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Clin. Pharmacol. Therap. 5,
611-614 (1964)

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Persistence of lysergic acid diethylamide in the plasma of human subjects

Two micrograms per kilogram of LSD-25 was administered intravenously to five normal human subjects. The concentration of drug in plasma was determined serially over the subsequent 8 hours. LSD-25 was found to be present in human plasma in relatively large quantities during the period of peak effect. The half-life of LSD-25 in human plasma was calculated to be 175 minutes.

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Although d-lysergic acid diethylamide (LSD-25) has not actually been measured in human tissues, there is an impression in the literature that the drug rapidly disappears from the body and that the characteristic and persisting psychic effects are the result of secondary biochemical events which are somehow "triggered" by the drug.^{2, 4, 7}

This formulation is apparently the consequence of combining laboratory data on the duration of LSD-25 in the tissues of the *mouse* with clinical data on the duration of effects in *man*. The effects of the drug in man generally last 8 to 12 hours, whereas, in mice, radioactive material has been reported to disappear from the blood and brain within about an hour after intravenous administration of C¹⁴ labeled LSD-25.^{2, 6} This apparent discrepancy (1 hour versus 8 to 12 hours) has led to the postulation of a "triggering" action for

LSD-25. It appears to be assumed that both man and the mouse metabolize LSD-25 at a similar rate and that, in both species, most of the drug has disappeared from the tissues in one hour.

Other studies have shown, however, that there is much species variation in the rate of metabolism of LSD-25. The half-life of LSD-25 in mice is 7 minutes, in monkeys 100 minutes, and in cats 130 minutes.¹ Since there is this variation, it appears hazardous to apply data from a particular animal species to humans.

In this study, we measured the levels of LSD-25 in plasma for an 8 hour period following the intravenous administration of 2 mcg. per kilogram of the drug to normal human subjects.*

*The human subjects in the tests conducted at the Chemical Research and Development Laboratories are enlisted volunteers from the six U. S. Army areas within the United States. The most stringent medical safeguards surround every human test.

Method

Five normal male subjects ages 21 to 25, were administered LSD-25 intravenously over a 1½ minute period. Each subject received a dose equivalent to 2 mcg. per kilogram of the free base (given in the form of the tartrate salt). Blood samples drawn at 5, 15, 30, 60, 120, 240, and 480 minutes were heparinized and centrifuged. The plasma was separated, frozen, and later analyzed for LSD-25 with a slight modification of the method of Axelrod and co-workers.¹

Since the quantities of LSD-25 to be measured at the dose used were relatively small, all glassware and equipment concerned with the analysis were scrupulously cleaned with nonfluorescent soap (Drene), rinsed, and then washed five times with distilled water. Pipettes were rinsed twice with the appropriate reagent before use. Five milliliters of plasma placed in a 40 ml. glass tube was salt saturated, alkalinized with 0.25 ml. 2N NaOH, and gently extracted for 30 minutes with 20 ml. of fluorescent grade n-heptane (Harleco), containing 2 per cent isoamyl alcohol, with the use of an Extractomatic shaker (Virtis). It was found that more violent agitation caused elevation of control readings. After extraction and centrifugation, 18 ml. of the heptane layer was placed in a tube containing 1 ml. of 0.004 N HCl, and acid-heptane mixture was shaken (Extractomatic) for 15 minutes.

The heptane supernatant was removed and the 1 ml. acid phase was placed into a 1.4 ml. quartz cuvette. Fluorescence of the solution was measured with an Aminco-Bowman spectrophotofluorometer. Excitation and fluorescent wavelengths were 325 and 445 m μ , respectively.

Internal standards with pretest plasma drawn just prior to the experiment were carried through the analysis. The internal standards contained 0, 10, 20, and 40 ng. of added LSD-25. The sensitivity of the instrument was set so that each nanogram represented one to two deflections of the photomultiplier scale.

We found, as did Axelrod and his associates, that the fluorometric method is sensitive to 1 ng. of LSD-25.¹ The assay proved quite reliable once fluorescent contaminants were eliminated. We obtained excellent linearity with the plasma internal standards. The mean deviation from linearity was 1.5 per cent (range 0 to 6.5 per cent).

To obtain a crude index of performance, subjects were given one of a series of equivalent tests, consisting of simple addition problems, after each blood sample was drawn. These were to be solved as quickly as possible during a three-minute period, and scores were expressed as a percentage of control values. It has been shown that performance on arithmetic tests is impaired by LSD-25 and that scores are inversely related to dose.³ Each plasma determination was associated with a performance test score.

Results

Plasma levels fall steeply and then begin to level off after 30 minutes (Fig. 1). This rapidly declining phase presumably represents equilibration between plasma and tissues.

Concomitantly, performance test scores show a rapid decrement until a peak is reached at approximately 30 minutes. This corresponds to reported peak effects of LSD-25 after intravenous administration, as scored by the Abramson symptom check list.⁵

During the subsequent hours, plasma levels of LSD-25 gradually fall and performance test scores slowly improve. At 8 hours, a small amount of LSD-25 remains in the plasma and there is still some impairment of performance.

On the basis of these figures, the half-life of LSD-25 in human plasma was calculated graphically on semilog paper to be 175 minutes.

Discussion

Although plasma levels of LSD-25 in this study may appear extremely low, they

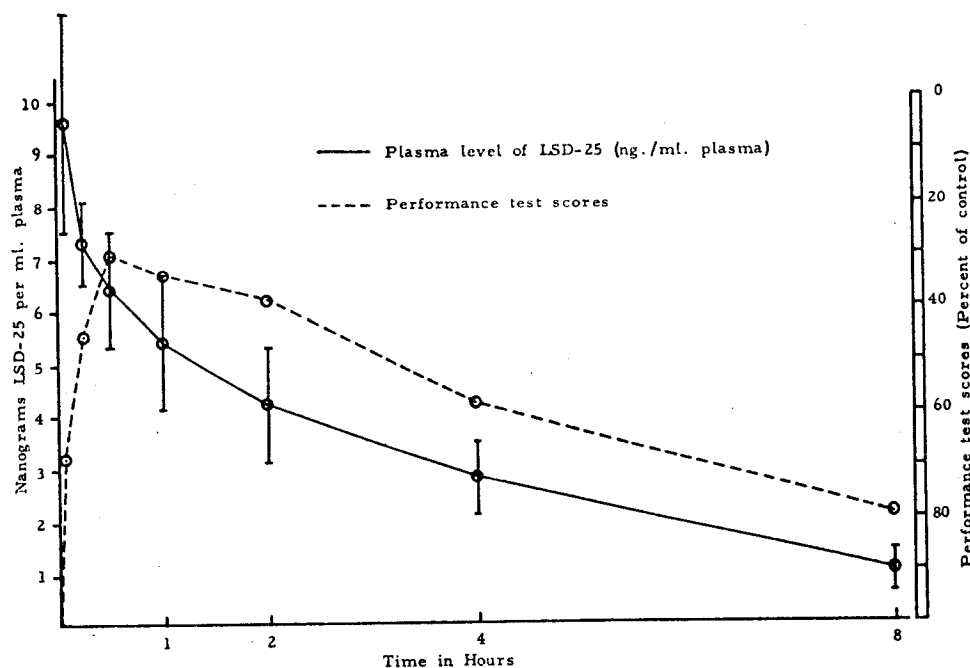


Fig. 1. Mean plasma levels of LSD-25 (expressed as nanograms per milliliter of plasma) may be read from the scale on the left of the graph. The standard deviation for each value is indicated. Mean performance test scores (expressed as a percentage of control scores) are read from the scale on the right of the graph.

are actually reasonably high in relation to the dose administered. Levels during the hour after the equilibration phase are about 4 to 6 ng. per milliliter of plasma. The administered dose is 2 ng. per gram of body weight or approximately 3.3 ng. per gram of body water. Thus, at 90 minutes, which is within the period of peak effect, the concentration of LSD-25 in the plasma is actually more than would be expected if the entire administered dose were evenly distributed throughout the total body water. These relatively high levels are comparable to those reported by Axelrod and associates¹ in the cat and monkey at a similar time. Correspondingly, a half-life of 175 minutes for LSD-25 in man is similar to that in the cat and monkey. In contrast, the 7 minute half-life of LSD-25 in mice is much shorter than that in man.

The findings of this study indicate that in humans, contrary to previous impres-

sions, LSD-25 does not rapidly disappear from the body before psychic effects are manifest. Actually, there seems to be a close relationship between the presence of LSD-25 and the effects produced. In view of this, it appears unnecessary to postulate a "trigger" mechanism to account for the action of LSD-25 in man. We do not wish to imply, however, that the effects of LSD-25 are necessarily due to a direct action of the drug.

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