LSD 407

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PHARMACOLOGY OF *d*-LYSERGIC ACID MORPHOLIDE (LSM)[1]

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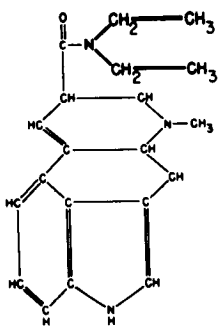
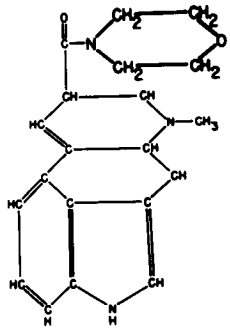
The actions of *d*-lysergic acid diethylamide (LSD) have been extensively described (Graham *et al.*, 1954; Gaddum, 1953; Rinkel *et al.*, 1952; Rinkel *et al.*, 1954). *d*-Lysergic acid morpholide (LSM) differs from LSD in that the diethylamine side chain is replaced by a morpholine group as shown in the following structures:



Lysergic Acid Diethylamide (LSD)



Lysergic Acid Morpholide (LSM)

LSM is a crystalline powder and is soluble in water to the extent of 8 mgm. per ml. The compound is in the form of the tartaric acid salt and all doses are expressed as such. Work in this laboratory indicates that in the more concentrated solutions this substance will remain stable for only three or four hours whereas in dilute solution (400 to 600 micrograms per ml.) the stability is maintained for approximately 7 days.

This report presents some of the pharmacological and behavioral effects of this lysergic acid derivative and compares these with those produced by LSD.

EXPERIMENTAL PROCEDURES AND RESULTS. A. *Animal studies. Acute toxicity studies.* Determinations of the LD_{50} for both LSM and LSD were made in white albino mice having an average weight of 25 grams. All injections were made intravenously by the tail vein. The results are shown in table 1. The Litchfield-Wilcoxon (1949) method for statistical analysis of dose response data was employed in the analysis of this data. It will be noted that the values for the LD_{50} differ with the rate of the injection.

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TABLE 1

Summary of LD_{50} determinations for LSM and LSD by intravenous administration to mice

Duration of Injection	Lethal Dose* 50% (LSM)	Lethal Dose* 50% (LSD)
10 sec.	55.5 mgm./kgm. (52.37–58.83 mgm./kgm.)	54 mgm./kgm. (45.29–64.26 mgm./kgm.)
30 sec.	128.0 mgm./kgm. (119–136.96 mgm./kgm.)	88 mgm./kgm. (82.2–94.16 mgm./kgm.)

* Confidence limits are shown in parenthesis.

Systematic determinations of the LD_{50} were not made in other species. However, some values were found for other species in the behavior studies reported later. These may be summarized as follows: 400 micrograms per kgm. produced death in rabbits; 6400 micrograms produced death in cats; 600 micrograms per kgm., the highest dose used in dogs, did not produce death. The special sensitivity of rabbits to LSM was also observed for LSD.

General pharmacology. Cardiovascular effects: Previous workers, while attempting to define some of the pharmacodynamic actions of LSD, found that it produced a prolonged drop in blood pressure when administered intravenously to chloralose-anesthetized cats. They tentatively ascribed this effect to a central action of LSD since the drug produced no observable effects in the spinal cat (Horita and Dille, unpublished observations). Effects of LSM on blood pressure were studied in chloralose-urethane anesthetized cats. Kymograph recordings were made by a mercury manometer attached to the left common carotid artery. Drugs were administered through the left femoral vein with the aid of an injection burette.

Single injections of 100 micrograms of LSM per kgm. over a period of 10 to 30 sec. resulted in a biphasic blood pressure response which showed a pressor-depressor sequence. This was accompanied by depression and failure of respiration. The secondary depressor response lasted approximately 20 minutes followed by a gradual return to the base level (figure 1). LSM, in this dosage, appeared to prolong the normal responses to acetylcholine and to epinephrine. However, the depressor response to LSM was not affected by previous atropinization of the animal. LSM did not affect the nicotinic response to acetylcholine nor did it alter the blood pressure response to peripheral splanchnic nerve stimulation or to peripheral vagal stimulation.

Three doses of 100 micrograms of LSM per kgm. within a period of 60 minutes resulted in a shift from a biphasic blood pressure response to a pure pressor effect. This pressor response had a duration of approximately 4 to 7 minutes. The pressor response was not abolished by previous administration of Dibenzyline or dihydroergotamine but, instead, appeared to be augmented by the previous administration of the latter.

In an attempt to elucidate the general depressor response of LSM, studies were made on the effect of LSM on the pressor response produced by carotid occlusion

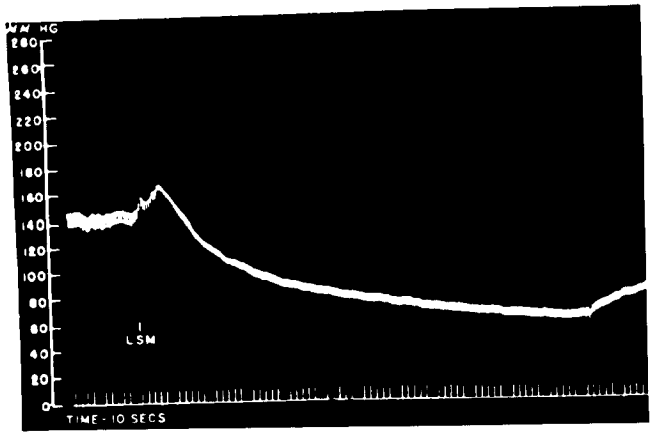

FIG. 1. Carotid blood pressure response of a cat under chloralose-urethane anesthesia to 100 micrograms per kgm. of LSM administered over 20 seconds intravenously.

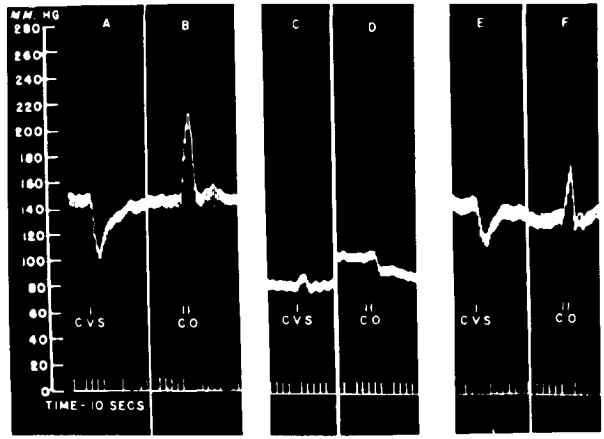

FIG. 2. Carotid blood pressure response of a cat under chloralose-urethane anesthesia. A and B, responses before administration of LSM to central vagus stimulation and carotid occlusion. C and D, abolition of these responses 20 minutes after administration of 100 micrograms of LSM intravenously. E and F, recovery of these responses 75 minutes after administration of LSM.

and on the depressor response produced by central vagal stimulation. The right vagus nerve was severed at the mid-cervical region in order to stimulate centrally without the direct peripheral effects. Shielded electrodes were used in all stimulation experiments. As is shown in figure 2, LSM, in a dose of 100 micrograms per kgm., completely abolished both of the above responses. These results compare to those obtained for LSD in a similar study (Ginzel, 1955). Although those

workers found that LSD was effective only when injected intraventricularly, we were able to obtain a complete abolition of the above reflexes for both LSM and LSD for approximately 60 minutes when injections were made intravenously.

Pyretogenic effects: LSD, when administered intravenously to rabbits produces a rise in rectal temperature which varies with the dosage (Horita and Dille, 1954a). This pyretogenic effect is of interest because of possible relationships with the central effects (Horita and Dille, 1954).

Three different dose levels of LSM were used in a series of six rabbits and the resultant temperature curves compared with that produced by a standard dose of LSD (figure 3). Temperatures were taken every half hour by means of a rectal thermometer. Injections of all compounds were made intravenously into the marginal ear vein. From the figure, it can be seen that a dose of 150 micrograms per kgm. of LSM was necessary to produce a temperature curve similar to that obtained for a dose of 50 micrograms per kgm. of LSD. Also, the duration of a comparable effect of LSM was much shorter than that for LSD.

Serotonin antagonism: The fact that LSD, in minute quantities, is an effective antagonist of serotonin-induced contractions of the sensitized rat's uterus has been well demonstrated (Gaddum, 1953a; Gaddum and Hameed, 1954). This, coupled with the evidence that serotonin is present in the mammalian brain (Amin *et al.*, 1953; Twarog and Page, 1953), has resulted in the hypothesis that LSD might exert its psychotomimetic effect by a serotonin-antagonizing mechanism in the central nervous system (Gaddum, 1953b; Woolley and Shaw, 1954a, b). Therefore the relation of LSM to serotonin was investigated.

Female rats were injected subcutaneously with 0.1 mgm. per rat per day of estradiol for six days previous to removing the uterine horns. On the sixth day, the animals were killed and the uterine horns were immediately removed and mounted in constant temperature (37° C.) 50 ml. muscle baths containing the

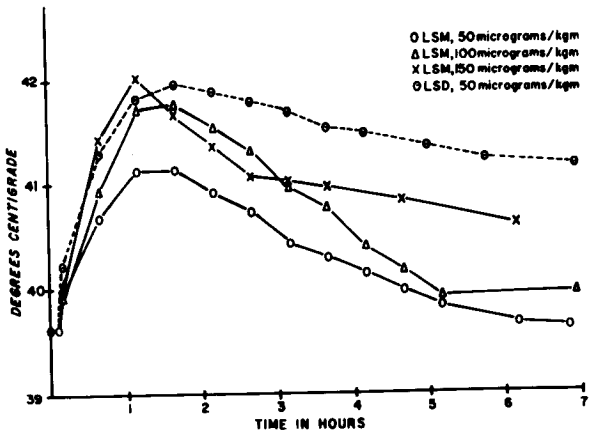

FIG. 3. Rectal temperature of the rabbit after intravenous administration of LSM in the dose levels indicated compared to the effect of 50 micrograms of LSD. Each curve represents the mean values of six rabbits.

following oxygenated modified Tyrode's solution (NaCl, 8; KCl, 0.2; $CaCl_2$, 0.18; $MgCl_2$, 0.102; NaH_2PO_4, 0.494; dextrose, 1; $NaHCO_3$, 1 gm./l.). Recording was made by means of an isotonic lever having a load of 1 gm. Control contractions to a standard dose of serotonin creatinine sulfate were established after which either LSD or LSM was added to the bath followed in one and one-half minutes by the standard dose of serotonin. In previous studies (Gaddum, 1953a), the interval between LSD administration and serotonin administration was given as ten minutes. However, we found that LSD or LSM would themselves induce contractions within the ten-minute period in the concentrations which were used by us. The serotonin was allowed to act for two minutes before being washed out. From figure 4 it may be seen that LSM must be used in more than ten times the amount of LSD to produce a comparable inhibition of contractions. A 50 per cent decrease in serotonin-induced contractions was the maximum amount of inhibition that could be demonstrated before the LSM-induced contractions interfered with the results. Also, it was observed that the serotonin control contractions returned almost immediately upon washing out of the LSM whereas with the LSD, serotonin contractions comparable to those of the control contractions did not return for approximately 60 minutes.

Observations on the effects of LSM on behavior in animals. Mice: Minimally effective intravenous doses of LSM of from 1 to 10 micrograms per kgm. produced in mice a general hyperexcitability with increased respiration and piloerection. The animals also appeared to be somewhat hyperreflexic at this dose level. As

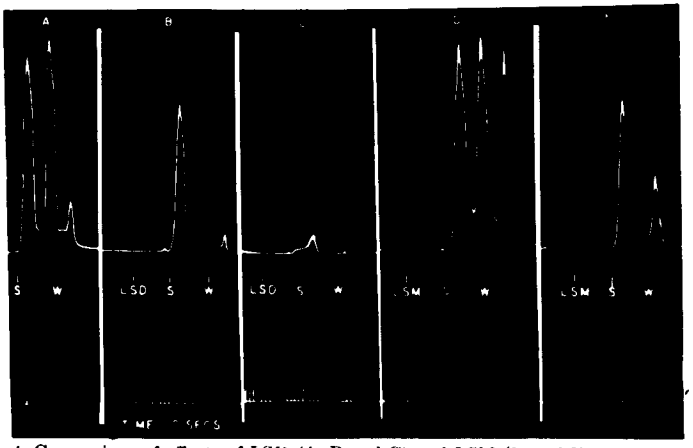

FIG. 4. Comparison of effects of LSD (A, B and C) and LSM (D and E) in serotonin induced contractions of the sensitized rat uterus.

S—indicates the addition of serotonin to the bath to make a concentration of 12 micrograms per 100 ml. W—indicates wash. A—control response to serotonin. B—response to serotonin after 1.2 micrograms per 100 ml. of LSD. C—response to serotonin after 2.3 micrograms of LSD per 100 ml. D—response to serotonin after 2.3 micrograms of LSM per 100 ml. Compare this to C. E—response to serotonin after 14 micrograms per 100 ml. Compare this to B where comparable inhibition was produced by 1.2 micrograms of LSD.

the dose was increased to 20 to 50 micrograms per kgm., a picture of generalized tremors with hyperexcitability began to appear. The animals seemed to be confused and disoriented, running purposelessly about when tactily stimulated. There was an increased sensitivity to auditory stimuli. When not being stimulated, the animals showed in some cases spontaneous backing movements similar to those described for LSD (Woolley, 1955). A stiffening of the tail resembling the Straub tail phenomena was seen. Exopthalmos and piloerection were present. The animals showed a spreading of the hind limbs with movements resembling those of swimming. Recovery from these effects took place in approximately 7 to 10 minutes at which time hyperexcitability with some evidence of prostration was seen. Further increase in dosage to 50 to 100 micrograms per kgm. resulted in convulsions, the respiration becoming irregular with gasping and anoxia evident. The mice died of respiratory failure.

Rabbits: Intravenous doses of 50 to 100 micrograms per kgm. of LSM in rabbits produced effects of autonomic stimulation evident in mydriasis and piloerection within the first five minutes. Hyperreflexia and hyperactivity were also observed within the first five minutes. Increased respiratory rate was noted within 15 minutes. The righting reflex was present at all times in the lower doses of 100 to 200 micrograms per kgm.; however, in the higher doses of 300 to 400 micrograms per kgm., the animals demonstrated a depressed righting reflex within 40 minutes after injection. The placing response was slightly depressed in the lower doses, with the depression increasing as the dosage increased. In general, lower doses produced hyperexcitability and hyper-reflexia, but no observable depression. Higher doses produced hyperactivity followed by ataxia, depressed righting reflex, depressed respiration and, finally, death from respiratory failure.

Cats: The behavior of cats under the influence of varying doses of LSM was observed. A geometrically increasing dose schedule from 100 micrograms per kgm. to 6400 micrograms per kgm. was used in a series of 14 cats. All injections were made intravenously utilizing the saphenous vein of the hind limb. It was found that the effects of LSM could be divided into three stages according to the dose level used. In a range of 400 to 600 micrograms per kgm. a behavior reaction was produced which was very similar to that described by Barger for ergometrine in doses of 2.0 to 2.5 milligrams per kgm. (Barger, 1938). This was accompanied by pronounced autonomic stimulation, chiefly sympathetic, with maximal pupillary dilatation, hypersalivation and piloerection. The behavior was especially significant. There was a marked coordinated aggression with spitting, snarling, baring of the teeth and striking with barred claws in response to auditory, visual or tactile stimuli of any kind. At this dose level it was impossible to handle the animal since it would attack upon the slightest provocation. This aggressive behavior had a duration of approximately 20 minutes at which time there was a gradual return to "normal" behavior. This coordinated, directed aggressive behavior is practically identical with that produced in cats by the intravenous administration of 200 to 400 micrograms of LSD per kgm.

In dose levels of 800 micrograms per kgm., LSM produced similar autonomic effects seen in the lower dose level except that exophthalmos was also evident.

Behavior was now changed. Instead of directed attack such as that seen in the previous dose level, the animal demonstrated a disorientation which progressed to an incoordinated aggression with signs of fearfulness and apprehension. Although the animal appeared aggressive, he was, in fact, quite fearful and any aggressive appearing movements were more in a line of defense than of attack. The animals were hypersensitive to auditory, tactile and visual stimuli. The animals demonstrated a "tracking behavior" in which they seemed to fix their gaze on something in the cage although nothing was there. During the latter part of the reaction, there was a somewhat depressed righting reflex and a slight hind limb ataxia.

In the higher dose levels, from 800 micrograms per kgm. to 6400 micrograms per kgm., LSM produced a lethargic behavior which increased as the dosage was increased. The animals showed a loss of righting reflex and placing reactions, slow, shallow, irregular respiration followed by panting with an elevated body temperature, and stupor which was similar to catalepsy. There was none of the behavior characteristic of the lower dose levels.

Dogs: An intravenous dose of 300 micrograms per kgm. of LSM produced signs of autonomic stimulation similar to those seen in cats consisting of pupillary dilatation, hypersalivation and piloerection. However, there was no aggressive rage observed; rather there was marked disorientation with fear and apprehensive behavior predominating. This was shown by whining with attempts to escape, especially from tactile stimulation. "Behavioral blindness" and a moderate ataxia were noted and the animals showed signs of great discomfort. Recovery was complete within 1 hour and 45 minutes.

By increasing the dose to 600 micrograms per kgm., the syndrome described for the preceding dose was accentuated with the fear and apprehension being greater. There was, in addition, depression marked by loss of motor coordination.

B. *Comparative effects of LSM and LSD in humans.* Two subjects served as volunteers for an exploration of dose ranges and subjective and objective effects of LSM on humans. Before the investigations of LSM both subjects took LSD in a total oral dose of 50 micrograms. Preparatory to this both subjects took the Rorschach and Thematic Apperception test which were again administered during the action of the drugs. During the effect of the drug, polygraphic records were taken on the subjects. These comprised measurements of the galvanic skin reflex, the heart rate by the means of an ECG record, respiratory rate and depth, face, and skin temperature, and muscle tension. Dr. Evan L. Frederickson, anesthesiologist and Dr. Albert Ax, clinical psychologist, both of the Medical School staff, aided in the experiments by administering the tests and making observations of the behavior responses of the subjects. Both subjects showed reactions to LSD which have been generally those already described in the literature (DeShon *et al.*, 1952; Sloane *et al.*, 1954). In one subject there was a high component of anxiety which was manifest in the polygraphic records and in the Rorschach test while the other subject showed little anxiety but depersonalization increased imagination as measured by the Rorschach test and some euphoria. Both subjects recorded their subjective experiences the following day.

With this experience of the effects of LSD as a guide, LSM administration was begun cautiously with lower doses allowing at least five days between tests. The first dose was a total oral dose of 25 micrograms. Neither subject showed any definite departures from normal subjective feeling or observable behavior changes. At a total oral dose of 50 micrograms, both subjects reported some subjective changes in feelings and attitudes but there were no observable departures from normal behavior except perhaps for a slight tendency to talkativeness. At a total oral dose of 75 micrograms the subjective feeling of the subjects and the objective observations indicated the degree of this action was approximately the same as that produced by a total oral dose of 50 micrograms of LSD. The difference lay in the shorter duration of the LSM effect. This effect required about 45 minutes to develop and lasted about an hour. By contrast, the LSD effect required about an hour to develop, had a peak effect of about four hours with residual effects from six to eight hours. These preliminary experiments with human subjects are being extended and attempts are being made to develop and make use of psychological tests which more precisely and objectively measure some of the subtleties of the action of these two phrenotropic drugs.

DISCUSSION. Results of systemic pharmacological studies of the effect of *d*-lysergic acid morpholide (LSM) in animals may be summarized as follows:

Toxicity studies in mice and observations in other species indicate that LSM required a slightly higher dose than LSD for equivalent effects.

Cardiovascular studies demonstrate that LSM produce a biphasic response with a primary pressor effect followed by a prolonged depressor action. Simultaneous with the hypotensive response to LSM is a block of the reflex responses mediated through the vasomotor centers. These results, in addition to those demonstrating that LSM does not influence the nicotinic response to acetylcholine nor does it affect the blood pressure responses to splanchnic nerve stimulation or to peripheral vagal stimulation, would indicate that at least part of the blood pressure response to LSM is centrally determined. The fact that the responses to acetylcholine and epinephrine are prolonged after LSM might be explained by a depression of the compensatory mechanisms located in the vasomotor centers. Preliminary studies in this laboratory indicate that LSM is ineffective as a cholinesterase inhibitor *in vitro*.

Of special significance is the action of LSM in blocking the effects of serotonin. Approximately twelve times as much LSM is required to block the serotonin-induced contractions of the rat's uterus as LSD; yet, the equivalent central effects of the LSM are produced by only about one-third greater dosage. These results would seem to indicate that there is no correlation between the peripheral anti-serotonin activity of these compounds and their ability to produce changes in mental behavior. Support for this idea may also be found in the report by Cerletti and Rothlin (1955) in which the powerful serotonin blocking agent brom-lysergic acid diethylamide (BOL-148) does not produce any central effects in either animals or humans.

Generally, the systemic pharmacology of lysergic acid derivatives such as LSM and LSD may be regarded as secondary to the dominating interest in the effects of these agents on the activities of the brain as expressed in the subtle qualities

of emotion, intelligence, and mentation. Because of such effects, LSD has been used in the treatment of psychoneurosis (Frederking, 1953; Sandison *et al.*, 1954; Abramson, 1956). The exact role of LSD in this regard is not yet clear but since the indications are that LSM produces the same kind of effects but with a shorter duration of action it may have a practical advantage.

SUMMARY

d-Lysergic acid morpholide (LSM) produces pharmacological effects generally similar to those produced by *d*-lysergic acid diethylamide (LSD).

Intravenous administration of LSM to anesthetized cats produces a transient rise in blood pressure followed by a fall. The fall of blood pressure is attributed to central effects.

LSM, like LSD, produces a rise in body temperature. Approximately three times the dose is required to produce equivalent increases in temperature and the duration of maximum effect is less.

LSM is approximately one-twelfth as effective as LSD in antagonizing serotonin-induced contractions of the rat uterus.

Death with lethal doses of LSM is caused, as with LSD, by respiratory failure.

Behavior modifications in animals produced by LSM are similar to those produced by LSD. The dose required for equivalent effects is about one-third greater and the duration of such effects is about one-half as long.

Preliminary studies of the effects of LSM in humans indicates that these are qualitatively similar to those of LSD. The dose required is at least a third larger and the duration of action is shorter.

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