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RAPID COMMUNICATION

Value of mink vomit model in study of anti-emetic drugs

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Abstract

AIM: To establish a new, reliable vomit model of minks.

METHODS: Adult male minks were randomly divided into 8 groups ($n = 6$): cisplatin (7.5 mg/kg) intraperitoneal injection (ip) group, copper sulfate (40 mg/kg) intragastric injection (ig) group, apomorphine (1.6 mg/kg) subcutaneous injection (sc) group, and 18 Gy whole-body X-irradiation group, ondansetron injection group (2 mg/kg ip) 30 min later followed by cisplatin (7.5 mg/kg) ip, normal saline (NS) ip injection control group, metoclopramide injection group (4 mg/kg ip) 30 min later followed by apomorphine (1.6 mg/kg) sc, NS ig control group. The frequency of retching and vomiting was calculated. After behavioral experiment, distribution of 5-HT in the ileum was detected by immunohistologic method.

RESULTS: Cisplatin, apomorphine, copper sulfate and X-irradiation administered to minks evoked a profound emetic response in the animals. However, retching and vomiting were significantly inhibited by pretreatment with ondansetron and metoclopramide in cisplatin and copper sulfate groups ($P = 0.018$). Immunohistologic result showed that 5-HT released from enterochromaffin cells (EC cells) was involved in vomiting mechanism.

CONCLUSION: Mink vomit model has a great value in studying the vomiting mechanism and screening new antiemetic drugs.

Key words: Vomit; Mink; Cisplatin; Ondansetron; Apomorphine; X-irradiation

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INTRODUCTION

In the treatment of malignant disease, potentially curative chemotherapy and radiotherapy are commonly associated with a wide range of adverse events, including intractable nausea and vomiting, which can challenge patient compliance with a treatment regimen. Other forms of emesis, including those experienced post-operatively or in other diseases, can also present as serious problems. Studying the vomiting mechanism and screening for new anti-emetic drugs urge us to establish appropriate animal models with similar vomiting behavior to that of human beings. Ferret (*Mustela putorius furo*) is a relative ideal animal model in vomiting study worldwide[1]. However, its use is limited because of its high feeding cost and difficulties to survive. Fortunately minks (*Mustela vison*) and ferrets belonging to the same stoat genus are characterized by their inexpensiveness, wide availability and ease of feeding and raising. However, there are no reports on the use of minks in medical researches. This study was to establish a new and reliable vomit model of minks based on the effects of a variety of emetogens.

MATERIALS AND METHODS

Materials

Cisplatin powder was obtained from Qilu Pharmaceutical Factory, Jinan, China. Ondansetron hydrochloride injection was from Ningbo Tianheng Pharmaceutical Factory, Ningbo, China. Copper sulfate was from Shanghai Hengda Chemical Co., Shanghai, China. Apomorphine was from Sigma in St Louis, USA. Metoclopramide dihydrochloride injection was from Tianjin People's Pharmaceutical Factory, Tianjin, China. SABC immunohistology test kit was from Boster Biotechnology Co., Wuhan, China. Varian 6 MeV 2100-C X-irradiation Linear Accelerator was from Varian Corp., USA. Microscope was from Olympus, Japan. Adult male minks weighing 1.3-1.8 kg were provided by Qingdao Special Animal Center.

Animal experiments

Animals were used in the present study in accordance with the Qingdao University Guide for the Care and Use of Laboratory Animals.

To examine the effects of emetogens, the minks were divided into 4 groups ($n = 6$), and housed individually in an iron cage of 75 cm × 50 cm × 50 cm with free access to

Table 1 Effects of emetogens on minks (n = 6, mean±SD)

Emetogens	Dose (mg/kg)	Latency (min)	Retching (n)	Emesis (n)	Vomiting ratio
NS	-	-	0	0	0/6
Cisplatin	7.5	92.0±21	91.5±37	12.0±3	6/6
NS	-	-	0	0	0/6
Apomorphine	1.6	39.4±36	28.5±16	5.3±1.9	6/6
NS	-	-	0	0	0/6
Copper sulfate	40	7.0±2.0	29.0±9	8.7±2.3	6/6
Pseudo irradiation	0	-	0	0	0/6
X-ray	18 Gy	17.0±4	19.3±7	10.4±3	5/6

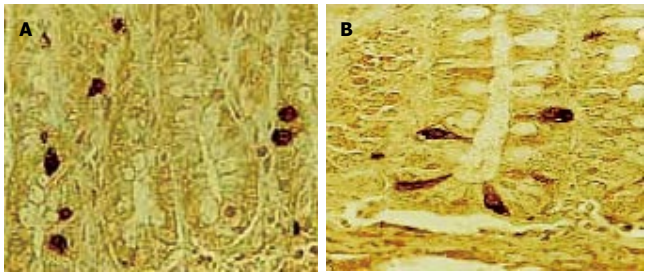

Figure 1 A: control group, 5-HT did not release from EC cells with a clear round rim; **B:** the cisplatin group, 5-HT released from EC cells with a tail.

Table 2 Effects of ondansetron or metoclopramide on emesis induced by cisplatin or apomorphine in minks (mean±SD, n = 6)

Emetogens	Dose (mg/kg)	Anti-emetics	Dose (mg/kg)	Latency (min)	Retching (n)	Emesis (n)
Cisplatin	7.5	NS		92.0±21	91.5±37	12±3
Cisplatin	7.5	Ondansetron	2	143.8±80	47.3±41	5.3±5[a]
Apomorphine	1.6	NS		39.4±36	28.5±16	5.3±1.9
Apomorphine	1.6	Metoclopramide	4	-a	1.3±3[b]	0.3±0.8[d]

[a]P = 0.018, t = 2.93 *vs* vehicle-pretreated cisplatin group; [b]P = 0.0022, t' = 4.08, [d]P = 0.003, t' = 5.94 *vs* vehicle-pretreated apomorphine group; -a: only 1 monk had retching and vomiting.

food and water

The minks in the first group were first given NS (5 mL/kg ip). After 24 h, the animals were administered cisplatin (7.5 mg/kg ip) in a volume of 5 mL/kg diluted with NS.

The minks in the second group were first given NS (15 mL/kg ig). After 24 h, the animals were given copper sulfate (40 mg/kg ig) in a volume of 15 mL/kg diluted with NS.

The minks in the third group were first given NS (0.4 mL/kg sc). After 24 h, the animals were given apomorphine (1.6 mg/kg sc) in a volume of 0.4 mL/kg diluted with NS.

The minks in the fourth group were first exposed to pseudo-irradiation. After 24 h, the animals received 18 Gy whole-body X-irradiation for 4.5 min.

To investigate the effects of anti-emetic agents on emesis induced by cisplatin or apomorphine, the minks in the first group were injected intraperitoneally with ondansetron injection (2 mg/kg) in a volume of 1 mL/kg 30 min before the intraperitoneal administration of cisplatin (7.5 mg/kg).

The minks in the second group were pretreated with NS (1 mL/kg ip) as control. After 30 min, the animals were administered cisplatin (7.5 mg/kg).

The minks in the third group were pretreated with metoclopramide injection (4 mg/kg ip) in a volume of 0.8 mL/kg, followed by apomorphine (1.6 mg/kg sc) after 30 min.

The minks in the fourth group were pretreated with NS (0.8 mL/kg ip) as control, followed by apomorphine (1.6 mg/kg sc) later 30 min.

All experiments were carried out starting at 9:00 am. After treatment, retching and vomiting were observed for 6 h, following the vomit criteria for ferrets described by Minami *et al*[2]. No observers were aware of the treatments. Salivating, flinching and other behaviors resembling the nausea of human beings were observed. During vomiting, the mink's head was protruding downwards ahead with open mouth, shrugging shoulder, contracting abdomen and occasional sound of vomiting. A vomiting cycle started the minute when vomiting began until smooth breaths recovered. A retching/vomiting referred to a vomiting action without or with stomach content spat out. The frequency of retching and vomiting was calculated.

Immunohistologic analysis

Minks in control group (n = 3) and cisplatin group (n = 3, 3 h after 7.5 mg/kg ip) were killed by cervical dislocation. A 3 cm long section was dissected 20 cm from the pylorus, and the distribution of 5-HT was detected under microscope by the immunohistologic method according to the instructions of the SABC test kit.

Statistical analysis

Data were expressed as mean±SD and analyzed by Student's t test. P < 0.05 was considered statistically significant.

RESULTS

Animal experiments

Cisplatin, apomorphine, copper sulfate and X-irradiation administered to the minks evoked a profound emetic response, and the manifestations of retching and vomiting in minks were similar to those in ferrets[2]. No vomiting occurred in control groups. The effects of emetogens over a 6 h period are shown in Table 1.

All minks in the NS + cisplatin group suffered from retching and vomiting. Vomiting started after 60 min and reached its peak after about 2 h. Five minks in the ondansetron pretreatment group suffered from retching and vomiting. The frequency of cisplatin-induced retching and vomiting after 6 h was significantly reduced by pretreatment with ondansetron.

All minks in the NS+apomorphine group and only one in the metoclopramide pretreatment group, suffered from retching and vomiting. The frequency of apomorphine-induced retching and vomiting after 6 h was significantly reduced by pretreatment with metoclopramide.

No significant difference was found between the pretreatment and control groups in terms of the latency and duration of emesis induced by cisplatin or apomorphine (Table 2).

Immunohistologic analysis

In the cisplatin group, 5-HT was released from EC cells which seemed to have a tail. In the control group, 5-HT was not released from EC cells which was round with a clear rim. Similar phenomena were also observed in other groups (Figure 1).

DISCUSSION

It is widely known that vomiting cannot be induced in rodents such as mice (except for the special strains), rats, and guinea pigs. Pigeons, cats and dogs are occasionally used in vomiting research and screening for new anti-emetics. Since pigeons often carry infectious viruses to human beings, no reports are available on vomiting induced by anticancer drugs in pigeons. Cats and dogs have a good learning ability. When vomiting is induced by emetogens, it often continues even anti-emetics[3] are administered. Ferret is a widely accepted animal model in vomiting study at present, mainly because its vomiting behavior resembles that of human beings[4] in terms of behavior, responses to emetogens and anti-emetic agents, and biochemistry change in vomit response. Ondansetron, a potential anti-emetic agent, was developed in ferret vomit model by Glaxo Company. However, since ferret is so expensive and difficult to raise, its wide use cannot be realized. In fact, no laboratory has carried out experiments in ferrets so far in China. Minks belong to the same stoat family of ferrets. As a vomit model, they not only share the advantages with ferrets, but also are inexpensive and can be raised quite easily and widely.

In the present study, the effects of a variety of emetogens, including cisplatin, copper sulfate, apomorphine and X-irradiation at the doses evoking a profound emetic response in ferrets, were identical in minks. The manifestations of retching and vomiting were similar to those in ferrets. As shown in our experiment, ondansetron and metodopramide can inhibit emesis induced by cisplatin and apomorphine in minks.

5-HT immunohistologic analysis showed that emetogens increased the release of 5-HT from EC cells in intestine, which may be an important mechanism involved in vomiting. This finding is consistent with the results reported previously[5]. However, it must be acknowledged that this study has its limitations because our experiments were mainly focused on the behavior of minks and the vomiting mechanism was studied in the initial stage. A further study is needed.

In conclusion, the mink vomit model is of great value in studying the vomiting mechanism and screening for new anti-emetic drugs.

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