THE EFFECT OF LYSERGIC ACID DIETHYLAMIDE (DELYSID, LSD-25) ON THIOPENTAL RECOVERY

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THE SYNTHESIS of lysergic acid diethylamide by Hofmann (1) and subsequent studies of the effects of this compound in man by Stoll (2) initiated the study of a group of drugs with unique psychotomimetic qualities. LSD-25 in very minute quantities produces psychic effects in man which last twelve hours or more, even though the drug is excreted from the body within one hour (3).

In most normal humans, oral doses of less than 1 μg. per kilogram of LSD-25 produce a syndrome which simulates a moderate acute schizophrenic upheaval with or without catatonic features. These individuals also experience a variety of disturbances of thought processes, depersonalization, hallucinations, abnormal perceptions, delusions, distortions, and misinterpretations (4). These reactions are interpreted in part as an indication of augmentation of perception of dulled areas of the brain (5). Motor effects of LSD-25 include a subjective sense of trembling and objectively an increase in deep reflexes. Sympathetic overactivity is indicated by the appearance of mydriasis and a slight increase in blood pressure and pulse rate (6). The increased sympathetic activity also causes an increase in skin temperature, hyperglycaemia, and pilo-erection. These reactions can be prevented or reversed by chlorpromazine, or general anaesthesia (7).

The hypnotic effect of barbiturates appear to be accompanied by an increased excretion of the major metabolite of 5-hydroxytryptamine (serotonin, 5 HT). In the conscious cat, LSD-25 produces alerting behaviour, and abolishes the E E G spindles of barbiturate anaesthesia (8). Since LSD-25 antagonizes the action of 5 HT in the circulation, one might expect a shortening of the hypnotic action of barbiturates by LSD-25 (9).

Apter showed that LSD-25 was effective in preventing death from lethal doses of pentobarbital (10). However, the effect of LSD-25 against lethal and sub-lethal doses of thiopental was not apparent in dogs, even though the intra-ventricular injection of LSD-25 in the awake dog has a stimulating (analeptic) effect (11).

In view of the potent cortical stimulating effect of LSD-25 in awake humans, the following test was carried out to determine if an analeptic effect against thiopental narcosis could be demonstrated.

METHOD

This study was designed to find out whether LSD-25 shortens the recovery time from thiopental–nitrous oxide anaesthesia for a standard, short operative procedure in women.

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Uterine dilatation and curettage was the procedure selected because the patients' age variation is not great, the posture required is always lithotomy, surgical trauma is very slight, and the physical state is usually good (1 or 2). In order to avoid selection, 55 consecutive patients were used as the control series followed by 55 consecutive patients for the test. The test group received 25 μg. LSD-25 intravenously as soon as the operation and nitrous oxide anaesthesia were discontinued.

At the preoperative visit, the usual assessment of the patient's physical state was made, and 4 to 6 mg. of perphenazine (Trilafon®) was given by mouth at bedtime. Scopolamine 0.4 mg. was given intramuscularly about one hour before the operation. This was the only medication given before anaesthesia. An infusion of 5 per cent dextrose in water was started on each patient to assure rapid absorption of all intravenous drugs. The patient was asked to gaze at the ceiling and to breathe deeply with the mouth open as induction was started with 3ml. of 2.5 per cent thiopental injected quickly. One minute by the clock was then allowed in order to determine the hypnotic response. Additional thiopental was then injected at a rate of approximately 15 mg./sec., until involuntary closure of the eyelids occurred. A snug-fitting face mask was then applied and nitrous oxide–oxygen (9 L.: 3 L.) was administered from a Mapleson A system (Magill's attachment) with the blow-off valve open on a Boyle or MIE anaesthetic machine until the end of the operation. The flow used in this system was sufficient to prevent longitudinal mixing in the corrugated tube. Immediately after induction the patient was placed in the lithotomy position and preparation was begun for the operation. If the patient showed signs of resistance to stimulation by movements, breath-holding, or swallowing, increments of 50 mg. of thiopental were administered. At least one minute was allowed between added increments, when they were necessary.

Except for the intravenous administration of LSD-25, there were no technical differences in the conduct of anaesthesia in the two groups. Four patients in the control group, and five in the test group were given a small dose of succinylcholine (10–20 mg.) when bimanual pelvic examination proved somewhat difficult because of tight abdominal muscles. This would not affect the duration of anaesthesia, as it was given at the beginning of the procedure.

Recovery time was the time in minutes noted from the moment the operation ended and the mask was removed from the face, until the following four end points were reached and recorded by the nursing staff in the recovery room who were instructed and assigned to observing these patients.

(i) Opened her eyes on request (response to verbal command)
(ii) Answered her name on request (sluggish verbal response)
(iii) Answered her home address on request (alert verbal response)
(iv) Identified simultaneous touch stimulus to face and contralateral arm three times in quick succession (Bender face-hand test)

During the period that these patients were under observation in the recovery room, the vital signs were checked at frequent intervals, and the incidence of vomiting was noted.

Results

The calculated means and standard deviations of the patients' age, height, weight, dose of thiopental (for induction, total, and per kilogram body weight), time of final dose increment (from time of induction), duration of anaesthesia, and times for recovery responses to four end points are summarized in Table I. The Fisher *t* value and significance of the difference of recovery times between the control and test groups are also shown.

It appeared evident from the analysis of these data that LSD-25 in a single intravenous dose of 25 μg. did not exert any analeptic effect which shortened the wakening time from thiopental–nitrous oxide anaesthesia. There was no significant

TABLE I

SUMMARY OF DATA SHOWING THE RECOVERY TIME FROM THIOPENTAL WITHOUT AND WITH LSD-25

				Thiopental					Recovery time in minutes			
Patients	Age	Height (cm.)	Weight (kg.)	Induction dose (mg.)	Total dose (mg.)	Dose/kg. (mg.)	Time of final dose (min.)	Duration of anaesthesia (min.)	R.V.C.	S.V.R.	A.V.R.	B.F. H.T.
Control (55)	40	156	64	353	480	7.5	10.0	19.7	14.3	16.8	17.8	18.4
S.D.±	13	7	15	33				8.1	13.2	13.9	13.8	13.8
LSD-25 (55)	38	155	60	352	444	7.4	9.6	19.4	12.8	16.1	17.3	18.4
S.D.±	13	6	13	29				8.7	10.2	10.8	11.2	11.1
Fisher *t* value:									0.666	0.295	0.208	0
Probability *p*:									No significant difference			

R.V.C. = response to verbal command
S.V.R. = sluggish verbal response
A.V.R. = alert verbal response
B.F.H.T. = Bender face-hand test

difference in the blood pressure and pulse rates between the control and test groups in the immediate postoperative period while these patients were under observation in the recovery room. Vomiting occurred in ten of the 110 patients in the recovery room: six of these did not receive LSD-25 and four did. These observations indicate that LSD-25 had no distinguishing cardiovascular effect, nor did it promote vomiting.

DISCUSSION

The comparison of the control and test groups was considered clinically and statistically valid because the age range, size, mean dose of thiopental, duration of the operation, and dose of thiopental per minute of anaesthesia were as similar as is possible to obtain from cases assigned on a surgical schedule.

The clinical method and technique of anaesthesia used was identical to that used by Gale (12), except that the patients in this study were not given a narcotic sedative in their premedication. It was, therefore, no surprise that the mean dose of thiopental and the duration of anaesthesia were comparable to those of the patients in his study who received a "median dose range" of thiopental. The response time to recovery and alertness after anaesthesia were also comparable.

The dose of LSD-25 employed in this study may have been too small to demonstrate an analeptic effect. However, an intravenous dose of 25 μg. LSD-25 is very close to the dose range which causes a variety of disturbances of affective behaviour such as hallucinations, depersonalization, reliving of repressed memories, and other undesirable reactions which may last up to twelve hours. The authors of this study did not feel justified in risking the development of such behaviour merely for the purpose of shortening the drowsy state after anaesthesia. On the other hand, much larger doses of LSD-25 should probably be tested with justification when a patient has taken a very large dose of barbiturates with suicidal intent. If no apparent effect is seen, no harm is done and other forms of therapy may be tried. Recently, one such trial was made on a psychiatric patient in this hospital who had ingested 10 to 15 gm. of Tuinal® with suicidal intent. This

patient was given 400 μg. of LSD-25 orally by the attending physician shortly after he was discovered. He slept deeply for about ten hours, and awakened without ill effects.

It was interesting to note in this study that none of the 55 patients who received LSD-25 had any overt suggestion of the various somatic, mental, or perceptual changes that are observed in subjects who have had LSD-25 without anaesthesia. The authors did not wish to draw the patients' attention to any subjective symptoms that may have occurred; so no attempt was made to elicit data of psychological import. However, the possibility exists that there was an increase in symptom intensity which was not "verbalized," and so could not be specifically observed. Only on the basis of the test data observed may one conclude that LSD-25 has no analeptic action. It may be surmised that the slow release of thiopental from the fat depots into the blood stream over several hours during recovery was sufficient to suppress any overt behavioural changes that may occur even with a small dose of LSD-25.

Summary and Conclusions

Two groups of 55 consecutive female patients were observed closely to determine the recovery time from thiopental–nitrous oxide anaesthesia after a short standard operative procedure. Uterine dilatation and curettage was the operation chosen because it produces very little surgical trauma and requires only a relatively light level of anaesthesia. The first group of patients served as a control. In the second group, each patient received 25 μg. of LSD-25 immediately after the end of anaesthesia.

There was no significant difference in the time required for awakening in the two groups as measured by four end points: response to verbal command (open your eyes), sluggish verbal response (what is your name), alert verbal response (where do you live), and Bender face-hand test (identify simultaneous touch stimulus to face and contralateral arm). There were also no distinguishing cardiovascular or overt psychic changes observed in any of the patients who received LSD-25. It was suggested, however, that one may be justified in testing the effectiveness of a much larger dose of LSD-25 when a very large overdose of a barbiturate has been injected or taken orally with suicidal intent.

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Résumé

Nous avons observé de près deux groupes de 55 malades consécutives pour préciser le moment du réveil à la suite d'une anesthésie au thiopenthal et protoxide

d'azote après une courte opération ordinaire. Nous avons choisi comme opération: dilatation et curettage parce que cette opération n'occasionne qu'un très petit traumatisme et ne requiert qu'un niveau d'anesthésie plutôt superficiel.

Le premier groupe de malades nous sert de témoins. Chacune des malades du deuxième groupe a reçu 25 mg. de LSD-25 immédiatement à la fin de l'anesthésie.

Entre les deux groupes, nous n'avons pas observé de différence notable dans la durée du sommeil, évaluée de quatre façons: une réponse à un ordre verbal (ouvrez vos yeux), une réponse verbale marmottée (quel est votre nom), une réponse verbale attentive (quelle est votre adresse), le test Bender (identification simultanée des stimuli du toucher à la face et au bras opposé). Nous n'avons pas observé non plus de changements cardiovasculaires ou d'éveil psychique chez aucune des malades qui avaient reçu LSD-25.

A la lumière de ces tests, nous concluons que LSD-25 est dépourvu d'activité analeptique. Nous concédons, toutefois, que si un grand surdosage de barbituriques a été donné en injection ou a été absorbé par la bouche en tentative de suicide, on puisse tenter de l'employer.

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