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CLINICAL TRIAL

Intravenous buspirone for the prevention of postoperative nausea and vomiting

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Abstract

Rationale Buspirone, a partial 5HT_{1A} agonist and D₂ and D₃ antagonist, has shown promising antiemetic efficacy when given parenterally in animal models, but its efficacy for the prevention of postoperative nausea and vomiting (PONV) is unknown.

Objective To study the efficacy and dose-responsiveness of intravenous buspirone for the prevention of PONV.

Methods A randomised, double-blind, placebo-controlled study was performed in adults at moderate to high PONV risk undergoing surgery with a general anaesthetic. Patients were randomised to receive an intravenous dose of buspirone

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(0.3, 1.0, 2.0, 3.0 mg) or placebo at the end of surgery. The primary endpoint was the cumulative 24-h PONV incidence (i.e. any nausea and/or vomiting). Vomiting included retching. Nausea was defined as a score of ≥ 4 on an 11-point verbal rating scale running from zero (no nausea) to ten (the worst nausea imaginable).

Results A total of 257 patients received the study drug and fulfilled the criteria for inclusion in the primary efficacy and safety analyses. With placebo, the mean 24-h PONV incidence was 49.0 % (90 % confidence interval [CI] 37.5–60.5 %). With buspirone, that incidence ranged from a mean of 40.8 % (29.3–52.4 %) in the 1 mg arm to 58.0 % (46.5–69.5 %) in the 0.3 mg arm ($P > 0.05$ for all comparisons). There was no difference between placebo and buspirone at any dose for any other efficacy endpoint, nor in the number or severity of adverse events or any other safety measures.

Conclusion We were unable to show that intravenous single-dose buspirone, at the tested dose-range, was effective at preventing PONV in surgical adult patients. The present study emphasises the difficulty in extrapolating from animal models of emesis to clinical efficacy in PONV.

Keywords Buspirone · Postoperative nausea and vomiting · Randomised clinical trial · Antiemetic

Abbreviations

D	Dopaminergic
5HT	Serotonergic
NK	Neurokinin
PONV	Postoperative nausea and vomiting
PP	Pyrimidinylpiperazine

Introduction

Postoperative nausea and vomiting (PONV) remain a significant medical problem, despite the availability of numerous anti-emetics [1]. Risk factors for PONV include female sex, non-smoking status, prior history of PONV or motion sickness, postoperative opioid usage, use of volatile anaesthetics and the type and duration of surgery [2].

Numerous mechanisms have been implicated in PONV, most notably the release of serotonin from the gut wall and activation of the chemoreceptor trigger zone in the brain. Several types of receptors seem to be involved in PONV, and these represent effective targets for drug therapies. Among the most important are the dopaminergic (D_2), serotonergic ($5HT_3$) and neurokinin (NK_1) receptors, and the majority of effective antiemetics are active against one or more of these receptors. Clinical and pre-clinical evidence also suggests a possible role for $5HT_{1A}$ and D_3 receptors as effective antiemetics [3–5].

PONV is typically managed using a prophylactic multimodal approach, including the frequent use of combination pharmacotherapy, especially in high-risk patients [6]. At the present time, there is general agreement that effective prophylaxis should involve the administration of one or more antiemetic agent in patients estimated to be at moderate or high risk of PONV [7].

Despite considerable improvement in the pharmacological control of PONV during recent years, there remains a significant need for new antiemetic agents. For example, even with the use of prophylaxis, PONV still occurs frequently and must then be treated, ideally with an agent having a different mechanism of action from those used for prevention [8]. Also, there is a particular requirement for agents with good anti-nausea activity [9]. Finally, surgical patients often receive strong opioids for pain control post-operatively, and it is this group of analgesics that is likely to provoke emetic symptoms. Thus, there is an ongoing need for antiemetic drugs to control opioid-induced emesis.

Buspirone hydrochloride, an anxiolytic agent introduced in the 1980s, is a $5HT_{1A}$ partial agonist and D_2 and D_3 antagonist [10]. It has been considered to be a potential antiemetic due to the importance of these pathways in nausea and vomiting. Given subcutaneously, buspirone has shown antiemetic efficacy in numerous animal models [11–14]. However, oral buspirone was found to be ineffective against cisplatin-induced emesis in a human trial [15]. This led to the hypothesis that the failure of oral buspirone may result from its extensive first pass metabolism in the liver to 1-pyrimidinylpiperazine (1-PP) [16], an α_2 -antagonist shown to have pro-emetic potential in the ferret. Parenteral administration of buspirone avoids such first-pass metabolism. However, the antiemetic efficacy of parenteral buspirone in humans remains unknown.

The study reported here was conducted to explore the prophylactic antiemetic efficacy of different doses of intravenous buspirone in surgical patients. We hypothesised that intravenous buspirone, in the dose range tested and in a dose-dependent manner, would prevent PONV without inducing unacceptable adverse effects.

Methods

Study participants

Adults who had given written, informed consent were enrolled if they were due to have an in-patient operation under general anaesthesia (other than intra-thoracic, transplant or central nerve system surgery) that was expected to last at least 1 h and during which inhalational anaesthetics were to be used as maintenance agents and if they had at least two of four pre-specified risk factors for developing PONV: (1)

female sex; (2) non-smoking status; (3) a prior history of PONV or motion sickness; (4) the expectation of receiving opioids for postoperative analgesia. Patients had to have adequate haematological, renal and hepatic function (alanine aminotransferase and aspartate aminotransferase levels of $<2.5 \times$ upper limit of normal [ULN]; bilirubin and creatinine levels of $<1.5 \times$ ULN; haemoglobin ≥ 9.5 g dL⁻¹; white cell count range $4.0\text{--}11.0 \times 10^9$ L⁻¹; platelet count range $150\text{--}400 \times 10^9$ L⁻¹) and were excluded if they were expected to require postoperative ventilation or if they had Parkinson's disease, a clinically significant cardiac arrhythmia or epilepsy.

Study design

This double-blind, placebo-controlled, parallel-group study was conducted at 17 centres in France, Germany, Switzerland and the USA. Each centre obtained independent approval from their institutional ethics committees and their national drug safety agencies (Germany: Bundesinstitut für Arzneimittel und Medizinprodukte; France: Agence française de sécurité sanitaire des produits de santé; Switzerland: Swissmedic; USA: Food and Drug Administration [FDA]).

Intravenous buspirone hydrochloride (strength 4.0 mg mL⁻¹, diluted in phosphate buffered saline, pH 5.5) and matching placebo (phosphate buffered saline, pH 5.5), both manufactured specifically for the study, were supplied to each site pharmacy by the sponsor. By means of an interactive telephone- and internet-based randomisation service, the site obtained a randomised treatment allocation for each subject to one of five groups: 0.3, 1, 2 or 3 mg of buspirone or placebo. The range of doses was determined at the upper end by considering the tolerability profile of intravenous buspirone in healthy volunteers and at the lower end by extrapolation from efficacy data seen in ferrets, using a conversion factor of 5.3 to take into account the species difference in surface area to volume ratio, in line with FDA guidance [17]. The randomisation was stratified by country and by number of risk factors (2 vs. 3 or 4). An unblinded pharmacist at each site, with no other study involvement, made up a treatment syringe of equal volume (28 ml) containing placebo or the appropriate dose of buspirone for each subject. Syringes were matching and were labelled with the randomisation number only to ensure that allocation was concealed and that the investigators, other study personnel and subjects were all blinded as to treatment group.

Pre-medication and anaesthetic regimens were at the investigators' discretion, except that total intravenous anaesthesia with propofol, which may have antiemetic properties, was not permitted, nor was it allowed to give any anti-emetic pre-operatively. The study drug was administered by slow intravenous push over 1 min at the end of surgery, defined as up to 15 min before completion of wound closure.

Assessments

The primary endpoint of the study was the cumulative incidence of PONV (i.e. vomiting or significant nausea) in the 24-h period after the end of surgery. Vomiting included retching. Significant nausea was defined as a score of ≥ 4 on an 11-point verbal rating scale running from zero (no nausea at all) to ten (the worst nausea imaginable). Patients were asked prospectively by blinded dedicated research assistants about nausea every 30 min after surgery up to and including the 1-h mark and then again at 6 and 24 h. Any nausea spontaneously reported by the patient was also recorded.

Secondary efficacy endpoints included the time to first vomiting and the use of any antiemetic rescue medication, which could be requested by the patient at any time. Further evaluation was specified in the early postoperative period (0–2 h) as well as at 2–6 h and 6–24 h postsurgery. Safety was analyzed in terms of the nature and incidence of adverse events and the change in Aldrete score between baseline and 1 h postoperatively. The Aldrete score is a validated instrument for assessing recovery from anaesthesia which assigns a score of 0–2 to each of five domains (activity, respiration, circulation, consciousness and oxygen saturation), giving a total score of up to 10 [18].

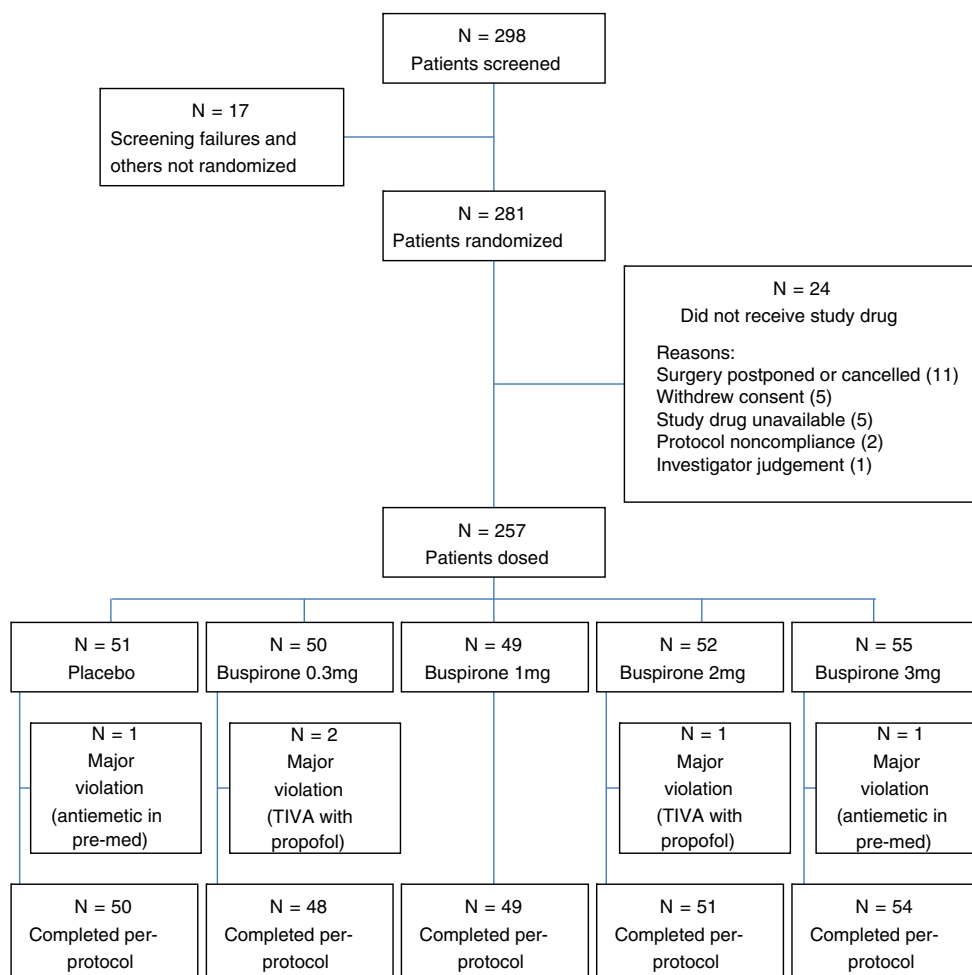
Although pharmacokinetics was not a primary aim of this clinical dose-finding study, we evaluated pharmacokinetics for a selection of patients in each study arm in order to determine if there was any difference between the anaesthetised individuals in this study and healthy volunteers. For practical reasons, sampling was limited to five study sites. Samples at time zero, 5 and 30 min, 1 and 4 h were selected from three to five subjects per study arm for analysis. Data were analyzed for concentration of buspirone and its major metabolite, 1-PP.

The primary statistical test was a comparison of the incidence of PONV between each treated group and the placebo group using Pearson's chi-square test with continuity correction, with a one-sided significance level of 0.1. A sample size of 50 evaluable patients per group was calculated to give a power of 85 % to detect a difference between the expected placebo PONV rate of 60 % and a target PONV rate of 35 % in the best active treatment group.

Results

In total, 298 patients were screened and 281 were randomised into the study (Fig. 1). Twenty-four patients did not receive the study drug, mostly because their operation was cancelled or postponed (11 cases), the study drug was unavailable (5 cases) or they withdrew consent prior to surgery (5 cases). This left 257 patients who

Fig. 1 Flowchart of study.
TIVA Total intravenous
anaesthesia with propofol



received the study drug and fulfilled the criteria for inclusion in the primary safety and efficacy analyses. Study arms were well balanced for age, sex, body mass index and race (Table 1). The mean age of patients at enrolment was 50.6 years, and 89.9 % were female.

There were no significant differences between study arms in terms of past medical history, baseline physical examination, vital signs and type of operation. Hysterectomy occurred in 22.6 % of patients, laparoscopic surgery other than

hysterectomy or cholecystectomy in 19.8 %, and breast surgery in 14.4 %.

There were no significant differences between study arms in terms of anaesthetic technique. All patients except one received opioids, and 93 % received a volatile anaesthetic (desflurane, isoflurane or sevoflurane). Among the few who did not receive a volatile anaesthetic, two received total intravenous anaesthesia with propofol and were therefore protocol violators and subsequently excluded from the

Table 1 Baseline demographics. There were no significant differences between groups

Demographic characteristics	Placebo (N=51)	Buspirone 0.3 mg (N=50)	Buspirone 1 mg (N=49)	Buspirone 2 mg (N=52)	Buspirone 3 mg (N=55)
Age (years)	51.2 (20–76)	49.4 (19–86)	49.5 (21–85)	52.3 (25–86)	50.3 (25–78)
Body mass index (kg m ⁻²)	27.1 (18.1–40.9)	26.9 (15.1–42.9)	26.8 (17.7–40.2)	26.7 (19.1–47.0)	26.9 (17.1–42.6)
Female	45 (88.2 %)	49 (98.0 %)	43 (87.8 %)	45 (86.5 %)	49 (89.1 %)
White/Caucasian	50 (98.0 %)	48 (96.0 %)	47 (95.9 %)	51 (98.1 %)	47 (85.5 %)

Data are presented as the mean with the range in parenthesis, or as the number with the percentage in parenthesis

analysis. Thirty-nine patients (15 %) received nitrous oxide and 43 (17 %) had their neuromuscular block reversed with neostigmine. These patients were evenly distributed among the groups. In terms of predefined risk factors, 45 patients had two of the risk factors, 38 % had three and 17 % had four.

Efficacy

In the placebo group, the mean 24-h incidence of PONV was 49.0 % (90 % confidence interval [CI] 37.5–60.5 %). There was a lower incidence of PONV among patients receiving placebo who were prospectively identified as having two risk factors than among those with three or four risk factors (40.9 vs 59.9 %, respectively; odds ratio 0.46, 90 % CI 0.28–0.74; $P=0.0081$).

With buspirone, the mean 24-h incidence of PONV ranged from 40.8 % (90 % CI 29.3–52.4 %) in the 1 mg arm to 58.0 % (46.5–69.5 %) in the 0.3 mg arm. There was no significant difference in the incidence of PONV between placebo and any of the buspirone study arms (Table 2).

In the placebo group, the mean 24-h incidence of vomiting alone and nausea alone was 27.5 and 43.1 %, respectively. There was no significant difference in the incidence of vomiting or nausea between patients receiving placebo and any of those enrolled in the buspirone study arms (Table 2).

The median time to first episode of vomiting across the study population was 3.8 h, with the shortest time in the 2 mg buspirone group (median 2.1 h) and longest time in the placebo and 0.3 mg buspirone groups (median 4.9 h). There was no significant difference between the groups. There was also no difference between placebo and any active group in terms of severity of nausea, measured as the area under the curve, nor in the incidence of PONV, vomiting, including

retching, or nausea in each of the pre-specified time periods after surgery.

Pharmacokinetics

The pharmacokinetic profile of intravenous buspirone in anaesthetised patients was essentially similar to that seen in healthy volunteers, with the peak plasma concentration and total exposure not deviating significantly from dose-proportionality (Fig. 2). The average plasma concentration of buspirone 1 h after administration was 2–3 ng mL⁻¹ per milligram of drug dosed. The plasma concentration of the primary metabolite, 1-PP, was below 1 ng ml⁻¹ at all times for all doses of buspirone.

Safety

The most commonly reported adverse events were gastrointestinal disturbances, such as nausea, vomiting, flatulence and constipation, postoperative pain and nervous system disorders, including headache and insomnia (Table 3). There were no significant differences between the placebo group and any of the four buspirone dose groups. Overall, 90.7 % of patients experienced at least one adverse event during the study, with no significant difference in adverse event rate between the groups. A little over one-quarter of patients experienced adverse events considered to be at least remotely related to study medication, ranging from 22.0 % (0.3 mg buspirone) up to 33.3 % (placebo).

In the 1 mg buspirone group, the Aldrete score showed a median decline between baseline and 1 h after surgery of 1 point. This was a significantly greater decrease than that for placebo ($P<0.01$) or 3 mg buspirone ($P<0.05$). The median decrease in the 0.3 mg group was also significantly greater than that for placebo ($P<0.05$).

Table 2 Incidence of postoperative nausea and vomiting, nausea, vomiting and/or rescue medication use in the 24-h postoperative period

Study endpoints	Placebo (N=51)	Buspirone 0.3 mg (N=50)	Buspirone 1 mg (N=49)	Buspirone 2 mg (N=52)	Buspirone 3 mg (N=55)
Postoperative period 0–24 h					
PONV	25 (49.0)	29 (58.0)	20 (40.8)	30 (57.7)	28 (50.9)
Nausea	22 (43.1)	24 (48.0)	17 (34.7)	25 (48.1)	23 (41.8)
Vomiting	14 (27.5)	13 (26.0)	11 (22.4)	19 (36.5)	18 (32.7)
Rescue medication use	20 (39.2)	28 (56.0)	15 (30.6)	28 (53.8)	23 (41.8)
PONV, postoperative period 0–2 h	14 (27.5)	16 (32.0)	10 (20.4)	23 (44.2)	19 (34.6)
PONV, postoperative period 2–6 h	8 (15.7)	7 (14.0)	3 (6.1)	5 (9.6)	5 (9.1)
PONV, postoperative period 6–24 h	3 (5.9)	6 (12.0)	7 (14.3)	2 (3.9)	4 (7.3)

PONV, Postoperative nausea and vomiting (including retching)

Data are presented as the number (of patients), with the percentage in parenthesis

There were no significant differences between groups

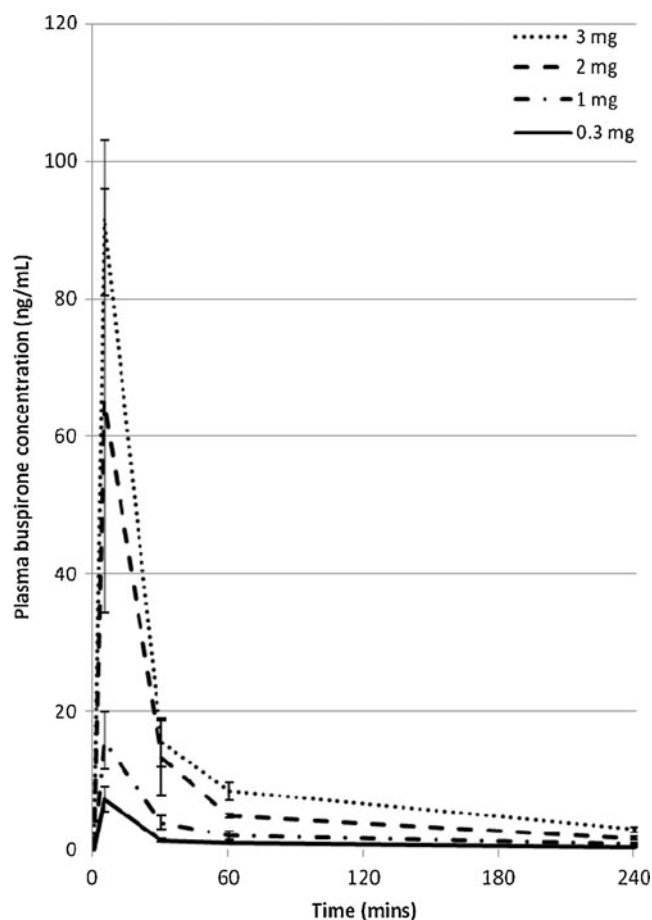


Fig. 2 Plasma concentration of buspirone against time for the different doses of intravenous buspirone

Discussion

Nausea and vomiting remain a significant problem in the postoperative period. Although the design and conduct of this study were broadly similar to those of many previous PONV

studies, the approach taken to patient selection differs from the majority of previous studies. It has been common practice to specify as an inclusion criterion a particular operation or class of operations, such as, for example, abdominal hysterectomy or open abdominal surgery. Our approach was to select patients on the basis of empirically established PONV risk factors [2]. The resulting placebo PONV rate was adequate to discriminate a potentially effective treatment. However, although half of the patients given placebo experienced at least one PONV episode, in the 24-h period after their operation there was no significant difference in the incidence of PONV between patients given placebo and those receiving any of the different doses of buspirone.

The negative result was a surprise, given the pharmacology of buspirone and its convincing antiemetic efficacy when given parenterally against various emetogens in the dog [11], cat [12, 13] and *Suncus murinus* [14]. There are several possibilities for this discordance between pre-clinical and human data. The most obvious methodological issues involve the dose range of buspirone and the route and timing of administration. If the animal studies are indeed accurate in their characterization of the antiemetic activity of buspirone, then this discordance would suggest an inapplicability of the animal models of emesis to the complex situation of PONV or perhaps a true species difference in the physiology of emesis or the behaviour of buspirone. In pre-clinical models, the antiemetic efficacy of an experimental intervention is usually tested in animals exposed to a single emetogenic stimulus, for example, apomorphine or morphine. However, none of these echoes PONV, which is clearly a multifactorial phenomenon, including patient, anaesthesia and surgical factors.

It seems unlikely that the study data are substantially inaccurate. Our study had a robust design with a minimal risk of selection or observer bias. Trial size was adequate; a negative result by random chance is therefore unlikely. The treatment

Table 3 Treatment-emergent adverse events (excluding nausea and vomiting) occurring in at least 3 % of the patient population

Adverse events	Placebo (N=51)	Buspirone 0.3 mg (N=50)	Buspirone 1 mg (N=49)	Buspirone 2 mg (N=52)	Buspirone 3 mg (N=55)	Total (N=257)
Procedural pain	24 (47.1)	25 (50.0)	32 (65.3)	25 (48.1)	24 (43.6)	130 (50.6)
Flatulence	5 (9.8)	7 (14.0)	7 (14.3)	7 (13.5)	4 (7.3)	30 (11.7)
Insomnia	6 (11.8)	3 (6.0)	8 (16.3)	7 (13.5)	6 (10.9)	30 (11.7)
Constipation	4 (7.8)	5 (10.0)	5 (10.2)	4 (7.7)	5 (9.1)	23 (8.9)
Hypertension	2 (3.9)	0 (0.0)	1 (2.0)	4 (7.7)	4 (7.3)	11 (4.3)
Hypokalaemia	3 (5.9)	1 (2.0)	3 (6.1)	3 (5.8)	0 (0.0)	10 (3.9)
Headache	1 (2.0)	1 (2.0)	4 (8.2)	4 (7.7)	0 (0.0)	10 (3.9)
Dizziness	1 (2.0)	1 (2.0)	2 (4.1)	3 (5.8)	2 (3.6)	9 (3.5)
Hypothermia	1 (2.0)	1 (2.0)	2 (4.1)	2 (3.8)	2 (3.6)	8 (3.1)

Data are presented as the number (of patients), with the percentage in parenthesis

There were no differences between groups (i.e. all *P* values >0.05)

arms were well-balanced. Indeed, the study delivered completely consistent efficacy data across all parameters and subsets.

One explanation for the discordance may relate to the dose range of intravenous buspirone in the trial. Extrapolating dose from animal to man is difficult. For example, the published K_1 value for buspirone against D_2 is some tenfold higher in the rat [19] than in humans [20], although this does not necessarily mean the same is true in any other small mammal species. The pharmacokinetics and binding affinity of buspirone for the D_2 and $5HT_{1A}$ receptors in the ferret are unknown and may be very different from those in humans. When the difference in the ratio of volume to surface area between these species are taken into consideration, it has been proposed that a dose of a drug in ferrets is equivalent to 5.3-fold the dose in humans [17]. However, that would assume a broad similarity in terms of pharmacokinetics and pharmacodynamics. This cannot be verified in the case of buspirone because its pharmacokinetics and its binding affinity for the D_2 and $5HT_{1A}$ receptors in the ferret are unknown and may be very different from those in humans.

It may be that subcutaneous rather than intravenous administration is required to achieve an antiemetic effect, perhaps by reducing the ratio of peak plasma concentration to overall exposure. We had decided to avoid dosing intravenous buspirone above 3 mg due to the fear of $5HT_{1A}$ -related central nervous system effects. This decision may have prevented exploration of the effective dose range of the agent, and in particular its effective dose as a D_2 antagonist.

The complex interaction of buspirone with $5HT_{1A}$ receptors may also provide an explanation. Buspirone acts at two main groups of $5HT_{1A}$ receptors: pre-synaptic auto-receptors in the dorsal raphe nucleus, inhibiting serotonin release, and post-synaptic receptors in the cortical and limbic regions [19, 21, 22]. Because of their greater density, pre-synaptic auto-receptors are activated at lower doses of buspirone. These receptor populations may have opposite effects in terms of emesis. The selective $5HT_{1A}$ partial agonist tandospirone, when given at a moderate oral dose, was found to be effective as an antiemetic in a clinical study [4], but provoked vomiting when given orally at high doses ($100 \text{ mg kg}^{-1} \text{ day}^{-1}$) to dogs in an acute toxicity study [23]. Peak plasma concentrations of buspirone resulting from intravenous dosing may have acutely activated both pre- and post-synaptic receptor populations, triggering pro-emetic as well as, or instead of, antiemetic pathways. The observation that activation of $5HT_{1A}$ receptors in the prefrontal cortex of rats led to increased mesocortical dopamine release [24] may provide a clue as to the mechanism by which high concentrations of buspirone could provoke—or at least fail to prevent—emesis.

The partial agonist behaviour of buspirone, meaning that it exhibits both agonist and antagonist activity at the $5HT_{1A}$ receptor, may also add complexity. The agonist effect would tend to be inversely proportional to the concentration of

serotonin present at the receptor. In a situation where there is a high level of endogenous serotonin, such as may be the case in a patient suffering from PONV, buspirone may act as a relative antagonist by competing with the fully agonist endogenous serotonin [25]. At pre-synaptic autoreceptors, this could lead to increased serotonin release.

Finally, it is possible that the $5HT_{1A}$ activity of buspirone may have species-dependent effects. Pathways involving $5HT_{1A}$, as well as the interaction between D_2 and $5HT_{1A}$, may be substantially more complex in humans than in other animals. Full $5HT_{1A}$ agonists, such as flesinoxan and repinotan, have been reported to provoke nausea and vomiting in humans [26–28] but to prevent emesis in the cat [29]. Given the heavy involvement of $5HT_{1A}$ pathways in higher cortical functions such as learning and memory [30], it does seem plausible that significant differences would exist in such pathways between animal brains and that they are far more developed in the human brain.

In conclusion, in this first clinical study of the perioperative use of intravenous buspirone, we were unable to confirm a beneficial effect, within the tested dose-range, on the prevention of PONV. The results of this study emphasise the difficulty in extrapolating from animal models of emesis to clinical efficacy in PONV.

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Conflict of interest and disclosure There was a pre hoc agreement that the investigators would have the right to examine the data independently and to submit a manuscript for publication without first obtaining the consent of the sponsor and that the results of this study would be published as a full report, in their entirety and not as individual centre data, and independent of the result of the study. MRT had full access to all the data and coordinated the decision to submit for publication. All authors participated in writing the manuscript. GMF is an employee of Acacia Pharma Ltd.

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