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Comparison of the Antiemetic Effects of a 5-HT_{1A} Agonist, LY228729, and 5-HT_3 Antagonists in the Pigeon

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WOLFF, M. C. AND J. D. LEANDER. *Comparison of the antiemetic effects of a 5-HT_{1A} agonist, LY228729, and 5-HT_3 antagonists in the pigeon.* PHARMACOL BIOCHEM BEHAV 52(3) 571-575, 1995.—Vomiting may be induced by a variety of agents such as drugs, oncolytics, and provocative motion, as well as being conditioned to occur to environmental stimuli. Such emesis has recently been shown to be blocked by agonists at the 5-HT_{1A} subtype of serotonin receptor. The antiemetic effects of LY228729 [(−)-4-(dipropylamine)-1,3,4,5-tetrahydrobenz-(c,d)indole-6-carboxamide], a 5-HT_{1A} receptor agonist, were tested and compared to the antiemetic effects of the 5-HT_3 receptor antagonists ondansetron, tropisetron, and MDL 72222 (3-tropanyl-3,5-dichlorobenzoate). The emetic stimuli tested are known to be blocked by 5-HT_3 antagonists in species other than the pigeon. In the pigeon, LY228729 totally abolished vomiting induced by fully emetic doses of cisplatin (10 mg/kg), ipecac (3 ml/kg), emetine (10 mg/kg), and a 5-HT_3 agonist, m-(chlorophenyl)-biguanide (1.25 mg/kg). MDL 72222 blocked ipecac-induced vomiting in a dose-related manner and was partially effective in attenuating cisplatin-induced emesis. Ondansetron and tropisetron were partially effective in blocking emetine- and mCPBG-induced vomiting. Ondansetron exhibited an intrinsic emetic response that could not be blocked by MDL 72222, but which was eliminated by LY228729. It was concluded that 5-HT_{1A} agonists are more effective in the pigeon than are 5-HT_3 antagonists against these types of emetic stimuli. These results broaden the range of emetic stimuli that are blocked by 5-HT_{1A} agonists in the pigeon.

Emesis Pigeon 5-HT_{1A} agonist 5-HT_3 antagonist

ANTAGONISTS at the 5-HT_3 subtype of serotonin (5-HT) receptors have generated a great deal of interest because they are effective antiemetics for radiation- and chemotherapy-induced emesis (1) in a variety of species. Despite their effectiveness in these emetic situations, 5-HT_3 antagonists are ineffective in the treatment of emesis induced by motion (13), certain nonserotonergic compounds including apomorphine (17), morphine (19), and ditolyguanidine (25), or by conditioning to environmental stimuli (25). It has recently been reported that compounds that are selective agonists at the 5-HT_{1A} subtype of receptor, on the other hand, effectively block emesis in a wide variety of situations. For instance, the 5-HT_{1A} receptor agonist 8-hydroxy-2-(di-*n*-propylamino)tetralin (8-OH-DPAT) blocks emesis induced by motion, xylazine, and the chemotherapy agent cisplatin in the cat (14). Likewise, in *Suncus murinus* (a house musk shrew; a species of insectivore), vomiting induced by such different stimuli as nicotine, veratrine, cisplatin, copper sulfate, and motion (19) is also blocked by 5-HT_{1A} receptor selective compounds. LY228729 [(−)-4-(dipropylamine)-1,3,4,5-tetrahydrobenz-(c,d)-indole-6-carboxamide], a well-characterized 5-HT_{1A} agonist (7), also blocks motion-induced emesis in the cat (7) and both ditolyguanidine (DTG) and conditioned emesis in the pigeon (25).

Although the mechanisms by which cisplatin elicits emesis are incompletely understood, release of serotonin from the gastrointestinal tract with activation of both peripheral and central sites has been implicated (2). Compounds that are considered to be agonists at the 5-HT_3 receptor induce vomiting that can be blocked in a manner similar to that by which cisplatin-induced emesis is blocked. For instance in the ferret, *m*-(chlorophenyl)-biguanide (mCPBG), a 5-HT_3 agonist (9), induces emesis that can be blocked by a combination of abdominal vagotomy and greater splanchnicectomy, as well as

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by a 5-HT_3 antagonist, YM060 (8). In addition, vomiting induced by the 5-HT_3 agonists 2-methyl-serotonin (2-methyl-5HT) and phenylbiguanide (PBG) is attenuated by vagotomy and a 5-HT_3 antagonist, MDL72222 (3-tropanyl-3,5-dichlorobenzoate), in the cat (16) and by zacopride and tropisetron (ICS 205-930) in the ferret (22).

Emesis induced by syrup of ipecacuanha (ipecac) has recently been suggested as a human model in which 5-HT_3 antagonists can be safely tested (18). Costall et al. (6) reported that ipecac, as well as cisplatin, produced emesis in ferrets that was blocked by a 5-HT_3 receptor antagonist, tropisetron. In dogs, the 5-HT_3 antagonist zatosetron attenuated both cisplatin- (5) and ipecac-induced vomiting with a similar potency (23), suggesting that a common underlying emetic mechanism may be responsible. Emetine, one of the active constituents of ipecac, has also been shown to induce emesis in *S. murinus* (24), dogs (3) and ferrets (2).

Pigeons have previously been used to study emesis induced by a variety of stimuli [for example, apomorphine, copper sulfate, piperazine, and cyclizine (11); cisplatin (20); and DTG and conditioned vomiting (25)]. The present study was conducted to determine whether pigeons would respond to a range of emetic stimuli that are effectively antagonized by 5-HT_3 antagonists in other species. The emetogenic stimuli chosen were cisplatin, mCPBG, ipecac and emetine. In view of the broad-spectrum antiemetic effects of 5-HT_{1A} agonists in cats (12), dogs (21), *S. murinus* (19), and pigeons (25), the relative efficacy of 5-HT_3 antagonists and 5-HT_{1A} agonists against the various emetic stimuli were compared in the present study. As some 5-HT_3 antagonists paradoxically not only block but induce emesis in the ferret (10,15) and the pigeon (20,25), the emetic as well as the antiemetic properties of ondansetron and MDL72222 were determined and compared with the antiemetic properties of tropisetron, 8-OH-DPAT, and LY228729. Only the highest subemetic doses of ondansetron and tropisetron were tested as antiemetics.

METHOD

Subjects

A group of 26 male White Carneaux pigeons (Palmetto Pigeon Plant, Sumter, NC) were kept in individual stainless-steel cages with water and crushed oyster shells continuously available except during experimental sessions. Temperature (22 ± 1°C) and humidity in the colony room were kept constant. Pigeons were maintained at 90% of their free-feeding body weights by a once-daily feeding of approximately 20 g of Purina Pigeon Checkers (Purina Mills, St Louis, MO).

All testing was conducted during the illuminated phase of the light-dark cycle (0600–1800 h). On test days, the birds were fed 5 min before the start of an emetic trial. If vomiting occurred, the pigeons were given an additional 20 g of feed after they were returned to their home cages at the conclusion of the observation period. Individual subjects were allowed a recovery period of at least 3 days between each drug test.

Procedure

Cisplatin. A 10-mg/kg dose of cisplatin [as shown previously (20) to be an effective emetic dose in pigeons] was administered into a wing vein 45 min before the intramuscular (IM) injection of either vehicle (n = 10), 0.08, or 0.32 mg/kg of LY228729 (n = 4/dose) or 5 mg/kg of MDL72222 (n = 3). The time until the onset of emesis and the number of emetic episodes (retches and vomits) were recorded for the next 4.5 h. As cisplatin is fatal to pigeons 5–7 days after administration, these birds were euthanized at the conclusion of the observation period to minimize their suffering.

Ipecac. Ipecac was administered via a feeding needle passed through the crop to the opening of the proventriculus (PO) at a dose of 1, 2, or 3 ml/kg. The birds were then placed in observation boxes that were checked for the presence of vomitus at 10-min intervals for the next 2 h. In tests of antiemetic activity, LY228729 (0.0025–0.16 mg/kg), MDL72222 (0.64–5 mg/kg), and ondansetron (0.32 mg/kg) were injected IM 15 min before ipecac (3 ml/kg, PO) administration. Three pigeons were tested at each drug and dose level. The dependent variable was the percentage of birds that vomited during the 2-h test interval.

Emetine. Emetine was injected IM at doses of 1, 5, 10, and 20 mg/kg (n = 3/dose). The pigeons were observed continuously for 10 min and then checked for the presence of vomitus at 15-min intervals for the next 2 h. Either 8-OH-DPAT (0.64 mg/kg, n = 4) or tropisetron (0.128 mg/kg, n = 4) was injected IM 15 min before 20 mg/kg of emetine, and the observation boxes were checked for the presence of vomitus at 15-min intervals for the next 2 h and at 30-min intervals for the following 2 h. However, as the 20-mg/kg dose of emetine was found subsequently to be fatal to 53% of the birds within 3–7 days, the dose of emetine was lowered to 10 mg/kg before further testing with antiemetics occurred. LY228729 (0.0025–0.01 mg/kg, n = 3/dose) and 5 mg/kg of MDL72222 (n = 3) were tested as antiemetics against 10 mg/kg of emetine.

mCPBG. After IM injection of mCPBG (0.32–5 mg/kg, n = 4/dose), the latency to the onset of the emetic response and the number of emetic episodes were recorded for 1 h. Tropisetron (0.128 mg/kg, n = 8), MDL72222 (1–5 mg/kg, n = 3/dose), ondansetron (0.16 mg/kg, n = 6), 8-OH-DPAT (0.64 mg/kg, n = 4), and LY 228729 (0.005–0.04 mg/kg, n = 3/dose) were injected IM 15–30 min prior to the IM injection of 1.25 mg/kg of mCPBG. The presence or absence of vomitus in the test cage was recorded after 1 h.

5-HT_3 antagonists. The presence or absence of vomitus was recorded 1 h after the IM injection of ondansetron (0.16–1.25 mg/kg, n = 3/dose) or MDL72222 (1–10 mg/kg, n = 3/dose). Subsequently, LY228729 (0.01–0.32 mg/kg, n = 3/dose), 8-OH-DPAT (0.64 mg/kg, n = 3), MDL72222 (5 mg/kg, n = 3), and tropisetron (0.128 mg/kg, n = 3) were tested as antiemetics against emesis induced by 1.25 mg/kg ondansetron.

Drugs. Cisplatin and emetine dihydrochloride were purchased from Sigma Chemical Co. (St Louis, MO). 8-OH-DPAT HBr, mCPBG HCl, and MDL 72222 were purchased from Research Biochemicals, Inc. (Natick, MA). Ondansetron was provided by Glaxo (Greenford, Middlesex, UK). Tropisetron (ICS-205 930) and LY228729 were synthesized by Eli Lilly and Co. (Indianapolis, IN). Ipecac was prepared by Eli Lilly and Co. in a solution of 7 g/100 ml of syrup. Emetine, 8-OH-DPAT, tropisetron, ondansetron, MDL 72222, and mCPBG were dissolved in normal saline. Cisplatin was prepared in sterile water at 70–75°C and then gradually cooled to 40°C before administration. LY228729 was dissolved in sterile water with the addition of a drop of lactic acid. All injections were given into the breast muscle (IM) in a volume of 1 ml/kg of body weight, except cisplatin, which was injected into a wing vein (IV) in a volume of 2 ml/kg of body weight, and ipecac, which was administered PO in various volumes (see earlier decription).

Data Analysis

ED_{50}s and 95% confidence limits were calculated using a method developed by Dr. Kerry Bemis (Eli Lilly and Co.) for use with JMP software (SAS Institute, Cary, NC).

RESULTS

Induction of Emesis

Cisplatin, emetine, mCPBG, and ondansetron (Fig. 1), as well as ipecac, each induced emesis in 100% of the birds tested at an appropriate dose.

In control treated birds, an IV injection of 10 mg/kg of cisplatin produced vomiting in 100% of the pigeons tested (Fig. 1). During a 4.5-h observation session, there was an average of 8.6 (±1.2 SEM) emetic episodes consisting of 6.2 vomits and 2.4 retches. The average latency to the onset of emesis was 1.46 h (±0.1 SEM).

Emetine (Fig. 1) induced emesis in a dose-related manner with an ED_{50} of 5.1 mg/kg. No signs of vomit were present during the 2-h observation period after administration of 1 mg/kg of emetine. A dose of 5 mg/kg induced vomiting in two of the three pigeons after 1.5 h. Doses of 10 mg/kg and above induced vomiting in all pigeons tested. The latency to the first emetic episode decreased from an average of 71.7 (±11.7 SEM) min after the 10-mg/kg dose to an average of 8.2 (±0.8 SEM) min after the 20-mg/kg dose.

An oral dose of 3 ml/kg of ipecac reliably induced emesis with a latency of approximately 35 min and a duration of at least 2 h (data not shown). Oral doses of 1 or 2 ml/kg failed to induce vomiting.

mCPBG (Fig. 1) induced vomiting in a dose-dependent manner with an ED_{50} of 0.75 mg/kg. A dose of 1.25 mg/kg of mCPBG caused vomiting with a mean latency of 4.9 (±0.7 SEM) min and an average of 4.5 (±0.5) emetic episodes. Vomiting continued for approximately 45 min after the injection of the mCPBG. Further increases in the dose of mCPBG did not significantly decrease emetic latency, but at 5 mg/kg, the average number of emetic episodes was increased to 8.8 (±1 SEM). Doses of mCPBG below 0.32 mg/kg did not induce emesis. As 1.25 mg/kg was a fully emetic dose of mCPBG, this dose was used in all subsequent experiments.

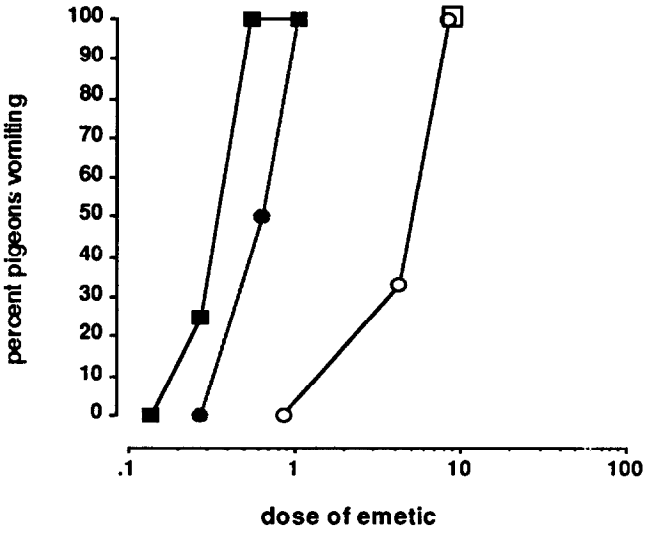

FIG. 1. Emesis induced by various compounds in the pigeon. ■, Ondansetron (n = 3/dose); ●, mCPBG (n = 4/dose); ○, emetine (n = 3/dose); □ (unconnected), cisplatin (n = 10). Dose is in milligrams per kilogram.

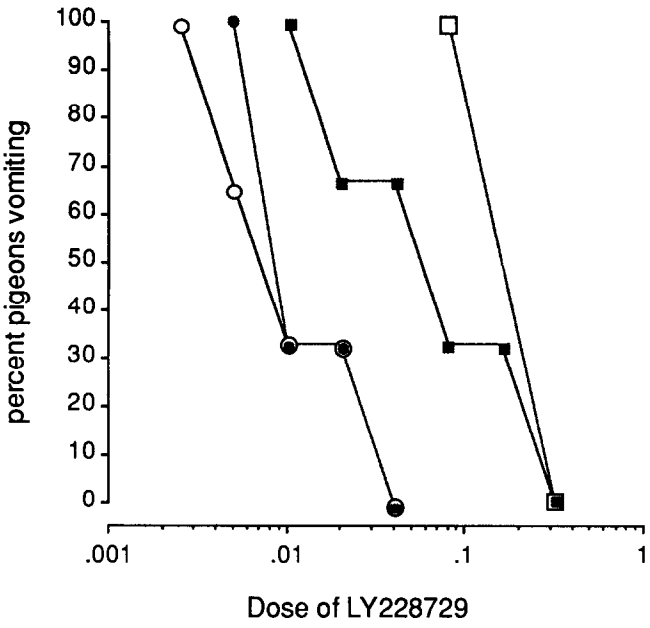

FIG. 2. Antiemetic effects of LY228729 against vomiting induced by emetine (○, n = 3/dose), ondansetron (■, n = 3/dose), mCPBG (●, n = 3/dose) or cisplatin (□, n = 4/dose).

Ondansetron alone (Fig. 1) induced dose-related vomiting in the pigeon, with an ED_{50} of 0.45 mg/kg. Vomiting continued for approximately 45 min. In contrast, the 5-HT_3 antagonist MDL72222 did not induce vomiting even at 10 mg/kg, the highest dose tested (data not shown).

Antiemetic Effects

As shown in Fig. 2, LY228729 produced a dose-related block of the vomiting induced by the 100% emetic doses of cisplatin, emetine (ED_{50} = 0.008 mg/kg), ipecac (ED_{50} = 0.009 mg/kg), mCPBG (ED_{50} = 0.01 mg/kg), and ondansetron (ED_{50} = 0.06 mg/kg). A single dose of 8-OH-DPAT (0.64 mg/kg) also completely prevented vomiting induced by either emetine (20 mg/kg) or mCPBG (data not shown).

Both MDL72222 (ED_{50} = 1.8 mg/kg) and LY228729 (ED_{50} = 0.009 mg/kg) blocked ipecac-induced vomiting in a dose-related manner (Fig. 3). However, a dose of 5 mg/kg of MDL 72222, which was fully protective against ipecac-induced vomiting, had variable effects against the cisplatin-induced vomiting in the three birds tested. In one bird, MDL 72222 totally prevented cisplatin-induced emesis. In a second bird, the cisplatin-induced emetic effects were markedly reduced (latency = 1.9 h, with a total of four emetic episodes consisting of one vomit and three retches), whereas the emetic response of the third bird was unaffected by administration of the MDL 72222. The 5-mg/kg dose of MDL 72222 was ineffective in blocking emesis induced by the 10-mg/kg dose of emetine.

A subemetic dose of tropisetron (0.128 mg/kg) prevented vomiting in two of the four pigeons administered a 20-mg/kg dose of emetine. One of eight pigeons administered 0.128 mg/kg of tropisetron was protected from mCPBG-induced vomit-

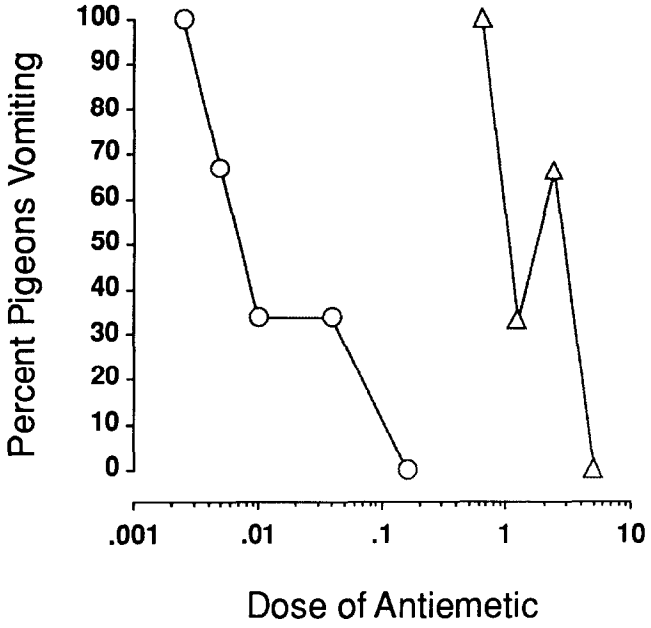

FIG. 3. Comparison of the antiemetic effects of LY228729 (○) and MDL72222 (△) against vomiting induced by 3 ml/kg ipecac. n = 3/drug per dose.

ing, but this dose was ineffective in preventing vomiting induced by 1.25 mg/kg of ondansetron.

When administered 30 min before mCPBG, ondansetron (0.16 mg/kg) prevented vomiting in two of six animals. Neither dose (0.32 or 0.5 mg/kg) of ondansetron prevented vomiting induced by ipecac.

DISCUSSION

Ipecac, emetine, and mCPBG, as well as cisplatin (20), induce dose-dependent vomiting in the pigeon that is similar to that which occurs in other species. For instance, although the dose of ipecac necessary to produce emesis in the dog [0.5 ml/kg, PO (23)] is much lower than that needed in the pigeon or human, the latency to the first emetic response was similar in the dog [34.4 min (23)] and pigeon (35 min), as well as in the ferret [25 min (6)]. The ED_{50} for emetine-induced vomiting (5.1 mg/kg) in the pigeon is considerably lower than in *S. murinus* [47.6 mg/kg (24)], but the latency to the onset of vomiting and its duration are similar in both species and in dogs (3). High doses of emetine are fatal in *S. murinus* [above 40 mg/kg (24)], dogs (3) and pigeons (20 mg/kg) within a few days. This problem can be avoided in studies with the pigeon, as consistently reliable vomiting occurs at one-half the fatal dose, although with a much longer latency than that which occurs after larger doses. The fully emetic dose of cisplatin (10 mg/kg), as well as the time to the onset and the duration of emesis, is similar in the pigeon and ferret (2). This 10-mg/kg dose of cisplatin is identical to the dose previously used in pigeons to provide 100% emesis (20).

In contrast to our emetic effects using the 5-HT_3 agonist mCPBG, Preziosi et al. (20) reported that the 5-HT_3 agonists 2-methyl-5-HT and PBG did not induce emesis in the pigeon. The doses used by Preziosi et al. may have been too small (0.5 mg/kg for 2-methyl-5HT and 2 mg/kg for PBG) to elicit vomiting, as relatively large doses of PBG were needed to induce vomiting in the ferret (22). As mCPBG is a more potent agonist at the 5-HT_3 receptor than either 2-methyl-5-HT or PBG (9), this may account for the difference between the result of Preziosi et al. and the present study. Peripherally administered mCPBG in the ferret (8) induces vomiting with a latency to onset that is similar in cats (16), ferrets (8), and pigeons in the present study.

Ondansetron, but not MDL72222, produced dose-related vomiting in the pigeon. Vomiting in response to 5-HT_3 receptor antagonists has been reported previously both in pigeons (20,25) and ferrets (10,15). Although the mechanism by which some 5-HT_3 antagonists induce vomiting in the pigeon remains unclear (20), the emetic response to zacopride in the ferret may be due to the 5-HT_3 receptor agonist properties of the S-enantiomer of zacopride (15) and could be blocked by ondansetron. Doses of MDL72222 that attenuated vomiting induced by cisplatin, ipecac, emetine, and mCPBG did not block ondansetron-induced emesis in the present experiments. Likewise, a dose of tropisetron that partially protected the pigeons from emetine- and mCPBG-induced emesis did not attenuate ondansetron-induced emesis. This would suggest that the vomiting produced by ondansetron in the pigeon is not due to an agonist action at the 5-HT_3 receptor.

The 5-HT_{1A} receptor agonists LY228729 and 8-OH-DPAT were more effective in blocking the emetic responses induced by cisplatin, ipecac, emetine, and mCPBG than were the 5-HT_3 antagonists. LY228729 blocked the fully emetic doses of each of these compounds in a dose-related manner. Vomiting induced by either mCPBG or emetine was also abolished by 0.64 mg/kg of 8-OH-DPAT. This extends the number of compounds known to be blocked by 5-HT_3 receptor antagonists in other species that are also blocked by 5-HT_{1A} receptor agonists. 5-HT_{1A} receptor agonists block the emetic response to cisplatin in the ferret (21), cat (14), and *S. murinus* (19), and to tropisetron in the pigeon (25).

Despite the similarity of the emetic response in the pigeon with that of other species, the 5-HT_3 antagonists were less effective in blocking vomiting in the pigeon than they have been reported to be in other species (1,6,8,16,22,23). MDL72222 blocked emesis induced by ipecac in a dose-dependent manner and provided partial protection against cisplatin-induced vomiting at the dose tested. Ondansetron and tropisetron totally protected only a few pigeons against mCPBG- and emetine-induced vomiting. However, the antiemetic potential of both ondansetron and tropisetron may have been limited by the action of both of these compounds to induce emesis in the pigeon.

Part of the apparent lack of effectiveness of the 5-HT_3 antagonists could be due to the all-or-none (presence or absence of vomitus) criteria used as the dependent variable in parts of the present study. This demanding criteria would not reveal any partial antiemetic effects, such as an increased latency to vomiting or a decrease in emetic episodes, that are frequently reported with 5-HT_3 receptor antagonists and were observed when MDL72222 was used to block cisplatin-induced emesis in the present study. Thus, use of these all-or-none criteria may have caused the effectiveness of these compounds to be underestimated. Species differences in the emetic response (2,10) could also account for the reduced efficacy of the 5-HT_3 receptor antagonists in the present study and in the study by Preziosi et al. (20). The vomiting reflex in the pigeon is initiated with apparent ease (4) and, in addition to ridding the body of possible toxins, is also used to feed the young.

In the present study, LY228729 was more effective than

the 5-HT_3 receptor antagonists to block emesis induced by cisplatin, ipecac, emetine, mCPBG, or ondansetron. These data, along with previous data (25) showing that the 5-HT_{1A} agonists 8-OH-DPAT and LY228729, but not the 5-HT_3 antagonist tropisetron, prevented vomiting induced by ditolyguanidine as well as vomiting conditioned to environmental stimuli, suggest that 5-HT_{1A} receptor agonists will have a broad spectrum of antiemetic activity that is not shared by 5-HT_3 receptor antagonists. This conclusion is further supported by the fact that 5-HT_{1A} receptor agonists block a wide range of emetogenic stimuli in a number of other species as well (12,19,21).

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