USE OF COMBINED TELEMETRY AND PLETHYSMOGRAPHY IN THE CONSCIOUS RAT IN ASSESSMENT OF CARDIO-RESPIRATORY FUNCTION

Sonia Rompion, Marion Maujeul, Emmanuelle Gascoin, Mickael Lepage, Eric Hayes and Guillaume Froget

INTRODUCTION

in vivo safety pharmacology assessment of cardiovascular (CV) and respiratory function is a regulatory requirement during pre-clinical drug development. Combination of both assessments in a single rodent model could be advantageous with respect to reducing animal use in safety pharmacology.

We established a model of combined telemetry and plethysmography to evaluate the time-dependent effects of various reference compounds on CV and respiratory function in conscious rats.

MATERIAL & METHODS

• Experimental protocol:
  - Male Sprague Dawley rats weighing 632-715 g at the initiation of the treatment were used (n=5 or 6).
  - Animals were implanted with DSI telemetric devices and placed into plethysmographic chambers (EMKA) with receivers (DSI).
  - Clonidine, verapamil and theophylline were examined for their effects on CV and respiratory function before and for 360 minutes after drug administration.

• Treatment:
  - The rats were given the vehicle (0.2% HPMC in distilled water) and then the reference substances, with a washout period of at least 48 hours between each treatment.
  - Verapamil at 30 mg/kg following a single p.o. administration.
  - Clonidine at 1 mg/kg following a single i.p. administration.
  - Theophylline at 100 mg/kg following a single p.o. administration.

• Parameters:
  - Cardiovascular: Heart Rate (HR) and Mean Arterial Blood Pressure (MAP).
  - Respiratory: Minute Volume (MV), Tidal Volume (TV), Respiratory Rate (R) and Enhanced Pause (Penh).

• Statistical analysis:
  - Data were compared by two-way ANOVA (group, time).

RESULTS

In the control group, a transient decrease in TV (-22% max at time point 45 minutes post-administration) and Penh (-6% max at time point 60 minutes post-administration) and a transient increase in Resp. R (+121% max at time point 10 minutes post-administration) were observed shortly following vehicle administration. These effects are classically ascribed to the stress induced in the animals during the administration phase. Thereafter, all parameters progressively returned to values close to the pre-administration mean values at time point 90 minutes and remained almost steady up to the end of the 360-minute test period. No change in MAP and HR occurred following the administration of vehicle.

Overall the expected pharmacological actions of the reference compounds on cardio-respiratory function were adequately determined using a combined telemetry and plethysmography system in the conscious rat.

• Clonidine (1 mg/kg, i.p.) reduced HR (-55%, p < 0.01), MV (-39%, p < 0.05) and TV (-39%, p < 0.05) but increased Resp. R (+95%, p < 0.05) and Penh (+96%, p < 0.001 compared to vehicle group).
• Verapamil (30 mg/kg, p.o.) reduced MAP (-39%, p < 0.001) but had no effect on ventilation compared to vehicle group.
• Theophylline (100 mg/kg, p.o.) exhibited respiratory stimulant and bronchodilatory properties (MV, +125%, p < 0.01; Resp. R, +313%, p < 0.001; TV, -40%, NS; Penh, -28%, p < 0.05) with concomitant tachycardia (HR, +63%, p < 0.001) compared to vehicle group.

CONCLUSION

The use of combined CV and plethysmography in rodents is a useful model for the development of new compounds providing detailed information on respiratory and hemodynamic function that can be validated against reference compounds.

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