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Analeptic Action of Lysergic Acid Diethylamide (LSD-25) Against Pentobarbital

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Adventitious findings in this laboratory indicate that lysergic acid diethylamide (LSD-25) protects cats against the toxic effects of large doses of pentobarbital. One hundred forty cats have survived inordinate amounts of pentobarbital at the termination of experiments in which LSD-25 solution was given systemically.

Gastaut,[13] Bradley,[3,4] and others [6,8,14,18] provide electrophysiological evidence that LSD-25 antagonizes the action of anesthetic doses of barbiturates. In these studies the actions of both drugs on the frontal cortex and on the reticular formation were investigated. There appear to be no reports, however, of the extent to which LSD might inhibit or reverse lethal effects of larger doses of barbiturates. It seemed worth while, therefore, to investigate in greater detail this protective property of LSD.

Under the conditions of the present studies, LSD-25 safely and effectively reversed respiratory and central nervous system depression induced in cats by lethal doses of pentobarbital. What is more, LSD-25 was more effective than picrotoxin or pentylenetetrazol U. S. P. (Metrazol) in this regard.

Material and Procedures

METHOD I.—*Ability of Drugs to Prevent Suppression of Respiratory and Cortical Activity by High Doses of Pentobarbital.*—One hundred eighty-six cats anesthetized with 42 mg. of pentobarbital sodium per kilogram intraperitoneally were used in this part of the study. (Sixty milligrams per kilogram kills a cat within 30 minutes of intraperitoneal injection.) The animal was immobilized in a Horsley-Clarke apparatus, and one femoral vein was exposed. The parietal cortex was exposed, and platinum electrodes were placed in contact with the surface. Silver electrodes were placed under the skin of the abdomen and of the thorax. All electrodes were led to a Grass electroencephalograph. In this way cortical, respiratory, and cardiac activities were recorded. Forty minutes after the original anesthetizing dose of pentobarbital, one of the following drugs was given intraperitoneally:

To 101 cats, LSD-25 solution, 50μg. per kilogram of body weight; to 7 cats, brom-LSD (2-brom-*d*-lysergic acid diethylamide), 50μg. per kilogram of body weight; to 17 cats, picrotoxin, 1.5 mg. per kilogram; to 7 cats, pentylenetetrazol, 0.05 gm. per kilogram; to 14 cats, crystalline LSD-25,* 50μg. per kilogram, and to 7 cats, no drug other than pentobarbital. Fifteen minutes after the test drug was injected, two-thirds of an anesthetizing dose of pentobarbital (called the first lethal dose) was administered intraperitoneally. The LSD series is large because at first we suspected that our pentobarbital was weaker than labeled. We used three different supplies of pentobarbital. To 13 animals still surviving because of a previous dose of LSD solution, repeated lethal doses of pentobarbital were given at 10-minute intervals until all 13 cats were dead, as confirmed by EEG, respiratory, and cardiac records.

Thirty-nine cats were given 50μg. of LSD-25 per kilogram, followed 15 minutes later by a single injection of a double anesthetizing dose of pentobarbital. No surgery was done on these cats.

METHOD II.—*Ability of Drugs to Reverse Respiratory and Central Nervous System Depression Induced by Lethal Doses of Pentobarbital.*—Eighty-three cats were prepared for recordings as in the first group of tests. Forty minutes after the initial anesthetizing dose of pentobarbital, all cats were given a lethal dose of the drug. The lethal dose was a second dose two-thirds of the

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* Previous studies on the ocular properties of LSD-25 indicated that crystalline LSD-25 was not as active as the solution.

Efficacy of Various Analeptic Agents Against Lethal Doses of Pentobarbital

	Lethal Dose Pentobarbital	No. Survived	% Survival
No. of Cats Treated with LSD-25 Solution			
Before	140	140	100
After	42	33	78.6
No. of Cats Treated with Picrotoxin			
Before	17	17	100
After	29	11	37.8
No. of Cats Treated with Pentylenetetrazol			
Before	7	7	100
After	9	0	0
No. of Cats Treated with Brom-LSD			
Before	7	1	14.3
After	6	0	0
No. of Cats Treated with LSD-25 Crystals			
Before	14	1	7.2
After	6	0	0

anesthetizing dose. Recordings were watched. When cortical activity became markedly depressed and respirations ceased but the heart beat remained, the test drugs were given in the following manner:

In this series, 42 cats received LSD-25 solution, 10μg/kg. I. V., injected very slowly, and 50μg/kg. intraperitoneally; 29 cats received picrotoxin 0.5 mg/kg. I. V. in two doses, five minutes apart and 1.5 mg/kg. intraperitoneally; 6 cats received crystalline LSD-25 on the same dose schedule as that on which other cats received LSD-25 solution; 6 cats received brom-LSD also on the same dose schedule as LSD-25.

In Method II the EEG tracings were watched until restoration of normal sleep EEG activity, until death, or, in some cases 8 to 16 hours after administration of the test drugs (until no further change could be expected).

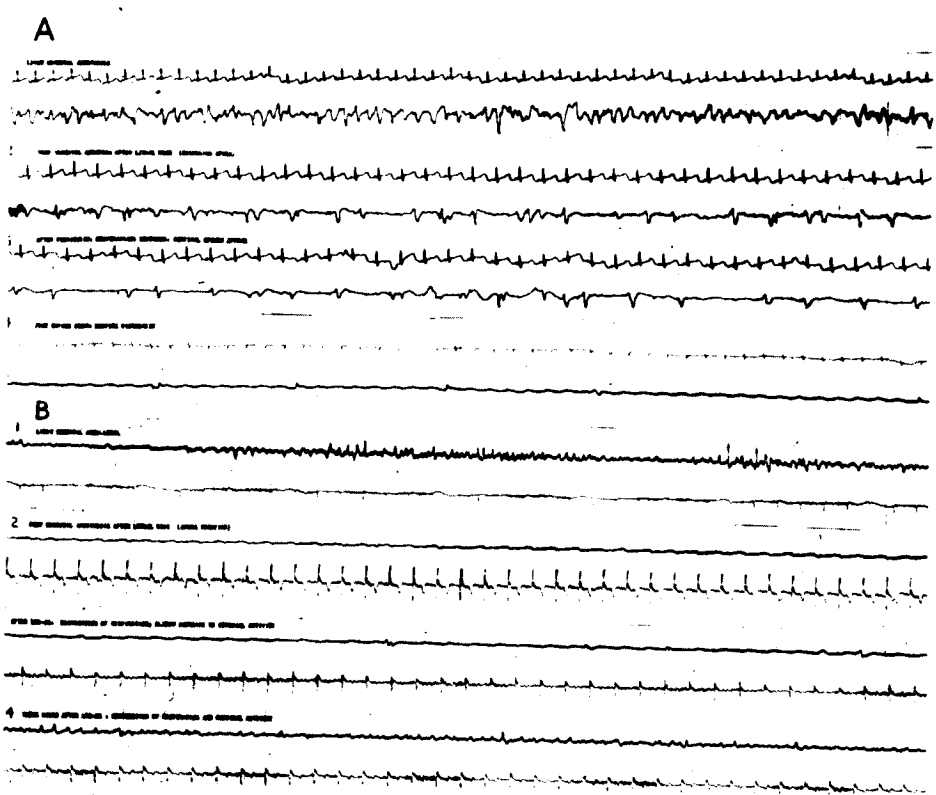
Results

I. All cats not given a test drug died 6 to 10 minutes after receiving the first lethal dose of pentobarbital sodium. Crystalline LSD-25 did not change this course of events. Cats receiving brom-LSD before the lethal dose of pentobarbital showed marked suppression of the EEG and respirations after pentobarbital and died within two hours after the lethal dose. All the cats receiving pentylenetetrazol, picrotoxin, or LSD-25 solution survived at least six hours after one lethal dose of pentobarbital and showed no suppression of the EEG and very slight suppression of respiratory rate. On the other hand, two lethal doses killed all the cats receiving pentylenetetrazol or picrotoxin but not those protected by LSD-25. The 101 LSD cats with exposed parietal cortex survived two lethal doses at least eight hours. They showed some suppression of EEG and respiration. These tracings returned to normal sleep-spindle-type records within 6 to 14 hours. It required three lethal doses of pentobarbital given at once or at 10-minute intervals to kill the cats protected by LSD solution. The 39 cats spared surgery and given two lethal doses of pentobarbital after LSD all recovered completely and were used in subsequent experiments.

II. All the cats given a lethal dose of pentobarbital showed marked suppression of the EEG in 4 minutes, of respiratory depth in 6 minutes, and of cardiac action in 10 minutes. Brom-LSD or crystalline LSD did not change this course of events. Picrotoxin restored respiration and some EEG bursts of spikes for a few minutes and kept 62.2% of the cats alive for 20 to 40 minutes and 37.8% for more than 6 hours. LSD solution restored respiration depth and rate in two minutes after intravenous administration. There were minimal signs of restored EEG activity until 60 to 80 minutes after LSD was given. At that time, EEG activity was like normal sleep records, or nearly so. Seventy-eight per cent of these cats lived for at least eight hours, and then two lethal doses were required to terminate the experiment.

Several precautions were taken during these experiments and are worthy of note. The animals were never moved after injection of a lethal dose of pentobarbital. Whenever an animal was carried, however carefully, it promptly died. These cats are not included in this series. The animals were kept warm, and all handling was gentle. If the animals lost a great deal of blood during surgery, they were discarded from this series.

The discrepancy in action between LSD-25 solution and crystalline LSD should be



(*A*) In each pair of tracings the upper one is the EKG, with slow oscillations from movement of the abdomen during respiration; the lower tracing is of potentials from the surface of the parietal cortex. *1*, recordings after anesthesia with pentobarbital; *2*, depression of cortical potentials and cessation of respiration six minutes after a lethal dose of pentobarbital; *3*, cortical spikes and restored respiration two minutes after injection of picrotoxin intravenously and intraperitoneally; *4*, irreversible changes leading to death: tachycardia, absence of cortical activity, apnea.

(*B*) In each pair of tracings the lower one is the EKG, with an electromyogram of respiratory muscles superimposed; the upper tracing is of potentials from the surface of the parietal cortex. *1*, recordings after anesthesia, showing sleep spindles; *2*, depression of cortical activity and apnea (LSD-25 was given intravenously and intraperitoneally given at this point); *3*, restored respiration but not much change in cortical potentials 20 minutes later; *4*, restored cortical potentials three hours later. This animal survived eight hours and was killed by a double anesthetizing dose of pentobarbital.

Time marking 0.4 second. Amplitude calibration is not contributory.

emphasized. In studying the ocular properties of LSD,[1,2] we found that the crystalline form induced the same respiratory and cardiac stimulation that LSD solution did, but the crystalline form did not induce similar ocular results. Therefore, the success of LSD-25 solution in the present study should be attributed not to respiratory and cardiac stimulation alone but, rather, to some special property yet to be identified.

Comment

The pentobarbital-induced EEG changes reported by Clark and Ward,[7] Brazier,[5] and Finesinger and Brazier [10] helped orient the depth of anesthesia in the present study. Sleep spindles were prominent in the parietal cortex before the lethal dose of pentobarbital was given. As the lethal dose took effect, random slow activity, then long quiescent periods with a few bursts of spikes were recognized. Six minutes after the

lethal dose the bursts of spikes disappeared and respirations ceased. At this point the analeptic drugs were given intravenously. All the successful drugs (LSD, picrotoxin, pentylenetetrazol) started respiration within a few seconds. Only pentylenetetrazol and picrotoxin initiated cortical spikes,[20] however. Each intravenous dose of an analeptic drug was supported by an intraperitoneal dose. In about 10 minutes the effect of the sustained supply of analeptic drug appeared in the EEG as low-amplitude spikes. All the pentylenetetrazol- and 62% of the picrotoxin-supported cats eventually died. Of the LSD-supported cats, 78.6% eventually recovered normal sleep spindles. The LSD cats that were not exposed to surgery survived this hazardous experience and were used in subsequent experiments.

These studies give no information concerning the basis for an antagonism between LSD-25 and pentobarbital. The work of others, however, provides clues. French et al.[11] find that barbiturates inhibit synaptic transmission in the reticular formation. Bradley and Key[4] report that LSD-25 increases the amplitude of spontaneous potentials in the peripheral (but not in the cortical) afferents to the reticular formation. Moreover, peripheral stimulation is one method employed in preventing collapse from large doses of barbiturates in humans[12] and is based on physiological evidence.[15-17] These facts suggest that LSD-25 may be capable of increasing the input from the periphery into the reticular formation. In this way LSD could help the organism to overcome resistance built up by pentobarbital at the synapses in this region. If this resistance[17] is the cause of death from large doses of pentobarbital, then overcoming the resistance would prevent death. Until more is known concerning the actions of pentobarbital and of LSD, further theorizing is merely speculation.

The contribution of the present study is in the demonstration that LSD safely and effectively overcomes cortical and respiratory inhibition induced in cats by lethal doses of pentobarbital. This fact can be useful to workers who find an animal succumbing to an overdose of pentobarbital during an experiment. It may also prove useful in cases of acute pentobarbital intoxication in human subjects when heroic measures are called for to protect the subject from the toxicosis. The best manner in which to use LSD under such circumstances cannot be deduced from the present report.

It should be emphasized that the doses of LSD used in this study are harmless to vital functions in both anesthetized and unanesthetized cats.[9,19] On the other hand, the doses of picrotoxin necessary to reverse pentobarbital intoxication are convulsive in unanesthetized animals and produce cortical spikes indicating a near-convulsive state in anesthetized animals.

Summary

The relative value of LSD-25 solution, LSD-25 crystals, pentylenetetrazol U. S. P. (Metrazol), picrotoxin, and brom-LSD to prevent and to reverse pentobarbital (Nembutal) intoxication was investigated in 269 cats.

LSD-25 solution proved more effective in safe doses than did picrotoxin, pentylenetetrazol, and brom-LSD (in that order) in preventing death from subsequent lethal doses of pentobarbital. Crystalline LSD had no protective effect.

LSD-25 solution was more effective than picrotoxin in safe doses in reversing cortical suppression and cessation of respiration induced by previously administered lethal doses of pentobarbital. Crystalline LSD and brom-LSD had no such effect under the conditions of this experiment.

The doses of LSD-25 solution necessary to prevent and to reverse pentobarbital death are harmless to vital functions in both unanesthetized and anesthetized cats, whereas the doses of picrotoxin necessary to reverse pentobarbital toxicosis are convulsive or subconvulsive even in anesthetized cats.

The relevance of this protective property of LSD-25 to the therapy of barbiturate

intoxication in humans requires further exploration.

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