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Publication

Comparison of three preclinical models for nausea and vomiting assessment.

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Abstract

INTRODUCTION: Nausea is a subjective sensation often preceding emesis in humans. Drug-induced nausea remains difficult to predict in preclinical tests. The aim of this study was to compare the effects of emetic agents in rats (pica behavior), ferrets (acute and delayed phases of emesis) or dogs (emesis and cardiovascular endpoints).

METHODS: Rats and ferrets were administered cisplatin (±aprepitant/ondansetron or aprepitant) or apomorphine (±domperidone). Telemetered dogs were administered apomorphine (±domperidone). Food and kaolin intake was measured in rats whereas the number of emetic events was counted in ferrets and dogs. Cardiovascular changes were also monitored in dogs.

RESULTS: In rats, cisplatin (6mg/kg, i.p.) increased kaolin intake (+2257%, $p<0.001$). The cisplatin effects were not reversed by the combination of aprepitant/ondansetron (2mg/kg, p.o./2mg/kg, i.p.) or by aprepitant (30mg/kg, p.o.). Apomorphine (10mg/kg, i.p.) did not induce pica behavior. In ferrets, cisplatin (8mg/kg, i.p.) induced acute and delayed emesis (371.8±47.8 emetic events over 72h) which was antagonized by aprepitant (1mg/kg, p.o.). Apomorphine (0.25mg/kg, s.c.) induced acute emesis (38.8±8.7 emetic events over 2h) which was abolished by domperidone (0.1mg/kg, s.c.). In dogs, apomorphine (100µg/kg, s.c.) induced emesis and tachycardia which were decreased by domperidone (0.2mg/kg, i.v.).

CONCLUSIONS: The assessment of emesis in the ferret or in the dog displays a strong predictive value. In contrast, assessing nausea remains challenging in all animal species and the use of pica behavior remains questionable in the context of antiemetic drug development.