antinociceptive activity of acetaminophen involves a reinforcement of the activity of the serotoninergic descending pathways through spinal release of serotonin that stimulates the $5\text{-HT}_{3/4}$, 5-HT_{1A} and/or 5-HT_7 receptors to inhibit the transmission of noxious stimuli (Mallet et al., 2008; Dogrul et al., 2012). Therefore, co-administration of acetaminophen with a setron could theoretically lead to a decrease or a loss of the analgesic properties of acetaminophen through a pharmacodynamic interaction at serotonin receptors (Tjolsen et al., 1991; Pelissier et al., 1996). Indeed, interactions between setrons and acetaminophen have been reported in different animal studies (Tjolsen et al., 1991; Alloui et al., 1996; Pelissier et al., 1996; Bonnefont et al., 2005; Girard et al., 2009) and in human volunteers (Pickering et al., 2006; Bandschapp et al., 2011), although this interaction has not been demonstrated in clinic settings (Jokela et al., 2010; Pickering et al., 2012).

Therefore, the primary aim of this study was to determine whether the concomitant perioperative administration of acetaminophen and ondansetron leads to a pharmacodynamic interaction that decreases the analgesic effect of acetaminophen.

2. Methods

2.1 Study design and conduct

This clinical trial was reviewed and approved by the institutional ethics committee (Protective Person Committee of *Sud-Ouest Outre-mer IV*, France) and registered with ClinicalTrials.gov (ref: PARATRON – NCT01432977; http://clinicaltrials.nlm.nih.gov/ct2/show/results/NCT01432977). All parents provided written informed consent. The *Paratron* trial was designed as a prospective, randomized, controlled and double-blind clinical trial using two parallel groups.

Perioperative care of the patients (anaesthesia, operation and post-operative care) was standardized. For the two groups of children, inhalational induction was performed using sevoflurane at a concentration of 2.5–3% in O_2/N_2O. Fluid administration during anaesthesia and in the recovery room consisted of the administration of a solution containing 5% glucose, 0.2% NaCl, 0.15% KCl and 0.1% calcium gluconate in 250 mL of water and it followed the 40/20/10 mL/10 kg rule.

After surgery began, all patients received betamethasone and acetaminophen together with ondansetron (ondansetron group) or droperidol (droperidol group) (Fig. 1). At the end of surgery, patients received an intravenous bolus of morphine (75 μg/kg). Post-operative analgesic and antiemetic strategies are also presented in Fig. 1. The CHEOPS (Children's Hospital of Eastern Ontario Pain Scale) is a behavioural scale for evaluating post-operative pain in young children (McGrath et al., 1985). It has been validated for children aged between 1 and 7 years [scores of 4 (normal) to 13 (maximum pain)] and it was used in this

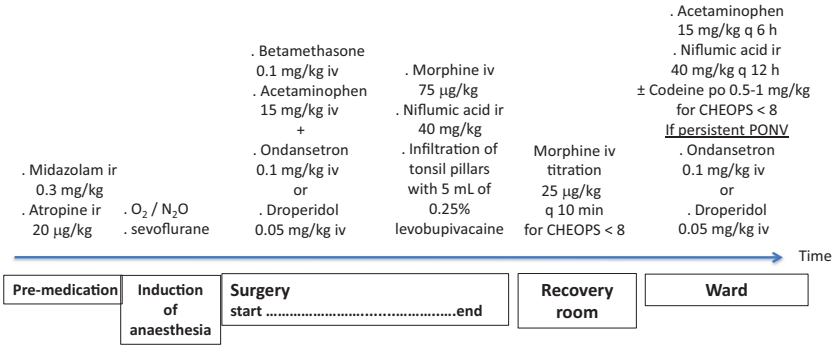

Figure 1 Trial assignment to study medications. ir, intrarectal; iv, intravenous; po, *per os*; q, every.

study. Pain scores were recorded by research nurses 30 min after admission and when leaving the recovery room, and then on the ward at 4 h after acetaminophen administration and every 4 h for up to 24 h. Opioid consumption (morphine in the recovery room and codeine on the ward) and the incidence of nausea and vomiting were recorded during the same time frame as pain scores. Adverse events were also recorded.

The randomization list was created by a statistician who used blocks of size 2 and 4 (1:1 ratio). Randomization was centralized and performed by the hospital pharmacist and occurred via the opening of a sealed envelope. All nurses, anaesthetists, surgeons, patients, parents and data collectors were blinded as to whether the patient received ondansetron or droperidol together with acetaminophen.

2.2 Study population and intervention

Patients aged between 2 and 7 years scheduled for tonsillectomy ± adenoidectomy were recruited at Limoges University Hospital Center (France).

Exclusion criteria included a hospital stay of less than 24 h, patients already on pain medication, and allergic patients with a contraindication to one of the study drugs (Fig. 2).

2.3 Outcome measures

The primary outcome measure for the trial was the post-operative pain score 4 h after the intraoperative co-administration of acetaminophen and ondansetron or droperidol, which was assessed using CHEOPS.

Secondary outcomes included post-operative analgesic consumption of intravenous morphine in the recovery room and oral codeine on the ward 24 h following surgery, as well as the cumulative incidence of nausea and vomiting at 24 h following surgery.

2.4 Power analysis

A preliminary study was performed at our institution in 19 children (11 boys and 8 girls) aged 2–7 years undergoing tonsillectomy ± adenoidectomy. It showed that mean pain scores on the CHEOPS were 6.5 ± 2 at 4 h after surgery, and the mean remained between 5 and 6 during the first 24 h, with occasional peak scores (CHEOPS > 7).

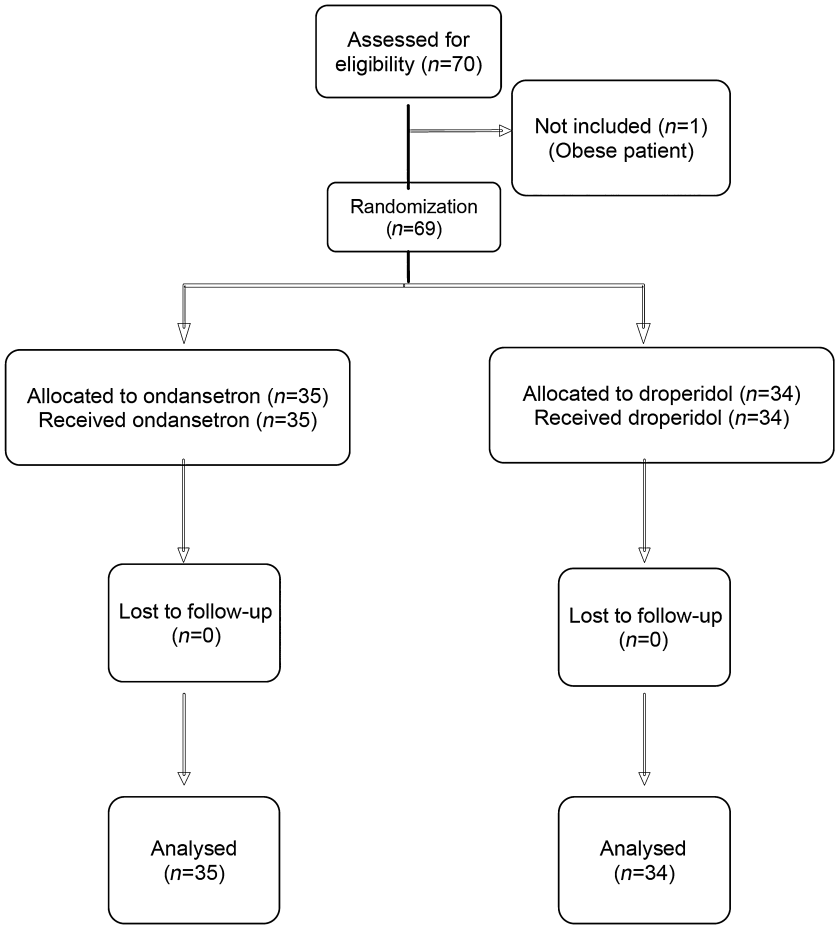

Figure 2 Flow of patients through the trial.

On the basis of the data from the preliminary study with a common standard deviation for CHEOPS of 2 and based on a power of 80% and an α of 5%, 33 patients per group were required to obtain a difference of 1.5 points on the CHEOPS (expected mean pain scores of 6.5 and 5 for the ondansetron and droperidol groups, respectively) (NQuery Advisor v7.0; Noether, 1987). To allow for the possibility of dropouts (5%), a total of 35 patients per group were recruited for this study.

2.5 Statistical analysis

Statistical analyses were performed by the *Unité Fonctionnelle de Recherche Clinique et de Biostatistique* of Limoges University Hospital using SAS® Software V 9.1.3 (SAS Institute, Cary, NC, USA). The level of significance was 5% for all analyses. Analyses were performed on an intent-to-treat basis. Additionally, analyses were performed and presented in agreement with revised CONSORT Statement guidelines (Moher et al., 2010).

Quantitative variables are expressed as median and interquartile range (IQR). Qualitative variables are described using frequency and percentage.

Comparisons of quantitative variables between the groups were performed using the Wilcoxon signed rank test. Normality was assessed using the Shapiro–Wilk test. Because the groups differed at baseline in terms of gender, the main analysis and secondary analyses were adjusted for gender. Therefore, we used an analysis of covariance (ANCOVA) based on ranks for quantitative variables (Kruskal–Wallis test was excluded because of inability to adjust on gender distribution) and a multivariate logistic regression for qualitative variables. Those methods allowed us to systematically adjust our analysis on gender. Statistical interactions between gender and treatment group were checked in those analyses but none was identified. Based on the assumption used for the a priori calculation of the sample size, we still had a power of more than 80% when using a non-parametric test instead of a parametric one. Indeed, the CHEOPS score did not follow the normal distribution. Comparison of the CHEOPS score, taking into account all assessments performed during follow-up ($n = 8$), was performed using analysis of variance (ANOVA) for repeated measures based on ranks. The crude variable that did not follow the normal distribution was ranked.

3. Results

The study was carried out in the *Hôpital Mère-Enfant* of the Limoges University Hospital Center (France) between October 2011 and June 2012. The study protocol (Fig. 1) was followed by a total of 69 patients who were included in the study: 35 were in the ondansetron group and 34 were in the droperidol group. One patient initially assessed for eligibility was excluded before randomization due to morbid obesity.

Table 1 Demographic and baseline clinical data at induction (mean ± SD) and the quantity of drug administered during surgery in mg [median (IQR)] between the two groups.

	Ondansetron group ($n = 35$)	Droperidol group ($n = 34$)
Age (years)	4.43 ± 1.36	4.18 ± 1.4
Sex (boys/girls)	25/10	14/20
Weight (kg)	18.94 ± 6.09	17.96 ± 5.91
Duration of surgery (min)	22.77 ± 7.49	23.91 ± 11.67
Time spent in recovery (min)	62.26 ± 29.85	56.94 ± 35.24
Acetaminophen (mg)	270 [226–315]	254.25 [225–300]
Niflumic acid (mg)	720 [604–840]	678 [600–800]
Betamethasone (mg)	1.80 [1.51–2.1]	1.7 [1.5–2]
Levobupivacaine (mg)	5 [5–8]	5 [5–6.5]

IQR, interquartile range.

Data from the 69 patients were available for final analysis, and a flow chart diagram was presented (Fig. 2).

Baseline demographic and clinical characteristics of each group are presented (Table 1). The groups were comparable, except, despite randomization, for a higher proportion of girls in the droperidol group (59%) versus the ondansetron group (28.5%). We could have controlled this beforehand by performing stratification on gender; nevertheless, this factor was not considered sufficiently important to justify such a procedure as gender distribution was equivalent in the preliminary study. Therefore, as the proportion of girls and boys was unexpectedly different, the results displayed for the main and secondary outcomes were adjusted on gender.

CHEOPS scores were not statistically different between the groups 4 h after co-administration of acetaminophen with ondansetron or droperidol [median scores: 5, IQR (4–6) and 5, IQR (4–6), respectively, $p = 0.22$]. This result was stable at all times when it was recorded during the first 24 h and when considering all times in a single ANOVA for repeated data, $p = 0.87$ (Table 2).

Median morphine consumption (in μg) in recovery was 322.5 IQR [0.0–500.0] and 0 IQR [0-0] in the ondansetron and droperidol groups, respectively, $p = 0.01$ (Fig. 3). The percentages of patients who received morphine titration were significantly different: 57.1% and 20.6% in the ondansetron and droperidol groups, respectively, $p = 0.008$. Finally, the ranges of morphine titration doses differed between the groups (Fig. 4).

Four children in each group were administered codeine on the ward during the first 24 h ($p = 0.68$). The median doses of codeine were 0 mg [0-0] for both the ondansetron and droperidol groups, respectively,

Table 2 Comparison of CHEOPS scores in the recovery room (30 min after admission and on leaving) and 4 h on the ward following acetaminophen + ondansetron or droperidol administration. Data are expressed as median and interquartile range.

CHEOPS score	Ondansetron group	Droperidol group	*p*-value
Recovery room at 30 min	9 [6–11]	6 [6–10]	0.11[a]
Exit from recovery room	6 [5–6]	6 [5–6]	0.67[a]
Ward at 4 h	5 [4–6]	5 [4–6]	0.22[b]
Ward at 8 h	5 [4–6]	5 [4–6]	0.78[a]
Ward at 12 h	6 [4–6]	6 [6–6]	0.07[a]
Ward at 16 h	6 [5–6]	6 [5–6]	0.18[a]
Ward at 20 h	5 [4–6]	6 [4–6]	0.90[a]
Ward at 24 h	4 [4–6]	4 [4–5]	0.37[a]

CHEOPS, Children's Hospital of Eastern Ontario Pain Scale.
[a]Wilcoxon signed rank test.
[b]Main analysis: ANCOVA test.

and the ranges were [0–19] and [0–13], respectively, $p = 0.73$. Likewise, the median amounts of acetaminophen administered perioperatively between the two groups were 270 [226–315] and 254.2 [225–300] mg for the ondansetron and droperidol groups, respectively, $p = 0.35$. Finally, niflumic acid during the first 24 h was administered at a dose (median and IQR) of 800 [400–800] mg in both the ondansetron and droperidol groups, $p = 0.054$.

The overall cumulative incidence of PONV in the first 24 h affected 11 patients: 5 (14.3%) in the ondansetron group and 6 (17.6%) in the droperidol group, $p = 0.57$.

The administration on the ward of a second dose of antiemetics (ondansetron in the ondansetron group and droperidol in the droperidol group) occurred in zero and three cases for the ondansetron and droperidol groups, respectively ($p = 0.11$).

The administration on the ward of a third dose of antiemetics (droperidol in the ondansetron group and ondansetron in the droperidol group) occurred in one patient per group ($p = 1$).

Adverse events were mild, and none modified the application of the protocol. Finally, three patients had to be readmitted to the hospital: one was in the ondansetron group (febrile diarrhoea) and two were in the droperidol group (otalgia and headache).

4. Discussion

The main objective of this study was to determine whether the use of acetaminophen and ondansetron is less effective than the use of acetaminophen and droperidol in the treatment of post-operative pain after tonsillectomy in children, therefore supporting the presence of an analgesic interaction between acetaminophen and a setron.

The CHEOPS pain scores between the groups were not different at all times following surgery. Likely explanations for the presence of similar pain scores between the two groups at 4 h (primary outcome) include the following: (1) children were titrated with intravenous morphine to decrease pain in recovery before being sent to the ward; and (2) if an interaction between acetaminophen and ondansetron was present, it may not have been present at 4 h due to the short half-lives of these compounds, which are 2–3 h for acetaminophen and 3–4 h for ondansetron. Indeed, earlier pain scores such as the ones recorded 30 min after arriving in the recovery room [medians of 9 (6–11) and 6 (6–10) in the ondansetron and droperidol groups, respectively], although not statistically different, were dissimilar.

With respect to secondary outcome measures, the results show that an analgesic interaction between ondansetron and acetaminophen is likely to be present. Thus, morphine consumption in the recovery room was approximately three times greater among patients who received acetaminophen and ondansetron compared with the other group, although post-operative pain scores were similar. Furthermore, the doses of morphine used in recovery among the two groups were very different (Fig. 4). Finally, the percentage of children who received morphine titration in recovery was almost three times higher (57%) in the acetaminophen and ondansetron groups than in the acetaminophen and droperidol groups (21%), and this was highly significant.

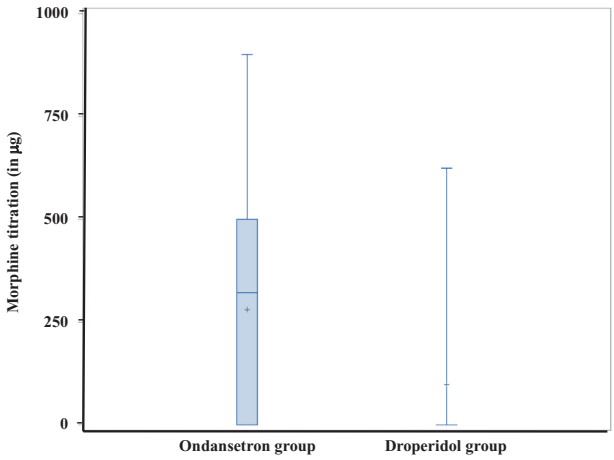

Figure 3 Boxplot of morphine titration (in µg) in the recovery room expressed as median and interquartile range (box) ($p = 0.01$). Ondansetron group: acetaminophen/ondansetron. Droperidol group: acetaminophen/droperidol. Note that in the droperidol group, there is no box because the median and the interquartile range are confounded (0).

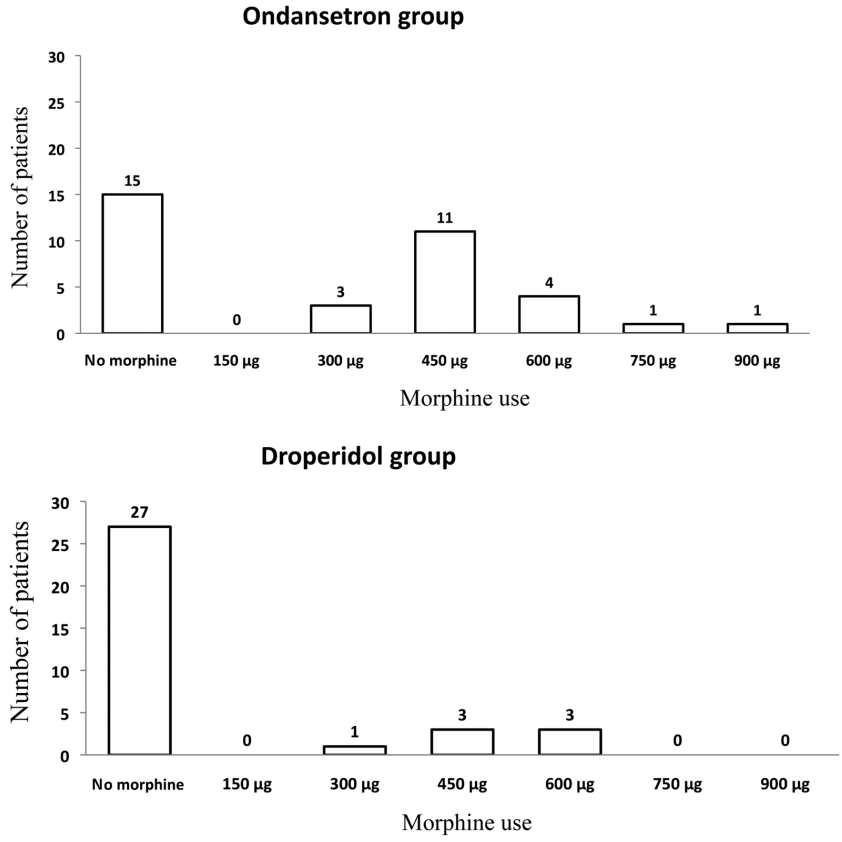

Figure 4 Range of doses of morphine used (in µg) and the distribution between the two groups during titration in the recovery room. Ondansetron group: acetaminophen/ondansetron. Droperidol group: acetaminophen/droperidol.

Two other clinical studies have been performed to date in which an interaction between acetaminophen and a setron has not been reported. The first clinical trial that examined patients after laparoscopic hysterectomy showed that ondansetron did not block the analgesic effect of acetaminophen (Jokela et al., 2010). However, the design of this trial could be responsible for the failure to detect an interaction between acetaminophen and ondansetron. Acetaminophen was administered at the induction of anaesthesia, and ondansetron was administered at the end of surgery while surgeries lasted a mean of almost 2 h. Therefore, considering the short half-lives of these two compounds, the interaction between acetaminophen and ondansetron may have been missed because the drugs were not administered at the same time. Moreover, a continuous remifentanil infusion was used until the end of surgery, and this could have confounded the analgesic effects of other drugs as its use is associated with opioid-induced hyperalgesia (Simonnet and Rivat, 2003) that could have modified post-operative pain assessment or treatment. Finally, the authors reported that during a previous trial for the same indication (Jokela et al., 2008), oxycodone consumption was higher after perioperative administration of placebo or acetaminophen with ondansetron compared with acetaminophen alone, which reveals a possible positive interaction between acetaminophen and ondansetron.

In a second clinical trial, the authors failed to show any significant interaction between acetaminophen and tropisetron after ear surgery, although pain was 30% higher in the tropisetron group compared with the control group (Pickering et al., 2012). They suggested that the interaction between acetaminophen and tropisetron could not be demonstrated because pain scores were low in the ear surgery model studied. A larger than expected inter-individual variability was also mentioned to explain the negative findings (Pickering et al., 2012).

Previous studies have shown in animals and then in healthy volunteers the decreased antinociceptive effect of acetaminophen by tropisetron and granisetron (Pelissier et al., 1996; Pickering et al., 2006). Therefore, it would have been wise to study acetaminophen and setron interactions by using tropisetron or granisetron. However, we have chosen to study ondansetron, rather than tropisetron or

granisetron/acetaminophen interaction, because tropisetron and granisetron are not approved for use in the paediatric population in France.

An interaction between droperidol and acetaminophen could have been possible although no data have been found in the literature concerning this issue. Droperidol could have also increased morphine sedation. Furthermore, ondansetron (Vergne-Salle et al., 2011) and droperidol (Richards et al., 2011) have intrinsic analgesic properties that may have interfered with the results of this trial. Finally, the similar incidence of PONV between the two groups demonstrates that droperidol is a valid antiemetic in the management of PONV after tonsillectomy in children, although its use is no longer recommended by most medical societies due to its ability to cause a prolonged QT interval. This is, however, also a concern with ondansetron (Charbit et al., 2005, 2008; McKechnie and Froese, 2010).

4.1 Limitations

In pain studies, guidelines from international experts recommend the use of pain scores rather than morphine consumption as a primary endpoint (Dworkin et al., 2011; Gilron and Jensen, 2011). Nevertheless, a recent publication contradicts this recommendation in the paediatric population, as the authors recommend that analgesic consumption is the best primary endpoint to use in paediatric pain research (Berde et al., 2012). In the present study and following Berde et al.'s recommendations (that were not published at the time of study design), because the patients were titrated with morphine to decrease their pain in the recovery room, pain scores at 4 h may not have been an appropriate primary outcome. Morphine consumption would have certainly been a better choice. Indeed, in children, a significant opioid sparing effect may be taken as a clinically relevant result.

Although the results presented in this trial are in favour of an analgesic interaction between acetaminophen and ondansetron, the fact that this occurred in a paediatric population is to be kept in mind as the interaction was not observed in the two previous clinical studies performed in adults (Jokela et al., 2010; Pickering et al., 2012). We did not measure plasma concentrations of acetaminophen and ondansetron to exclude a pharmacokinetic interaction. Other authors have already demonstrated that the administration of tropisetron and granisetron did not affect plasma concentrations of acetaminophen (Pickering et al., 2006). Furthermore, it is unlikely that ondansetron has any impact on the plasma concentrations of acetaminophen, as their metabolic pathways are largely different. In order to best demonstrate an ondansetron/acetaminophen interaction, a placebo/acetaminophen group could have been used. However, the use of an antiemetic placebo in a paediatric population of high risk of nausea and vomiting was not considered ethical. Finally, although many analgesic drugs (niflumic acid, infiltration with levobupivacaine) were administered in this trial during surgery, these could have interfered with pain scores and morphine consumption, but it was decided to allow their use to study the interaction between acetaminophen and ondansetron in 'real life' conditions.

In conclusion, although the combined administration of ondansetron with acetaminophen in paediatric tonsillectomy did not significantly modify the pain scores 4 h after administration compared with droperidol with acetaminophen, morphine consumption was three times higher in the former group, suggesting a drug interaction. Considering that more than 230 million major surgical procedures are performed annually worldwide (Devereaux et al., 2012) and that many hundreds of million more are minor operations such as tonsillectomy, such an interaction may prove to be extremely frequent and may interfere with post-operative pain management although a reduction of opioid-mediated side effects was not observed in this study. Further studies are needed to evaluate whether this interaction is present in other types of surgery; and if this interaction is confirmed, the management of post-operative pain will be modified on a large scale.

Author contributions

L.R., J.C., Pa.B. and F.R-C. designed and performed the research. B.M. designed the research, analysed the data and wrote the manuscript. A.B. and M.A.V. performed the research. G.E.L. analysed the data. V.G., N.N. and P.B. designed the research and wrote the manuscript.

Acknowledgement

We would like to acknowledge the contribution of members from the Délégation à la Recherche Clinique of the CHU de Limoges, France.

References

Alloui, A., Pelissier, T., Dubray, C., Lavarenne, J., Eschalier, A. (1996). Tropisetron inhibits the antinociceptive effect of intrathecally administered paracetamol and serotonin. ***Fundam Clin Pharmacol*** 10, 406–407.

Bandschapp, O., Filitz, J., Urwyler, A., Koppert, W., Ruppen, W. (2011). Tropisetron blocks analgesic action of acetaminophen: A human pain model study. *Pain* 152, 1304–1310.

Baugh, R.F., Archer, S.M., Mitchell, R.B., Rosenfeld, R.M., Amin, R., Burns, J.J., Darrow, D.H., Giordano, T., Litman, R.S., Li, K.K., Mannix, M.E., Schwartz, R.H., Setzen, G., Wald, E.R., Wall, E., Sandberg, G., Patel, M.M. (2011). Clinical practice guideline: Tonsillectomy in children. *Otolaryngol Head Neck Surg* 144, S1–S30.

Berde, C.B., Walco, G.A., Krane, E.J., Anand, K.J., Aranda, J.V., Craig, K.D., Dampier, C.D., Finkel, J.C., Grabois, M., Johnston, C., Lantos, J., Lebel, A., Maxwell, L.G., McGrath, P., Oberlander, T.F., Schanberg, L.E., Stevens, B., Taddio, A., von Baeyer, C.L., Yaster, M., Zempsky, W.T. (2012). Pediatric analgesic clinical trial designs, measures, and extrapolation: Report of an FDA scientific workshop. *Pediatrics* 129, 354–364.

Bonnefont, J., Chapuy, E., Clottes, E., Alloui, A., Eschalier, A. (2005). Spinal 5-HT1A receptors differentially influence nociceptive processing according to the nature of the noxious stimulus in rats: Effect of WAY-100635 on the antinociceptive activities of paracetamol, venlafaxine and 5-HT. *Pain* 114, 482–490.

Charbit, B., Albaladejo, P., Funck-Brentano, C., Legrand, M., Samain, E., Marty, J. (2005). Prolongation of QTc interval after postoperative nausea and vomiting treatment by droperidol or ondansetron. *Anesthesiology* 102, 1094–1100.

Charbit, B., Alvarez, J.C., Dasque, E., Abe, E., Demolis, J.L., Funck-Brentano, C. (2008). Droperidol and ondansetron-induced QT interval prolongation: A clinical drug interaction study. *Anesthesiology* 109, 206–212.

Devereaux, P.J., Chan, M.T., Eisenach, J., Schricker, T., Sessler, D.I. (2012). The need for large clinical studies in perioperative medicine. *Anesthesiology* 116, 1169–1175.

Dogrul, A., Seyrek, M., Akgul, E.O., Cayci, T., Kahraman, S., Bolay, H. (2012). Systemic paracetamol-induced analgesic and antihyperalgesic effects through activation of descending serotonergic pathways involving spinal 5-HT(7) receptors. *Eur J Pharmacol* 677, 93–101.

Dworkin, R.H., Turk, D.C., Katz, N.P., Rowbotham, M.C., Peirce-Sandner, S., Cerny, I., Clingman, C.S., Eloff, B.C., Farrar, J.T., Kamp, C., McDermott, M.P., Rappaport, B.A., Sanhai, W.R. (2011). Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION. *Pain* 152, S107–S115.

Gilron, I., Jensen, M.P. (2011). Clinical trial methodology of pain treatment studies: Selection and measurement of self-report primary outcomes for efficacy. *Reg Anesth Pain Med* 36, 374–381.

Girard, P., Pansart, Y., Coppe, M.C., Niedergang, B., Gillardin, J.M. (2009). Modulation of paracetamol and nefopam antinociception by serotonin 5-HT(3) receptor antagonists in mice. *Pharmacology* 83, 243–246.

Hanasono, M.M., Lalakea, M.L., Mikulec, A.A., Shepard, K.G., Wellis, V., Messner, A.H. (2004). Perioperative steroids in tonsillectomy using electrocautery and sharp dissection techniques. *Arch Otolaryngol Head Neck Surg* 130, 917–921.

Jokela, R., Ahonen, J., Seitsonen, E., Marjakangas, P., Korttila, K. (2010). The influence of ondansetron on the analgesic effect of acetaminophen after laparoscopic hysterectomy. *Clin Pharmacol Ther* 87, 672–678.

Jokela, R., Ahonen, J., Tallgren, M., Haanpaa, M., Korttila, K. (2008). A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. *Pain* 134, 106–112.

Litman, R.S., Wu, C.L., Catanzaro, F.A. (1994). Ondansetron decreases emesis after tonsillectomy in children. *Anesth Analg* 78, 478–481.

Mallet, C., Daulhac, L., Bonnefont, J., Ledent, C., Etienne, M., Chapuy, E., Libert, F., Eschalier, A. (2008). Endocannabinoid and serotonergic systems are needed for acetaminophen-induced analgesia. *Pain* 139, 190–200.

Mallet, C., Eschalier, A. (2010). Pharmacology and mechanism of action of acetaminophen. In *Pharmacology of Pain*, P. Beaulieu, D. Lussier, F. Porreca, A.H. Dickenson, eds. (Seattle, WA: IASP Press) pp. 65–85.

McGrath, P.J., Johnson, G., Goodman, J.T., Schillinger, J., Dunn, J., Chapman, J. (1985). The CHEOPS: A behavioral scale to measure post operative pain in children. In *Advances in Pain Research and Therapy*, H.L. Fields, R. Dubner, F. Cervero, eds. (New York: Raven Press) pp. 395–402.

McKechnie, K., Froese, A. (2010). Ventricular tachycardia after ondansetron administration in a child with undiagnosed long QT syndrome. *Can J Anaesth* 57, 453–457.

Moher, D., Hopewell, S., Schulz, K.F., Montori, V., Gotzsche, P.C., Devereaux, P.J., Elbourne, D., Egger, M., Altman, D.G. (2010). CONSORT 2010 explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol* 63, e1–e37.

Noether, G.E. (1987). Sample size determination for some common nonparametric tests. *JASA* 82, 645–647.

Pelissier, T., Alloui, A., Caussade, F., Dubray, C., Cloarec, A., Lavarenne, J., Eschalier, A. (1996). Paracetamol exerts a spinal antinociceptive effect involving an indirect interaction with 5-hydroxytryptamine3 receptors: In vivo and in vitro evidence. *J Pharmacol Exp Ther* 278, 8–14.

Pickering, G., Faure, M., Commun, F., de Boissy, E.C., Roche, G., Mom, T., Simen, E., Dubray, C., Eschalier, A., Gilain, L. (2012). Tropisetron and paracetamol association in post-operative patients. *Fundam Clin Pharmacol* 26, 432–437.

Pickering, G., Loriot, M.A., Libert, F., Eschalier, A., Beaune, P., Dubray, C. (2006). Analgesic effect of acetaminophen in humans: First evidence of a central serotonergic mechanism. *Clin Pharmacol Ther* 79, 371–378.

Richards, J.R., Richards, I.N., Ozery, G., Derlet, R.W. (2011). Droperidol analgesia for opioid-tolerant patients. *J Emerg Med* 41, 389–396.

Simonnet, G., Rivat, C. (2003). Opioid-induced hyperalgesia: Abnormal or normal pain? *Neuroreport* 14, 1–7.

Société Française d'Anesthésie-Réanimation (2005) *Conférences d'experts*. Anesthésie pour amygdalectomie chez l'enfant.

Tjolsen, A., Lund, A., Hole, K. (1991). Antinociceptive effect of paracetamol in rats is partly dependent on spinal serotonergic systems. *Eur J Pharmacol* 193, 193–201.

Ved, S.A., Walden, T.L., Montana, J., Lea, D.E., Tefft, M.C., Kataria, B.K., Pudimat, M.A., Nicodemus, H.F., Milmoe, G.J. (1996). Vomiting and recovery after outpatient tonsillectomy and adenoidectomy in children. Comparison of four anesthetic techniques using nitrous oxide with halothane or propofol. *Anesthesiology* 85, 4–10.

Vergne-Salle, P., Dufauret-Lombard, C., Bonnet, C., Simon, A., Treves, R., Bonnabau, H., Bertin, P. (2011). A randomised, double-blind, placebo-controlled trial of dolasetron, a 5-hydroxytryptamine 3 receptor antagonist, in patients with fibromyalgia. *Eur J Pain* 15, 509–514.

