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Effect of palonosetron on the QTc interval in patients undergoing sevoflurane anaesthesia

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Editor's key points

- Many anti-emetics, including all first-generation 5-HT_3 receptor antagonists, increase the duration of the QT interval of the electrocardiogram.
- Recent preliminary data suggest that palonosetron, a longer-acting anti-emetic, may have lower risk of inducing QT prolongation.
- This study finds that sevoflurane anaesthesia was associated with a small increase in the mean duration of the QT interval, including a minority with a QT-corrected interval >500 ms.
- Palonosetron given before induction of anaesthesia had no effect on the QT interval after its administration and during surgery.

Background. Palonosetron is a recently introduced 5-HT_3 receptor antagonist for postoperative nausea and vomiting. Detailed standardized evaluation of corrected QT (QTc) interval change by palonosetron under sevoflurane anaesthesia is lacking. We evaluated QTc intervals in patients who are undergoing surgery with sevoflurane anaesthesia and receive palonosetron.

Methods. Our study included 100 patients who were undergoing elective surgery under sevoflurane anaesthesia. The patients were randomly assigned to two groups: those who received an i.v. injection of palonosetron 0.075 mg immediately before induction of anaesthesia (pre-surgery group, n=50) and those who received it after surgery in the recovery room (post-surgery group, n=50). QTc intervals were measured before operation, intraoperatively (baseline, immediately after tracheal intubation, and at 2, 10, 15, 30, 60, and 90 min after administration of palonosetron or placebo), and after operation (before and at 3, and 10 min after administration of palonosetron or placebo). QTc intervals were calculated using Fridericia's, Bazett's, or Hodges formulas.

Results. The perioperative QTc intervals were significantly increased from the baseline values, but were not affected by the pre- or post-surgical timing of palonosetron administration.

Conclusions. There was no significant difference in the QTc intervals during the perioperative period, whether 0.075 mg of palonosetron is administered before or after sevoflurane anaesthesia. Palonosetron may be safe in terms of QTc intervals during sevoflurane anaesthesia.

Clinical trial registration. ClinicalTrials.gov: NCT01650961.

Keywords: anti-emetics; electrocardiography; palonosetron; postoperative nausea and vomiting; serotonin 5-HT_3 receptor antagonists; sevoflurane

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5-HT_3 receptor antagonists have been widely used for the prevention and treatment of postoperative nausea and vomiting (PONV) in patients receiving general anaesthesia.[1] However, the first-generation 5-HT_3 receptor antagonists such as ondansetron, dolasetron, and granisetron have been associated with cardiovascular adverse events such as ventricular arrhythmia, atrial fibrillation, myocardial ischaemia, and cardiac arrest.[2–7] One reason for cardiac complications seems to be a tendency to block cardiac potassium and sodium ion channels, resulting in increasing corrected QT (QTc) intervals.[8–10]

Palonosetron is the second-generation 5-HT_3 receptor antagonist which has recently been approved for PONV prophylaxis. It has the greatest potency and the longest duration of action of 24 h among 5-HT_3 receptor antagonists.[11 12] Several clinical studies have shown that palonosetron is effective for PONV prophylaxis.[13 14] However, by possessing similar pharmacological mechanisms as ondansetron, palonosetron may theoretically prolong the QTc interval and increase the risk of life-threatening arrhythmias. Therefore, some anaesthesiologists are reluctant to use palonosetron in patients who have an increased risk of QTc interval prolongation. Although the prescribing information deleted the warnings of QTc prolongation of palonosetron for the PONV dose recently,[15] the study will be helpful in investigating QTc prolongation by palonosetron in detailed and standardized methods.

Some randomized studies have shown that palonosetron does not increase the QTc interval when compared with control groups in patients undergoing surgery.[13 14] However, since the primary outcome of these studies was not QTc data, QTc intervals were measured only two times regardless of anaesthetic duration. The types of anaesthetic agents which influence the heart during anaesthesia have not yet been fully identified, although sevoflurane is known to induce QTc interval prolongation.[16 17] The mechanism of QTc interval prolongation of sevoflurane is the inhibition of cardiac potassium ion channels similar to that of the first-generation 5-HT_3 receptor antagonists. Therefore, if palonosetron and sevoflurane have combined effect on the cardiac ion channels, palonosetron may induce QTc interval prolongation under sevoflurane anaesthesia. However, to the best of our knowledge, there have been no randomized studies to investigate the effects of palonosetron on the QTc interval under sevoflurane anaesthesia.

We hypothesized that palonosetron would increase the QTc interval in patients who were undergoing sevoflurane anaesthesia. Therefore, this study was conducted to evaluate the effects of palonosetron on QTc intervals in patients undergoing surgery under sevoflurane anaesthesia.

Methods

This prospective, randomized, double-blind study was approved by the Institutional Review Board of Seoul National University Hospital (Ref: H-1203-050-401) and registered at ClinicalTrials.gov (NCT01650961). Written informed consent was obtained from each patient after complete description of the study protocol.

Patients

We enrolled 100 patients aged 20–75 who were undergoing elective abdominal or gynaecological surgery under general anaesthesia with an expected duration of more than 1.5 h between July 2012 and December 2012. Exclusion criteria were as follows: histories of previous PONV; ischaemic heart disease; valvular heart disease; diabetes mellitus; significant arrhythmias, including atrial fibrillation, bundle branch block, or atrioventricular block; QTc prolongation of more than 500 ms on preoperative ECG; hypokalaemia on preoperative laboratory tests; patients who received QT-prolonging medications, such as antiarrhythmics, antibiotics, calcium channel blockers, β-blockers, or antipsychotics;[18 19] patients who received antiemetics, opioids, steroids, cancer chemotherapy, or radiotherapy within 1 month before surgery.

Groups

Patients were randomly divided into two groups—the pre-surgery (n=50) and post-surgery (n=50) groups—using a computer-generated random number table. Medication was administered to the two groups as follows.

- The pre-surgery group received palonosetron (Aloxi®, Helsinn Healthcare, SA, Switzerland) 0.075 mg i.v. immediately before induction of general anaesthesia and 1.5 ml of normal saline, which is the same volume as 0.075 mg of palonosetron, i.v. immediately after the first postoperative QTc interval was recorded in the recovery room.
- The post-surgery group received 1.5 ml of normal saline, which is the same volume as 0.075 mg of palonosetron, i.v. immediately before induction of general anaesthesia and 0.075 mg palonosetron i.v. immediately after the first postoperative QTc interval was recorded in the recovery room.

Palonosetron or normal saline was prepared by a single nurse who was not involved in the collection of data and patient care. These two medications of the same colour and volume were indistinguishable to the anaesthesiologists who were in charge of anaesthesia.

Anaesthesia

Routine monitoring of arterial pressure, three-lead ECG, oxygen saturation, and bispectral index (BIS) were applied. General anaesthesia was induced with propofol in doses of 2–2.5 mg kg^{-1} and tracheal intubation was facilitated with rocuronium in a dose of 0.6 mg kg^{-1}. Anaesthesia was maintained using sevoflurane 1–3% with oxygen/air (fractional inspired oxygen 0.4) targeting BIS values between 40 and 60. To measure serum concentrations of potassium, calcium, and magnesium, 4 ml blood samples were obtained from all patients before the start of surgery. The anaesthesiologists who conducted general anaesthesia were blinded to the study groups. Medications were used for haemodynamic stabilization and analgesic supplementation during surgery at the discretion of the anaesthesiologists. Patient-controlled analgesia (PCA) was applied at the end of surgery in the operating theatre. The PCA regimen consisted of fentanyl 25 μg kg^{-1} diluted with 100 ml of normal saline in a bolus dose of 0.5 ml at lockout intervals of 15 min and with a background infusion of 1 ml h^{-1}. After tracheal extubation, patients were transferred to the recovery room and observed for at least 1 h. A cardiac defibrillator and a resuscitation cart containing emergency medications such as magnesium sulphate were available in the operating theatre and the recovery room for the immediate treatment in the case of developing a life-threatening arrhythmia.

QTc interval measurement

In all patients, preoperative QTc intervals were recorded routinely using a 12-lead ECG machine in the ward or outpatient clinic. Intraoperative QTc intervals were obtained at the following time points: before anaesthetic induction (baseline), immediately after tracheal intubation, and 2, 10, 15, 30, 60, and 90 min after administration of palonosetron or placebo in the operating theatre. Postoperative QTc intervals were assessed three times (before and at 3 and 10 min after administration of palonosetron or placebo) in the recovery room; these time points were expressed as R, R3, and R10, respectively.

ECG signals were recorded using the continuous monitoring ECG system (Solar® 8000 M, GE Medical System, Milwaukee, WI, USA) in the operating theatre and recovery room. ECG data in