

## Methadone dosing based on testosterone-to-creatinine urine ratio

### *Dosificación de metadona basada en el índice urinario testosterona-creatinina*

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**D**ear editor: Methadone Maintenance Treatment programs (MMT) are the procedures of choice for opioid addiction since the 60's (Dole & Nyswander, 1965), but the interindividual variability in methadone disposition, resulting in a high variability of methadone dosage, difficults the dosage regimen design in opioid dependence treatment of patients included in MMT programs (Torrens, Castillo & Pérez-Solá, 1996; López, Baño & Guillen, 2000; Crettol et al., 2006). Thus, we aimed to identify a laboratory surrogate marker which, alongside to clinical response data (e.g. dose titration according to patient symptoms), allows us to improve the accuracy of methadone dosing in these MMT programs.

Based on disruption of pituitary-gonadal axis, caused by opiates, and on the different "opiate potency", defined as the lowest concentration of opiate required to produce 50% of maximum effect, which results in a dose-dependent decrease of testosterone plasma levels (Cicero, 1970; Mendelson, Mendelson & Vernon, 1974), we conducted the present work aimed to study the relationship between urinary testosterone-to-creatinine ratio values (U-T/Cr) and methadone doses, and its application to dosing in MMT, as follows:

Sample of 62 patients with heroin addiction, age 40.0 ( $\pm$  6.4) years old, women 32.5%, methadone (given as racemic oral solution at 0.5 %) dose at steady-state 91.8 ( $\pm$  38.9) mg, addict since the age of 18.2 ( $\pm$  4.3) years old, remaining in a MMT program for 8.3 ( $\pm$  4.4) years and no symptoms of withdrawal syndrome for at least 1 month before sample collection.

We analyzed urine samples for testosterone (Testosterone RIA Kit test Coat-A-Count®, limit of detection, 0.4 mcg/L)

and creatinine (autoanalyzer Hitachi Modular DPP, Roche®), then we calculated the U-T/Cr ratio for all patients and, finally, we applied the gaussian Kernel density estimation (Kernel's test) to data series, for population analysis.

The following overall results were obtained: creatinine 1.5 ( $\pm$  0.7) g/L, testosterone 45.4 ( $\pm$  66.1) mcg/L and U-T/Cr ratio 31.3 ( $\pm$  36.1) mcg/g.

After applying Kernel's test to the U-T/Cr data serie, we observed two main subpopulations (Student's "t" two-tailed test,  $p = .001$ ), the first and most important with an estimated mean value of 23.4 ( $\pm$  13.9) mcg/g ( $n = 58$ ; 93.5% patients) and the second with an estimated mean value of 103.4 ( $\pm$  15.2) mcg/g ( $n = 4$ ; 6.5%).

After applying Kernel's test to methadone-dose data serie, we observed two main subpopulations (Student's "t" two-tailed test,  $p = .001$ ) with an estimated mean value of 56.4 ( $\pm$  18.4) mg ( $n = 29$ ; 47% of patients) and 122.8 ( $\pm$  21.8) mg ( $n = 33$ ; 53%) of methadone, respectively.

According to the main population from U-T/Cr data, we taken the value of U-T/Cr = 23.4 mcg/g as "clinical surrogate endpoint" for methadone dosing. Accordingly with this target, only 6.5% of patients, those with U-T/Cr = 103.4 ( $\pm$  15.2) mcg/g, required a 1.5 to 2-fold dose increases, which was made using the relation of Figure 2.

There are many different studies showing the reduction of testosterone levels induced by opioid drug. So, this ability to decrease plasma and/or urine testosterone can be used to evaluate the pharmacokinetic constants and reach conclusions about their pharmacological potency and its optimal therapeutic dose (Cicero et al., 1975; Mendelson, Inturrisi, Renault & Sinay, 1976).

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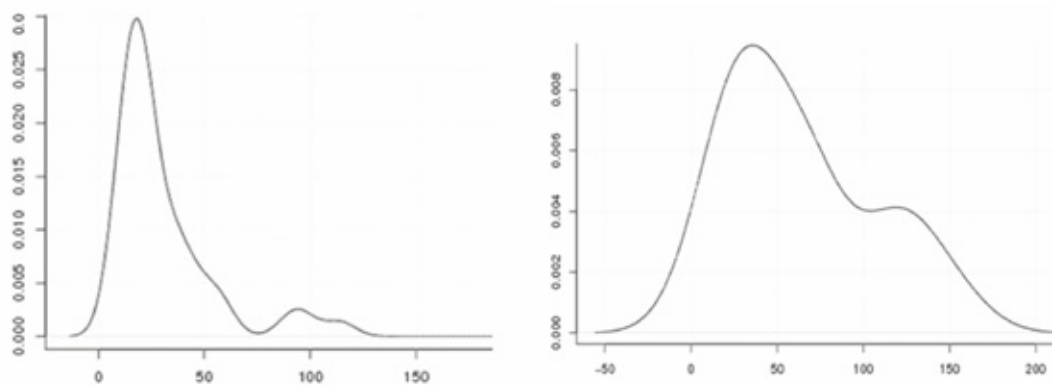


Figure 1. Graphics of “Gaussian Kernel Density Estimation” for methadone-dose (left) and U-T/Cr (right) data series. U-T/Cr = Urinary testosterone-to-creatinine ratio; X-axis = methadone-dose (left) and U-T/Cr (right) values, respectively; Y-axis = density of methadone-dose (left) and density of U-T/Cr (right) values, respectively

$$\frac{[U - T/Cr]_{pac}}{23} = 2 \left[ \frac{D_{pac}}{D_{des}} \right]^{-1}$$

Figure 2. Equation for adjusting patient’s methadone-dose. U-T/Cr = patient’s urinary testosterone-to-creatinine ratio value;  $D_{pac}$  = current methadone dose;  $D_{des}$  = desired dose to obtain U-T/Cr equal 23

Methadone, among other opiate drugs that reduce serum testosterone levels in function of their narcotic potency, causes a decrease in the values of urinary testosterone and in testosterone-to-creatinine urinary index, in a dose-dependent manner (Cicero, 1970; Mendelson, 1974). Because of this, we can dosing methadone by increasing or decreasing the daily dosage in order to reach an U-T/Cr ratio value of 23.4 ( $\pm 13.9$ ) mcg/g, which is approximately 30-40% lower than in healthy population, 37 ( $\pm 21.7$ ) mcg/g, or, in approximate, an U-T/Cr ratio value in the range of 20-25 mcg/g.

In this way, once the steady-state and a pharmacological response, ranging between the 20-80% of maximal effect, corresponding to the linear portion of the sigmoid dose-effect curve, is reached, we can estimate the methadone optimal dose, required to achieve its “clinical surrogate endpoint”, in absence of other confounder factors for U-T/Cr ratio (e.g. disease states, alcohol), by using the relation of Figure 2.

In short, we can conclude that U-T/Cr is a good and cost-effective surrogate marker for optimal methadone dosing and for minimizing both withdrawal and adverse opioid side effects, in MMT programs. We have calculated its “clinical surrogate endpoint” as equal to 20-25 mcg/g which when used alongside to clinical response and/or patient’s dose demand, allow us to improve the accuracy of methadone dosing.

However, it is necessary more studies in a largest sample to validate its applying, as such, and to determine what and how, genetic (e.g. polymorphisms affecting metabolism and/or pharmacological activity) and/or environmental (e.g. alcohol consum, drug interactions), factors affect each of different populations. Also, finally, it would be interesting to compare the intra-patient pre- and post-therapy ratios.

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