

Methadone Plasma Level: Sustained by a Reservoir of Drug in Tissue

(heroin/humans/opiate/maintenance treatment/addiction)

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Contributed by Vincent P. Dole, October 24, 1972

ABSTRACT Binding of methadone in body tissues limits the rise in plasma concentration and prolongs the pharmacological action in patients receiving a daily maintenance dose. An opiate with equal intrinsic activity but greater binding affinity would, therefore, be a better drug than methadone for maintenance treatment; it would be safer when taken in a single dose and longer in its duration of action when taken on a regular schedule.

In maintenance treatment of narcotic addicts, methadone is administered as a single daily dose of constant magnitude (1). On this schedule the patients remain functionally normal (2), without symptoms of abstinence, during the 24-hr span between doses. If a single dose is omitted, they generally experience only minor discomfort (some nausea and gripe-like aching) during the subsequent 24-hr period without medication.

On the other hand, quantitative studies of the analgesic effect of methadone in acute experiments have shown that the duration of the drug effect is only about 6 hr, no greater than that of morphine (3). There is thus a significant difference between the periods of action of the drug on acute and chronic administration. Paradoxically, the effect of methadone persists longer in the patients who have become refractory to the narcotic action of the drug (the maintenance patients) than in subjects who have not received previous doses of methadone and, therefore, are more sensitive to it.

The explanation suggested by recent studies of maintenance patients in this laboratory is that methadone accumulates in tissue when given repeatedly. Bound methadone, equilibrated with drug circulating in plasma, sustains a pharmacologically effective plasma level for 24 hr or longer. Since a single dose is rapidly cleared from the plasma, this dose, in the absence of tissue stores, soon loses its effect. On the other hand, a daily dose of methadone, given to a maintenance patient, stabilizes him pharmacologically by maintaining a reservoir of drug in tissue; this reservoir, in turn, holds the plasma level within narrow limits. This buffering action makes short-term fluctuations in dosage unimportant. In any 24-hr period, the dose taken by a maintenance patient may be halved or doubled without significant effect, whereas a change of this magnitude if continued over several days would be felt by the patient.

The approximate capacity of the methadone reservoir and the rate of elimination of drug from the body can be estimated from data recently obtained by us (M. J. K., manuscript in preparation) and other investigators (4, 5). In our study, nine patients who had been maintained on methadone for 1-5 years prior to the study, and known to be reliable (urines consistently free of other drugs, steady employment, good reputations), were stabilized on a daily dose of 100 mg for a period of 8 weeks. At 2-week intervals, each patient spent a day in the clinic during which time blood samples were taken before ingestion of the daily dose of methadone, and at intervals of 2 and 6 hr afterwards. Urine samples were also taken for analysis of methadone and routine monitoring for drugs of abuse (none

were found). Plasma methadone concentrations were determined by isotope dilution and gas-liquid chromatography (manuscript in preparation). The recovery of methadone added to plasma was $97.6 \pm 7.5\%$, over a concentration range from 0.3 to 2.0 $\mu\text{g/ml}$.

Plasma concentrations before ingestion of the morning dose (i.e., 24 hr since the last dose) averaged 0.58 $\mu\text{g/ml}$. Analysis of variance showed no significant trend in these levels over the 8-week period of observation, and no consistent difference between the two values obtained from the samples taken 2 and 6 hr after the dose—the latter result presumably reflecting variations in the time that the plasma maximum occurred after ingestion. The average increment in plasma level (difference between the zero-time level and the greater of the two values after ingestion) was 0.33 $\mu\text{g/ml}$; thus, only about 1 mg (assumed plasma volumes of 3500 ml) of the 100 mg administered was recovered in circulating plasma.

The ratio between the maximal observed concentration of methadone in plasma and the level 18-22 hr later was 1.6. Therefore, the half-time of excretion has a magnitude of the order of 24 hr, and the average rate of clearance of drug from plasma is about 140 ml/min. These values are only preliminary estimates, but the magnitude of these parameters is not in doubt. A large reservoir outside of plasma must exist to account both for the limitation of plasma concentration to a low level after absorption of a large dose, and for maintenance of a relatively high plasma concentration 24 hr later.

The concept of a tissue reservoir as the determinant of plasma level suggests a direction in which to search for a better drug than methadone—one that is both safer if taken by a nontolerant subject and longer in duration of action when used for maintenance treatment. If an opiate could be found with intrinsic activity equal to that of methadone, but with a tissue-binding affinity ten times greater, it would be almost devoid of narcotic effect in a single oral dose, yet when it was given repeatedly this hypothetical drug would establish a tissue reservoir that could be maintained by doses spaced at intervals of 2 weeks.

1. Dole, V. P., Nyswander, M. E. & Kreek, M. J. (1966) "Narcotic blockade," *Arch. Intern. Med.* 118, 304-309.
2. Gordon, N. B. (1973) "The functional status of the methadone maintained person," in *Discrimination and the Addict*, eds., Simmons, L. R. & Gold, M. B. (Sage Publications, Beverly Hills, Calif.), in press.
3. Houde, R. W., Wallenstein, S. L. & Rogers, A. (1971) Reported to the Committee on Problems of Drug Dependence, Thirty third Annual Scientific Meeting, p. 199.
4. Inturrisi, C. E. & Verebely, K. (1972) "A gas-liquid chromatographic method for the quantitative determination of methadone in human plasma and urine," *J. Chromatogr.* 65, 361-369.
5. Sullivan, H. R. & Blake, D. A. (1972) "Quantitative determination of methadone concentrations in human blood, plasma and urine by gas chromatography," *Chem. Pathol. Pharmacol.* 3, 467-478.