ANTIEMETIC ACTIVITY OF *D*-LYSERGIC ACID DIETHYLAMIDE[1]

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Dhawan *et al.* (1961) reported that *d*-lysergic acid diethylamide (LSD-25) was one of the most effective antagonists of apomorphine-induced pecking in pigeons (Dhawan and Saxena, 1960a). It was further seen that many drugs influenced the pecking (in pigeon) and emetic (in dog and cat) responses to apomorphine in an identical manner. Since no reports regarding the effects of LSD-25 on apomorphine-induced emesis were available, we decided to investigate this problem. In addition, we undertook (a) to determine whether the structurally related compound 2 *d*-bromolysergic acid diethylamide (BOL-180), which is devoid of central nervous system stimulant properties (Rothlin, 1957), had a similar effect and (b) to elucidate the site of antiemetic effect of LSD-25 by studying its interaction with emetic agents acting at various sites.

METHODS. These results were obtained in 56 mongrel dogs of either sex. The dogs were used twice a week. They were fed and, after about 30 minutes, a dose of LSD-25 or BOL-180[2] was given. Fifteen minutes after this they were given one of the following emetic agents: apomorphine hydrochloride, 50 μg per kg (100% emetic dose in 26 dogs); emetine hydrochloride, 3.0 mg per kg (Hatcher and Weiss, 1923); Hydergine, 30 μg per kg (Wang and Glaviano, 1954); ouabain, 50 μg per kg (Hatcher and Weiss, 1923); morphine hydrochloride, 1.0 mg per kg (Wang and Glaviano, 1953) and protoveratrine, 10 μg per kg (100% emetic dose in 16 trials). All the agents were given intravenously except morphine which was given intramuscularly (Wang and Glaviano, 1954). All the dosage levels chosen represent the 100% effective emetic dose or greater. In all tests the dogs were observed for at least 1 hour after they had received the emetic agent, and active expulsion of the gastric contents was the criterion of emesis. Animals that did not vomit by the end of 1 hour were considered protected. In a preliminary trial the emetic agent under study was given alone and the animal observed for a positive emetic response. A latent period of 15 minutes was the maximum interval observed between the emetic challenge and the onset of emesis. An occasional unresponsive dog was excluded from further study.

The data were analyzed by the method of probits (Finney, 1952), and ED50's and their respective 95% fiducial limits were estimated in the usual manner. If, however, no protection was obtained even with 50 μg per kg LSD-25, it was concluded that the drug had no activity against the particular emetic agent and further testing was abandoned.

RESULTS. After intravenous administration of LSD-25 at doses of 50 μg per kg or above there were signs of excitation, pacing, dyspnea and salivation; subsequent venipuncture also was more difficult. Emesis induced by 50 μg per kg apomorphine could be blocked by suitable doses of LSD-25. The ED50 (dose preventing emesis in 50% of dogs) of LSD-25 against apomorphine was 12.7 ± 5.7 μg per kg (see table 1). In a few cases, injection of apomorphine after LSD-25 was followed by a transitory cataleptic stage which lasted for only 3 to 5 minutes. By contrast, BOL-180 was ineffective in checking the emesis (see table 1) and no excitation or cataleptic state was observed in the dogs.

LSD-25 was found to be less effective against emesis induced by 1 mg per kg morphine injected intramuscularly (ED50 = 25.8 ± 12.7 μg per kg; see table 1) than against apomorphine-induced emesis. LSD-25 proved to be even less effective against 30 μg per kg Hydergine given intravenously (ED50 = 38.90 ± 19.3 μg per kg; see table 1). At a dose as high as 50 μg per kg, LSD-25 was ineffective against emesis in-

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[2] LSD-25 and BOL-180 were kindly furnished by Dr. E. J. Vaz, Sandoz (Private) Ltd., Bombay.

TABLE 1

Effect of LSD-25 on emetic response to apomorphine, morphine and Hydergine, and of BOL-180 on apomorphine-induced emesis

Dose (μg/kg)	No. of Dogs Tested	No. of Dogs Protected	% Protected	ED50 (μg/kg) ± 95% Fiducial Limits
Apomorphine hydrochloride, 50 μg/kg i.v.				
LSD-25				
1.5	14	0	0	
3.0	14	2	14.0	
6.0	14	4	29	12.7
12.5	13	7	54	±
25.0	14	9	64	5.7
50.0	14	12	86	
BOL-180				
25.0	7	0	0	
50.0	7	0	0	
Morphine hydrochloride, 1 mg/kg i.m.				
LSD-25				
6.0	7	0	0	25.8
12.5	8	2	25	±
25.0	9	5	44	12.7
50.0	5	4	80	
Hydergine, 30 μg/kg i.v.				
LSD-25				
6.0	6	0	0	38.9
12.5	7	1	14	±
25.0	8	2	25	19.3
50.0	9	5	56	
100.0	7	7	100	

duced by emetine in all of 7 dogs, by ouabain in 7 of 8 dogs and by protoveratrine in all of 7 dogs. Some of the dogs that received ouabain after LSD-25 were found dead the next morning. A similar phenomenon was also observed in pigeons (unpublished observations). The cause of this, however, remains obscure at present.

DISCUSSION. The emetic chemoreceptor trigger zone (CT zone; Wang and Borison, 1952), located in the area postrema, has been demonstrated to be the sole site of action for certain emetic agents including apomorphine (Wang and Borison, 1950), morphine and Hydergine (Wang and Glaviano, 1954). It is significant to note that LSD-25 protected the dogs only against the effects of the above-mentioned emetic agents. Further, LSD-25 could not prevent emesis induced by an agent acting on the nodose ganglion of the vagus (veratrum; Borison and Fairbanks, 1952), or on some presumed site other than the CT zone (*e.g.*, emetine). These observations strongly suggest that LSD-25 has a depressant action on the CT zone. The ineffectiveness against emesis induced by cardiac glycosides—shown to be due to stimulation of the CT zone (Borison and Wang, 1951)—may be due to the presence of qualitatively different receptors for them (Brand *et al.*, 1954) or to their firmer binding with the same receptors as for apomorphine, morphine and Hydergine (Wang, 1958). The antiemetic spectrum of LSD-25 in dogs is similar to that reported for the phenothiazines (Brand *et al.*, 1954; Wang, 1958).

The effect of a drug on emesis induced by intragastric copper sulfate can serve to exclude or establish any direct action on the vomiting center (Wang and Borison, 1952). Thus, a drug that depresses the vomiting center should block every type of emesis to a certain degree. The failure of LSD-25 to modify even slightly the emetic responses to emetine, ouabain and protoveratrine therefore indicates that LSD-25 does not act directly on the vomiting center. For this reason, a study of the effect of LSD-25 on the emetic activity of intragastric copper sulfate was not indicated in this investigation.

The blockade of morphine- and apomorphine-induced emesis by LSD-25 is of particular significance. It has been reported earlier (Dhawan and Gupta, 1959) that morphine analgesia in rats is antagonized by LSD-25. Mention has already been made of blockade of apomorphine-induced pecking in pigeons by LSD-25 (Dhawan and Saxena, 1960b; Dhawan *et al.*, 1961). Morphine has also been shown to antagonize LSD-25-induced pyrexia in rabbits (Dhawan and Gupta, 1960; Dhawan, 1960). All these results strongly suggest the possibility of a specific antagonism between some of the central effects of LSD-25 and morphine and related drugs. It may be worthwhile to investigate the effect of morphine and related drugs on LSD-25-induced model psychosis in man.

The inability of BOL-180 to antagonize the emetic effect of apomorphine suggests that the antiemetic action is also related to the other central effects of LSD-25—which are not possessed by BOL-180. BOL-180 has also been found

to be ineffective against apomorphine-induced pecking in pigeons (Dhawan *et al.*, 1961). Inhibition of emesis induced by apomorphine has been recommended as one of the possible techniques for screening of potential ataractic agents (Freedman and Giarman, 1956). The findings of the present investigation with LSD-25 and those of Boyd and Cassell (1957) with amphetamine, however, show that the test has serious limitations and should not be used for this purpose.

SUMMARY

d-Lysergic acid diethylamide (LSD-25) and 2 *d*-bromolysergic acid diethylamide (BOL 180, a congener of LSD-25 devoid of CNS stimulant properties) were tested for their efficacy against apomorphine-induced emesis in dogs. In addition, LSD-25 was tested against emesis induced by emetine, Hydergine, morphine, ouabain and protoveratrine.

LSD-25 effectively antagonized apomorphine-induced emesis whereas BOL-180 showed no protective effect. LSD-25 also protected against vomiting evoked by morphine and Hydergine, but it was ineffective against emetine, ouabain and protoveratrine. These findings suggest that the mechanism of antiemetic action of LSD-25 is a selective depression of the medullary emetic chemoreceptor trigger zone.

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