Antiemetic Effects of Lerisetron in Radiation-induced Emesis in the Dog

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The 5-HT_3 receptor antagonists are the most potent antiemetics known at present. Lerisetron is a new 5-HT_3 receptor antagonist chemically unrelated to other antagonists like Ondansetron. An emesis model in the dog induced by irradiation with ^{60}Co was used, and 8 Gy were administered over the total body surface. An irradiated control group was established and received no medication, and two irradiated groups received treatment with either Ondansetron or Lerisetron. The 'up-down' technique was employed to determine the effective dose (ED_{50}). A logarithmic scale was used to increase or decrease the doses in each case. The initial doses were 300 μg/kg for Ondansetron and 100 μg/kg for Lerisetron. All animals in the control group vomited. The ED_{50} of Ondansetron was 178 ± 151 μg/kg body wt and that of Lerisetron was 63 ± 18 μg/kg. Lerisetron is more potent and presented less individual variability than Ondansetron, but its antiemetic effects were equally effective.

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Anticancer treatments involving chemotherapy or radiotherapy are associated with a high rate of gastrointestinal side effects, most commonly vomiting and diarrhoea. The neurochemical mechanisms of nausea and vomiting are not well understood. Several neurotransmitters have been identified in the chemoreceptor trigger zone, including dopamine, histamine, acetylcholine and endogenous opioids. Serotonin has been included among these substances as a mediator of the emetic stimulus (1, 2) in central and peripheral neurons as well as in enterochromaffin cells of the intestinal mucosa (3).

A new group of serotonin analogues (5-hydroxytryptamine, 5-HT) has been developed and applied which includes antagonists of the serotonin receptor subgroup-3 (5-HT_3) (4). Ondansetron (Glaxo Lab.), a carbazole that is structurally similar to 5-HT, is the first antiemetic drug available for human use (5). This drug has a powerful antiemetic effect with a reduction in side effects commonly observed with standard antiemetic drugs, i.e. Ondansetron has been widely used in anticancer chemotherapy with better results than metoclopramide in controlling nausea and vomiting (6). It is also effective after radiotherapy (7), even in children and elderly people with low tolerance to metoclopramide.

Lerisetron (Lerisetron, FAES Lab., Bilbao, Spain) is a new antagonist of the 5-HT_3 receptors but, unlike Ondansetron, it has a competitive antagonist effect of histamine H_1 receptors (8). Lerisetron is a piperazinylbenzimidazole derivative with higher affinity binding for the 5-HT_3 receptors ($pKi = 9.2$, $DE_{50} = 2.0$ μg/kg iv) (9) than granisetron or tropisetron. The aim of this work is to determine the efficacy of Lerisetron in the treatment of radioinduced emesis in the dog.

MATERIAL AND METHODS

A model of radiation-induced emesis has been set up in young adult beagle dogs (> 8 months weighing 7–15 kg). All the animals were healthy and underwent deparasitization and vaccination 35 days before the study. Three groups were established: control ($n = 5$), Ondansetron ($n = 7$) and Lerisetron ($n = 12$). The three groups of animals were irradiated under the same conditions.

Technique and type of irradiation

Preparation. At the same time of day, each animal received 0.44 kg of canned dog food (Canine Maintenance, Hills Science Diet). Immediately afterwards, a catheter (Abbott 18G) was placed in the cephalic vein for drug or

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saline (placebo) administration. The drug (or placebo) was supplemented with saline for a final volume of 0.5 ml/kg, administered 15 ± 2 min before irradiation and repeated 90 min post-irradiation. The animals were then transferred to the radiotherapy room.

Irradiation. Abdominal whole body irradiation was administered using a telecobaltotherapy unit (^{60}Co, Phoenix model). The animals were placed in a plastic cage measuring $50 \times 40 \times 16$ cm with the area exposed to the radiation beam covered by a 3-mm thick polyvinyl chloride (PVC) plaque. The centre of the irradiation field was located in the middle of the cage at the level of the animal's navel, situated caudally 2.5 cm from the last rib. The radiation dose was 8 Gy applied from two opposing fields lateral and parallel to the animal (4 Gy from each side). The irradiation time per field was 5.22 min and the dose rate was 1.775 Gy/min, with an irradiation field size of 47×47 cm, placing the collimators at their maximum opening (36×36 cm). The distance between the source and the PVC plaque was 105 cm, and to the longitudinal axis of the animal was 113 cm. Individual monitoring of the radiation exposure was done by indirect dosimetry (FLi photothermoluminescent crystals) in the first three irradiation protocols and randomly thereafter in other animals.

Study of emesis

Following irradiation, the animals were placed in individual cages for 10 h of continuous observation with a videotape recorder. The onset and peak effect, duration and number of vomiting episodes were registered. Vomiting was defined as a succession of strong brief contractions of the thoracic and abdominal muscles, with expulsion of gastric content through the mouth; nausea was defined as an episode of vomiting without expulsion of stomach contents through the mouth (10). When two successive episodes were separated by an interval of less than 20 s, they were registered as double vomiting episodes.

'Up-down' technique to determine the ED_{50} (mean effective dose) of Lerisetron and Ondansetron after radiation

For this part of the study, group I (non-medicated controls) was excluded. In groups II (Ondansetron) and III (Lerisetron), an 'up-down' study protocol was developed to determine increases or decreases based on a logarithmic scale, expressed as Log_{10} of the dose, at intervals of 0.5 ($10\text{-}30\text{-}100\text{-}300\text{-}1\,000 = 10^1\text{-}10^{1.5}\text{-}10^2\text{-}10^{2.5}\text{-}10^3$), depending on the response of the preceding animal; that is, if the dose administered to the first animal (100 μg/kg) did not make the animal vomit, the dose was reduced in the second animal according to the scale being applied (30 μg/kg), and if the animal vomited in this case, it was raised in the third animal (100 μg/kg), and so on. The initial doses were 300 μg/kg for groups II and III, respectively. For group III, a new scale was used to obtain a more precise measure of the ED_{50} at intervals of 0.2 ($30\text{-}50\text{-}80\text{-}126 = 10^{1.5}\text{-}10^{1.7}\text{-}10^{1.9}\text{-}10^{2.1}$) with an initial dose of 80 μg/kg. Animals were randomly included in groups I and II. Analysis of group III was performed afterwards. The antiemetic drug was given unblinded to the observer.

This study not only allowed us to determine the efficacy of the drugs being assessed, but to have their ED_{50} at a set emetogenous dose, since the study focused on the mean effective dose, estimating the true mean dose (ED_{50}) with fewer animals than those necessary using standard statistical techniques (11).

Statistical analysis

A simple descriptive study of the variables was carried out using the statistical software Statview (Abacus Concepts, Inc., California, USA, release 4.0). The dose at which 50% of the dogs vomited (ED_{50}) was determined for each treatment group in agreement with the 'up-down' technique for small samples (12).

RESULTS

The total irradiation time in all cases was 10.44 min over a mean period of $13.7 \text{ min} \pm 2.1$ s (mean ± standard deviation).

Antiemetic effect

Controls. All animals in the control group vomited during the 10 h of post-irradiation observation ($n = 5$).

Ondansetron. The results when different doses of Ondansetron were used, in agreement with the 'up-down' method, reveal the course of the dose–vomiting relationship, with an ED_{50} (mean effective dose) of 178.8 ± 151.0 μg/kg body wt which inhibited vomiting in the dog (Table 1).

To assess the effect of Lerisetron, two starting doses were tested sequentially: 100 μg/kg and 80 μg/kg (Table 2). The results, as shown in the tables, illustrate the course of the response to the different doses as assessed by the 'up-down' method, with an ED_{50} of 56.2 ± 53.1 μg/kg for a starting dose of 100 μg/kg and an ED_{50} of 63.1 ± 18.6 μg/kg for a starting dose of 80 μg/kg.

Table 1

Results obtained using the 'up-down' technique with Ondansetron at a starting dose 300 μg/kg. Numbers indicate different animals [1–7]. 'x' indicates that the animal vomited, whereas 'o' indicates the absence of vomiting

Ondansetron (μg/kg)	1	2	3	4	5	6	7
3 000							
1 000		o					
300	x		o				
100				o		o	
30					x		x
10							

Table 2

Results obtained using the 'up-down' technique with Lerisetron two starting doses 100 μg/kg and 80 μg/kg. Numbers indicate different animals [1–7]. 'x' indicates that the animal vomited, whereas 'o' indicates the absence of vomiting

Lerisetron (μg/kg)	1	2	3	4	5	6	–
300							
100	o		o		o		
30		x		x		x	
10							
126							
80	o		o		o		
50		x		x		x	
30							

Number of vomiting episodes

Controls. The onset of vomiting occurred between 50 and 108 min post-irradiation (mean: 82 ± 26.5 min) with a mean number of episodes of 2.4 ± 0.9 (Fig. 1).

Ondansetron. The onset of vomiting occurred between 117 and 207 min post-irradiation (mean: 159 ± 46.1 min) with a mean number of episodes of 1.3 ± 0.6 (Fig. 2).

Lerisetron (at 100 μg/kg). The onset of vomiting was produced between 85 and 155 min post-irradiation (mean: 118.3 ± 35.1 min) with a mean number of episodes of 2.7 ± 0.6 (Fig. 3).

Lerisetron (at 80 μg/kg). The onset of vomiting was produced between 65 and 159 min post-irradiation (mean: 124.7 ± 51.4 min) with a mean number of episodes of 1.3 ± 0.6 (Fig. 4).

No differences were observed in the duration of the vomiting episodes, which always lasted less than 45 s. The peak of vomiting episodes coincided with the onset of the first and second episodes, with the strongest contractions and the expulsion of the greatest amount of gastric contents. The incidence of double vomiting, that is, the occurrence of two episodes in rapid succession, did not differ from one group to another, probably due to the low number of cases among the treated groups, although there was a greater tendency toward double vomiting in the control group (80%). Almost all the double vomiting episodes occurred during the first or second vomiting episodes.

Nausea, as defined above, was not detected; gastric contents were expulsed during every episode, initially in greater amounts which decreased as the episodes continued.

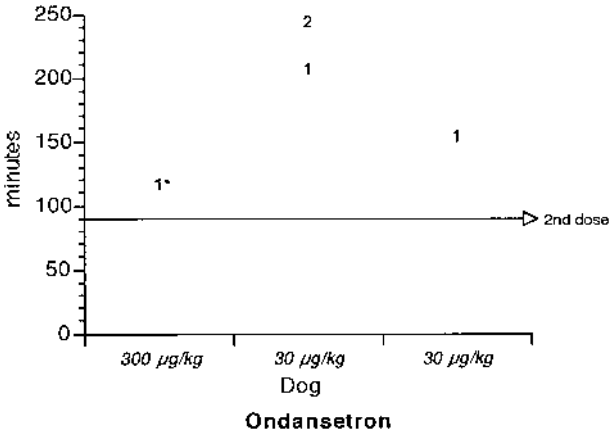

Fig. 2. Ondansetron: number of vomiting episodes. Number 1 indicates the first episode and the rest in succession with respect to the time elapsed since irradiation (min 0). The line indicates the time of administration of the second Ondansetron dose. On the abscissa, the dogs used are numbered starting with 1 and the Ondansetron dose administered. * Double vomiting episodes.

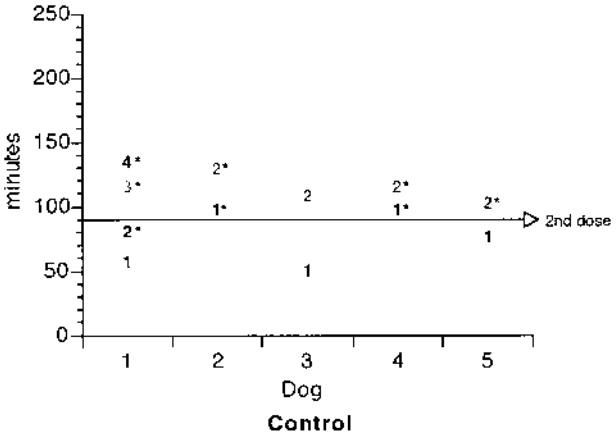

Fig. 1. Control: number of vomiting episodes. Number 1 indicates the first episode and the rest in succession with respect to the time elapsed since irradiation (min 0). The line indicates the time of administration of the second placebo dose (saline). On the abscissa, the dogs used are numbered starting with 1. * Double vomiting episodes.

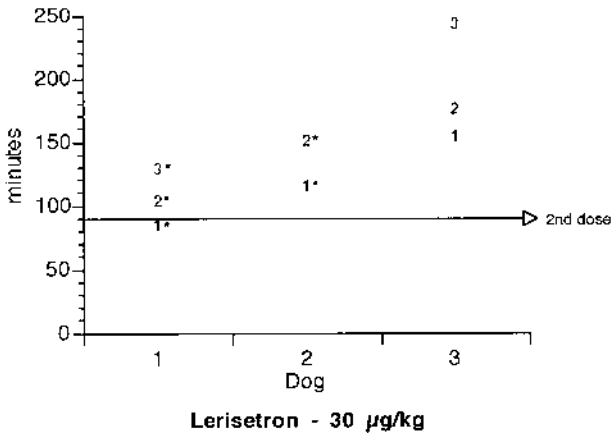

Fig. 3. Lerisetron (30 μg/kg): number of vomiting episodes. Number 1 indicates the first episode and the rest in succession with respect to the time elapsed since irradiation (min 0). The line indicates the time of administration of the second dose of 30 μg/kg Lerisetron. On the abscissa, the dogs used are numbered starting with 1. * Double vomiting episodes.

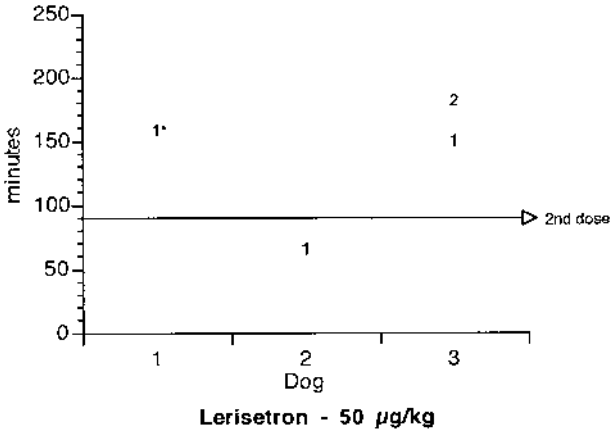

Fig. 4. Lerisetron (50 µg/kg): number of vomiting episodes. Number 1 indicates the first episode and the rest in succession with respect to the time elapsed since irradiation (min 0). The line indicates the time of administration of the second dose of 50 µg/kg Lerisetron. On the abscissa, the dogs used are numbered starting with 1. * Double vomiting episodes.

Other effects

Some degree of drowsiness was observed with either Lerisetron or Ondansetron during the study period. Neither sedation nor extrapyramidal effects were observed. The vital signs of the animals (heart and respiratory rates, arterial pressure) were not registered. The following day (24 h later), there was no sign of vomit or diarrhoea in the cages; these signs did appear, however, in those cases in which sacrifice was not carried out until 48 h later, but were due to the effects of the irradiation.

DISCUSSION

Radiotherapy effects are similar to those of chemotherapy in that mediators are produced or released that stimulate the peripheral and central activation sites of the vomiting reflex (8). Damage to the intestinal mucosa, produced by radiotherapy, chemotherapy or surgical trauma, causes the release of 5-HT by the enterochromaffin cells, stimulating the afferent vagal neurons toward the vomiting centre. Ondansetron blocks the afferent stimulus coming from bowel, preventing or reducing emesis. It can also exert a direct effect on the chemoreceptor triggering region. Ondansetron is not effective in motion sickness (13) or nausea induced by dopamine receptor agonists. Lerisetron, which does not inhibit apomorphine-induced vomiting, also has a low affinity for the dopamine receptor (9).

Few species experience vomiting, and those that do differ widely from one to another (14); nevertheless, several have been used successfully in the study of newly developed antiemetics (15). In cats, the ED_{50} of whole body radiation with ^{60}Co, which provokes vomiting, is over 20 Gy, whereas in the ferret, it is 1 Gy. Dogs and humans have great similarities in terms of their sensitivity to radiation (ED_{50} 2.3 Gy and 2 Gy, respectively). In dogs, a mean irradiation dose of 3.74 Gy produces vomiting in 84% of cases (16). Experimental studies suggest that doses of 4 Gy provoke vomiting in more than 85% (16) of the animals. This calculation is based on the fact that this dose is twice the ED_{50} of 1.70–2.3 Gy in the dog (11, 14), whereas the ED_{50} for humans is 1.5–2 Gy (17). Doses of 7 Gy produce 5–8 vomiting episodes in the dog (11), whereas doses of 8 Gy have been employed with a decreased incidence of vomiting which, in our trial, fell to a mean of 2.4 episodes, but occurred in 100% of animals not treated with the antiemetic agent. This decrease is probably related to irradiation injury and later development of oedema in the chemoreceptor triggering region.

The administration of Lerisetron can effectively prevent experimental radio-induced vomiting in the dog. Ondansetron is equally effective, although there was a stronger individual response to this drug and the mean dose was higher than that of Lerisetron. Doses of Lerisetron of 80–100 µg/kg iv, administered 15 min pre- and 90 min post-irradiation, were sufficient to prevent the onset of vomiting.

The administration of Ondansetron or Lerisetron at doses lower than those necessary to prevent vomiting appears to delay its onset and reduce its intensity and frequency, although more detailed studies, probably involving lower doses of radiation (4–7 Gy), will be necessary to confirm this finding.

There is great similarity in the response to both drugs studied in this work, although less individual variability was observed with Lerisetron. The vomiting-suppressing effect of Ondansetron and Lerisetron was assessed by means of the 'up-down' technique, a method which not only shows the efficacy of the drug, but is also an estimation of the ED_{50}. However, this technique is poorly suited to the determination of its efficacy at a given dose with a given confidence interval (e.g. the dose at which 95% of the population does not vomit).

There was no evidence of side effects with either Lerisetron or Ondansetron during the study period, with the exception of some degree of drowsiness. However, the animals were filmed during the study period and were not bothered; thus, the responses observed were probably more characteristic of the individual behaviour of each animal. Preliminary studies indicate that both Ondansetron and Lerisetron present a wide safety margin in dogs.

In conclusion, Lerisetron reduces vomiting after radiation therapy similar to the reduction with Ondansetron, but had a more predictable effect for a given dose of the antiemetic drug.

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