PRODUCT MONOGRAPH

LOPERAMIDE

(Loperamide Hydrochloride Caplets)

2 mg

Antidiarrheal

Laboratoires Trianon Inc.
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Blainville, Canada
J7C 3V4

Date of Preparation:
May 29, 1998

Control Number 056274

NAME OF DRUG

LOPERAMIDE
(Loperamide Hydrochloride Caplets)
2 mg

THERAPEUTIC CLASSIFICATION

Antidiarrheal

ACTION AND CLINICAL PHARMACOLOGY

Diarrhea may be defined as a failure or imbalance of one or a combination of activities in the gut which include secretion, absorption and motility. Loperamide hydrochloride has been shown to act on all of these functions via cholinergic, non-cholinergic, opiate and non-opiate receptor mediated mechanisms. In this way, loperamide hydrochloride effectively reduces fecal output and frequency, improves stool consistency and relieves symptoms of abdominal cramping and fecal incontinence.

A comparative bioavailability study was performed using IMODIUM 2 mg caplets (Janssen Pharmaceutica Inc., Canada) *versus* LOPERAMIDE 2 mg caplets (Laboratoires Trianon Inc.) in 30 normal volunteers. A single dose of 10 mg (5 caplets) was administered. The results are presented in the following summary tables for *loperamide* and *N-desmethylloperamide*.

SUMMARY OF COMPARATIVE BIOAVAILABILITY DATA

[after oral administration (5 x 2 mg caplets) in the fasting state]

LOPERAMIDE 2 mg Caplets (Laboratoires Trianon Inc., Canada -- Lot #630906)

versus

IMODIUM 2 mg Caplets (Janssen Pharmaceutica Inc., Canada -- Lot #93B973)

Loperamide

Parameter	Geometric Mean Arithmetic Mean (C.V.%)		Ratio of Means (%)
	Test	Reference	(90% C.I.)
AUC_T (ng·h/mL)	21.83 24.62 (47.4)	21.93 25.29 (57.6)	99.5 (91.4 - 108.4)
AUC (ng·h/mL)	24.39 26.92 (44.5)	24.14 27.38 (54.5)	101.0 (92.8 - 110.0)
C_{max} mg/mL	1.50 1.68 (49.6)	1.59 1.73 (40.8)	94.2
T_{max} (h)	3.42 (1.43)	3.78 (2.03)	---
$T½_{el}$ (h)	15.00 (4.77)	14.44 (4.88)	---

T_{max} and $T½_{el}$ -- arithmetic mean with standard deviation in parenthesis.

N-Desmethylloperamide

Parameter	Geometric Mean Arithmetic Mean (C.V.%)		Ratio of Means (%)
	Test	Reference	(90% C.I.)
AUC_T (ng·h/mL)	149.88 153.08 (20.1)	154.00 159.09 (27.8)	97.3 (93.6 - 101.2)
AUC_∞ (ng·h/mL)	157.13 160.80 (21.2)	160.28 165.56 (27.6)	98.0 (94.5 - 101.7)
C_{max} mg/mL	3.47 3.55 (21.4)	3.61 3.69 (21.3)	95.9
T_{max} (h)	7.83 (2.59)	7.47 (2.30)	---
$T½_{el}$ (h)	35.84 (6.32)	34.92 (5.53)	---

T_{max} and $T½_{el}$ -- arithmetic mean with standard deviation in parenthesis.

INDICATIONS

LOPERAMIDE (loperamide hydrochloride) is indicated as an adjunct to rehydration therapy for the symptomatic control of acute nonspecific diarrhea; for chronic diarrhea associated with inflammatory bowel disease; and for reducing the volume of discharge for ileostomies, colostomies and other intestinal resections.

CONTRAINDICATIONS

LOPERAMIDE (loperamide hydrochloride) is contraindicated for use in children under 2 years of age.

LOPERAMIDE is contraindicated in patients with known hypersensitivity to the drug and in those in whom constipation must be avoided.

WARNINGS

LOPERAMIDE (loperamide hydrochloride) should not be used in the case of acute dysentery which is characterized by blood in stools and elevated temperature. Fluid and electrolyte depletion may occur in patients who have diarrhea. The use of LOPERAMIDE does not preclude the administration of appropriate fluid and electrolyte therapy.

In some patients with acute ulcerative colitis and in pseudomembranous colitis associated with broad spectrum antibiotics, agents which inhibit intestinal motility or delay intestinal transit time have been reported to induce toxic megacolon. LOPERAMIDE therapy should be discontinued promptly if abdominal distension occurs or if other untoward symptoms develop.

The use of LOPERAMIDE is not recommended for children under 12 years of

age except on the advice of a physician. (See DOSAGE AND ADMINISTRATION).

LOPERAMIDE should be used with special caution in young children and those with compromised blood brain barrier (eg. meningitis) because of the greater variability of response in these groups. Dehydration, particularly in young children, may further influence the variability of response to LOPERAMIDE.

In case of accidental ingestion of LOPERAMIDE by children, see SYMPTOMS AND TREATMENT OF OVERDOSAGE.

PRECAUTIONS

Safe use of LOPERAMIDE (loperamide hydrochloride) during pregnancy and lactation has not been established. Reproduction studies performed in the rat and the rabbit revealed no evidence of impaired fertility or harm to the fetus at dosage levels up to 30-fold, the therapeutic dose for man.

Patients with hepatic dysfunction should be monitored for signs of CNS toxicity due to the extensive first pass metabolism of loperamide in the liver.

If improvement in symptoms of acute diarrhea is not observed within 48 hours, the use of LOPERAMIDE should be discontinued.

Dependence liability: Physical dependence to LOPERAMIDE in humans has not been observed. However, studies in morphine- dependent monkeys demonstrated that loperamide hydrochloride at doses above those recommended for humans prevented signs of morphine withdrawal. However, in humans, the naloxone challenge pupil test, which when positive indicated opiate-like effects, performed after a single high dose, or after more than two years of therapeutic use of LOPERAMIDE, was negative.

ADVERSE REACTIONS

The adverse effects reported in adults during clinical trials are difficult to distinguish from symptoms associated with the diarrheal syndrome. In adults, they were generally of a minor and self-limiting nature e.g., abdominal pain, distension or discomfort; constipation; drowsiness or dizziness; dry mouth; nausea and vomiting; hypersensitivity, including skin rash. Opiate-like effects (CNS) have been observed in young children (under 3 years of age).

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Clinical trials have demonstrated that a slurry of activated charcoal administered promptly after ingestion of loperamide hydrochloride can reduce the amount of drug which is absorbed into the systemic circulation by as much as ninefold. If vomiting occurs spontaneously upon ingestion, a slurry of 100 grams of activated charcoal should be administered orally as soon as fluids can be retained.

If vomiting has not occurred, gastric lavage should be performed followed by administration of 100 grams of the activated charcoal slurry through the gastric tube. In the event of overdosage, patients should be monitored for signs of CNS depression for at least 24 hours. If CNS depression is observed, naloxone may be administered. If responsive to naloxone, vital signs must be monitored carefully for recurrence of symptoms of drug overdose for at least 24 hours after the last dose of naloxone.

In view of the prolonged action of loperamide and the short duration (one to three hours) of naloxone, the patient must be monitored closely and treated repeatedly with naloxone as indicated. Since relatively little drug is excreted in the urine, forced diuresis is not expected to be effective for

loperamide hydrochloride overdosage.

In clinical trials, an adult who took three 20 mg doses within a 24-hour period was nauseated after the second dose and vomited after the third dose. In studies designed to examine the potential for side effects, intentional ingestion of up to 60 mg of loperamide hydrochloride in a single dose to healthy subjects resulted in no significant adverse effects.

DOSAGE AND ADMINISTRATION

Adults:
Acute diarrhea: The recommended initial dose of LOPERAMIDE (loperamide hydrochloride) is 4 mg followed by 2 mg after each unformed stool. Daily dosage should not exceed 16 mg.

Chronic diarrhea: The recommended initial dosage of LOPERAMIDE is 4 mg followed by 2 mg after each unformed stool until diarrhea is controlled; thereafter the dosage of

LOPERAMIDE should be reduced to meet individual requirements. When the optimal daily dosage has thus been established, this amount can be administered as a single dose daily or in divided doses.

The average daily maintenance dosage used in clinical trials has been 4-8 mg. If improvement is not observed after treatment with 16 mg per day for 10 days, symptoms are unlikely to be controlled by further administration.

Children:
Acute or chronic diarrhea: LOPERAMIDE should be used in children only on the advice of a physician. For children up to 12 years of age, the following schedule will usually fulfill initial dosage requirements:

Recommended First-Day Dosage Schedule

2-5 years: (10 to 20 kg)	1 mg t.i.d. (3 mg daily dose)
5-8 years: (20 to 30 kg)	2 mg b.i.d. (4 mg daily dose)
8-12 years: (greater than 30 kg)	2 mg t.i.d. (6 mg daily dose)

Following the first treatment day, it is recommended that subsequent LOPERAMIDE doses (1 mg/10 kg body weight) be administered only after a loose stool.

Duration of Treatment

LOPERAMIDE (loperamide hydrochloride) may be administered for prolonged periods of time. Blood, urine, liver and kidney function, ECG and ophthalmological examinations have revealed no significant abnormalities after several years of administration. No tolerance to the antidiarrheal effect has been observed. Naloxone pupil challenge studies in patients with chronic diarrhea who have received LOPERAMIDE orally for prolonged periods indicate a lack of CNS effects.

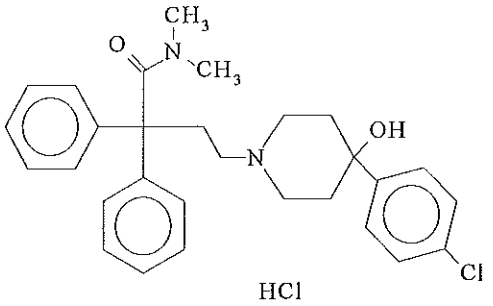
PHARMACEUTICAL INFORMATION

Drug Substance

Proper Name: Loperamide Hydrochloride

Chemical Name: 4-(4-chlorophenyl)-4-hydroxy-N, N-dimethyl-α,α-diphenyl-1- piperidinebutyramide monohydrochloride.

Structural Formula:



Molecular Formula: $C_{29}H_{33}ClN_2O_2 \cdot HCl$

Molecular Weight: 513.51

Description: White to faintly yellowish amorphous or microcrystalline powder; soluble in methanol, chloroform and ethanol, slightly soluble in water and ether; melts at 215° to 230°C.

Composition

Each LOPERAMIDE caplet contains 2 mg loperamide hydrochloride and the following nonmedicinal ingredients: Croscarmellose Sodium, D&C Yellow No. 10 Aluminum Lake, FD&C Blue No. 1 Aluminum Lake, Lactose, Magnesium Stearate, Microcrystalline Cellulose and Povidone.

Storage Recommendations: Store between 15° and 30°C.

AVAILABILITY OF DOSAGE FORMS

LOPERAMIDE caplets are scored, oblong, biconvex, green tablets inscribed "1 *2 mg*" on the scored side and "*LOPERAMIDE*" on the other side; available in a PVC-aluminum blister pack of 6 and 12 caplets.

PHARMACOLOGY

Preclinical Studies

1. Tissue and Whole Animal

a) Motility

Motility in the gut is the result of cholinergic and noncholinergic biphasic stimulation of the intestinal musculature. The cholinergic mediator, acetylcholine (ACh), is responsible for the first phase of peristalsis, while prostaglandins (PG) are thought to mediate the second phase. Loperamide has been shown to inhibit release of both ACh and PG for isolated guinea pig ileum, as well as directly block the action of PG on smooth muscle preparations from rats. The net result is a reduction in the number of peristaltic waves, the fluid expelled by each wave and overall gut motility. Loperamide produces a sustained inhibition of the peristaltic activity of the guinea pig ileum *in vitro* at doses as low as 0.005 mg/L. The inhibitory effects are dose related, the activity of both the longitudinal and circular muscles being affected. At dose levels inhibiting peristaltic activity, loperamide antagonizes the spasmogenic effects of electrical-and nicotine-induced stimulation of this preparation. As well, the angiotensin- 5-hydroxy-tryptamine-, bradykinin-barium chloride- and histamine-induced contractions of the guinea pig ileum preparation are inhibited by doses of 0.14 mg/L or more.

On the other hand, loperamide is inactive against 5-hydroxytryptamine on the rat fundus, epinephrine on the rabbit spleen, acetylcholine on the rabbit duodenum and isoproterenol on the hen rectal caecum preparations at dose levels of up to 10 mg/L. A moderate negative inotropic effect is produced on the cat papillary muscle at 3 and 10 mg/L, and a moderate negative chronotropic effect is produced on the guinea pig atrium at 0.16 mg/L. This antagonism is thought to be unspecific.

In mice, loperamide is a potent blocker of gastrointestinal motility both by the subcutaneous route (ED_{50} = 0.59 mg/kg) and the intraperitoneal route (ED_{50} = 0.35 mg/kg). At oral doses up to 40 mg/kg in mice and rats, loperamide is devoid of any general pharmacological activity. Pulmonary function is not affected by high oral doses and the cardiovascular effects of intravenous loperamide are mainly due to the vehicle used.

Loperamide also acts on the anal sphincter to increase both maximum basal and maximum squeeze pressure, as well as reduce urgency and incontinence.

b) Absorption/Secretion

Changes in ion permeability of the mucosal surface are associated with the presence of various endotoxins, prostaglandins, hormones and other substances, resulting in secretory diarrhea. Substances such as vasoactive intestinal polypeptide, prostaglandin E_2, cholera toxin and both the heat-stable and labile enterotoxins of E. coli increase intracellular cyclic nucleotides which result in the opening of mucosal chloride channels allowing excess loss of chloride followed by sodium and water into the intestinal lumen. On isolated tissue, devoid of motility, loperamide has been shown to reduce the chloride loss associated with the presence of prostaglandin, cholera toxin, theophylline, 1,8-dihydroxanthraquinone, and castor oil. Loperamide, administered orally, blocks castor oil-induced diarrhea in rats and has an ED_{50} value of 0.15 mg/kg (1 hour). The antidiarrheal action is rapid, regular and long lasting. Loperamide has also been shown to decrease secretion caused by E. coli enterotoxin both *in vivo* and *in vitro*. This is accomplished by increasing the chloride secretion into the plasma at the serosal membrane, thus effectively decreasing chloride as well as sodium and water loss at the mucosal surface. This effect on chloride secretion can be blocked with naloxone.

Substances such as serotonin, acetylcholine and other cholinergic agonists are believed to cause diarrhea by increasing intracellular calcium levels.

Intracellular calcium combines with calmodulin to activate adenyl cyclase, which again results in an increase in cellular cyclic nucleotides, hence an increase in chloride permeability. Loperamide inhibits the calcium-calmodulin-mediated increase in enzyme function *in vitro* at concentrations as low as 4 μM. This action appears to be separate from the opiate receptor binding properties of loperamide.

c) Safety

Loperamide, carefully evaluated in a series of experimental procedures for central narcotic actions and associated subjective stimuli, showed that the dissociation between gastrointestinal and CNS effects is complete with this compound. The antidiarrheal activity of loperamide is evident at low oral and parenteral doses; however, atoxic oral doses are not analgesic in rats and morphine-like behavioural effects cannot be induced in mice even at toxic subcutaneous and intraperitoneal doses. Unlike fentanyl, morphine, codeine and diphenoxylate, loperamide after chronic administration of doses as high as 300 times the antidiarrheal dose, does not produce physical dependence in mice or narcotic withdrawal symptoms in rats, and no preference for loperamide can be experimentally established. Also, loperamide cannot substitute for fentanyl in rats with a learned preference for narcotics. Initial difference in taste qualities of loperamide and fentanyl are excluded as a possible explanation of the observations. Finally, the discrimination learning procedure provides the most direct and conclusive evidence to the inability of loperamide to induce subjective stimuli specifically associated with the central action produced by all narcotic drugs tested.

2. Metabolism and Pharmacokinetics

Tritium-labelled loperamide was administered orally to eight groups of five fasted male Wistar rats (250 ± 10g) at a dosage of 1.25 mg/kg. Urine and feces were collected for up to 4 days. The rats were killed at different times from 1 to 96 hours after drug administration in order to examine blood, organs and tissues. In one rat, the bile was cannulated for 48 hours. The

radioactive content of each sample was measured and the fractions due to loperamide, metabolites, and volatile radioactivity were determined by the inverse isotope dilution technique and lyophilization. Only 5% of the drug and its metabolites was recovered from the urine, the bulk being excreted with the feces. Drug plasma levels were low at all times. Maximum plasma levels of unchanged loperamide were at least 0.22% of the administered dose corresponding to about 75 ng/mL of plasma. The gastrointestinal tract contained about 85% of loperamide 1 hour after dosing. Brain levels were extremely low, never exceeding 22 ng/g brain tissue or 0.005% of the administered dose. The existence of an enterohepatic shunt was shown, but the uptake of the drug into the general circulation was low. Differentiation between total radioactivity and nonvolatile radioactivity demonstrated that most of the residual organ radioactivity was due to tritiated water.

Clinical Studies

1. Metabolism and Pharmacokinetics

Three male volunteers received orally 2.0 mg of ^{3}H-loperamide (specific activity 64 mCi/mM) in gelatine capsules. Control samples of blood, urine and feces were obtained before administration. Blood was collected on heparin 1,2,4,8,24,72 and 168 hours thereafter. Urine was collected for seven days and feces for eight days. The radioactive content of each sample was measured and the fractions due to loperamide, metabolites and volatile radioactivity were determined by the inverse isotope dilution technique and lyophilization. The fate of orally administered ^{3}H-loperamide in man appeared to be similar to that in rats. The peak plasma level of loperamide occurred 4 hours after treatment and was less than 2 ng/mL or about 0.3% of the administered dose. About 1% of the administered dose was excreted unaltered with the urine and 6% as nonvolatile metabolites. About 40% of the administered dose was excreted with the feces, mainly within the first four days; 30% of this amount was due to unchanged drug.

2. Treatment of Chronic Diarrhea

Eleven studies conducted in Europe and the United States have evaluated the use of loperamide for the symptomatic control of chronic diarrhea.

These studies included 231 male and female patients (20-76 years of age) who had a documented history of chronic diarrhea or had undergone extensive intestinal resections.

Seven studies were based on essentially a common protocol: a double-blind, crossover comparison of loperamide with a control agent, either a placebo (3 studies, 53 patients) or a known effective anti-diarrheal, diphenoxylate (4 studies, 58 patients), at once or twice the marketed dosage strength. The patients were always randomly allocated to either treatment sequence. A drug-free prestudy relapse period and drug-free relapse interval between treatment sequences was provided in all studies comparing loperamide with diphenoxylate. Drug efficacy was based on the frequency and consistency of stools, fecal output, carmine transit time, number of capsules or daily dosage, investigators' or patients' preferences.

One study involving 15 patients was based on an original protocol. After a relapse period, all patients were treated with loperamide; the successfully treated patients thereafter entered a double-blind trial to substantiate the effects of the open phase.

Three studies included 104 male and female patients (20 to 76 years of age), and were conducted according to a common protocol. After a drug-free period, the patients were treated with loperamide for one month. After this open trial, the patients were randomly assigned to double-blind treatment with either placebo or loperamide. When patients relapsed, the code was broken. Loperamide was then prescribed for those patients who were found to be on placebo, and the prestudy antidiarrheal was again prescribed for patients relapsing on loperamide. The codes of those patients who did not relapse were broken after about one month of double-blind medication. Those patients who were controlled by loperamide continued taking the medication to obtain long-term control.

In these controlled studies, loperamide has been found useful for the symptomatic control of:

a) chronic diarrhea of various organic and functional etiologies (e.g. Crohn's disease, chronic ulcerative colitis, post-radiotherapy diarrhea, irritable colon);

b) intestinal peristalsis and transit time in patients with ileostomies, colostomies, and other intestinal resections:

The long-term evaluations in chronic diarrhea included 104 male and female patients studied for up to 44 months. Loperamide was found to be an effective agent for long-term treatment of chronic diarrhea and that improvement was maintained for several years without increasing the dose.

3. Treatment of Acute Diarrhea

Five studies carried out in Europe and the United States have assessed the use of a flexible dose schedule with loperamide in the treatment of acute diarrhea. These studies included 554 patients treated with loperamide. Drug efficacy was assessed on the basis of stool frequency and consistency, dosage and recurrence of unformed stools. The noticeable features of these studies were:

a) after a single 4 mg dose, the first liquid or unformed stools recurred after 24 hours or more, indicating the restoration of intestinal peristalsis and transit time to normal.

b) a single 4 mg dose had a rapid, regular and long-lasting effect;

c) the number of stools is reduced and their consistency is improved.

In these studies, loperamide used in a flexible dosage regimen effected the symptomatic control of acute diarrhea.

4. Clinical Laboratory Studies

In selected studies, haematology, blood chemistry, urinalysis and

electrocardiograph examinations as well as slit-lamp and clinical ophthalmology examinations were carried out. A review of all laboratory data obtained from these patients treated with loperamide failed to show any short-term or long-term drug-related effects.

5. Adverse Reactions

In general, few side effects after treatment with loperamide were reported. These were gastrointestinal in origin and subsided with continuation of treatment. The most frequent adverse effect reported was constipation. No adverse experiences were reported after prolonged use of loperamide.

6. Evaluation of Drug Abuse Liability

Four special studies have examined loperamide for opiate-like effects in humans. These studies showed that single high doses (16 mg) did not produce pupillary constriction and naloxone, a morphine antagonist, had no effect on pupil size even after prolonged use of loperamide.

The optimum dose level as a function of time was evaluated in three studies with patients on long-term loperamide treatment. In these studies:

a) Patients given loperamide at a median dose of 2 mg twice daily for 12 months maintained improvement without increasing dose;

b) Patients treated up to 44 months progressively reduced their daily requirements;

c) Patients treated with 2 to 12 mg of loperamide daily upto 38 months maintained improvement without increasing dose.

In addition, clinical studies with loperamide have not shown this drug to produce subjectively pleasant effects in man or animals. Those subjective effects which may be expected are related to the control of diarrhea or, in the case of overdosage, constipation.

TOXICOLOGY

1. Acute

The acute toxicity of loperamide (7-day mortality) has been assessed in several species by various routes. The following values were obtained:

Species	Routes of Administration	LD_{50} (mg/kg)
Mouse	p.o. s.c. i.p.	105 75 28
Adult Rat	p.o. i.v.	185 5.1
Young Male Rat	p.o.	135
Young Female Rat	p.o.	261
Guinea Pig	p.o.	41.5
Dog	p.o. i.v.	> 40 2.8

The therapeutic ratio (LD_{50}/ED_{50} "8 hour" castor oil test) for loperamide when given orally to rats is 1:125. This compares to diphenoxylate, morphine and codeine which have therapeutic ratios of 1:55, 1:13 and 1:5.5, respectively. As well, the oral safety margin is wider than the intravenous.

2. Subacute

Rats

Wistar rats (10 males and 10 females per dose group) were given loperamide in their diet at 40, 10 and 2.5 mg/100 g of food seven days a week for 15 weeks. Control animals received diet only. No drug-induced mortality was observed. Health, behaviour and appearance were normal in all groups except that the 40 mg/100 g food-dosed animals showed a swollen abdomen during the first four weeks. No effects could be evidenced on hemograms, serum analyses and urinalyses except a decrease of creatinine in the dosed animals. Weight gain and food consumption were lower in the 40 mg/100 g food-dosed animals. At this 40 mg/100 g food dose, some minor macroscopic and microscopic changes are probably related to reduced food consumption.

3. Chronic

Rats

Wistar rats (30 males and 30 females per dose group) were given loperamide in their diet at 40, 10 and 2.5 mg/100 g of food seven days a week, while control animals received diet only. Interim sacrifices of 20 animals per dose group were carried out at 6, 12 and 18 months on study. No drug induced mortality was observed. Health, behaviour and appearance were normal in all groups throughout the entire experimental period. Weight gain and food consumption were lower in the 40 mg/100 g food-dosed animals especially during the initial 3 months of dosing. As for the subacute toxicity study, no effects could be evidenced on hemograms, serum analyses and urinalyses, except a decrease of creatinine at 10 and 40 mg/ 100 g food-dosed animals and dose-related hyperemia of the vascular system of the intestine and mesenterium, but no other dose- or drug-related changes.

Dogs

Beagle dogs (3 males and 3 females per dose group) were given loperamide

in gelatin capsules at 5.0, 1.25 and 0.31 mg/kg six days a week for 12 months. Some depression was seen during the first week of drug administration at 1.25 and 5 mg/kg. Behaviour and appearance were normal during the rest of the experiment, except that haemorrhagic stools were seen from time to time at 5 mg/kg and soft stools at 0.31 and 1.25 mg/kg, especially during the first 6 weeks of drug administration. Blood pressure, heart rate, electrocardiogram, hemograms, serum analysis and urinalysis were normal throughout the experiment. Gross pathologic and histologic examinations failed to reveal any dose or drug-related changes.

4. Reproductive studies

Fertility and General Reproductive Performance in Rats
Adult Wistar rats (2 groups per dose level) were given loperamide in their diet at 40, 10 and 2.5 mg/100 g of food as follows:

Group A: 20 males - drug given 60 days premating
20 females - no drug

Group B: 20 males - no drug
20 females - drug 14 days premating and throughout gestation.

Loperamide has no effect on male fertility when administered orally to males for at least 60 days prior to mating at doses of 40, 10 and 2.5 mg/100 g food, or approximately 40, 10 and 2.5 mg/kg. No pregnancies occurred among the females dosed at 40 mg/100 g food for at least 14 days prior to mating and during the complete period of gestation. No data on offspring are available for this group. In the other groups there was no difference in the number of implantations per dam, litter size, percentage of live, dead and resorbed fetuses; distribution of live, dead and resorbed fetuses in the left and right uterine horns; and body weight of live young. There was no evidence of teratogenicity.

Peri- and Post-natal Studies in Rats

Mature female Wistar rats (20 animals per dose group) were given loperamide in their diet at 40, 10 and 2.5 mg/100 g of food from day 16 of pregnancy throughout a three-week lactation period. Control animals received diet only. Food consumption and body weight gain were affected in the 40 mg/100 g food-dosed females, resulting in a decrease of fetal weight gain and survival rate. There was no difference between the control group and the 2.5, 10 and 40 mg/100 g food-dosed groups in pregnancy rate, duration of gestation, litter size, percentage of live and stillborn fetuses. There were no abnormalities in any young.

	Dose (mg/100 g food)			
Adult rat data	0	2.5	10	40
Pregnancy rate (%)	95	95	100	95
Mortality rate (%)	0	0	5	0
Litter data				
Mean litter size	9.8	11.2	11.7	9.6
Average weight at birth (g)	5.9	6.0	5.9	5.5
Live fetuses (%)	91.5	95.5	98.5	92.7
Dead fetuses (%)	8.5	4.5	1.5	7.3
Survival rate at weaning (%)	79.6	90.6	71.0	13.8
Abnormalities	0	0	0	0

5. Teratology

Rats

Pregnant primiparous female Wistar rats (20 animals per dose group) were given loperamide in their diet at 40, 10 and 2.5 mg/100 g of food from day 6 through day 15 of pregnancy. On day 22, fetuses were delivered by caesarean section. At 40 mg/100 g food, only 1 female out of 20 became pregnant, thus confirming the results of the fertility study in rats. There was no significant difference between the control group and the 2.5 and 10 mg/100 g food-dosed groups in pregnancy rate; number of implantations per dam; litter size, percentage of live, dead and resorbed fetuses; distribution of live, dead and resorbed fetuses in the left and right uterine horns; and body weight of live young. No macroscopic, visceral, or skeletal malformations were seen.

	Dose (mg/100 g food)			
Adult rat data	0	2.5	10	40
Pregnancy rate (%)	100	100	95	5
Mortality rate (%)	0	0	0	0
Litter data				
Mean litter size	10.6	9.3	9.9	8.0
Average weight at birth (g)	5.3	5.5	5.2	4.5
Live fetuses (%)	93.5	92.5	91.7	88.9
Dead fetuses (%)	4.2	0.0	0.5	0.0
Resorbed fetuses (%)	2.3	7.5	7.8	11.1
Abnormalities	0	0	0	0

Rabbits

Primiparous female New Zealand white rabbits, fertilized by artificial insemination (15-20 animals per dose group) were given loperamide by gavage at 40, 20 and 5 mg/kg from day 6 through 18 post-insemination. Control animals received an equivalent volume of isotonic saline vehicle. Animals were sacrificed on day 28. No differences in pregnancy rate could be noted. The mortality rate was higher in the 40 mg/kg dosed rabbits and was mainly due to enteritis. There was no difference in pregnancy rate between dosed and controlled. The average weight gain and litter size of treated females was affected, and the average weight at delivery was lower in the young of the 40 mg/kg dosed females. There was little or no difference in the percentage of live, dead and resorbed fetuses. No macroscopic visceral or skeletal abnormalities were seen except in 1 fetus with bifurcated ribs of the control group and 1 fetus with cyclopia of the 40 mg/kg dosed group. It is not believed that this case of cyclopia is drug related as cases of cyclopia and agnathia have been encountered in control fetuses of earlier experiments with the same New Zealand rabbit strain.

	Dose (mg/kg)			
Adult rabbit data	0	5.0	20	40
Pregnancy rate (%)	70	60	70	80
Mortality rate (%)	20	10	25	60
Litter data				
Mean litter size	6.5	5.4	5.3	5.3
Average weight at birth (g)	40.9	41.4	38.1	34.3
Live fetuses (%)	98.6	95.2	89.2	87.0
Dead fetuses (%)	0	0	0	4.3
Resorbed fetuses (%)	1.4	4.8	10.8	8.7
Abnormalities	1	0	0	1

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