INVESTIGATING THE EFFECT OF INTRAVENOUS APD421 (AMISULPRIDE) AND THE ETHNIC DIFFERENCES BETWEEN JAPANESE AND CAUCASIANS ON CARDIAC CONDUCTION

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Introduction

Amisulpride is a substituted benzamide that acts as a selective antagonist of dopamine D_2 and D_3 receptors [1]. Some dopamine antagonists have been associated with prolongation of the QT interval.

Amisulpride APD421 (amisulpride) has shown promising efficacy against PONV at low doses [2]. This is the first thorough QT/QTc (TQT) to exclude an effect of i.v. APD421 on the QTc interval at the therapeutic dose proposed for PONV management.

Aim

- Characterise the effects of single intravenous (iv) doses of 5 mg and 40 mg APD421 on the QTc interval.
- Compare the PK QTc relationship in two ethnicities: Caucasian and Japanese.

Methods

Study Design: randomised, double-blind, placebo and positive-controlled, four-way crossover study with 40 subjects (n= 17Japanese and n=23 Caucasian). Treatment sequences were as follows:

Period 1		Washout ≥7 days	Period 2		Washout ≥7 days	Period 3		Washout ≥7 days	Period 4	
Day −1	Day 1		Day −1	Day 1		Day −1	Day 1		Day −1	Day 1
IV-P	T5		IV-P	T40		M-P	M		IV-P	IV-P
IV-P	T40		IV-P	IV-P		IV-P	T5		M-P	M
IV-P	IV-P		M-P	M		IV-P	T40		IV-P	T5
M-P	M		IV-P	T5		IV-P	IV-P		IV-P	T40

IV-P: IV placebo infused over 2 min or 8 min.
T5: Single 5 mg iv dose of APD421 of 2.5 mL infused over 2 min.
T40: Single 40 mg iv dose of APD421 of 20 mL infused over 8 min.
M: Moxifloxacin, provided as a single, oral 400 mg tablet.
M-P: moxifloxacin placebo, provided as a single, inactive oral tablet.

ECG recording: Triplicate ECG recordings were performed using a MAC1200® ECG recorder (GE Healthcare) and stored electronically on the Medical MUSE® information system (GE Healthcare) at the following time points: pre-dose, 2, 8 and 30 min, 1, 1.5, 2, 3, 4, 5, 6, 8, 12 and 24 h post-dose of each treatment period after the subjects have been resting in a supine position for at least 10 min. ECGs were assessed by cardiologists with extensive experience of manual on screen over reading with electronic callipers using the commercially available MUSE® to correct any implausible readings presented by the automated process as described in [3].

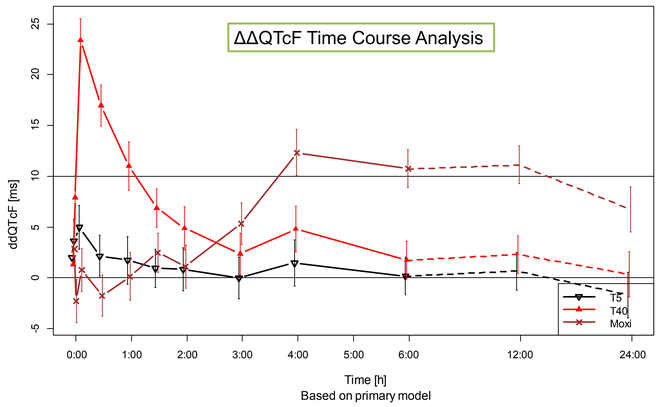
Statistical analysis: The primary analysis used the change from average baseline of QTcF of the baseline day. A linear mixed effects model with sequence, period, gender and race and treatment as fixed effects and baseline as covariate was adapted, with subject (nested in sequence) as a random effect. To show assay sensitivity, a Hochberg procedure was applied. A linear concentration response model was fitted to all QTcF data. The placebo corrected change from average baseline (ΔΔQTcF) was used as a dependent variable. The model had a fixed intercept and slope but random intercepts only.

Pharmacokinetics: Timings for PK blood sampling were coincident with ECG time points. Plasma samples for determination of APD421 concentration were analysed by Quotient BioAnalytical Sciences, using a validated LC/MS/MS method.

Safety Assessment: Adverse events were recorded from the date informed consent was signed until follow-up.

Results

Effect of APD421 on QTcF



5 mg APD421:
5.0 ms at 8 min (90% CI: 2.8, 7.1 ms).

40 mg APD421:
23.4 ms at 8 min (90% CI: 21.3, 25.5 ms).
The ΔΔQTcF returned to below 5 ms by 2 h and was at baseline levels by 6 h.

Moxifloxacin: 12.3 ms at 4 h (90% CI: 10.1, 14.6 ms) with significant QTcF elevation at 24 h.

Figure 1: Difference to Time Matched Placebo of Change from Baseline (ΔΔQTcF).

Pharmacokinetics

Parameters	APD421 5 mg Over 2 min	APD421 40 mg Over 8 min
n	39	39
$AUC_{0-\infty}$ (ng.mL^{-1}.h)	154.00 (30.17)	1374.14 (239.47)
AUC_{0-t} (ng.mL^{-1}.h)	134.59 (30.17)	1334.01 (228.36)
C_{max} (ng.mL^{-1})	200.49 (139.16)	1305.44 (329.35)
t_{max} (h)[a]	0.033 (0.033-0.133)	0.133 (0.067-0.183)
$t_{½}$ (h)	4.05 (0.78)	5.04 (0.66)

a Median (range) presented for t_{max}.

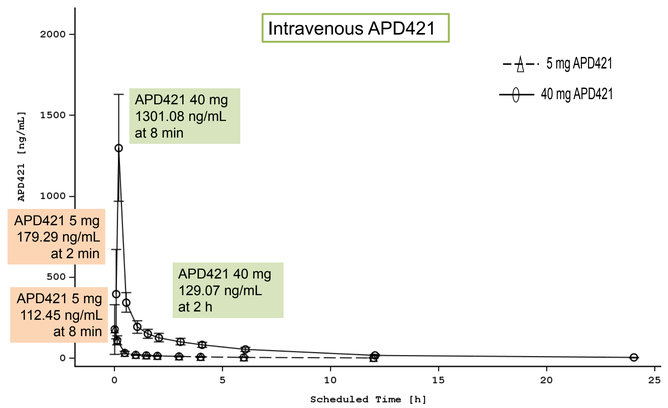
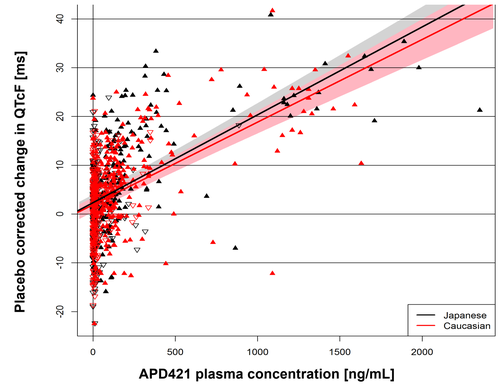


Figure 2: Mean Plasma Concentrations of APD421 (ng/mL) by dose group (linear scale).

Concentration response analysis



PK-PD relationship was linear and dose proportional.

No differences between Caucasian and Japanese. The difference between slope is not statistically significant.

PK-PD predicted that each additional increase of 10 ng.mL^{-1} in plasma APD421 concentration would lead to an increase in QTcF of 0.175 ms.

No evidence of hysteresis.

Figure 3: PK-PD for APD421 Following Single Intravenous Doses of 5 mg and 40 mg APD421. Regression line and 90% Confidence region from concentration-effect model.

Safety and Tolerability

A total of 74 adverse events (AEs) were reported in 34 of 40 subjects, 8 with moxifloxacin, 11 with placebo, 12 with 5 mg APD421 and 43 with 40 mg APD421, the majority of which were pain at the injection site. There were no SAEs, no AEs which led to withdrawal and no AEs with severe intensity. There were no clinically relevant changes in the laboratory parameters or physical examinations.

Conclusions

Dose effects

- The 5 mg dose of APD421, the proposed therapeutic dose in PONV, was not associated with a QTcF prolongation of concern at any time point when administered at 2.5 mg.min^{-1}.
- A more rapidly infused (5 mg.min^{-1}) eight-fold supra-therapeutic dose of 40 mg APD421 did cause a meaningful prolongation of the QTc interval. This returned to below 5 ms by 2 h.
- At 8 min, time of mean peak ΔΔQTcF, the APD421 plasma levels for 40 mg dose are X12 times higher than the plasma levels for the 5 mg dose. When plasma levels decrease to those levels seen at C_{max} for 5 mg, the QTc values drop to below 5 ms.
- No QTcF values of >480 ms were observed at any point during the study.

Ethnic differences

- Both doses were well tolerated by Caucasian and Japanese subjects.
- Based on a concentration response analysis, no statistically significant differences between ethnicities could be detected. Data was not adjusted for weight but QTc effects are comparable at similar APD421 plasma concentrations.

PK-PD

- The PK-PD relationship was linear and proportional.
- PK-PD analysis predictions were in close agreement with the observed data.
- This study was limited to two doses and two infusion rates.

References

1. Coukell AJ, et al. CNS Drugs 1996; 6(3): 237-56. **2.** Kranke P, et al. Br J Anaesth 2013; 111 (6): 938–45. **3.** Ferber et al. Biomed Res Intern 2015 doi:10.1155/2015/293564.

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