

Does therapeutic threshold of methadone concentration in plasma exist?

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Summary

This study was conducted among the group of 69 patients in the methadone maintenance programme in Bratislava. There were 56 males and 13 females, with an average age of 26.9 years (SD 5.4). Daily methadone doses (mean: 134 mg, SD 56.1, from 10 to 270 mg) were compared with methadone concentrations in plasma (mean: 376.6 ng/ml, SD 226.1, from 44 to 1103 ng/ml); of these, 17.4% of the patients had levels below the threshold of 200 ng/ml of plasmatic concentration of methadone, whereas 15.9% had levels above the level of 600 ng/ml. All of them had previously been stabilized clinically, with negative urinalysis for morphine.

Key words: Methadone - Plasma Concentration - Maintenance Therapy - Methadone Dose

Introduction

On the programme level there are two main indicators of the treatment effectiveness of maintenance programmes: (1) retention rate of the patients in it and (2) the proportion of negative/positive urinalysis for morphine [20, 21, 9, 19, 22, 1]. On the individual level the main clinical criteria for an appropriate methadone dose are: (1) no signs of withdrawal state, (2) no craving for use of opiates, (3) no illicit opiate use [12, 18].

Evaluation studies have brought considerable evidence that, with an increase in average methadone dose for those in the programme, there is lower drop-out and a lower proportion of urine tested positive for morphine [5, 2, 22, 23, 18]. The "ASAM Board of Directors' Issued Statement on Public Policy on Methadone Treatment" (April 1990), states, inter alia, that: "Determination of methadone dosage by program policy

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is inappropriate. Dosage should be individually determined by well-trained clinicians based on subjective and objective data and be adequate for the individual patient in all cases". The benefits of individualized methadone dosing are well documented [17].

The implementation criteria for objective clinical signs of withdrawal and the history of illicit opiate use for dose management without upper dose limitations, led some clinicians to prescribe doses up to 780 mg per day or even higher [18]. A high degree of inter-individual variation was found in the doses prescribed for single patients. Some of the research carried out has attempted to explore these differences by studying methadone plasma levels. Several studies have aimed to find a minimum methadone blood level which can reliably support effective methadone maintenance therapy. Some of the studies reported no such threshold [3, 25, 7], while the others put forward a range of values, between 50 and 600 ng/ml [10, 24, 4, 6, 11, 16, 15, 26]. Loimer and colleagues [14] suggest that methadone plasma concentrations of 400 ng/ml are necessary to suppress any further opiate action and provide stable maintenance.

Using these modern criteria for each patient's individual dose assessment, we have confirmed wide variations in the individual daily doses prescribed for patients in our methadone maintenance programme in Bratislava. The main goal of this study was to find out whether we would be able to determine a threshold for methadone plasma level and, if so, with what accuracy.

Material and Method

The methadone maintenance programme in Bratislava, from which the study sample was chosen, has an overall retention rate of 84% 12 months into the programme. There was a proportion of 13% urine randomly tested positive for morphine in last 2.5 years. The programme is a complex one, comprising group therapy, a cognitive-behavioural approach and contingency management. Methadone hydrochloride in liquid form is dispensed under medical staff supervision, after being mixed with juice, at a methadone out-patient clinic. Take-homes are allowed for week-ends. Recently the patients were also allowed to collect methadone twice a week, but only if they had been doing well in the programme for over one year.

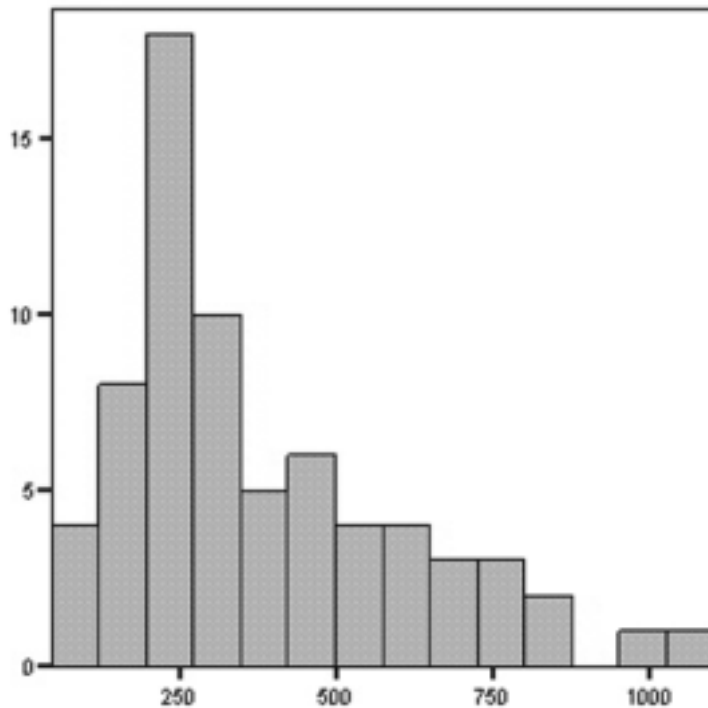
The study group was formed of 69 patients from the methadone maintenance programme, with an average age of 26.9 years (SD + 5.4; median 26). 56 (81%) were males and 13 females (19%). Their average daily methadone dose was 134 mg (SD 56.1), with a range from 10 mg to 270 mg. Collection of blood for methadone plasma level testing was conducted during regular assessment of their condition after completion of one year in treatment. All of them were under close staff supervision when drinking their daily dose at the clinic four days prior to blood taking. The blood was taken for assessment through plasma level from 23 to 25 hrs after their previous dose of methadone, usually on a Thursday. None of the patients had positive urinalysis for morphine on that day. All of them were well stabilized. They had had negative urine for morphine at least for the previous month, but in most cases much longer. Quantitative

analysis of blood samples for methadone was performed in an analytical laboratory, where GC/MS methodology was used. SPSS statistical software was used for data analysis.

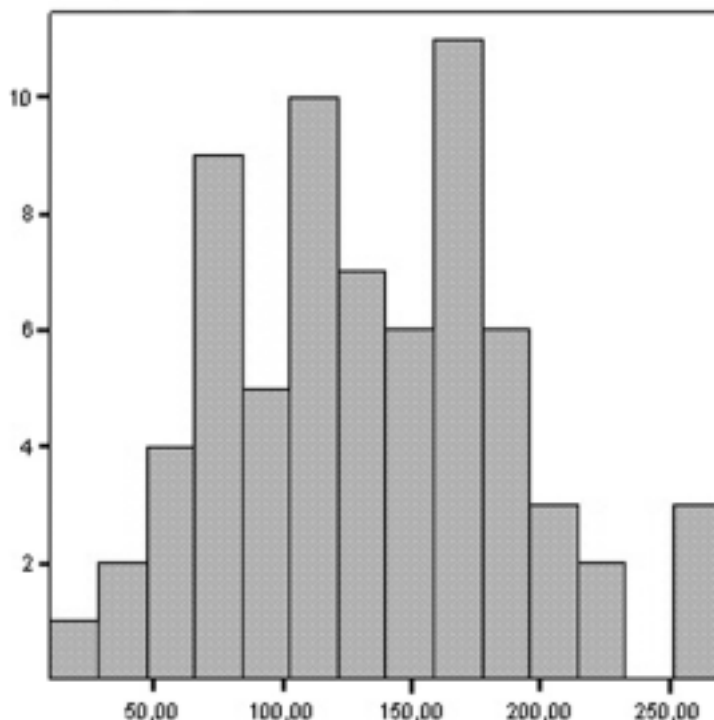
Results

Detected average concentration of methadone in plasma was 376.6 ng/ml (SD 226.1; median 307 ng/ml) in a range from 44 to 1103 ng/ml. Distribution of the frequencies of different plasma concentrations are shown by histograms (Graph 1). Distribution of the frequencies of different doses of methadone appears in Graph 2. A scatter plot diagram demonstrates correlation between dose and methadone level in plasma (Graph 3). When we applied a minimum threshold of 200 ng/ml and a maximum limit of 600 ng/ml of through-plasma methadone concentration on our sample, we detected that 12 (17.4%) patients had plasma levels below the threshold and 11 (15.9%) above the upper limit.

Graph 1.



Graph 2.

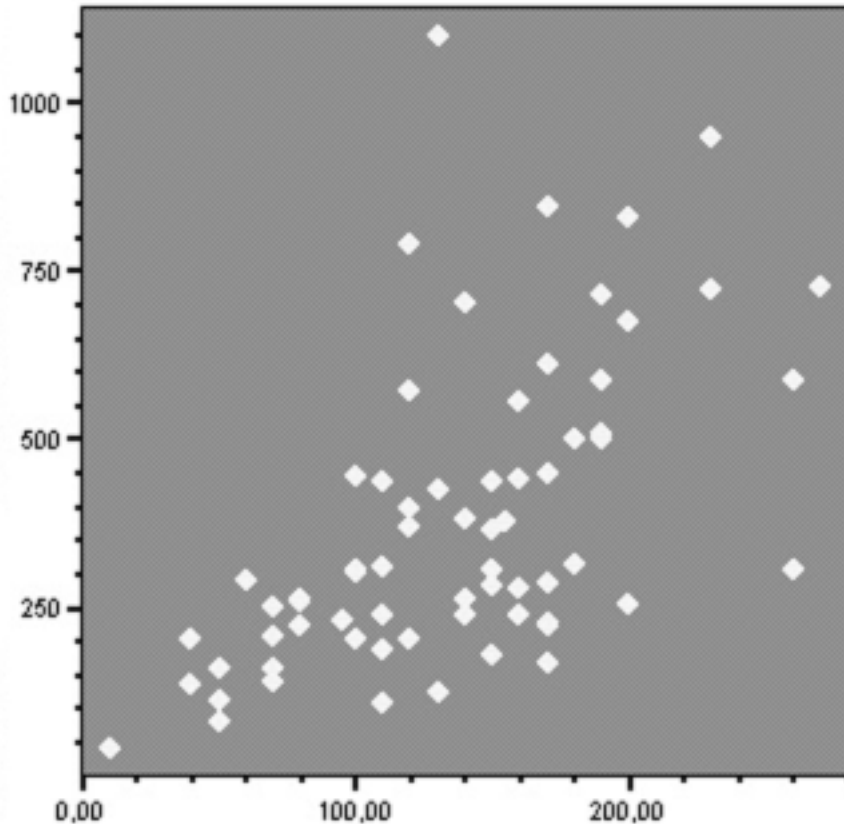


Discussion

Despite the fact that our study has confirmed that there is a clear correlation between the dose of methadone and its plasma level, and also that majority of patients who are stabilized on it had daily through-plasma concentrations between 200 and 400 ng/ml, we still had some interesting findings. Using clinical indicators to determine adequate methadone dose resulted in wide inter-individual dose variations.

Even if both distribution-of-frequency curves were bell-shaped, the dose distribution curve was less steep, with a peak further to the right than the curve for the distribution of frequencies of different plasma concentrations, which was steeper and had a peak further to the left. This finding suggests that a wider range of different daily doses is needed to achieve the optimum plasma concentrations. In other words, the doses required to achieve 250 ng/ml in plasma ranged between 60 and 270 mg of methadone per day (Graph 3). We have discovered that one third of our patients were stabilized at plasma concentrations, which were outside the lower or upper limit recommended by others (Graph 4).

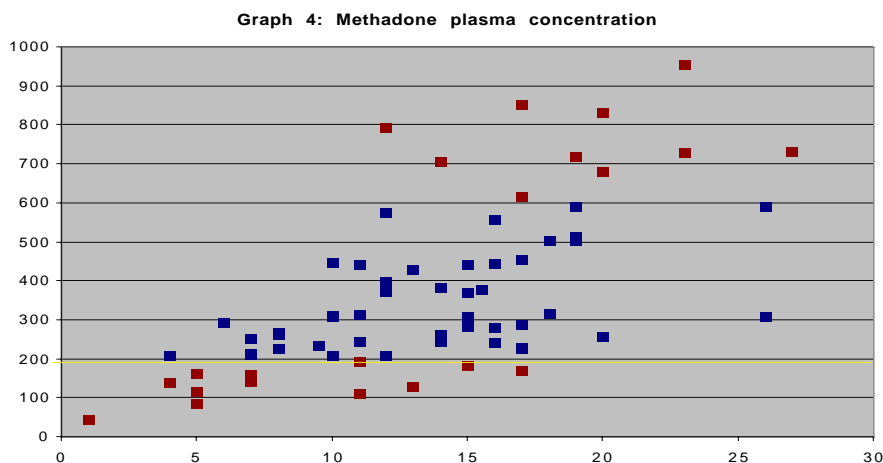
There were five concentrations above 700 ng/ml, and one over 1100 ng/ml among



stabilized patients. This is consistent with Maxwell and Shinderman [18], who reported that some patients with high doses had serum methadone levels of 800-1200 ng/mg when titrated to doses resulting in no signs of opioid overmedication; Leawitt et al. [13] even presented a case of 1800 ng/mg with no clinical signs of opioid overmedication and a severe opiate withdrawal syndrome at a concentration of 810 ng/mg with the same subject.

Similar situations have occurred on the other side of the spectrum at low concentrations. A similar proportion of patients with methadone concentrations below the lower recommended limit was found as for those with concentrations above the upper limit. We do not consider 17% as being insignificant. Again, no signs of withdrawal were observed and patients were stabilized. We found no reason to increase their dose.

One possible interpretation of our findings is that low methadone doses do not automatically result in low methadone concentrations in plasma. The same applies to unusually high daily doses of methadone, which do not necessarily produce high



concentrations in plasma. Bearing this in mind, we should not be restricted in our clinical practice to keeping to firm lower limit thresholds, or to any firm upper daily limit for methadone doses or even to a ceiling for plasma concentrations.

There are, in fact, patients who, to become stabilized, need unusually high or low methadone levels in plasma. The previous thinking could be turned the other way around, by saying that not only appropriate daily dose, but also appropriate plasma concentration show a high degree of inter-individual variation. The explanation for this wide spectrum lies partly in the variations in the degree of methadone metabolism specific to different patients, and partly in different interactions with other medications, or inter-individual differences in pharmacokinetics and pharmacodynamics.

Our findings suggest that neither daily methadone dose alone, nor methadone concentrations in plasma alone, can be interpreted as a univocal indicator of a patient's stabilization. It is, rather, the criteria derived from assessment of a patient's clinical condition that should set the ultimate guidelines for a doctor's decision as to whether daily doses of methadone in a methadone maintenance programme should be increased or decreased.

Plasma methadone concentrations should help provide clinical orientation in cases where the daily dose of methadone is relatively high, its level in plasma is low and clinical signs of withdrawal and/or craving are present. In case of this kind, the low level found in plasma supports an increase in the dose.

The limitations of the study lies in its naturalistic design and the limited size of the sample. In addition, rate of change is sometimes of greater clinical significance than absolute levels, so the peak through ratio could be measured.

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References:

1. Adelson M.O., Hayword R., Bodner G., Bleich A., Gelkopf M., Kreek M.J. (2000): Replication of an Effective Opiate Addiction Pharmacotherapeutic Treatment Model: Minimal Need for Modification in a Different Country. *Journal of Maintenance in the Addictions*. 1(4): 5-13.
2. Ball J.C., Ross A. (1991): *The Effectiveness of Methadone Maintenance Treatment*. Springer Verlag, New York.
3. Bell J., Bowron P., Lewis J., Batey R. (1990): Serum levels of methadone in maintenance clients who persist in illicit drug use. *Br J Addict*. 85: 1599-1602.
4. Bell J., Seres V., Bowron P., Lewis J., Batey R. (1998): The use of methadone levels in patients receiving methadone maintenance. *Clin. Pharmacol Ther*. 43: 623-629.1.
5. Caplehorn J.R.M., Bell J. (1991): Methadone dosage and retention of patients in maintenance treatment. *Med J Aust*. 154: 195-199.1.
6. Dole V.P. (1988): Implications of methadone maintenance for theories of narcotic addiction. *JAMA*. 260(20): 3025-3029.1.
7. Eap C.B., Déglon J.J., Baumann P. (1999): Pharmacokinetics and Pharmacogenetics of Methadone: Clinical Relevance. *Heroin Add & Rel Clin Probl*. 1(1): 19-34.1.
8. Finnegan L. (2000): Women, Pregnancy and Methadone. *Heroin Add & Rel Clin Probl*. 2(1): 1-8.1.
9. Fudala J.P., Vocci F., Montgomery A., Trachtenberg A.I. (1997): LAAM for the treatment of Opioid Dependence: A Multisite, Open-Label Study of LAAM Safety and an Evaluation of the Product Labeling and Treatment Regulations. *Journal of Maintenance in the Addictions*. 1(2): 9-39.1.
10. Holmstrand J., Anggard E., Gunne L.M. (1978): Methadone maintenance: plasma levels 1. and therapeutic outcome. *Clin Pharmacol Ther*. 23(2):175-180.2.
11. Kell M.J. (1995): Utilization of plasma and urine methadone concentration measurements to limit narcotics use in methadone maintenance patients: II. Generation of plasma 3. concentration curves. *J Addict Dis*. 14(1): 85-108.
12. Kreek M.J. (1992): Rationale for maintenance pharmacotherapy of opiate dependence. In: O'Brein, C.P., Jaffe, J.H. eds. *Addictive states*. Research publications: Association for Research in Nervous and Mental Disease. Raven Press, New York: 210.
13. Leavitt S.B., Schinderman M., Maxwell S., Chi B.E., Paris P. (2000): When "Enough" is Not Enough: New Perspectives on Optimal Methadone Maintenance Dose. *Mt Sinai J Med*. 67(5-6): 404- 411.
14. Loimer N., Schmid R., Grunberger J., Jagsch R., Linzmayer L., Presslich O. (1991): Psychophysiological reactions in methadone maintenance patients do not

- correlate with methadone plasma levels. *Psychopharmacol.* 103(4): 538-540.
15. Loimer N., Schmid R., Rauch B. (1992): Individual dosing in methadone substitution therapy. Determination of concentration with high performance liquid chromatography in comparison with immunoassay. *Arzneimittelforschung - Drug Research* 42(11): 1346-1349.
 16. Loimer N., Schmid R. (1992): The use of plasma levels to optimize methadone maintenance treatment. *Drug Alcohol Depend.* 30 (3): 241-246.
 17. Lowinson J.H., Payte J.T., Salsitz E., Joseph H., Marion I.J., Dole V.P. (1997): Methadone Maintenance. In: *Substance Abuse A Comprehensive Textbook*, third edition, Lowinson J.H., Ruy P., Millan R.B., Langrod J.G. eds., Baltimore, William and Wilkins, 405-415.
 18. Maxwell S., Shinderman M. (1999): Optimizing Response to Methadone Maintenance Treatment: Higher Dose Methadone. *Journal of Psychoactive Drugs.* 31(2).
 19. Nwakeze P.C., Magura S., Demsky S. (1997): Patient and Program Effects on Retention in Methadone Treatment: A Preliminary Report. *Journal of Maintenance in the Addictions.* 1(1): 63-74.
 20. Payte J.T., Khuri, E.T. (1993): Treatment Duration and patient Retention. In: Parrino, M.W.: *State Methadone Treatment Guidelines*. SAMHSA, Rockville, 119-132.
 21. Parrino M.W. (1993): *State Methadone Treatment Guidelines*, SAMHSA, Rockville.
 22. Strain E.C., Stitzer M.L., Liebson I.A., Bigelow G.E. (1998): Useful predictors of Outcome in Methadone-Treated Patients: Results from a Controlled Clinical Trial with Three Doses of Methadone. *Journal of Maintenance in the Addictions.* 1(3):15-28.
 23. Strain E.C., Bigelow G.E., Liebson I.A., Stitzer, M.L. (1999): Moderate - v.s. high-dose methadone in the treatment of opioid dependence: a randomized trial. *JAMA* 281(11):1000-1005.
 24. Tennant F.S. Jr., Rawson R.A., Cohen A., Tarver A., Clabough D. (1984): Methadone plasma levels and persistent drug abuse in high dose maintenance patients. *NIDA Research Monograph* 49(8): 262-268.
 25. Torrens M., Castillo C., San L., del Moral E., Gonzales M.L., de la Tore R. (1998): Plasma methadone concentrations as an indicator of opioid withdrawal symptoms and heroin use in a methadone maintenance program. *Drug Alcohol Depend.* 52 (7): 193-200.
 26. Wolff K., Sanderson M., Hay A.W., Ralstrick D. (1991): Methadone concentrations in plasma and their relationship to drug dose. *Clin Chem.* 37 (2): 205-209.

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