

I.V. APD421 (amisulpride) prevents postoperative nausea and vomiting: a randomized, double-blind, placebo-controlled, multicentre trial

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Editor's key points

- This is a dose-finding study to investigate amisulpride for i.v. injection (APD421), a D₂/D₃-antagonist, in postoperative nausea and vomiting (PONV) prophylaxis.
- This study demonstrates that a 5 mg dose of APD421 reduced PONV from 69 to 40%, compared with placebo.
- A lower dose of APD421 (1 mg) also reduced PONV significantly ($P < 0.05$) but higher dosages did not.

Background. Postoperative nausea and vomiting (PONV) remain significant clinical problems for patients, especially nausea. The D₂-antagonist droperidol was popular for prophylaxis until safety concerns limited its use. In early testing, APD421 (amisulpride for i.v. injection), a D₂/D₃-antagonist, has shown promising antiemetic efficacy at very low doses. We conducted a randomized, double-blind, dose-finding study to investigate APD421 in PONV prophylaxis.

Methods. Adult surgical patients with ≥ 2 Apfel risk factors for PONV undergoing surgery expected to last ≥ 1 h and receiving standard inhalation anaesthesia were randomized to receive placebo or one of three doses of APD421 (1, 5, or 20 mg) as a single i.v. administration at anaesthesia induction. The primary endpoint was PONV (vomiting/retching or antiemetic rescue) in the 24 h period after surgery.

Results. Two hundred and fifteen patients received study drug, 92% female and 60% with ≥ 3 risk factors. Groups were well balanced for baseline characteristics and risk factors. The PONV incidence was 37/54 [69%; 90% confidence interval (CI), 57–79%] in the placebo group; 28/58 (48%; 90% CI, 37–60%) with 1 mg APD421 ($P=0.048$); 20/50 (40%; 90% CI, 28–53%) with 5 mg ($P=0.006$); and 30/53 (57%; 90% CI, 44–68%) with 20 mg ($P>0.1$). APD421 at 5 mg also significantly improved vomiting, rescue medication use, and nausea rates. The safety profile of APD421 was similar to that of placebo at all doses, with no significant central nervous system (CNS) or cardiac side-effects.

Conclusions. APD421 given i.v. before surgery is safe and effective at reducing PONV in moderate/high-risk adult surgical patients. The optimal dose tested was 5 mg.

Trial Registration. ClinicalTrials.gov identifier: NCT01510704. <http://www.clinicaltrials.gov/ct2/show/NCT01510704?Term=APD421&rank=1>.

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Vomiting and nausea, especially the latter, remain important issues after surgery, despite the availability of numerous antiemetic agents. Dopamine (D₂), serotonin (5-HT₃), and histamine

(H₁) antagonists are commonly used as prophylactic agents, as is the corticosteroid dexamethasone, but the incidence of postoperative nausea and vomiting (PONV) is still appreciable. The

D₂-antagonist droperidol was an especially valued agent, described as the 'overwhelming first choice for PONV prophylaxis' in international consensus guidelines,^{1,2} until safety concerns, particularly QT-interval prolongation, led to its withdrawal or disuse in many countries. New agents are therefore still required, especially those with good activity against nausea.

APD421 is an i.v. formulation of amisulpride for the new use of prevention and treatment of nausea and vomiting. Amisulpride is an anti-psychotic agent first launched as Solian® tablets (Laboratoires Delagrangue, now sanofi-aventis) in France in 1986 and now approved in oral form in >50 countries worldwide. It is a potent but 'atypical' D₂-antagonist with a very low tendency to cause the side-effects which have plagued older members of the class, such as QT-interval prolongation and extra-pyramidal signs and symptoms.³ It is, furthermore, a potent antagonist at D₃ receptors, which have also been implicated in the emetic response.⁴

In pre-clinical testing, APD421 showed a significant anti-emetic effect against challenges with the D₂-agonist apomorphine, with cisplatin and with morphine. We, therefore, conducted this double-blind, placebo-controlled study with the primary objective of assessing the efficacy of different doses of i.v. APD421 as PONV prophylaxis.

Methods

Study design

This double-blind, placebo-controlled, parallel-group study was conducted between January and April 2012 at 10 sites, predominantly University Hospitals, in Germany, France, and the USA, each centre obtaining prior approval from an authorized ethics committee and their national regulatory authority. The trial was registered on EudraCT (ref.: 2011-004267-71) and ClinicalTrials.gov (ref.: NCT01510704).

Adults who had given written informed consent were enrolled if they were due to have an in-patient operation [other than intra-thoracic, transplant, or central nervous system (CNS) surgery], expected to last at least 1 h, under general anaesthesia, and had at least two of the following risk factors for developing PONV: (i) female sex; (ii) non-smoking status; (iii) a prior history of PONV or motion sickness; and (iv) being expected to receive postoperative opioid analgesia.

Adequate haematological, renal, and hepatic function (haemoglobin ≥ 9 g dl⁻¹; white cells $\geq 3 \times 10^9$ litre⁻¹; platelets $\geq 100 \times 10^9$ litre⁻¹; creatinine $< 2 \times$ upper limit of normal (ULN); bilirubin $< 3 \times$ ULN; and alanine aminotransferase (ALT) and aspartate aminotransferase (AST) both $< 5 \times$ ULN) were required. Patients were not eligible if they were expected to require postoperative ventilation or need a naso- or oro-gastric tube *in situ* after surgery, or if they had Parkinson's disease, a pre-existing vestibular disorder or history of dizziness, a history of alcohol abuse, a clinically significant cardiac arrhythmia, or epilepsy.

Subjects were randomized to one of four parallel groups: 1, 5, or 20 mg of i.v. APD421 or placebo, on a 1:1:1:1 basis. The randomization was stratified by centre and by the number of risk factors (2 vs 3 or 4), the latter intended to give as homogeneous as possible a risk of PONV in each of the groups, within the

constraints of the sample size. The APD421 dose range was determined partly by reference to data generated in an ongoing clinical trial of APD421 in patients receiving cisplatin chemotherapy and partly by extrapolation from pre-clinical efficacy data. Each site was supplied with vials of i.v. APD421 (at strengths of 0.5, 2.5, and 10 mg ml⁻¹ to maintain equal volume of study drug) and matching placebo containing the same excipients but no active ingredient, manufactured specifically for the study. All vials were identically labelled except for an individual subject number derived from a master randomization list available to the contract manufacturer of the study medication, but not to the sponsor, any site research personnel, or study participants. An internet-based randomization system provided sites on demand with a subject number for each patient randomized, which could then be matched to the subject number on the appropriate vial of study medication held at the site. A 2 ml aliquot of study medication was administered by slow i.v. push over 2 min at the time of induction of anaesthesia.

Pre-medication and anaesthetic regimens were at investigators' discretion, except that total i.v. anaesthesia with propofol, which would have significantly reduced the control PONV rate, was not permitted, nor was it allowed to give any anti-emetic apart from study drug before operation. The investigator's usual institutional practice was also followed for other aspects of peri- and postoperative care, such as analgesia. Rescue medication, specified as the investigator's choice of 5-HT₃-antagonist, was available to any patient who retched, vomited, or experienced nausea from which they wanted relief. One or more additional agents of a different class could be added at the discretion of the investigator in the event of PONV which was not, or was considered likely not to be, controlled by the 5-HT₃-antagonist.

Assessments

The primary population for both efficacy and safety analysis was the intention-to-treat (ITT) population, defined as all subjects who signed the informed consent form, were randomized into the study, and received study medication. A per-protocol analysis population was defined as a subset of the ITT population with no major protocol violations. A major violation was considered one that could reasonably be considered to have had a material impact on the subject's outcome, such as inadvertent use of antiemetics or use of excluded anaesthetic techniques or agents. The final constitution of study analysis populations was determined on a fully blinded basis before database closure.

The primary endpoint of the study was the incidence of PONV, defined as any episode of vomiting, retching, or any use of rescue antiemetic medication in the 24 h period after the end of surgery, timed from the completion of wound closure. Secondary efficacy endpoints included incidence and severity of nausea, time to PONV, and the use of antiemetic rescue medication. Nausea was measured using an 11-point verbal rating scale (VRS) running from 0 (no nausea at all) to 10 (the worst nausea imaginable). Any nausea spontaneously

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