Introduction

Objectives of the safety pharmacology core battery are to investigate adverse effects of new chemical entities (NCE) on vital functions, that is, the central nervous system (CNS), cardiovascular system (CV), and respiratory system (RES). Different individuals and sometimes even different animal species are generally used for each target function. For instance, few or no functional observational battery studies on CNS are commonly conducted using rodents, dogs and/or monkeys are most popular for telemetry method on CV. Whole-body plethysmography (WBP) method using rats or blood gas analysis using dogs or monkeys is widely used for RES. It would be advantageous if effects of NCE on the said three functions are simultaneously tested in identical individuals. Specifically, it will allow us to interpret inter-functional effects of NCE in more detail and to reduce animal sacrifice, time, and cost.

We recently invented an innovation system which realizes simultaneous evaluation of CNS on CVS, and RES in identical free-moving dogs. This simultaneous evaluation system has been designed to combine the observation of the general activity and behavior, telemetry method, and WBP method. We had reported that dogs could be housed in the WBP chamber, an equipment of our system, for up to 14 days, and the animals' conditions were maintained healthily in the chamber (Miyamori et al., 2006, at the 38th Annual Meeting of the Japanese Society of Toxicology).

This study was conducted in order to investigate the feasibility of our system using a compound known to induce respiratory suppression, morphine, and two compounds known to induce QT prolongation, d-sotalol and E-4031.

Methods

[Experimental system structure]

- **Recording and measuring systems**
  - Video recording system (AV编集システム, Panasonic Co., Ltd.)
  - Monitoring activity (LMA monitoring system: ABL77, Radiometer A/S)
  - LMA monitoring system: Biosystem XA, ver.2.9.0 (Buxco Inc.)
  - Whole-body plethysmography (WBP) system: SUPERMEX (Muromachi Kikai Co., Ltd.)
  - Charge-coupled device camera

- **Experimental system**
  - Observation of general activity and behavior
  - Monitoring of body temperature and behavior using charge-coupled device cameras
  - LMA monitoring system using SUPERMEX
  - Body temperature monitoring using ABL77

- **Monitoring of general activity and behavior**
  - Pupillary reflex, Palpebral reflex, Auditory response, Touch response, Pain response, Walking and running

- **Data collection**
  - Mean blood pressure (MBP), Heart rate (HR), Mean blood pressure, and electrocardiogram in dogs.
  - Time after starting infusion (hr)

Results & Discussion

**[Experiment 1, Morphine]**

- **Subjects**: 3 dogs (1.9-2.5 kg, 19-42 months old, 11-14 kg)
- **Procedure**: Morphine at 1, 3, and 10 mg/kg/hr showed significant increase in the respiration rate and decrease in the tidal volume when compared to the control, suggesting WBP method can monitor the effects of morphine on CNS and CVS. The QT-prolongation effect of morphine on CV, and the effect of morphine on CNS were not performed.

- **Conclusion**: The effects of morphine on CNS were relatively well detected.

**[Experiment 2, d-Sotalol & E-4031]**

- **Subjects**: 3 dogs (21 months old, 11-12 kg)
- **Procedure**: 2.5 mg/kg/hr and E-4031 at the doses of 0.5 and 1 mg/kg/hr were administered. The QT-prolongation effect of d-sotalol and E-4031 was statistically significant.

- **Conclusion**: The effects of d-sotalol and E-4031 on the QT-prolongation effect in dogs were statistically significant.

**Conclusion**

The results described above suggest that our system enables to detect effects of NCE on CNS, RES, and CV simultaneously in identical free-moving dogs. In conclusion, our system could be useful for the safety pharmacology core battery.