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A Comparison of the Antidiarrheal and Some Other Pharmacological Effects of Clonidine, Lidamidine, and Loperamide in the Rat

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ABSTRACT

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Clonidine, lidamidine, and loperamide each inhibited castor oil-induced diarrhea in the rat. Clonidine and lidamidine, but not loperamide, also induced diuresis but at doses above those producing antidiarrheal activity. Clonidine and lidamidine, but not loperamide, produced autonomic and central effects including piloerection, hypotonia, exopthalmus and ataxia at doses similar to those producing antidiarrheal activity. These data suggest that only loperamide possesses selective antidiarrheal activity.

Key words: clonidine, lidamidine, loperamide, diarrhea, diuresis

INTRODUCTION

Because of the widespread indications for the use of specific antidiarrheal drugs in many disease conditions, a number of new chemical structures are being investigated for their antidiarrheal potency. Loperamide, the most recently introduced drug for controlling diarrhea, has proven to be very efficacious and free of side effects [Reyntjens and Lal, 1976; Zelveder, 1976]. Among the new chemical structures currently under investigation for their antidiarrheal action are clonidine [Lal et al., in press] and several modifications of its structure, including lofexidine [Lal et al., in press] and lidamidine [Mir et al., 1978]. The present experiment was undertaken to compare the antidiarrheal potency of clonidine and lidamidine with loperamide and view their antidiarrheal activity in relationship to a number of other pharmacological actions.

MATERIALS AND METHODS

Male rats of inbred Wistar strain weighing 200–250 g body weight were used. Clonidine and lidamidine were dissolved in saline. Loperamide was suspended in methylcellulose and Tween 80.

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Measurement of Antidiarrheal Activity

The rats were food deprived during the night before testing. On the day of testing, they were treated orally with either saline or one of several doses of either clonidine, lidamidine, or loperamide prepared in aqueous solutions (1 ml/100 g body weight). Each animal was then challenged with 1 ml of castor oil given orally at 1 hr after treatment and placed in a small (11 × 17 × 12 cm) individual cage. At intervals of 1, 2, 3, 4, 6, and 8 hr after castor oil, the removable floor underneath the cage was examined for the presence or absence of diarrhea as described before [Lal et al., in press]. The rats were removed from the cages as soon as the diarrhea was noticed. Absence of diarrhea at a particular interval of observation was used as the criterion of drug effectiveness and ED50 values with 5% fiducial limits were computed by the method of Finney [1962].

Measure of Diuresis

The rats were deprived of food and water for 16 hr. They were then loaded with 5 ml of saline given orally and treated with the test drugs also given orally. The rats were placed in metabolic cages and urine volume was recorded after 8 hr. No food or water was available during this period.

Measurement of Autonomic and CNS Effects

These observations were made on a blind basis. Rats were given the test drug and placed in observation cages. They were observed for the following signs and rated at different intervals. Exophthalmus was rated without disturbing the animals, with the scores of 0 (eyes closed), 1 (eye ¼ open), 2 (eye ½ open), 3 (eye ¾ open), 4 (eye fully open), or 5 (exophthalmus). Piloerection was also rated without disturbing the animals, with the score of 0 (definitely no piloerection), 1 (questionable piloerection), 2 (moderate but clear piloerection), or 3 (pronounced piloerection). Hypotonia and sedation were scored by manipulating the animals to evaluate loss of muscle tone or sedation. Ataxia was given rating scores similar to those given for piloerection, except that ataxia was tested by placing each animal on the table top and forcing him to walk. Loss of righting reflex was considered positive when an animal, placed twice in a row on its back, failed to right itself within 30 seconds.

RESULTS

Data summarized in Table 1 show that all of the drugs tested are potent antidiarrheals, clonidine being the most potent of the three. Besides their potency, the duration of action of these drugs in the rat extended to as long as 9 hr. after their administration. These data are consistent with the previous reports on the antidiarrheal activity of these and other similar drugs.

Data shown in Table 2 suggest that clonidine and lidamidine may also be diuretics at higher doses. The diuretic effect of lidamidine was reported previously [Riley et al., 1978]. The doses that are active diuretics at 8 hr are similar to those active as antidiarrheals at 8 hr. However, at the clinically more relevant period of 6 hr after their oral administration these drugs were potent antidiarrheals and produced only minimal diuretic action. The maximally active diuretic dose of clonidine was tenfold higher than its antidiarrheal dose at 6 hr after administration, and a similar dose of lidamidine was six times higher. Loperamide did not produce diuresis at any dosage.

Clonidine and lidamidine produced autonomic and central side effects as illustrated in Table 3. Piloerection, hypotonia, and exophthalmus were produced at doses close to those producing antidiarrheal action. Sedation was produced at higher doses only. Loperamide was virtually free of autonomic and central side effects.

TABLE 1. Antidiarrheal Action of Clonidine, Lidamidine, and Loperamide After Oral Administration in the Rat

Hours after castor oil	Oral ED50 (lower-upper limit), mg/kg		
	Clonidine	Lidamidine	Loperamide
1	0.012 (0.007–0.023)	0.44 (0.29–0.68)	0.13 (0.09–0.19)
2	0.021 (0.016–0.027)	1.89 (1.32–2.69)	0.26 (0.16–0.41)
3	0.036 (0.027–0.047)	3.54 (2.43–5.14)	0.45 (0.28–0.72)
4	0.044 (0.025–0.076)	4.55 (3.56–6.07)	0.59 (0.34–1.01)
6	0.11 (0.06–0.2)	5.85 (4.47–7.64)	1.35 (0.83–2.17)
8	0.20 (0.11–0.35)	9.78 (6.53–14.6)	1.78 (1.10–2.81)

TABLE 2. Diuretic Action of Clonidine, Lidamidine, and Loperamide After Oral Administration in the Rat

Drug	Dose (mg/kg, p.o.)	Urine excretion/8 hr, % of control[a]	P[b]
Clonidine	0.04	114	> 0.05
	0.08	204	< 0.05
	0.16	246	< 0.05
	0.32	304	< 0.05
Lidamidine	5	107	> 0.05
	10	260	< 0.05
	20	365	< 0.05
Loperamide	10	112	> 0.05
	20	104	> 0.05
	40	84	> 0.05

[a]Urine excretion in nontreated rats was a mean of 13.3 ml over the 8-hr test period.
[b]Mann-Whitney U-test.

DISCUSSION

This experiment confirms the previous observations from our laboratory and others that clonidine [Lal et al., in press], lidamidine [Mir et al., 1978], and loperamide [Reyntjens and Lal, 1976; Zelvelder, 1976] are effective antidiarrheal drugs. Their antidiarrheal activity is significant both with respect to the potency and the duration of action. With respect to selectivity, a therapeutically useful drug is not expected to produce other effects that are unrelated to the therapeutic action at doses markedly below those needed to produce the desired action. In this respect, of the three drugs tested, only loperamide is the specific antidiarrheal drug.

TABLE 3. Lowest ED50 Values for Different Signs of Overt Autonomic and CNS Effects of Clonidine, Lidamidine, and Loperamide After Oral Administration in the Rat

Observed sign	Oral ED50 (lower-upper limit), mg/kg[a]		
	Clonidine	Lidamidine	Loperamide
Piloerection	0.056 (0.031–0.084)	28.2 (22.9–34.8)	> 160
Hypotonia	0.074 (0.046–0.12)	28.2 (22.9–34.8)	89[b] (not linear)
Exophthalmus	0.042 (0.025–0.073)	18.6 (12.4–27.9)	> 160
Ataxia	0.58 (0.36–0.94)	32.4 (23.9–44.0)	80 (not linear)
Loss of righting reflex	0.89 (not linear)	56.5 (45.8–69.7)	> 160

[a]Determined at the time of maximum activity.
[b]Related to sedation produced at this dose.

Clonidine is a safe and potent antihypertensive drug that has also recently been found useful in decreasing narcotic withdrawal signs in laboratory rats [Fielding et al., 1978] and humans [Gold et al., 1978; Washton et al., in press]. The psychopharmacological actions of clonidine are less known and were reviewed recently [Shearman and Lal, in press]. Since other pharmacological actions of clonidine are produced at doses similar to those producing antidiarrheal activity, clonidine cannot be considered a specific antidiarrheal drug. Similarly, lidamidine produced many other pharmacological actions at doses reasonably close to those producing antidiarrheal action. Both clonidine and lidamidine, therefore, do not compare with the specific antidiarrheal standard, loperamide, which produced its antidiarrheal action at doses at least 40 times lower than those producing any of the other actions measured in this study. The clonidine action reported here may be relevant to the observation that constipation may be caused in a small percentage of patients chronically treated with clonidine [Nickerson and Rudy, 1975].

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