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ELYMOCLAVINE (43-Y).

Elymoclavine (V-A-22) is a material isolated from a cultured saprophytic fungus by the Research Laboratories of Takeda Pharmaceutical Industries in Japan. It is related to agroclavine (V-A-18) and to dihydroagroclavine, both of which have sedative and hypnotic effects in man, although they are primarily excitant in animals. All these drugs are related to the ergot group. In elymoclavine the acid amide group of LSD has been replaced with a hydrogen and a CH_2OH group.

According to Yui and Takeo (1) agroclavine and elymoclavine cause a syndrome of "central sympathetic excitation" in mice, rabbits, cats and dogs manifested by mydriasis, tachypnea, convulsions, hyperactivity, etc; whereas dihydroagroclavine, dihydroergokryptine, etc., cause sedation. Elymoclavine and agroclavine had analeptic effects in reserpine sedated mice.

Because of discrepancy in the effects of agroclavine (in animals, excitation and in man, sedation) a preliminary study of elymoclavine was thought to be of interest. The study was designed to determine the effective dose range in man, and to determine if LSD-like (psychosomimetic) effects were induced.

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METHODS

Subjects. Nontolerant former opiate addicts who were serving sentences for violating the Federal narcotic laws volunteered for these experiments. All were healthy males between 21 and 40 years of age who presented no evidence of any of the major psychoses on mental status examinations. All had experienced the effects of LSD-25 in previous experiments.

General Conditions. The experiments were conducted in a special ward. Patients entered this ward on the night before experiments were conducted, and were observed hourly by specially trained attendants. Between observations the patients were free to remain in their own rooms, to sleep or to socialize with other patients in a common day room.

Drugs. Elymoclavine was given orally in solution at 8 a.m. The taste was masked with cherry syrup.

In preliminary experiments, the dose of elymoclavine was cautiously elevated from 1 mcg/kg to 7.5 mcg/kg. No psychosomimetic effects were observed, and with the larger doses patients began to report headaches and drowsiness. Accordingly

more formal experiments were carried out in which 12 patients received on two separate occasions 10 and 15 mcg/kg of V-A-22. In addition, 5 patients received 20 mcg/kg and 4 received 25 mcg/kg.

Observations. The following observations were made at hourly intervals twice before and eight times after administration of V-A-22: pupillary size, systolic blood pressure, and threshold for eliciting the kneejerk. In addition patients completed a questionnaire hourly, with the help of an aide, and short mental status examinations were made at appropriate intervals. The methods of making the observations and analyzing the data were described by Isbell et al (2,3). For comparative purposes, data on 9 other subjects who received a placebo and 1.0 mcg/kg of LSD in other experiments are included.

RESULTS

The combined data are presented in Table 1 which shows that, as compared with LSD, elymoclavine had relatively minor effects on pupillary diameter, threshold for kneejerk, and blood pressure (except at the 25 mcg/kg level). The table also shows the lack of any psychosomimetic effect, even with 25 mcg/kg. Positive responses on the questionnaire after elymoclavine were usually to such items as: "I feel sleepy," "I am nauseated," etc.

V-A-22 did, however, induce symptoms differing from those of LSD. The most commonly reported symptoms were sleepiness and relaxation (Table 2).

DISCUSSION

Like agroclavine and Lilly 23194, elymoclavine had sedative effect, rather than psychosomimetic effects in man. Whether such sedation could be exploited therapeutically remains to be determined. ✓

In further work, the sleep-inducing properties of elymoclavine should be compared with those of a barbiturate.

REFERENCES

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Table 1.

Comparison of the Effects of Elymoclavine (V-A-22) with those of LSD-25.

MEASURE	DRUG AND DOSE (mcg/kg) ¹					
	Placebo ¹	LSD-25 ¹ 1.0	ELYMOCLAVINE			
			10	15	20	25
Pupillary Size	0.2 ± 1.4	+10.2 ± 1.2	- 0.4 ± 1.3	- 1.2 ± 1.3	+ 3.0 ± 2.2	- 1.9 ± 2.5
Blood Pressure	+15.6 ± 13.5	64.8 ± 10.9	+25 ± 11	+43 ± 14	+24 ± 12	+94.5 ± 8.7
Threshold for kneejerk	+20.7 ± 11	-50.9 ± 31	- 7.6 ± 1.4	- 8 ± 1.5	-16.7 ± 9	+10 ± 9
Total positive responses on Questionnaire	0.1 ± 0.3	57 ± 23.2	5 ± 1.3	7.3 ± 1.9	5.2 ± 3.2	6.5 ± 3.9
Clinical Grade	0 ± 0	2.2 ± 0.4	0 ± 0	0 ± 0	0 ± 0	0 ± 0

1. Figures are means ± standard errors of observations on 9 subjects in the case of placebo and 1 mcg/kg of LSD; 12 subjects in case of 10 and 15 mcg/kg of V-A-22; 5 subjects in case of 20 mcg/kg of V-A-22; and 4 subjects in case of 25 mcg/kg of V-A-22.

Table 2. Incidence of Certain Symptoms after Elymoclavine.

SYMPTOMS	DOSE (mcg/kg)			
	10	15	20	25
	Number of Subjects			
	12	12	5	4
Sleepiness	9	9	3	2
Relaxed	7	8	3	2
Headache	2	4	2	0
Nausea	3	4	2	2
Dizziness	0	0	1	0
Feel "different"	7	8	2	2

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