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Correlation between duration of treatment and cortisol plasma level in methadone maintained patients

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Summary

Background. The various endocrine abnormalities reported in heroin addicts and patients in methadone maintenance treatment include: increased thyroxine, triiodothyronine and prolactin levels, and abnormalities in sexual hormone, ACTH and cortisol secretion. The pathophysiological mechanism that has been postulated does explain these findings, including the direct action of heroin or methadone along the hypothalamic-pituitary-adrenal axis. **Aim.** The aim of this study is to determine the correlation between duration of methadone treatment and cortisol plasma levels in patients treated with methadone maintenance therapy. **Methods.** The study was carried out at the Centre for Prevention and Treatment of Drug Abuse and Addiction, a part of the Skopje Psychiatric Hospital. The hormonal analysis was carried out at the Department of Clinical Biochemistry, Skopje University Hospital. It is an analytical, cross-sectional study that included 50 male patients in methadone maintenance treatment, divided into two groups. The first group consisted of 34 male patients who had been maintained on methadone treatment for over 2 years. The second group consisted of 16 male patients who had been maintained on methadone treatment for 2 years or less. To discover demographic characteristics we used medical records, and to determine cortisol plasma level we relied on the Chemiluminescence Immunoassay method. The results were analysed statistically by using a t-test for independent samples, χ^2 test, and Pearson coefficient of linear correlation. **Results.** The results show that patients treated with methadone for 2 years or less have significantly higher plasma cortisol levels than patients treated with methadone for over 2 years. **Conclusions.** Longer duration of methadone maintenance treatment tends to normalize the cortisol plasma level.

Key Words: Methadone maintenance therapy; duration of treatment; cortisol plasma level.

1. Introduction

Although endocrine abnormalities are recognized in opiate users, very little is known about the range of hormones affected, their pathophysiology, or their clinical relevance. Various endocrine abnormalities have been reported in opiate users such as: increased level of thyroxine (T4), triiodothyronine (T3), thyroxine binding globulin (TBG), insulin and glucose metabolism abnormalities similar to those seen in type 2 diabetes, increased prolactin level, reduction in testosterone level, abnormalities in follicular stimulating hormone level, abnormalities in ACTH and cortisol secretion [6,11]. The pathophysiological mechanism that has been postulated does

explain these findings, including the direct action of heroin or methadone along the hypothalamic-pituitary-adrenal axis. Some studies have concluded that many of the hypothalamic and anterior pituitary hormones are adversely affected in heroin misuse and methadone maintenance treatment [4]. One of the endocrine abnormalities in opiate users and methadone maintained patients is a higher cortisol plasma level. It has been suggested that opiates directly depress the hypothalamic pituitary axis, resulting in lower ACTH secretion and cortisol secretion [1]. Some authors went on to describe a state of compensated primary hypoadrenalism in these patients whereby reduced secretion of cortisol through a lack of negative feedback mechanism resulted in greater plasma ACTH

and cortisol secretion [16]. Attempts to explore the cause of adrenocortical hormonal abnormalities have focused on the roles of a direct depressogenic action of opiates on the hypothalamic-pituitary-adrenal axis, adrenal cortical dysfunction, and abnormalities in the circadian rhythms of ACTH and cortisol secretion [1,16].

The aim of this study is to determine the correlation between duration of treatment and cortisol plasma level in patients maintained with methadone. If duration of treatment is inversely correlated with the value of cortisol plasma level, we would expect to find a higher prevalence of patients with a normal level of cortisol in the group of patients that have been maintained with methadone for over 2 years than in the group maintained with methadone for 2 years or less.

2. Methods

2.1. Design of the study

The present study was carried out at the Centre for Prevention and Treatment of Drug Abuse and Addiction, a part of the Skopje Psychiatric Hospital. The hormonal analysis was carried out at the Department of Clinical Biochemistry, Skopje University Hospital; it was cross-sectional, and included 50 methadone maintained male patients.

2.2. Sample

Fifteen methadone maintained male patients signed a written informed consent document. Confidentiality of information was assured. All these patients met the criteria for opioid dependence. Criteria for exclusion were: chronic liver and renal diseases, AIDS or HIV infection, or other chronic physical disorders.

No female participants were included in this study, although the inclusion of both sexes is important in principle, especially when we are talking

about the hormonal axis, the main reason being that the number of female patients is still very small at the Centre, with the exception of programmes that are specifically addressed to female patients. In addition, on this occasion no female patients were willing to sign an informed consent document.

The patients were divided into two groups, and in the classification process, the independent variable selected for this study was the duration of methadone maintenance treatment. A treatment duration of 2 years was chosen because there are references that suggest that the normalization of cortisol plasma levels can be achieved after chronic methadone maintenance of 2 years or more [11, 12, 13, 15, 17].

The first group consisted of 34 male patients who had been maintained on a stable dose of methadone for more than 2 years. The second group consisted of 16 male patients maintained on a stable dose of methadone for 2 years or less.

2.3. Instruments

As follow-up, all these patients received routine medical examination, which included blood chemistry, urine analysis and serology for hepatitis and HIV infections.

As our source for demographic characteristics we referred to medical records.

To determine the cortisol plasma level we relied on the Chemiluminescence Immunoassay (CLIA) method, which is highly sensitive. Blood samples of all patients for hormone assays were obtained in the morning between 09.00 and 11.00 a.m., when the normal range of cortisol plasma level is 50-690 ng/ml.

2.4. Data analysis

The results were analysed statistically using: descriptive methods, the t-test for independent samples, the χ^2 test, and the Pearson coefficient of linear correlation. The statistical tests were considered significant at the level of $p < 0.05$ and $p < 0.01$.

Table 1. Mean age, methadone dose and duration of methadone maintenance treatment of the examined groups

	Group 1	Group 2	T-Test	p-value
	M \pm sd	M \pm sd		
Age	34.53 \pm 3.9	25.56 \pm 3,5	7.72	<.00001
Methadone dose	81.47 \pm 35.6	93.75 \pm 22.1	1.26	0.211
Duration of treatment (in months)	101.38 \pm 23.7	14,25 \pm 5.0	14.48	<.00001

Table 2. Distribution of patients by nationality, educational level, marital and employment status

	Group 1 N=34	Group 2 N=16		
	N (%)	N (%)	χ^2	p-value
Nationality				
Macedonians	26 (76.4)	12 (75.0)		
Croats	2 (5.8)	0 (0.0)		
Albanians	4 (11.7)	4 (25.0)		
Turks	1 (2.9)	0 (0.0)		
Serbs	1 (2.9)	0 (0.0)	3.07	0.547
Marital status				
Married	14 (41.1)	5 (31.2)		
Unmarried	20 (58.8)	8 (50.0)		
Divorced	0 (0.0)	3 (18.7)	6.80	0.033
Educational level				
Up to primary school	7 (20.5)	5 (31.2)		
Secondary school	23 (67.6)	10 (62.5)		
University	4 (11.7)	1 (6.2)	0.88	0.640
Employment status				
Employed	22 (64.7)	6 (37.5)		
Unemployed	12 (35.2)	10 (62.5)	3.26	0.070

3. Results

The first group consisted of 34 male patients, who had a mean age of 34.53 ± 3.95 years and whose mean methadone dose was 81.47 ± 35.62 , with a mean duration of treatment of 101.38 ± 23.7 months. The second group consisted of 16 male patients, who had a mean age of 25.56 ± 3.56 years and whose mean methadone dose was 93.75 ± 22.1 , with a mean duration of treatment of 14.25 ± 5.08 months. The mean age and duration of methadone maintenance treatment, specifying standard deviation as well as the p-value for differences between the examined groups, are shown in table 1.

There is no statistically significant difference between the two groups examined by us in the mean value of their methadone doses. There is a statistically significant difference between those groups in their age and duration of methadone maintenance treatment. The patients with a longer duration of methadone maintenance treatment turned out to be older than those who had had a shorter duration of methadone maintenance treatment. There was no statistically significant difference between their mean methadone doses, so the size of the methadone dose was not a pertinent factor in this study.

The distribution of the patients included in the study by nationality, educational level, marital and employed status, and the p-value that was used to

determine differences between the two examined groups are shown in table 2.

There were no statistically significant differences in nationality, educational level or employment status, nor was there any statistically significant difference in marital status between the two groups examined. There were more unmarried and fewer married patients in the group with a treatment duration of over 2 years, and there were more married and divorced patients and fewer unmarried patients in the group with a treatment duration of 2 years or less.

The value of cortisol plasma levels in the two groups examined is displayed in table 3. The results show that patients with a duration of methadone maintenance treatment of 2 years or less have a higher mean value for cortisol plasma level than those with a duration of methadone maintenance treatment of over 2 years. The difference between the mean value of the cortisol plasma level in the two groups is significant at $p < 0.01$.

A higher percentage of patients with a duration of methadone maintenance treatment of 2 years or less have higher cortisol plasma levels than those with a duration of methadone maintenance treatment of over 2 years. Table 4 shows that 75% of patients with a duration of methadone maintenance treatment of 2 years or less have higher cortisol plasma levels, while the other 25% have normal cortisol plasma levels. In the group of patients with a duration of methadone

maintenance treatment of over 2 years, 17.64% have high cortisol plasma levels and 82.26% have normal levels. This difference is significant at $p < 0.01$.

Figure 1 shows the correlation between duration of treatment and cortisol plasma level in examined groups ($r = -0.5389$ $p = 0.000056$). There is an inverse correlation between duration of methadone maintenance treatment with cortisol plasma level, which means there is a tendency for a long duration of methadone maintenance treatment to correspond to a low cortisol plasma level, and vice versa. The association between the duration of methadone maintenance treatment and cortisol plasma level is statistically significant at $p < 0.01$.

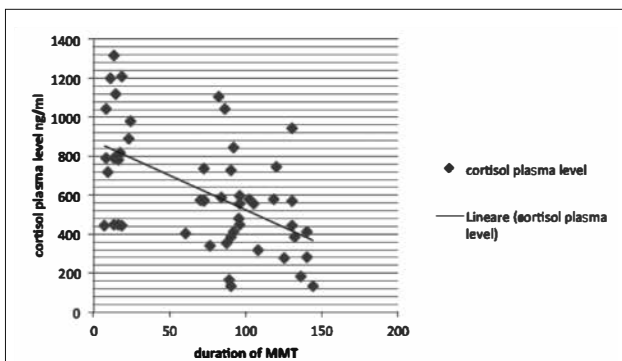


Figure 1. Correlation between duration of treatment and cortisol plasma level in examined groups ($r = -0.5389$ $p = 0.000056$)

Figure 2 shows that although technically there is an inverse correlation between duration of treatment and cortisol plasma level in the group that had a duration of treatment of over 2 years, the relationship between these two variables in this group is only weak (NB: the nearer the value is to zero, the weaker the relationship) and is not statistically significant at $p < 0.05$.

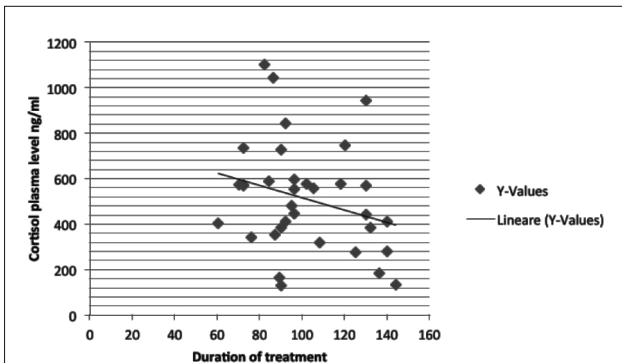


Figure 2. Correlation between duration of treatment and cortisol plasma level in group with duration of treatment that is more than 2 years ($r = -0.26$ $p = 0.13754$)

Figure 3 shows that although technically there is a direct correlation between duration of treatment and cortisol plasma level in the group that had a duration of treatment of 2 years or less, the relationship between these two variables in this group is only weak, and is not statistically significant at $p < 0.05$.

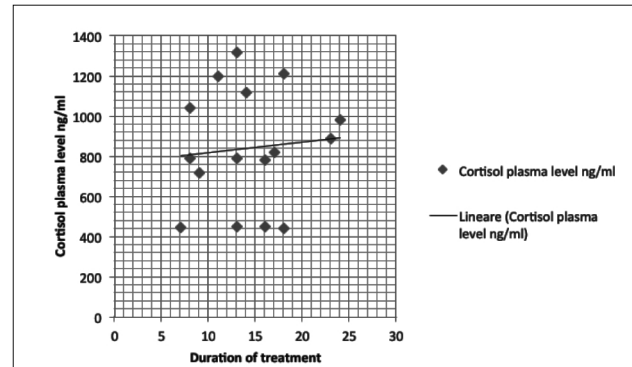


Figure 3. Correlation between duration of treatment and cortisol plasma level in group with duration of treatment that is 2 years or less ($r = 0.0949$ $p = 0.72664$)

4. Discussion

The aim of this study was to determine the correlation between duration of treatment and cortisol plasma levels in patients maintained with methadone. The hypothesis of an influence of methadone dose on cortisol plasma levels had to be excluded because the groups did not differ statistically compared with the dose taken. As shown in the results section, there is an inverse correlation between duration of methadone maintenance treatment and cortisol plasma level, and there is a higher percentage (82.26%) of patients with normal cortisol plasma levels in the group of patients whose duration of treatment was over 2 years than in the group whose duration of treatment was 2 years or less. The results also show that, after 2 years or longer, the correlation between duration of methadone maintenance treatment and cortisol plasma levels becomes so weak that it falls below the level of significance, and as the value for cortisol comes closer to zero, the relationship between duration of treatment and cortisol plasma levels becomes weaker. These results support the belief that a longer duration of methadone maintenance treatment stabilizes hormonal imbalances, including cortisol plasma levels [7]. On the other hand, high levels of cortisol can correlate with depression [9] so methadone does have an effect on the stabilization of cortisol as well as on depression. That is why opiates were used to treat major depres-

Table 3. Values of cortisol plasma levels in the two groups examined

Cortisol levels	N	Mean**	Min.	Max.	St. dev	Median
Group 1	34	513.26	132	1104	240.58	517.5
Group 2	16	840.69	443	1319	292.08	805.0

The t-value is -4.18961. The p-value is .000119. The result is significant at $p < .01$

sion until the mid-1950s, while both methadone and buprenorphine show an antidepressant effect [2]. In any case, long-term treatment with an optimal methadone dose does tend to stabilize hormonal imbalance [8]. It is known that, once a stable level of methadone is reached, that leads to adaptation and normalization of the endocrine and neuroendocrine functions [8, 13]. A stable dose of methadone maintenance therapy always helps to normalize several physiological systems: the hypothalamic-pituitary-adrenal, hypothalamic-pituitary-gonadal and immune systems. There are studies that support our findings by showing that hormonal levels return to normal after 2 or more years of chronic methadone treatment [11, 12, 13, 15, 17].

There are studies that report that there are no abnormalities in ACTH or cortisol secretion in heroin addicts and methadone maintained subjects when the duration of use is short [1,12]; that may explain why 25% of the patients making up the group with a duration of treatment of 2 years or less had normal cortisol plasma levels in both the two groups examined.

Some studies have demonstrated a fall in cortisol plasma concentrations to low levels in heroin addicts [5], but in our study there were no subjects with low cortisol plasma levels in either of the two groups examined.

Although a long duration of treatment with optimal agonist opioid dose tends to stabilize hormonal imbalances, 17.64% of the patients from the group with a long duration of methadone maintenance showed a high cortisol plasma level. This shows that, even after two years or more of methadone maintenance, high cortisol plasma level may persist. In this connection, some studies report that in certain patients in methadone maintenance increased cortisol plasma levels may persist for a long time – a phenomenon that may be due to patients in agonist opioid treat-

ment developing tolerance of hormonal effects [3], or else the persistence of a comorbid disorder, such as depression [10]. In those cases the correct response is a higher amount of medication [14], in some cases over-standard medication.

5. Conclusions

The study shows evidence of inverse correlation between the duration of methadone maintenance and cortisol plasma level, which means there is a tendency for a longer duration of methadone maintenance to correspond to lower cortisol plasma level and vice versa. The study also demonstrated that the prevalence of patients with normal cortisol plasma levels is higher in the group of patients who had methadone maintenance treatment for over two years when compared with the group of patients who had methadone maintenance treatment for two years or less. Thus, we can conclude that a duration of methadone maintenance treatment of over 2 years can lead to the normalization of cortisol plasma levels. We may also conclude that in some patients, despite long-term treatment, there are high cortisol values that can be explained by the persistence of comorbid disorders such as depression that need to be diagnosed and treated.

References

1. Afrasiabi M.A., Flomm M., and Friedlander H. (1989): Endocrine studies in heroin addicts. *Psychoneuroendocrinol.* 4: 145-153.
2. Bodkin J.A., Zornberg G.L., Lukas S.E., Cole J.O. (1995): Buprenorphine treatment of refractory depression. *J Clin Psychopharm.* 15(1): 49-57.
3. Carter T.M. (1998): The effects of spiritual practices on recovery from substance abuse. *J. Psychiat Ment. Health.* 5(5): 409-413.

Table 4. Distribution of patients by cortisol plasma level in the two groups examined

Cortisol plasma level	Group 1 N=34	Group 2 N=16
High level	6(17.6%)	12(75.0%)
Normal level	28(82.2%)	4(25.0%)

The chi-square statistic is 15.5331. The p-value is .000081. This result is significant at $p < .01$

4. Cushman Jr.P., Border B.(1990): Hypothalamic-pituitary-adrenal axis in methadone treated heroin addicts. *J. Clin. Endocrin. Metab.* 30: 24-29
5. Dackis C.A., Gurpegui M., Potash L.C. (2002): Methadone induced hypoadrenalism. *Lancet.* 2: 1167.
6. Fichna J., Janecka A., Piestrzeniewicz M., Costentin J., Do Rego J.C. (2007): Antidepressant-like effect of endomorphin-1 and endomorphin-2 in mice. *Neuropsychopharmacol.* 32(4): 813-821.
7. George S., Mural V., Pullickal R. (2005): Review of neuroendocrine correlates of Chronic opiate Misuse. [La successione di maiuscole e minuscole sembra anomala: o tre o zero.] Dysfunctions and pathophysiological mechanisms. *Addict Disord Their Treatment.* 4(3): 99-109.
8. Hardman J.G., Limbrid L.E. (1999): Section III: Drug action on the central nervous system. *The pharmacologic basis of the therapeutics.* 5: 120.
9. Ignjatova L., Spasovska Trajanovska A., Bonevski D. (2015): Correlation between methadone dosage, cortisol plasma level and depression in methadone maintained patients. *Heroin Addict Relat Clin Probl.* 17(6): 41-48.
10. Katz N., Mazer N. (2009): The impact of opioids on the endocrine system. *Clin J Pain.* 25(2): 170-175.
11. Kreek M.J., Wardlaw S.L., Hartman N. (1993): Circadian rhythms and levels of beta-endorphin, ACTH and cortisol during chronic methadone maintenance in humans. *Life sci.* 33: 409-411.
12. Kreek M.J., Raganath J., Plevy S. (1984): ACTH, Cortisol and beta endorphin response to metyrapone testing during chronic methadone maintenance treatment in humans. *Neuropeptides.* 5: 277-278.
13. Malmed S., Janeson J.L. (2005): Disorders of the Anterior Pituitary and Hypothalamus. McGraw-Hill Medical Publishing Division, New York, pp 133-136.
14. Maremmani I., Pacini M., Canoniero S., Deltito J., Maremmani A. G. I., Tagliamonte A. (2010): Dose Determination in Dual Diagnosed Heroin Addicts during Methadone Treatment. *Heroin Addict Relat Clin Probl.* 12(1): 17-24.
15. Martin J., Piute J.T., Webern J.V. (2001): Methadone maintenance treatment: a primer for physicians. *J. Psychoactive Drugs.* 23(2): 155-159.
16. Pullan P.T., Watson F.E., Seow S.S.W. (2003): Methadone induced hypoadrenalism. *Lancet.* 1: 714.
17. Vescovi P., Delarosaresibi G., Rasteli G., Valentine G.,

Gera G. (2005): Effects of dopamine receptor stimulate on opiate-induced modification on pituitary-gonad function. *Horm Res.* 21(93): 155-159.

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Contributors

All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest

All authors declared no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. This study does not require ethics committee approval because it was carried out according to a non-interventional protocol. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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