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Oculomotor disturbances in HIV-positive individuals treated with methadone

Zaburzenia ruchu gałek ocznych u osób HIV (+) leczonych metadonem

Julia Feit[1,2, A, B, C, D, E, F, G], **Marek Kunc**[4, E, F], **Piotr Walecki**[5, A, B, D],
Edward Jacek Gorzelańczyk[1,2,3, A, B, D, E, G]

[1] Non-public Health Care Center Sue Ryder Home in Bydgoszcz, Poland
[2] Department of Theoretical Basis of Bio-Medical Sciences and Medical Informatics, CM UMK, Bydgoszcz, Poland
[3] Institute of Philosophy, Kazimierz Wielki University, Bydgoszcz, Poland
[4] Airedale NHS Trust, Steeton, UK
[5] Jagiellonian University, Medical College, Faculty of Medicine, Krakow, Poland

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

Summary

Introduction: Methadone substitution is claimed to be the most effective way of pharmacological management of human immunodeficiency virus (HIV) positive patients addicted to opioids. Possible and clinically the most relevant drug interactions are those between methadone and antiretroviral agents [13,18,25,32]. HIV causes cognitive impairment by infiltrating the central nervous system (CNS) in the initial phase of infection. The consequence of this is damage to the hippocampus, caudate nucleus, and basal ganglia [2,26].

Methods: Eighty-six patients from the substitution program group were examined. The trial was conducted twice: before and about 1.5 hours after the administration of a therapeutic dose of methadone. The antisaccades task (AT) and latency task (LT) were performed using a saccadometer diagnostic system.

Results: The statistical analysis showed that the mean duration of latency measured by AT in HIV(-) and HIV(+) subjects after the administration of a therapeutic dose of methadone was significantly increased (p=0.03 HIV(-); p=0.04 HIV(+)). There was a statistically significant increase in the mean latency after the administration of methadone in HIV(+) subjects when compared to the control group measured by LT (p=0.03).

Conclusion: The statistical analysis confirms the change in the saccadic refixation parameters in patients addicted to opioids. Methadone influences saccadic dynamic parameters less in HIV(+) than in HIV(-) drug users. Oculomotor disturbances are probably related to the neurotropic effects of HIV leading to damage of the striatum, which plays an important role in psychomotor functions.

Key words: methadone • opioid • HIV • eye movements • oculomotor disturbances

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Author's address: mgr Julia Feit, NZOZ Dom Sue Ryder, ul. Roentgena 3, 85-796 Bydgoszcz, e-mail: j.feit@domsueryder.org.pl

Introduction

Administration of psychoactive drugs increases dopaminergic receptor stimulation, improves mood and stimulates motor activity. Chronic use of psychoactive substances can lead to structural and functional changes in the central nervous system (CNS) [26]. Patients addicted to opioids can experience symptoms similar to those in people with structural changes in the cerebral cortex [5,26]. According to the concepts of regulation of mental activity by cortico-subcortical loops, integrity of all the structures constituting the loops is a prerequisite for their physiological functioning [2]. There are five known control loops linking the subcortical nuclei with the cerebral cortex: motor, oculomotor, dorsolateral prefrontal, lateral orbitofrontal, and limbic. Any dysfunction of these loops, as observed in several psychiatric disorders, as well as in psychoactive substance addiction, results in emotional, motor and cognitive impairment [7,8,16]. The alteration of cortico-subcortical loop function occurs in patients infected with HIV because of the neurotropic properties it exhibits. Features of subcortical stupor are found [19,29]. The oculomotor loop participates in the control of saccadic eye movements. In order to investigate oculomotor disorders in people addicted to psychoactive substances, examination of eye movement parameters was carried out to assess the impact of psychoactive substances on the CNS [7]. The study of eye movement allows one to understand the function of the brain. Abnormalities of ocular motility frequently reflect the localization of a pathological process. The neural structures that control saccades are widespread in the brain structure; thus neurological disorders exhibit a variety of effects on the saccadic parameters [23,24]. The movements are highly and specifically responsive to all kinds of disturbances when motor commands to the contractile muscular fibers are generated and delivered. The impairment of the saccadic system is therefore the most sensitive indicator of even slight disturbances within the neuromuscular system [23].

Material and methods

Eighty-six patients from the methadone substitution program were examined. The study included 32 women and 54 men (mean age 39±7.7 years) including 46 HIV(-) subjects and 40 HIV(+) subjects managed in a methadone substitution program over a period of 53 months on average. All HIV(+) subjects were infected with hepatitis C virus (HCV). The mean duration of antiretroviral treatment (lamivudine, tenofovir disoproxil fumarate, ritonavir, lopinavir/ritonavir) was 51 months (±52.18). The trial was conducted twice: before and about 1.5 hours after the administration of a therapeutic dose of methadone (mean daily dose of methadone: 71.9±(33.4) mg). The study included 36 subjects from the control group. All the subjects performed the antisaccades task (AT) and latency task (LT) twice. The antisaccades task was used to assess the relative complexity and vulnerability of the underlying decision mechanisms. A subject told to look in the direction opposite to a stimulus has to suppress the automatic response of looking towards it. This leads to delays and errors which are believed to be generated by completion of the decision processes [22]. The latency task is aimed at monitoring visual attention processes reflecting conscious attention. It allows detection of anomalies in attention management [23]. In the research effects of deep brain stimulation (DBS), carried out in order to change the saccadic parameters, were analyzed. A saccadometer is a diagnostic system enabling identification of impairment of the CNS functioning at the earliest (presymptomatic) stages of a disorder. The system allows one to perform strictly quantitative evaluation of saccadic dynamics measuring eye movement with infrared technology (infra-red oculography). The voltage signal generated by the eye movement sensor is converted into digital 12-bit samples at a frequency of 1 kHz. Saccades are detected after exceeding the detection threshold of 5 deg/s [7,8,16]. The system measures eye movements in a horizontal plane with high temporal and spatial resolution. The visual stimulus is displayed, using miniature laser projectors mounted on the sensor forehead plate, in order to stimulate the subject's visual system. Visual stimulation allows one to carry out a number of tests for fast eye movements (saccades) research. In all the tests the system provides an opportunity to set numerous trials or test duration according to the examination needs. The test results (saccadic latency, duration, peak velocity and simplified position profile) are stored in the device's memory and can be reviewed once the test is finished [8].

STATISTICA version 10 was used for data analysis. The statistical significance of differences of parameter values

between groups (before and after HIV(-), HIV(+), the control group) was verified using Student's t test for unpaired samples. Statistical significance of the differences of parameter values of both groups (before and after HIV(-), HIV(+)) was verified using Student's t test for dependent samples.

Results

For statistical analysis HIV (+) and HIV (-) subject groups were distinguished and compared to the individuals from the control group. In the saccadic refixations test - latency task it was found that the mean latency before the administration of methadone was not statistically significantly different between HIV(-) (mean 198.3 ms ±53.8; p=0.58) and HIV(+) (mean 212.8 ms ±74.4; p=0.015) subjects when compared to the individuals from the control group (mean 189.2 ms ±49.2). The statistical analysis showed that the mean latency after the administration of methadone in HIV(+) subjects (mean 214.4 ms ±54.4) when compared to the control group (mean 189.2 ms ±49.2) was significantly increased (p=0.03; t=2.11).

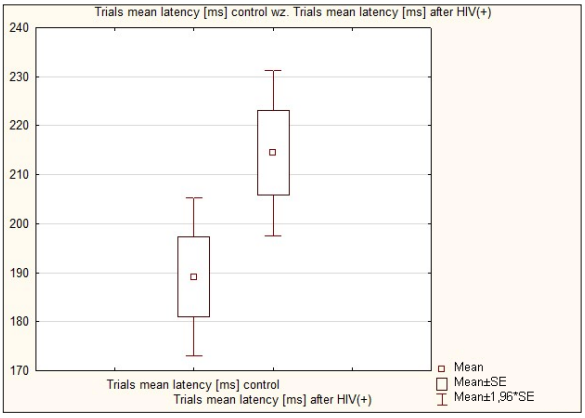

Fig. 1. Comparison of the mean latency in the latency task after the administration of methadone in HIV(+) subjects and individuals from the control group

The difference in mean peak velocity of latency before the administration of a therapeutic dose of methadone in HIV(-) (mean 421.3 deg/s ±69.8) compared to the control group (mean 447.5 deg/s ±54) was not statistically significant (p=0.06) but it decreased significantly after methadone administration (mean 406.5 deg/s ±84.1; p=0.01).

It was observed that the mean amplitude of saccades was increased before and after the administration of methadone in all research groups (before: HIV(-) mean 10.2 deg ±0.9; HIV(+) mean 11 deg ±5.1; after: HIV(-) mean 10.6 deg ±1.4; HIV(+) mean 10.8 deg ±3.9) when compared to the control group (mean 9.6 deg ±0.3). Before (p=0.0002) and after (p=0.0001) the administration of methadone the mean amplitude in the latency task differed significantly in HIV(-) patients treated with the substitution drug when compared to individuals from the control group.

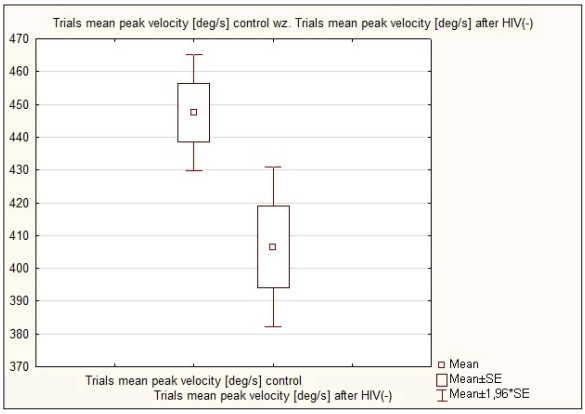

Fig. 2. Comparison of the mean peak velocity in the latency task after the administration of methadone in HIV(-) subjects and individuals from the control group

Statistical analysis of the same eye movements parameters (mean peak velocity, mean latency, mean duration, mean amplitude) was performed using the antisaccades task. From among the members of the study groups, who were addicted to opioids, HIV(-) and HIV(+) participants of the substitution program were identified. The statistical analysis shows that the mean latency measured by the AT after the administration of a therapeutic dose of methadone decreased statistically significantly in HIV (-) subjects (mean before: 328.51 ms ±159.3; after: 298.74 ms ±130.03; p=0.04), in contrast to the HIV(+) subjects (mean before: 345.8 ms ±128.2; after: 321.65 ms ±112.8), where there was no statistically significant difference (p=0.35).

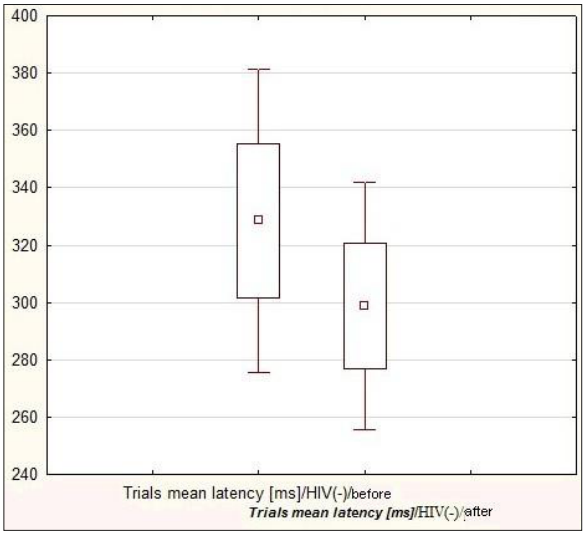

Fig. 3. Comparison of the mean latency in the AT before and after the administration of methadone in HIV(-) subjects

An increase of the mean duration values in HIV(-) (mean before: 55.8 ms ±10.8; after: 60 ms ±10.8; p=0.03) and HIV(+) (mean before: 60.1 ms ±11.1; after: 65.3 ms ±12.1; p=0.04) subjects after the administration of a therapeutic dose of methadone was observed. The statistical analysis revealed

that it is significant. No statistically significant differences were found in other parameters of the test (mean amplitude [deg] - before: 11.07±3.1 HIV(-), 11.70±3.9 HIV(+); after: 11.08±2.8 HIV(-), 11.82±3.4 HIV (+); mean peak velocity [deg/s] - before: 398.09±90.9 HIV(-), 395.60±109.8 HIV(+); after: 382.06±82.1 HIV(-), 342.40±97.4 HIV (+)).

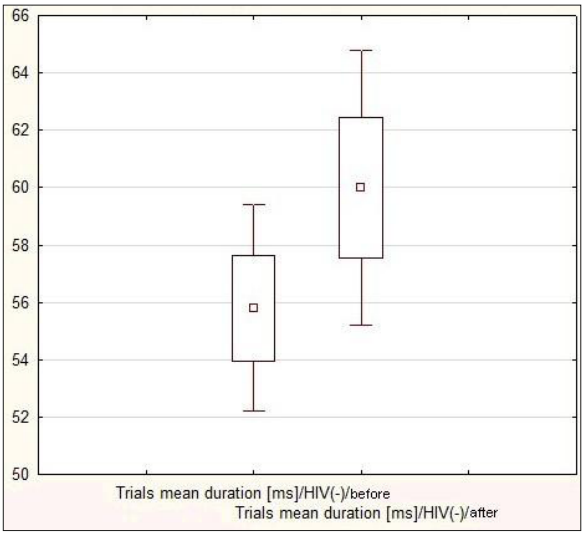

Fig. 4. Comparison of the mean duration in the AT before and after the administration of methadone in HIV(-) subjects

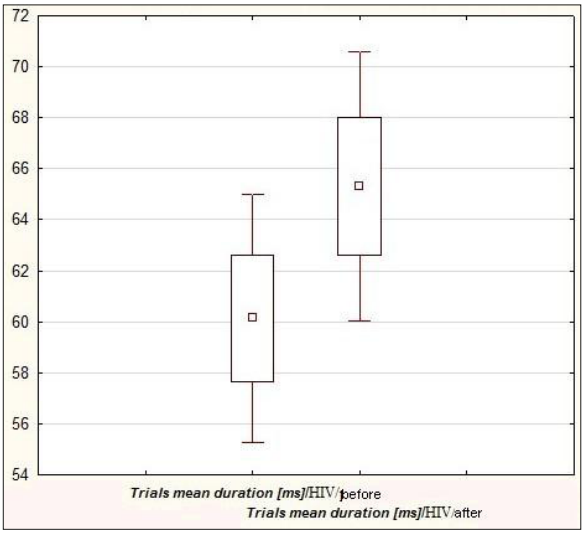

Fig. 5. Comparison of the mean duration in the AT before and after the administration of methadone in HIV(+) subjects

Discussion

The analysis of the latency task results have confirmed that the mean latency in HIV (+) subjects is significantly longer after the administration of methadone. The mean peak velocity is significantly shorter after methadone in HIV(-) subjects. The results may indicate that the administration of a therapeutic dose of methadone changes the saccadic refixation parameters in subjects from all the study groups when compared to the control group. Methadone influences saccadic dynamic parameters to a lesser extent in HIV(+) than in HIV(-) drug users. Eye movement disturbances are probably related to the neurotropic effects of HIV leading to damage of the striatum, which plays an important role in psychomotor functions. This has been confirmed by other authors [1,6,9,10,12,15,20,28,33]. Several studies have shown that the most pronounced effects of HIV infection are cortical atrophy and widespread neuronal loss [1,33]. It was demonstrated that in patients with AIDS there is a 3–8% prevalence of neuro-ophthalmological disorders [20]. In addition, it has been shown that asymptomatic HIV infected subjects, even in the early stages of infection, exhibit oculomotor disturbances [9,10,12,20,28]. Optic nerves of HIV infected patients can undergo chronic degeneration resulting in axonal loss. The mechanism by which HIV induces optic neuropathy emphasizes the key role of tumor necrosis factor alpha (TNF-a) [6,15]. Eye movement disturbances can also be related to the interactions of antiretroviral drugs and methadone leading to changes in methadone concentrations and influencing the regulation of psychomotor activity at the same time [30,31]. The results of other research describe drug interactions which occurred during dependency and HIV infection treatment. It has been proven that there are numerous interactions between methadone and antiretroviral agents. It has been speculated that antiretroviral medications themselves can contribute to the decline of cognitive functions [30]. The results of other research have proven that certain combination antiretroviral therapy cART medications could be neurotoxic [31]. Methadone concentration is reduced by concomitant administration of some of retroviral agents. The use of lopinavir/ritonavir may lead to opioid withdrawal symptoms. [3,4,11]. The antiretroviral agents can alter methadone pharmacodynamics, leading to changes in the clinical picture [14]. Pharmacokinetic interactions of methadone commonly cause a decrease of the concentrations and reduction of effects of concomitantly used agents, which will influence psychomotor activity [3].

A statistical analysis of the same latency task parameters was performed using the antisaccades task. From among opioid addicted individuals being treated with methadone HIV(+) and HIV(-) subjects were identified. It was found that the mean latency is statistically significantly shorter after methadone administration in HIV (-) subjects but the difference in corresponding values was not statistically significant in HIV(+) patients. In subjects of both groups the mean duration is significantly increased after methadone administration. These results suggest that methadone impairs the saccadic refixation parameters in HIV(+) subjects when compared to HIV(-) ones. HIV infection impairs motor functions, which is a consequence of the negative effects of the virus on the central nervous system. Studies support the notion that HIV can infect the microglial tissue and impair CNS functions [21,31]. The results of other research show a progressive decline of neuropsychological function despite effective

antiretroviral therapy and good control of viral load. This is associated with cerebral atrophy (including basal ganglia) and significant neuronal cell loss [21,27]. The virus can cause a variety of movement disorders due to basal ganglia involvement [21].

Eye movements are closely related to cognitive and emotional functions. Information on saccadic dynamics during certain tasks can indicate disorders of mental functions, which can explain the neurobiology of sensory-motor systems. This may be useful in neuropsychiatric diagnosis. Identifying the characteristic pattern of psychomotor disturbances (abnormal eye movement) can be a valuable diagnostic tool that supports clinical and neuropsychological evaluation of the effectiveness of pharmacotherapy and psychotherapy. Currently, not many facts are known about the degree to which subcortical nuclei can be damaged as a result of chronic substance abuse (particularly opioids) and how much it influences functioning of the limbic loop and the reward system. There is a lack in the world literature of reliable, objective research results of cognitive function and psychomotor performance in patients addicted to opioids treated with methadone.

Conclusion

The results indicate a change in the saccade dynamics after methadone administration. This suggests the influence of methadone on the efficiency of the external eye muscles.

The observed changes in values for eye movements may be due to the inhibitory effect of methadone on the CNS.

The changes in the parameters of eye movements can be a consequence of damage to the structures involved in processing visual information (frontal cortex, striatum).

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