

A Validation Study of the Effects of Milrinone and Clonidine on Left Ventricular Pressure in Conscious Telemetered Dogs

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ABSTRACT

The objective of this study was to verify the functionality of L21 telemetry implants in canines. These implants measure blood pressure (BP), electrocardiography (ECG), body temperature (BT), and left ventricular pressure (LVP). Assessment of LVP is currently considered the gold standard for measuring contractility. Evaluation of a drug's effects on contractility is important in safety assessment studies because either an increase or a decrease may be harmful under certain clinical situations. Changes in contractility were assessed following administration of Milrinone, Clonidine, and a Vehicle Control (VC) of deionized water. The in-life phase was 16 days, with dosing on days 1 (VC), 4 (Milrinone 0.05 mg/kg), 8 (Milrinone 0.25 mg/kg), 11 (Clonidine 0.015 mg/kg), and 15 (Clonidine 0.03 mg/kg). Data were continuously collected for at least 26 hours per dosing occasion using Ponemah acquisition software and analyzed using EMKA ecgAUTO. The parameters evaluated included heart rate (HR), systolic arterial pressure (SAP), diastolic arterial pressure (DAP), mean arterial pressure (MAP), pulse pressure (PP), left ventricular end diastolic pressure (LVEDP), $\pm$ dP/dt, BT, PR-interval, RR-interval, QRS-duration, QT-interval, and corrected QT-interval (QTcH) 1. Three analyses were conducted: 1) change from baseline (BL); 2) change from VC; and 3) BL corrected VC-subtracted (delta-delta) values. Statistically significant ($p < 0.05$) decreases in SAP, MAP, PP, and HR were observed following 0.015 mg/kg and 0.03 mg/kg of Clonidine. Positive inotropic effects were observed, with significant ($p < 0.05$), dose-dependent increases in $\pm$ dP/dt, following Milrinone at 0.05 mg/kg and 0.25 mg/kg. Conversely, a reduction in contractile force was observed following Clonidine at 0.015 mg/kg and 0.03 mg/kg, with significant ($p < 0.05$), dose-dependent decreases in $\pm$ dP/dt. BP and HR changes were also as expected based on the known pharmacological mechanisms for each test article, and thus the functionality of L21 implants was successfully verified in canines

BACKGROUND

The International Conference on Harmonization (ICH) S7A and S7B guidelines require pharmaceutical companies to conduct comprehensive nonclinical cardiovascular assessments on all new drug candidates^{1,2}. Typically, these safety pharmacology studies evaluate potential drug effects on cardiac, and often respiratory, function via implanted telemetry devices that continuously measure BP, ECG, BT, and respiration. While not a regulatory requirement, it can also be beneficial to evaluate the potential for drug effects on cardiac contractility by measuring LVP in addition to the regulatorily required parameters^{3,5}. The objective of this study was to verify the functionality of L21 telemetry implants, which measure cardiac contractility, in male beagle dogs. Milrinone lactate (Milrinone) was chosen as a positive control due to being a known positive inotropic agent that is used to treat heart failure. Clonidine hydrochloride (Clonidine), which is clinically used to reduce contractile force, also was chosen as a negative control³.

METHODS

Four male beagle dogs were surgically implanted with L21 telemetry devices. After a recovery period of at least 27 days, the dogs were dosed with VC, Milrinone, or Clonidine on Days 1, 4, 8, 11, and 15, as per the study design depicted in Table 1. For each dosing occasion, continuous telemetry data were collected via Ponemah acquisition software (version 5.41) beginning at least 2 hours prior to dose administration through at least 24 hours following dose administration. Using EMKA ecgAUTO (version 3.5.9), the waveform data were evaluated using a pattern recognition approach. Three analyses were conducted, including: 1) change from baseline (BL); 2) change from VC; and 3) BL corrected VC-subtracted (delta-delta) values. Parametric statistical analyses were also conducted. Delta-Delta % values are shown graphically.

Table 1: Study Experimental Design

Dose Route: Oral Gavage (5 mL/kg at each dose)						
Group	# of Animals/Sex	Day 1	Day 4	Day 8	Day 11	Day 15
1	4/male	VC	Milrinone 0.05 mg/kg	Milrinone 0.25 mg/kg	Clonidine 0.015 mg/kg	Clonidine 0.03 mg/kg

RESULTS

Administration of Milrinone produced statistically significant ($p < 0.05$), dose-dependent increases in $\pm$ dP/dt and $\pm$ dP/dt at 0.05 and 0.25 mg/kg (peak effects of +10 and +45 ($\pm$ dP/dt) and +6 and +10 ($\pm$ dP/dt) delta-delta percentage points, respectively).

Administration of Clonidine produced statistically significant ($p < 0.05$), dose-dependent decreases in $\pm$ dP/dt and $\pm$ dP/dt at 0.015 and 0.03 mg/kg (peak effects of -20 and -24 ($\pm$ dP/dt) and -14 and

-14 ($\pm$ dP/dt) delta-delta percentage points, respectively.

CONCLUSION

Following the administration of Milrinone, positive inotropic effects were observed, with significant ($p < 0.05$) dose-dependent increases in $\pm$ dP/dt and $\pm$ dP/dt. Conversely, a reduction in contractile force was observed following the administration of Clonidine, with significant ($p < 0.05$) dose-dependent decreases in $\pm$ dP/dt and $\pm$ dP/dt. These changes, as well as decreases in BP and HR, were expected via known mechanisms, thus verifying the functionality of L21 telemetry implants in beagle dogs.

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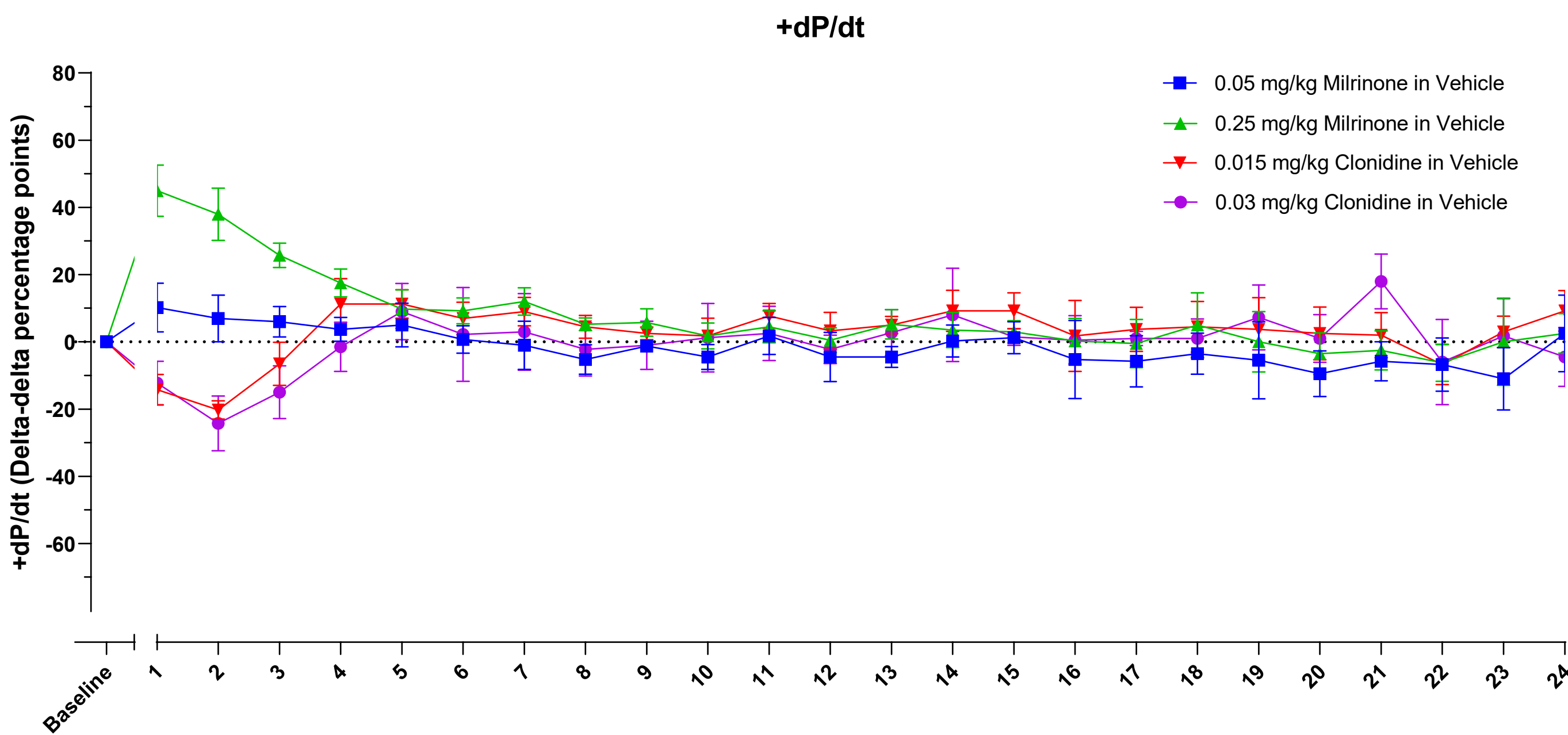


Figure 1: +dP/dt Delta-Delta Percentage Points

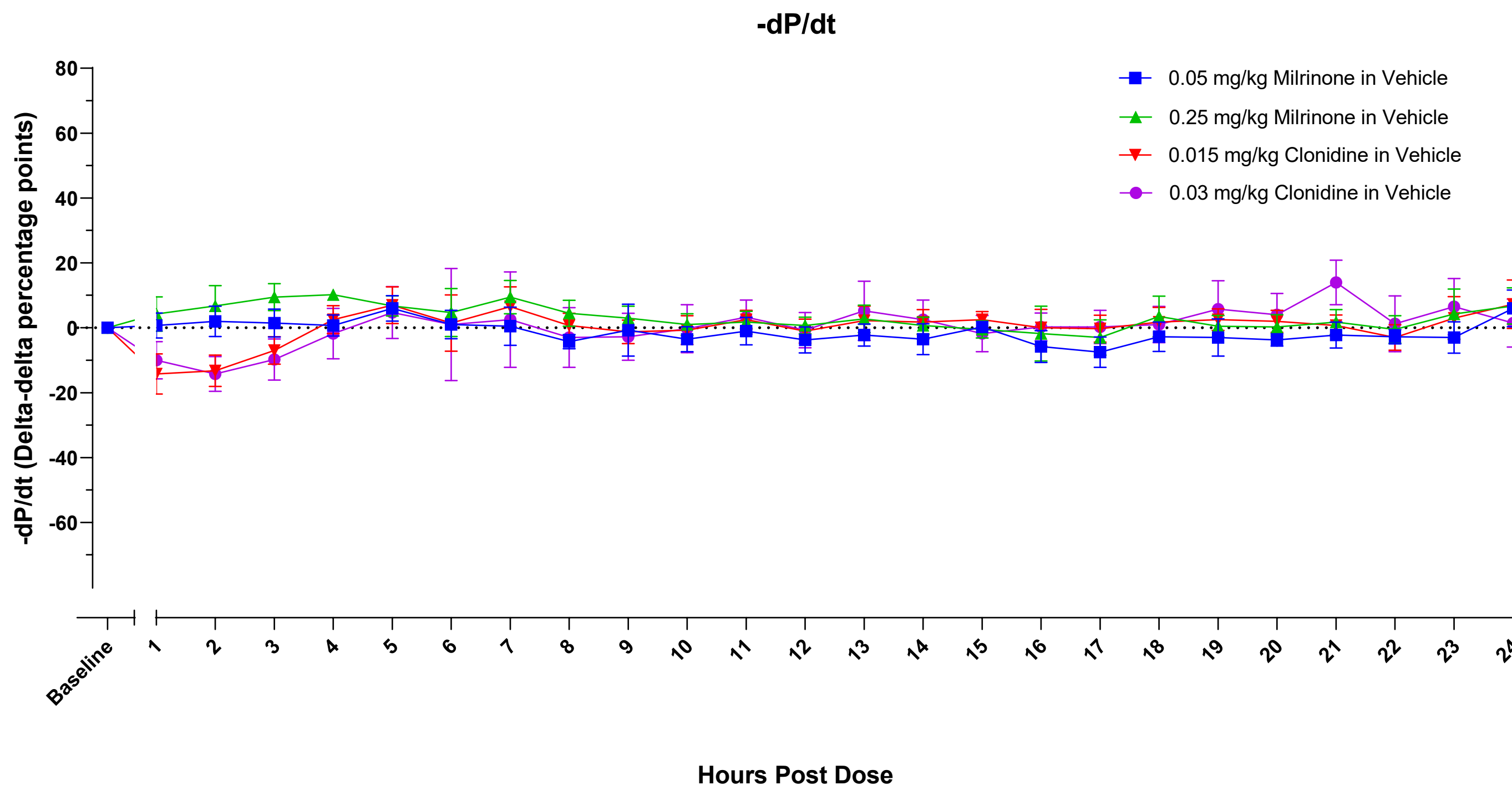


Figure 2: -dP/dt Delta-Delta Percentage Points