VOMITING INDUCTION BY IPECAC SYRUP IN DOGS AND FERRETS

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ABSTRACT — The dog has been used as an experimental animal in emesis research. In this study, we analyzed the emetic effects of ipecac syrup using a smaller animal, the ferret, and compared its response to that of the dog. Dogs and ferrets were divided into 4 groups (n=4, each). Each group was given either 0.1, 0.25, 0.5, or 1.0 ml/kg of ipecac syrup, and the latency and numbers of retching and vomiting were recorded. Animals given an equal volume of saline served as controls. The numbers of vomiting and retching increased dose-dependently in both dogs and ferrets, and there was no difference in latency and numbers of vomiting between them. The numbers of retching were greater in ferrets than in dogs at ≥0.25 ml/kg. Taking these results into consideration, the ferret seems to be as useful as the dog in studies on emetic effects of ipecac syrup.

KEY WORDS: Ipecac, Canine, Ferret, Emesis, Retch

INTRODUCTION

Although ipecac syrup has been used all over the world in the initial treatment of poisoning such as accidental ingestion (Adams, 1961), it has not yet been approved as a therapeutic drug in Japan. When physicians want to use ipecac syrup in Japan, they must formulate it by themselves or purchase it from overseas. Therefore the development of ipecac syrup as a therapeutic drug has been awaited in Japan.

In emesis research, the dog has been widely used as an experimental animal because of the similarity of vomiting induction by ipecac syrup in humans and dogs (Adams, 1961). The dog has, however, several disadvantages as an experimental model: difficulty of supply in sufficient numbers, place for maintenance, cost, etc. Therefore it is desirable to develop an experimental model using smaller animals. More recently, the ferret has been used in studies of anti-emetics for adverse effects of anti-cancer agents. Because anti-emetics act via the vomiting center in this animal as well as in the human being (Arnold et al., 1959), the ferret is seemingly suitable for studies on emesis and anti-emesis (Endo et al., 1990). However, to our knowledge, there is no report comparing the responses of the ferret with those of the dog or the human being. We compared the vomiting induction by ipecac syrup between the ferret and the dog in this study.

MATERIALS AND METHODS

Animals

Five-month-old male Marshall Beagles (9 -
11 kg, Charles River, Tsukuba, Japan) and 2-month-old male Marshall Ferrets (1.0 - 1.4 kg, Charles River, Tsukuba, Japan) were used in this study. All the experiments were approved by the Animal Care Committee of the University of Tsukuba. The animals were housed individually in a metallic cage at a temperature of 24±2 °C and a relative humidity of 55±10 % and were provided with 12 hr of light per day (6 a.m. ~ 6 p.m.). The dogs were fed with 250 g/day of DEQ (Oriental Yeast Co., Tokyo, Japan), whereas the ferrets were given 50 g/day of CFE-2 (Japan Clear Co., Tokyo, Japan). The animals were given free access to food and water. After a 1-week acclimation period, they were assigned to the study.

**Drug**

Ipecac syrup® (USP, Paddock Laboratories, Inc, Minnesota, USA : Lot No 4C6292) was used. The concentrations of emetine and cephaeline of this ipecac syrup were 0.756% and 0.526% by the USP XXII, respectively.

**Designs of the experiment**

The dogs and ferrets were divided into 4 groups (n=4, each). Each group was given either 0.1, 0.25, 0.5, or 1.0 ml/kg of ipecac syrup. Animals given an equal volume of saline served as controls. On the study day, food was given at 9:00 a.m., and the ipecac syrup was orally given at 9:20 a.m. by opening the mouth and administering the syrup to the innermost pharynx by syringe. Every animal swallowed the syrup without vomiting. Animals were observed for 4 hr after dosing to determine the latency and the numbers of retching and vomiting. Retching was defined as a vomiting-like response without expulsion of any vomit. The course from the start of a vomiting-like response to its end and recovery of a normal state was counted as one retching. After animal had vomited, the quantity of the vomiting matter was measured. When an animal showed no retching or vomiting during the first 4-hr observation period, the latency was determined as 240 min.

**Statistical analysis**

Differences between the individual doses were analyzed by the Williams' multi-comparison test after analysis of variance (ANOVA). Differences between the dogs and the ferrets were analyzed by two-way ANOVA. Significant differences are indicated (P<0.05).

**RESULTS**

The latencies of retching and vomiting decreased and their numbers of responses increased dose-dependently in the dogs (Table 1). The latencies and the numbers of retching and vomiting at ≥0.25 ml/kg were significantly different from those in the control. The ferrets showed similar dose-dependent tendencies, and the differences in the latency and the numbers of retching were significant at ≥0.25 ml/kg as com-

**Table 1.** Emesis induced by ipecac syrup in dogs. Values are the means ± S.E.

<table>
<thead>
<tr>
<th></th>
<th>control</th>
<th>0.1 ml/kg</th>
<th>0.25 ml/kg</th>
<th>0.5 ml/kg</th>
<th>1.0 ml/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retch latency (min)</td>
<td>240.0 ± 0.0</td>
<td>240.0 ± 0.0</td>
<td>45.3 ± 2.4*</td>
<td>30.0 ± 2.9*</td>
<td>23.3 ± 1.2*</td>
</tr>
<tr>
<td>responses</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>2.5 ± 0.3*</td>
<td>3.8 ± 0.3*</td>
<td>5.5 ± 1.0*</td>
</tr>
<tr>
<td>Vomit latency (min)</td>
<td>240.0 ± 0.0</td>
<td>240.0 ± 0.0</td>
<td>51.3 ± 2.4*</td>
<td>34.5 ± 3.2*</td>
<td>27.5 ± 1.9*</td>
</tr>
<tr>
<td>responses</td>
<td>0.0 ± 0.0</td>
<td>0.0 ± 0.0</td>
<td>1.0 ± 0.0*</td>
<td>2.0 ± 0.4*</td>
<td>3.0 ± 0.4*</td>
</tr>
<tr>
<td>Final vomiting (min)</td>
<td>240.0 ± 0.0</td>
<td>240.0 ± 0.0</td>
<td>51.3 ± 2.4*</td>
<td>44.5 ± 9.0*</td>
<td>77.5 ± 41.1*</td>
</tr>
<tr>
<td>Quantity of vomiting matter (ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1st vomiting</td>
<td>60 ± 10</td>
<td>11.8 ± 12</td>
<td>106 ± 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2nd vomiting</td>
<td>10 ± 6</td>
<td></td>
<td>10 ± 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3rd vomiting</td>
<td>10 ± 5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

n = 4. For dogs that did not respond, the latency was calculated as 240 min (i.e., observation time). *P<0.05 as compared to the control.
pared to the control, whereas the differences in
those of vomiting were significant at 1.0 ml/kg as
compared to the control (Table 2). The number
of retchings was significantly greater in the fer-
rets than in the dogs at ≥0.25 ml/kg. The time of
the final vomiting was significantly earlier at ≥
0.25 ml/kg as compared to the control in the
dogs, whereas it was significantly earlier at ≥0.5
ml/kg in the ferrets.

The quantity of vomiting matter in the first
vomiting in both of the animals administered a
dose of 0.5ml/kg ipecac syrup was 100 ± 12g, and
in the second and third vomittings the vomited
matter was small in volume.

DISCUSSION

Administration of 0.1 ml/kg of ipecac syrup
induced neither retching nor vomiting in the dogs
or the ferrets. As the dose increased to over 0.25
ml/kg, the numbers of vomiting and retching in-
creased dose-dependently in both the dogs and
the ferrets, and there was no difference in the
latency and the numbers of vomiting between the
dogs and the ferrets. The quantity of vomited
matter of the first vomiting in the dogs and the
ferrets administered a dose of 0.5ml/kg ipecac
syrup was larger than those in the second and third vomittings. Taking these results into consid-
eration, the ferret seemed to be as useful as the
dog in studies on emetic effects of ipecac syrup.

Studies on emesis require several conditions:
reproducibility of vomiting, easy oral administra-
tion, absence of hypersensitivity, etc. Based on
these conditions, the dog has been widely used,
but nowadays Suncus murinus and the ferret have
also been used because of easiness in handling.
Suncus murinus is used in studies of anti-cancer
agents, because its vomiting is a coordinated
reflex like that in the human being and can be
clearly distinguished from yawning (Ueno et al.,
1987). However, apomorphine and digitalis,
which induce vomiting by acting on the chemore-
ceptor trigger zone (CTZ), cannot induce vomit-
ing in Suncus murinus. On this point, the Suncus
murinus is different from the human being or the
dog (Torii et al., 1991). It is also difficult to
administer an emetic to Suncus murinus because
of its ferocity and biting nature. For these rea-
sons, we did not use Suncus murinus in this study.
The ferret has a well-developed area postrema,
and is far from ferocious. The ferret has a dose-
dependent emesis after intraperitoneal injection of
cisplatin (Endo et al., 1990), and shows the same
pre-vomiting symptoms as observed in the human
being, which facilitates the observation of vomit-
ing (Florczyk et al., 1982). The ferret showed
highly reproducible vomiting with oral adminis-
tration of cupric sulfate or with vagal stimulation,
and the relations between the vomiting center, the
CTZ, the area postrema, the vagal afferents, and
the GI tract were similar to those in the human
being and the dog. Based on these facts, we used
the ferret in this study to determine how it is dif-
ferent from the dog.

In the 0.5 ml/kg group, the average numbers

| Table 2. Emesis induced by ipecac syrup in ferrets. Values are the means ± S.E. |
|-----------------------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| control | 0.1 ml/kg | 0.25 ml/kg | 0.5 ml/kg | 1.0 ml/kg |
| Retch latency (min) | 240.0 ± 0.0 | 240.0 ± 0.0 | 38.8 ± 2.3* | 31.3 ± 1.3* | 27.5 ± 7.8* |
| responses | 0.0 ± 0.0 | 0.0 ± 0.0 | 8.0 ± 1.8* | 14.8 ± 2.1* | 18.5 ± 3.1* |
| Vomit latency (min) | 240.0 ± 0.0 | 240.0 ± 0.0 | 121.3 ± 57.2 | 87.5 ± 50.8 | 37.5 ± 5.2* |
| responses | 0.0 ± 0.0 | 0.0 ± 0.0 | 2.3 ± 1.4 | 2.3 ± 0.8 | 6.0 ± 1.3* |
| Final vomiting (min) | 240.0 ± 0.0 | 240.0 ± 0.0 | 152.5 ± 50.6 | 98.8 ± 47.1* | 76.3 ± 24.7* |
| Quantity of vomiting matter(ml) | | | | | |
| 1st vomiting | 2(approximately) | 6−7 | 6−7 |
| 2nd vomiting | 2(approximately) | 2(approximately) | |
| 3rd vomiting | 2(approximately) | | |

n = 4. For ferrets that did not respond, the latency was calculated as 240 min (i.e., observation time). *P<0.05 as compared to the control. † P<0.05 as compared to the dogs.
of retching and vomiting were 3.8 and 2.0 in dogs, respectively, whereas they were 14.8 and 2.3 in ferrets. In human beings, at most one episode of retching precedes one vomiting after administration of ipecac syrup. Thus the retching/vomiting ratio was: human beings<dogs<ferrets. The latency of vomiting after dosing of ipecac syrup USP to humans is constant; approximately 88 to 98% experience vomiting within 30 min, with an average latency of 17 to 18 min (Robertson 1962; Reid, 1970; Yamashita et al., 1986). These studies used the conventional dosing volume (8 ml for <1 year old, 12 ml for 1-12 years old, 15 ml for >12 years old), and the dose is considered to be about 0.2 - 0.3 ml/kg. When these data are compared with the results of 0.25 and 0.5 ml/kg in this study, the latency of vomiting was: human beings<dogs<ferrets. The final vomiting tended to occur earlier as the dose increased in both animals. That may be because a larger dose of ipecac syrup caused stronger vomiting and the gastric contents were expelled in an earlier period after dosing. At 1.0 ml/kg, however, some animals showed a marked delay in final vomiting. One ml/kg dose might be excessive for observing emetic phenomena.

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REFERENCES