Effect on ECG Parameters of ABP-700 Infusions in Combination with Opiates Targeting Sedation in Man

Presenting Author: P. Meyer, MD, PhD 1
Co-Authors: S. Sweeney, BS[2]; J. A. Campagna, MD, PhD[2]; John J. Marota MD, PhD[2]; B.I. Valk, BSc[1]; S. Meier, MD[1]; M.M.R.F.Struys, MD, PhD[1]; Borje Darpo, MD, PhD[3]

[1]Department of Anesthesiology, University of Groningen, University Medical Center Groningen, The Netherlands
[2]The Medicines Company, Parsippany, NJ, USA
[3]iCardiac Technologies, Rochester, NY, USA

Introduction: ABP-700 is a novel, second-generation metabolically labile etomidate analogue in development for procedural sedation and general anesthesia. The goal of this analysis is to investigate the effects of ABP-700 on electrocardiogram (ECG) parameters of conduction and repolarization during co-administration with commonly used opiates, fentanyl (FEN) and remifentanil (REM) during infusions targeting production of hypnosis ranging from light/moderate to deep sedation.

Methods: An open label, phase I study was performed following ethics approval in accordance with the Declaration of Helsinki and in compliance with GCP. Targeted arterial plasma concentrations of ABP-700 were selected based upon results of prior phase I trials. Dual-stage, 30min ABP-700 infusion regimens were designed to produce clinical effect within 5 minutes. Fifty-six subjects were dosed across 8 cohorts of either 4 or 8 subjects. ABP-700 was given either 5 min after FEN bolus (1mcg/kg, iv) as pre-treatment in 5 cohorts (n = 32), or 5 min after initiation of co-infusion with REM (0.125 mcg/kg/min infusion for 3 min, then reduced to 0.05 mcg/kg/min for 32 min) in 3 cohorts (n = 24).

Five ABP-700 fixed infusion paradigms (PAR) were used: PAR-1, 25 mcg/kg/min for 10 min then 20 mcg/kg/min for 20 min; PAR-2, 50 mcg/kg/min for 5 min then 30 mcg/kg/min for 25 min; PAR-3, 4 and 5, 70, 80 or 90 mcg/kg/min for 3 min then 40, 45 or 50 mcg/kg/min for 27 min. A sixth ABP-700 dosing paradigm tested anesthesiologist titration to effect of moderate sedation as 80 mcg/kg/min for 1 to 5 min then 45-60 mcg/kg/min for 27 min; this cohort received concurrent REMI infusion. FEN cohorts received PAR-1 through 5; REM cohorts received PAR-3, 4 and 6.

Hypnotic effect was assessed by MOAA/S and BIS. Arterial plasma ABP-700 concentration was determined in association with sedation assessments. ECG was recorded continuously by 12-lead Holter monitoring starting 1 h prior to dosing to 4 hours post dose. Serial ECGs were extracted post-dosing at the times of arterial sampling to determine effect on PR, QRS, and QTcF intervals. The effect of ABP-700 on QTc was evaluated by exposure response (ER) analysis.

Results: Subjects (48% male) were aged 18-55 years and predominantly white. Arterial mean peak plasma levels ranged from 574 (PAR-1) to 1957 ng/mL (PAR-5); sedation ranged from light to deep.

With both FEN and REM, ABP-700 had no effect on cardiac conduction; PR and QRS intervals were unchanged over the exposure range. There was a shallow linear relationship between ABP-700 plasma concentrations and the QT effect (ΔQTcF) with a slope of 0.005 msec per ng/mL (90% CI: 0.004 to 0.007). This is likely of little clinical significance.

Conclusions: These data indicate that ABP-700 can produce levels of clinical sedation ranging from light/moderate to deep in the presence of fentanyl and remifentanil without either clinically meaningful effect on cardiac conduction or clinically concerning effect on cardiac repolarization (QTc interval) and support further exploration of ABP-700 for use in procedural sedation.