

Haematic concentrations versus oral doses of methadone. Comparative assessment of two reference systems during substitute therapy in opiate addiction

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Summary

Therapeutic failures in MMP patients may be due to an inadequate oppioidergic replacement effect of the drug on specific receptors for endogenous opiates. Even with oral doses considered adequate in the current literature, haematic levels may be low, due to genetic or induced over-metabolization of the drug; in addition, even when haematic levels are high, the results may be poor, due to acquired receptor tolerance. 61 heroin addicts on MMP doses agreed on between therapist and patient have been evaluated with Europasi at the beginning and at the end of observational and therapeutic periods ranging between 12 and 57 months. Addicts who showed a positive development revealed haematic levels (non-oral ones) higher than non-responder patients, and some of the former reached haematic levels higher than those reported in current literature. Estimates of the haematic concentration of methadone may be useful, even if availed of "una tantum" during the treatment period.

Key words: Substitutive Therapy - Methadone Haematic Concentration - Clinical Consequences

Two objectives are pursued by pharmacological replacement treatment for opiate addiction: first, in the short term, interruption, or at least the reduction of drug abuse, or of high-risk or antisocial behaviour; second, in the long term, retention on treatment to avoid or lessen relapses and achieve reintegration in social, family and working environments.

Data-processing from systematic researches [6] suggests that a daily dose of between 70 and 120 mg of hydrochloride methadone, with a broader range extending above or below, is sufficient for individual patients, at particular moments, as the

appropriate therapeutic regime.

Therapeutic results vary very widely between patients, and, over time, the same patient may present different results with the same dose.

Pharmacokinetic studies [13;8;9;1;14] in normal volunteers, in cancer or post-surgical patients or in opiate addicts indicate highly variable characteristics for the drug: 1) its elimination half-life may vary between 13 and 58 hours; 2) the volume of apparent distribution may vary between 2.1 and 5.6 L/kg and its bioavailability between 65 and 90%.

The administration of increasing doses of methadone C 14 [1] has made evident a proportional increase in the elimination of the product itself and of its primary inactive catabolite (2 ethylidene-dimethyl-phenyl-pyrrolidine), but the relationship between the two substances changes considerably, shifting progressively in favour of the latter, so indicating increased metabolism due to enzymatic induction or the progressive mobilization of deposit substances.

Variations in the free fraction (the active fraction subject to metabolism) are produced by variations in the haematocrit, in the alpha-acid glycoprotein or in albumin, which are the three principal vectors [12].

Variations in urinary pH must modify excretion of the drug, considering that the clearance function is a logarithmically inverse function of urinary reaction [3].

The clinical importance of these variations has not yet been assessed, as the prevalence of the metabolized part compared with the part excreted through the kidneys is unknown. What has become clear is the pertinence of the involvement of cytochrome p 450 in the variability of intrahepatic metabolism (with a reduction of as much as 22 hours with regard to the normal 52-hour half-life of the drug) [8].

Numerous addictive substances used by patients (alcohol, benzodiazepines, barbiturates, tobacco, and other forms of smoking) and those used in therapy (rifampicin, amitriptyline, ritonavir, cimetidine and theophylline), as well as those used in foodstuffs (furanocumarine and bergamottine) [8] drastically modify the metabolism and the concentration of the drug in the plasma.

Above all, the drug currently used in therapy is offered in racemic form (d and l methadone in equal quantities, 50:50), while it is almost exclusively the levogyral form that is biologically active, and differences in the clearance media, in the affinity and the average half-life of the two forms have been stressed [8;11].

As the effect of a drug is considered directly proportional to its concentration in specific receptors and, therefore, indirectly proportional to its haematic concentration, numerous tests have been carried out to determine a specific therapeutic range for its concentration in the blood.

The data obtained, however, have not been at all univocal. Even if the haematic concentration of the drug grows in direct proportion to the dose administered, with an average coefficient of 3.5 in ng/over mg/die of the dose, there are large variations in the ratio between different patients and, over time, in the same patient [8].

Horns [11], Loimer [17] and Torrens [20] have not found any correlation between

the haematic concentration of the drug, and either subjective symptomatology, or the objectivity of abstinence or hyper-treatment, or the therapeutic results as perceived in the persistence of the abuse of opiates over a period of a few months.

Dole [7] established a dose of between 100 and 1000 ng/ml as the effective therapeutic range for the treatment.

Bell [4] suggested a haematic level of 100 ng/ml or above as being capable of solving withdrawal symptomatology without increasing the oral dose of methadone.

Holmstradt [10], in a group of MMP patients with a follow-up period of up to 43 months and a preestablished daily dose of about 60 mg/die, reported that the best results, in terms of social, family and work integration and of the reduction of abuse, were found in patients who had the highest haematic levels.

Loimer [17] noticed subjective and objective symptoms of abstinence even with a high methadone level in plasma, but he focused on an inverse statistical correlation between the haematic concentration of methadone and objective withdrawal symptomatology, which was more evident than in the case of oral doses.

Wolf [21] found a positive correlation between dose per kilo of weight and drug concentration in the plasma; data outside this range improve our understanding of some clinical cases (diversion of dose or enzymatic interference).

By using a methadonemic curve, on the other hand, instead of the oral dose curve, Kell [16] obtained a decrease from 10 to 3% of positivity in urinary control for drug abuse substances. Divergencies as sharp as these in the results reported in the literature prompt us to radically reconsider the question of the usefulness of relying on methadone dose values.

At present therapy is carried out by modifying doses in line with clinical attendance and the frequency of relapses.

The delay in therapeutic responses in term of dose adjustment makes therapy difficult to apply; it also suffers from the impact of ideological and emotional interference between therapist and patient, so that the seriousness of many cases is underestimated.

We have tried to clarify the terms of the problem further by examining a group of MMP patients on a constant dose, where a more reliable correlation might be found between the course of the illness (tendency towards changes in the frequency of relapses, behaviour likely to increase the risk of infections, syringe swapping, and promiscuous sexual relationship, as well as reintegration in the social, family and working context) and methadonemic concentration or, alternatively, the oral doses taken.

Materials and methods

From a population consisting of drug addicts and those utilizing a public service, which show an overall rise from 320 to 812 during the period under review, 196 addicts taken opiates or other substances were chosen. Their addiction had lasted for at least two years, on the basis of the standards set down by the DSM III-R, and had been on stable

MMP for at least 6 months, maintaining that dose for the whole period of observation. They were asked to allow a blood sample for the calculation of the proper methadonemic value to be taken in order to assess the progress of the illness. No changes in the therapy were carried out after this value had been calculated.

The oral doses were agreed upon by the therapist and the patient, avoiding withdrawal conditions as far as possible. Only 76 of the patients contacted participated in the trial, and only 61 respected the conditions that had been laid down.

The gravity of addiction was estimated at enrolment by applying the Europasi [19] interview, and summing the therapist's and patient's scores for medical, work, alcohol, drug, family and psychic problems. Each index had a range between 0.1 and 0.9, while the range for scores was between 0.7 and 6.3.

The interview was repeated by the same therapist at the end of the treatment period, in the case of patients who wished to interrupt or change therapy, and at the end of the observation period for those who completed the therapy.

Differences between the first and the second results were evaluated and divided into three outcome classes, according to whether the score was greater than, equal to, or less than before:

Class A: Worse situation

Class B: Unchanged situation

Class C: Improved situation

The patients were visited weekly, and urine samples were taken at random more or less three-monthly, when samples had been collected, they were analysed for opiates, ecognina, barbiturates and amphetamines.

The percentage of positivity for addictive substances and the frequency of urine sampling helped to determine the therapist's score along the drug-problem gravity axis.

After the minimum fixed observation period, patients who wished, or who had to change their oral dose permanently, were assessed on the basis of their outcome and then registered as new patients.

Detection of methadone value in serum

Once the observation period had elapsed, a sample of venous blood was taken between the administration of one dose and the next. Separated serum was frozen until it could be examined. Quantitative analysis was performed in RIA using coat a count methadone solidphase I 125 radioimmunoassay from DPC (Diagnostic Products Corporation), 700 West 96th Street, Los Angeles, California.

For each of the three groups the following were evaluated: average age, duration of addiction, time of retention on treatment, oral dose and methadonemic level, and the ratio between rate in ng/ml and oral daily dose in mg/die.

Results

Group A, with a worse situation, comprised 8 patients (13% of all patients who completed the study); they showed a very small increase in ASI.

Group B, with an unchanged situation, comprised 21 patients (33% of the patients

completing the study); their ASI value averaged 3.1.

Group C, with an improved situation, comprised 33 patients (54% of the patients completing the study); their ASI value fell from 2.8 to 2.3.

Significant differences were found:

On the duration of addiction: group A reported a period of 14.9 years, against 10.4 in group B (+43%) and 9.7 in group C (+52%).

On the oral daily dose of methadone: 55 mg in group A, against 76 in group B (-28%) and 77 mg in group C (-29%).

Mean methadonemic level: 313 ng/ml in group A, against 260 in group B (+20%) and 661 in group C (-53%); in group C methadonemia varied from 17 to 4000 ng/ml.

Ratio between methadonemia in ng/ml and oral dose (mg/ml):

Group A: 5.70

Group B: 3.24 = 43.70% of A

Group C: 8.64 = 151% of A

Discussion

The rationale which inspires methadone treatment is the constant saturation of the receptors for endogenous opiates, so as to give physiological tone and opioidergic reactivity at three rising levels:

- 1) Resolution of the withdrawal crisis;
- 2) Inhibition of the gratification response to the abuse of opiates;
- 3) Attenuation of the craving for opiates.

As therapy progresses, conspicuous individual differences in the capacity to modify drug metabolization are elicited, as widely demonstrated by studies on pharmacokinetics, followed by conspicuous diversity in the methadonemic concentrations deriving from the same oral dose.

In any case, some patients treated in "open" studies, with doses agreed upon between therapist and patient, developed very high haematic concentrations, up to ten times the average values; those levels would certainly have been lethal in patients who had not become tolerant. This induces us to think that the highest tolerance level and the greatest diversity develop in line with receptor sensitivity.

In clinical practice there is no opportunity to correlate anomalous therapeutic responses with either of the two mechanisms, so it may be worth determining the methadonemic level in the blood, even if only once.

Low haematic values of methadone caused by genetic disparity or pharmacokinetically induced by other drugs may require the removal of the interfering factors, the fractionating of doses, or the choice of levo-acetyl-methadolo with a longer half-life.

Disappointing therapeutic responses even in the presence of high haematic levels, due to high receptor tolerance, may call for a further increase in the dose, with an expectation of attenuation in the stressors that induced the relapse.

Most observers agree that it is not possible to determine a therapeutic haematic concentration within constant or precise limits. A reduction of high levels, significant

Table 1. Sinossi

	n. of patients	% of total patients	Duration of addiction	Average oral dose	Average ematic rate	ratio ematic/oral	Initial ASI	Final ASI	Retenti-on time (months)	Averall age
Group A "pejorative evolution"	8	13	14.9	55	313	5.22	4.0	4.2	46	40
Group B "invariated situation"	21	33	10.4	76	260	3.67	3.1	3.1	47	37.7
Group C "improved situation"	32	54	9.7	77	661 min 17 max 4000	8.61	2.8	2.3	48	35.4

enough to be noted clinically, may still keep values well above the usual ones; low haematic levels may maintain a good behavioural equilibrium in the mild phases of the illness.

Our data match those of Holmstradt: long-term improvement in the illness comes about in the presence of high methadonemic level rather than high oral doses. Methadonemia only marks an intermediate point in the cascade which proceeds from the daily oral dose to the methadonemic level, on to concentration on receptor unity, to the affinity of receptors, and to behavioural response, but it does make a useful contribution to management of the therapy.

Above all, it may prove to be a useful instrument in the therapeutic relationship: high oral doses are adversative [5;2;15] or are almost always refused by patients because of their resistance to therapy or fear of long-term dependence on it. The relationship between therapist and patient is a useful instrument, because high levels can produce a negative reaction from the patient, due to therapeutic resistance or fear of long-term dependence on therapy.

To shift the terms of the problem from subjective cenaesthetic sensations to objective laboratory data may help to convince patients that they should accept adequate oral doses.

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