CRITICAL EVALUATION OF THE FERRET EMESIS MODEL IN SAFETY AND EFFICACY PHARMACOLOGY STUDIES

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■ INTRODUCTION

Pharmacological studies on emesis, the ferret is the most widely used model because of the high sensitivity of its vomiting reflex, in contrast to rodents, and because it is similar and more economical than many larger species (i.e., dogs or pigs). Evaluation of vomiting in ferrets can be used for safety evaluation of compounds designed for anesthesia/analgésia, as well as antiemetic and other pharmacological drugs. In addition, it is valuable work for evaluating efficacy against the gastric side effects of antiemetic drugs, cytotoxic agents or ionizing radiations. However, depending on the type of the emetic (emetic or anti-emetic effects), the methodology of action envisaged (type of research) and the pharmaceutical class of the substances under evaluation, the experimental protocols and methodologies need to be considered.

This work describes the critical aspects of the ferret emesis model and provides examples of results and methodologies to consider in the context of screening, safety or efficacy investigations.

■ RESULTS

Potency of the emetic effects of substances may be dependent to the route of administration:

- Figure 1 shows that the emesis induced by morphine is less marked following and (p.o.) administration than intraperitoneal (i.p.) administration.
- Latencies to first retching (1-10 min).
- Latencies to first vomiting (1-10 min).

Potency of the anti-emetic effects of substances may be not dose-dependent:

- Figure 2 shows that the potency of the anti-emetic effects induced by ondansetron, following (p.o.) administration, appears to decline at doses higher than 2.2 mg/kg (b/w-shaped curve).
- Latencies to first retching 1-10 min.
- Latencies to first vomiting 1-10 min.
- NB: Marked sedation is observed in the ferrets treated with the highest dose of 10 mg/kg p.o.

SMG recording using telemetry is a sensitive method for the investigation of delayed emesis induced by the chemotherapeutic agent cisplatin.

- Figure 3 shows an example of SMG recording from the diaphragm in one ferret 24h after treatment with cisplatin (0.4 mg/kg i.p.).
- Figure 4 shows the emetic effects of cisplatin (5 or 10 mg/kg i.p.) during the early and late phases of delayed emesis.

■ CONCLUSION

These findings highlight some critical issues that need to be considered when using the ferret emesis model for the investigation of the emetic or anti-emetic effects of new substances in safety or efficacy studies: route of administration, dose-dependence relationship of the effects, repeatability of the effects in a same colony of ferrets (desensitization phenomenon). They also demonstrate the usefulness of a sensitive EMG telemetry methodology for the investigation of delayed emesis.

■ MATERIAL & METHODS

Animals

Male musculus putneus ferus (Marshall Europe, 69220, St-Etienne, France).

Experimental protocol

- **Visual observation method:**
  - Observation sessions: 2-hour (morphine) or 3-hour (cisplatin) observation period starting immediately after administration. Pre-treat with ondansetron: 1 hour before cisplatin administration.
  - Parameters analyzed: number of retches or vomits and number of ferrets showing retches or vomits.
  - n = 4 to 8 ferrets per group.

**Electromyographic (EMG) telemetry recording method:**

- Ferrets implanted with EMG electrodes (implantable telemetric devices, Data Sciences International) placed few centimetres under the diaphragm.
- Telemetry recording acquired using the Data Sciences International software (Dataquest A.R.T. TM version 2.0 or 2.3) over a 72-hour period after administration of cisplatin.
  - n = 3 (cisplatin 0.4 mg/kg) or n = 5 (cisplatin 0.2 mg/kg) ferrets per group.

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