STUDY OF Lysergic Acid Diethylamide as an Analgesic Agent

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AN IDEAL ANALGESIC agent has not yet been discovered. The criteria for such an analgesic would be: to give relief from pain, offer no impairment of the sensorium, maintain interest in life, have no unpleasant side effects, and be long lasting and effective in a high per cent of cases. In the quest for such a remedy, we explored the analgesic action of lysergic acid diethylamide (LSD-25), an ergot derivative which has a number of psychic effects in humans.[1, 2] This is a preliminary report on the analgesic actions of LSD-25.

LYSERGIC ACID ACTION

The LSD-25 experience varies greatly from patient to patient and is probably due to enzymatic action.[3] It consists of an initial excitatory phase where fine tremors, perspiration, pupillary dilatation, panicky feeling, and feelings of impending disaster are noted. Following this (about 90 minutes after administration), the patient commonly experiences the world as beautiful, becomes gregarious, and enjoys certain images. After a further hour has elapsed, the images and the transcendental experience in general may become ominous, and it is then that the psychic reactions described below have the greatest intensity. The total reaction lasts about 8 to 12 hours. The psychic impact, however, can be observed for a long time, up to 2 weeks.

Of special importance to us were two aspects of the LSD-25 reaction. First, this drug produces a peculiar distortion of the body image[4] and certain obliterations of ego boundaries, in addition to visual images or hallucinations, auditory, olfactory, or tactile images. Second, LSD-25 deprives the human psychic structure of its ability to concentrate on a specific significant sensation[5] and, although attention can be paid to certain sensations, the selection is not guided by the usual criteria.

The attention of the individual may be fully absorbed by a single sensation for a short time, and then tends to shift from one sensation to another more rapidly than usual. Normally, attention is focused primarily on sensations related to survival or purposefulness, whereas under LSD-25, a single visual impression may take precedence over sensations of pain or those concerned with survival.

DEFINITION OF PAIN

Pain can be viewed as a neurophysiologic and psychologic event.[6, 7] Neuro-

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physiologically, the pain phenomenon depends on availability of end-organs, their specific type, the number stimulated, and their frequency of discharge. Psychologically, it depends on the intensity and symbolic significance of the tension that exists between the desire to maintain bodily integrity and the wish to sequestrate the ailing part.[8] This conflict which exists between the fear of losing part of the organism (castration fear)[9] and the inability to include into one's body image that section which causes pain (narcissistic restoration) plays an important role, not only in the pain experience, but in many functional disease states.

The bulk of pathologic pain experience is a composite phenomenon, consisting of pain sensation — the neurophysiologic component, and pain affect —the psychologic component. However, when the pain-producing source is definitely outside the body, as in experimental pain, pain sensation only is involved. At the other extreme, when the psychic problem of castration fear versus narcissistic restoration (pain affect) becomes projected on a section of the body, pain is experienced without pain sensation.[6]

This view of pain led us to consider LSD-25 as a possible analgesic, for two reasons. First, since LSD-25 lessens the need to maintain bodily integrity and produces certain obliterations of the ego boundaries, it should permit sequestration of the diseased part and thus facilitate narcissistic restoration, alleviating the pain affect.

Second, LSD-25 produces an inability to maintain selective attention on a sensation of importance, whether this importance is due to sensory intensity or affect. This inability should alleviate both components of the pain experience. In order to assess this theoretically conceived analgesic possibility of LSD-25, we compared its analgesic action with that of two established and potent drugs, dihydromorphinone HCl (Dilaudid®) and meperidine HCl (Demerol®).

PROCEDURE

While fully recognizing the need for double-blind procedures in analgesic studies, it soon became apparent that LSD-25 is immediately recognizable by its psychic and vegatative action. Furthermore, during initial pilot studies, we found that the effect of LSD-25 may be protracted and lasting as long as 2

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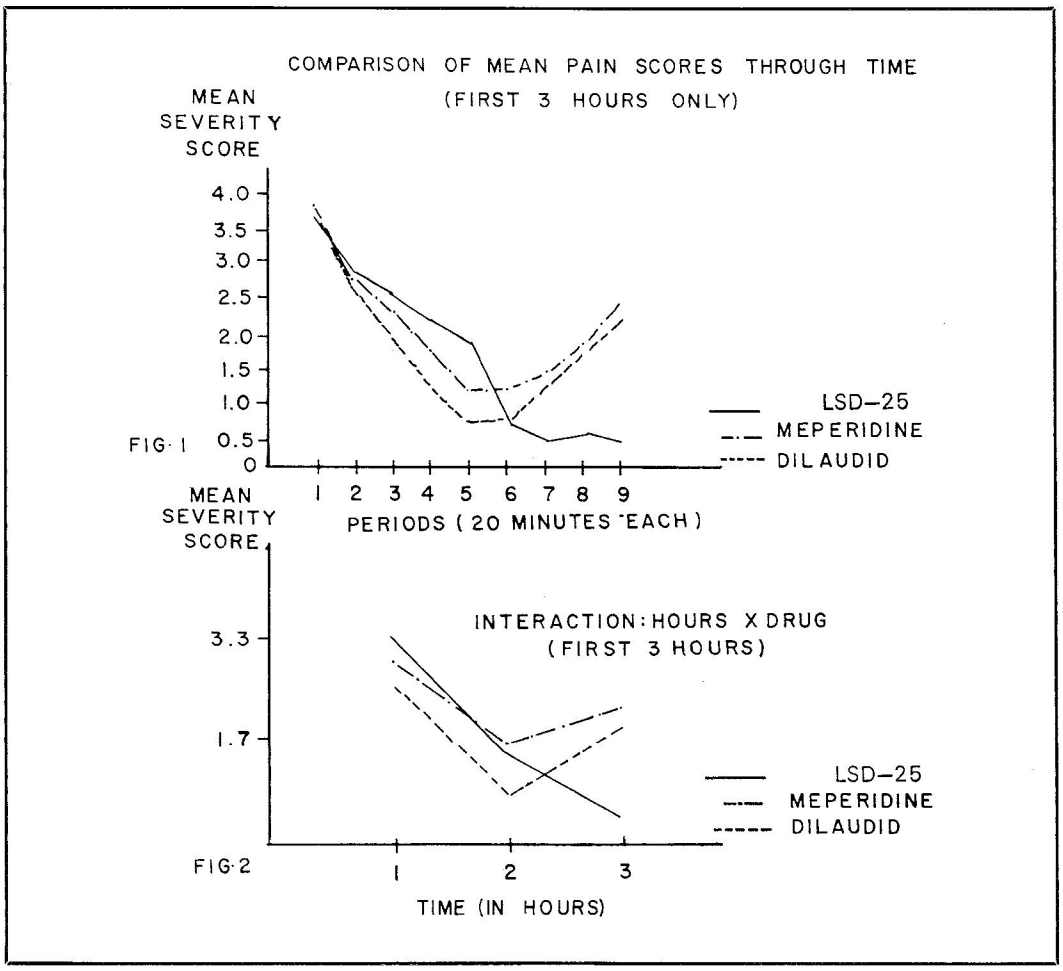

Table 1

ANALYSIS OF DRUG X HOURS INTERACTION
(Duncan's Multiple-Range Test)

I. Between Drugs Within Periods:
1. *First Hour:* No significant difference between drugs.
2. *Second Hour:* Dihydromorphinone is significantly better than meperidine, ($p<0.05$) and LSD-25, ($p<0.001$). The test of significant difference between meperidine and LSD-25 proved to be "borderline:" ($0.05<p<0.10$).
3. *Third Hour:* LSD-25 is significantly better than both meperidine and dihydromorphinone at the 0.001 level. There is no significant difference between meperidine and dihydromorphinone (that is, $p>0.10$).

II. Within Each Drug Between Periods:
1. *Meperidine:* The second hour mean was significantly better than the first hour ($p<0.001$), and better than the third hour ($p<0.005$). The third hour mean was significantly less than the first hour mean ($p<0.001$).
2. *Dihydromorphinone:* All hourly mean scores were significantly different from each other at the 0.001 level.
3. *LSD-25:* All hourly mean scores were significantly different from each other, also at the 0.001 level.

Table 2

ANALYSIS OF PAIN-FREE SCORES
(Including observations beyond the first 3 hours post of drug administration)

A
Percentage of Patients Free of Pain for Designated Periods (Exclusive of First 3 Hours of Drug Administration)

Duration	Meperidine	Dihydromorphinone	LSD-25
0 to 6	8.5	8.5	—
7 to 12	6.4	14.9	14.9
13 to 18	—	—	10.6
19 and over	—	—	48.9
patients with no protracted pain-free periods	85.1	76.6	25.6
Total	100.0	100.0	100.0

B
Mean Number of Pain-Free 20-Minute Periods for Each Drug*

Drug	Code	Mean	Probability Statement
Meperidine	m	5.7	m versus d; $p<0.04$
Dihydromorphinone	d	8.4	d versus L; $p<0.001$
LSD-25	L	95.6	m versus L; $p<0.001$

*The usual analysis of variance methods could not be employed, as the data were violative of key assumptions; the errors associated with randomness were not normally distributed and the within-drug variances were heterogeneous. We attempted to transform the data in order to meet these requirements, but none of the transformations worked. Resort,therefore, was made to the nonparametric Wilcoxon matched-pairs signed-rank test for each drug pair, that is, meperidine versus dihydromorphinone, dihydromorphinone versus LSD-25, and LSD-25 versus meperidine.

Table 3

OBSERVED MEANS

Drug/Period	First Hour	Second Hour	Third Hour
Meperidine	2.93	1.35	1.87
Dihydromorphinone	2.81	0.84	1.76
LSD-25	3.06	1.66	0.63

weeks, which makes its incorporation in a double-blind study impractical. Since LSD-25 is known to have strong effects on the human psyche, we felt it would be appropriate to assess its analgesic value in gravely ill patients who complain of severe intolerable pain. We selected 50 gravely ill patients with the following diagnoses: cancer of the breast with metastasis, 10; herpes zoster with severe burn, 1; cancer of the cervix with metastasis, 13; gangrene of foot or leg, 10; cancer of the pancreas with metastasis, 2; cancer of the pancreas, 2; cancer of the liver, 2; cancer of the tonsils and larynx with metastasis, 4; cancer of the lung with metastasis, 6.

We administered dihydromorphinone HCl, 2 mg., and meperidine HCl, 100 mg., in double-blind fashion. Upon the complaint of pain, the patient received either drug initially. Upon the subsequent complaint of pain, and at least 6 hours later, the patient received the other drug in a randomized design. At least 6 hours after the second administration and upon the complaint of pain, the patient re-

ceived 100 mcg. of LSD-25. The patients were observed after each administration for 3 hours, at 20-minute intervals. After the LSD-25 administration, and after 3 hours, the patients were observed indefinitely, at 6-hour intervals. We rated the degree of pain in four categories: mild, moderate, severe, and very severe. The observations consisted of: (1) the observer's opinion of

Table 4

TOTAL PAIN RELIEF SCORES FOR INDIVIDUAL PATIENTS

Score is derived by adding degrees of pain (0-4) for the total of the first 3 hours (9 observations, including the initial observation). d—dihydromorphinone; m—meperidine; L—Lysergic acid.

Patient number	Drug	Score	Patient number	Drug	Score	Patient number	Drug	Score	Patient number	Drug	Score
1	d	20	13	d	21	25	d	15	38	d	13
	m	21		m	20		m	15		m	22
	L	10		L	15		L	17		L	23
2	d	18	14	d	16	26	d	28	39	d	14
	m	19		m	20		m	26		m	17
	L	8		L	14		L	17		L	14
3	d	16	15	d	17	27	d	11	40	d	12
	m	15		m	31		m	15		m	17
	L	15		L	17		L	19		L	18
4	d	24	16	d	10	28	d	19	41	d	18
	m	23		m	17		m	21		m	15
	L	9		L	18		L	15		L	17
5	d	13	17	d	15	29	d	15	42	d	12
	m	18		m	20		m	24		m	19
	L	8		L	15		L	20		L	18
6	d	7	18	d	16	30	d	16	43	d	17
	m	20		m	16		m	20		m	22
	L	14		L	14		L	14		L	17
7	d	14	19	d	23	31	d	15	44	d	17
	m	16		m	29		m	10		m	17
	L	13		L	18		L	18		L	21
8	d	13	20	d	24	32	d	18	45	d	19
	m	11		m	13		m	19		m	18
	L	14		L	22		L	16		L	17
9	d	11	21	d	19	33	d	16	46	d	24
	m	27		m	16		m	19		m	24
	L	9		L	14		L	16		L	17
10	d	16	22	d	18	34	d	16	47	d	13
	m	10		m	18		m	14		m	21
	L	11		L	16		L	13		L	21
11	d	9	23	d	21	35	d	13	48	d	21
	m	17		m	17		m	15		m	20
	L	12		L	13		L	22		L	12
12	d	17	24	d	15	36	d	14	49	d	15
	m	21		m	18		m	17		m	13
	L	11		L	17		L	19		L	17
						37	d	17	50	d	11
							m	16		m	12
							L	24		L	10

the pain intensity, (2) the patient's statements, (3) the objective signs of pain distress (thrashing, crying, etc.), (4) statements from neighboring beds and house staff.

Because of the gravity of the patient's illness, these four observations were usually in conformity with each other.

RESULTS

The results can be divided into two groups, the first comparing dihydromorphinone and meperidine and the second comparing LSD-25 with the other two drugs. Dihydromorphinone and meperidine showed no significant difference in analgesic action during the first hour. During the second hour, dihydromorphinone showed significantly better analgesia than meperidine, and during the third hour there was no significant difference between the two drugs. Dihydromorphinine was effective for a somewhat longer period (table 1). There were somewhat less distressing side effects during the dihydromorphinone than during the meperidine administration.

When compared with LSD-25, both drugs fell short in their analgesic action, although the onset of therapeutic action of LSD-25 was somewhat slower (table 2A and B). Observed means for the first 3 hours are shown in table 3, the individual pain scores for the first 3 hours in table 4, and a statistical analysis of variance in table 5. The mean severity score comparing the three pain scores can be seen in figure 1 and the hours times drug interaction in figure 2.

Side reactions were difficult to interpret in these patients, because of the symptoms of their primary disease, but apparently 7 patients developed nausea and/or vomiting during the meperidine administration, 4 during the dihydromorphinone, and 3 during the LSD-25 administration. Psychotic reactions were observed during the LSD-25 administrations, but none was of sufficient severity to warrant termination of the reaction by chlorpromazine. Although the analgesic action of LSD-25 was profound and the patients were relieved of the oppressive ideation accompanying grave illness, 8 patients refused the second administration, 30 were indifferent, and 12 wished for it.

DISCUSSION

In an attempt to find an analgesic medication which would diminish the patient's suffering and permit him to participate in life with heightened intensity, theoretical considerations led us to the exploration of LSD-25 as an analgesic. It has been noted that this drug prevents sleepiness and permits an increase in the sensory input either with images or a heightened affective response to common sensory impressions. In addition to pain relief, this increase

Table 5

ANALYSIS OF VARIANCE

Two-Dimensional 3x3 Design with Repeated Measurements (Observations limited to first 3 hours)

Source	Sum of square	df	MS	F	Significance level
Main effects					
Between drugs	54.36	2	27.18	3.99	$p<0.05$
Between hours	2130.82	2	1065.41	156.45	$p<0.001$
Between patients	433.10	46	9.42	1.38	$0.05<p<0.10$
Interactions					
Drugs x hours	502.56	4	125.64	18.45	$p<0.001$
Drugs x patients	518.97	92	5.64	0.83	ns
Patients x hours	1331.85	92	14.48	2.13	$p<0.005$
Residual:	1253.44	184	6.81	—	—
Total:	6225.10	422	—	—	—

in sensory input has been assumed to produce a euphoric state, which would induce the patient to seek additional administration of the drug.

This, however, did not materialize. On the contrary, as noted above, some patients refused the second administration in spite of complete pain relief for protracted periods of time, many were indifferent to repeated administration, and only relatively few wished for it. An explanation for this peculiarity is difficult to conceive. It seems that the LSD-25 experience required a great deal of psychic energy, and represents "hard work." This statement, which was frequent, probably reflects the heightened subconscious activity under lysergic acid, which places a strain on ego control and consequently is felt as a laborious task. If ego disintegration threatens, this experience may be felt as panic.[10]

The most striking psychic phenomenon observed to occur in the LSD-25 experience is a regression to infantile sexuality with an accompanying abandonment of goal-directed, genital activity. This regression may be considered as a basis for lessening of castration fears and the increase of primary narcissistic feelings. The abandonment of genital orientation may also be responsible for the reluctance of patients to repeat the drug experience.

The administration of LSD-25 is an innocuous procedure from a medical standpoint. All patients in this study were gravely ill, and some were preterminal, and yet no medical complication was encountered. The incidence of hallucinations was considerably less than reported for the population in general, probably because these patients were intensively preoccupied with their own disease processes. In addition to pain relief, these patients displayed a peculiar disregard for the gravity of their situations, and talked freely about their impending death with an affect considered inappropriate in our western civilization, but most beneficial to their own psychic states. This approach to their disease was noted usually for longer periods than the analgesic action lasted. It was a common experience for the patient to remark casually on his deadly disease and then comment on the beauty of a certain sensory impression. It is conceivable that the relevance of meaningful sensory input can for protracted periods outweigh the fear of dying.

In view of the fact that the analgesic action probably depends on the overall psychic experience, it will be a difficult, though important, task for the future to determine the possible addition of other drugs to attenuate the LSD-25 experience and thus make it more acceptable to the patient.

SUMMARY AND CONCLUSION

A comparative study between lysergic acid diethylamide (LSD-25), meperidine, and dihydromorphinone was conducted (double-blind for the latter two drugs). A theoretical basis for the analgesic action of LSD-25 is presented. Dihydromorphinone compared favorably with meperidine in the intensity and length of analgesic action, and LSD-25 showed a protracted and more effective action than either of the other drugs. Difficulties encountered are discussed, and a theory of the nature of pain is presented.

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