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Original Research Article

Adverse drug reactions of antiretroviral therapy in patients receiving methadone substitution treatment

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ABSTRACT

Aim of the study: The aim of the study was to analyze the incidence of adverse effects of antiretroviral therapy in patients receiving concomitant therapy with methadone substitution.
Background: With the advances in research on anti-retroviral drugs, we now have regiments with different mechanisms of action that can be combined to give an effective therapy that lengthens the life of HIV-infected people into old age. It should be emphasized, however, that anti-retroviral drugs, as other pharmacologically active substances, are characterized by adverse effects (AEs), significantly changing the quality of life for patients, as well as predisposing to the development of comorbidities. Their appearance can be triggered by administration of other therapy at the same time such as methadone in heroin addicts.
Materials and methods: The survey was conducted among 60 people, 21 of respondents were participants of methadone program.
Results: Based on the survey we found that among patients receiving methadone, compared to patients treated only with antiretroviral drugs, more often the following symptoms occurred: loss of appetite, constipation, cough, rhinitis, insomnia, libido and decreased hemoglobin level.
Conclusion: A study found that co-administration of methadone may increase the incidence of adverse effects, which in turn has a significant impact on patient quality of life. This issue has not been fully explained and requires further studies in a larger group of patients.

1. Introduction

Due to advances in pharmacotherapy HIV infection has become a chronic condition – if treatment is started at the right time, life expectancy of people with HIV *is slightly shorter* than the general public. However, antiretroviral drugs (ARV), like all other pharmacologically active substances, have adverse effects that may predispose to the occurrence of various diseases, as well as they may deteriorate quality of life. The most important adverse effects are: lipodystrophy syndrome, immune reconstitution syndromes as well as: gastrointestinal dysfunction, central nervous system disorders, in addition hepatotoxicity, nephrotoxicity, osteopenia, osteoporosis, cardiovascular system diseases. Simultaneously administered drugs may affect the incidence and severity of adverse effects of antiretroviral therapy (cART) [6,8,15].

Methadone is an opioid analgesic, which is currently used in substitutional therapy of heroin addicts. The dose is determined individually, and does not cause life-threatening adverse reactions. The most significant impact of methadone on patient quality of life include: dyspepsia, sedation, hypotension and dizziness. However, methadone with other drugs, including cART may cause *undesirable* pharmacokinetic interactions at the stage of absorption (decreasing gastrointestinal motility) and metabolism (cytochrome P450 enzyme induction, inhibition of glucuronidation) which affect the efficacy and safety of treatment [11].

2. Materials and methods

The study involved 60 people (20 women) who are patients of Centre of Prevention and Treatment of Infectious Diseases and Addiction Therapy Wroclaw's Health Center. 21 patients were also participants of methadone program (MP) run by Poradni

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Table 1
Categorization of patients due to the severity of the adverse effects.

Group	AEQR	Severity of adverse events
1	0–0.031	None or insignificant
2	0.032–0.063	Low
3	0.064–0.095	Medium
4	0.096–0.127	Severe
5	0.128–∞	Very severe

Table 2
Number of patients due to the duration of treatment.

Duration of treatment (years)	*N*
<4	27
4–7	17
8–11	13
>11	3

Terapii Uzależnień od Substancji Psychoaktywnych Wrocławskiego Centrum Zdrowia. There were 9 women and 12 men among MP participants and 11 women and 28 men among not addicted patients. Mean age was 38.53 ± 8.24 (range 26–63 years).

Drug injection was the most common cause of HIV infection declared in survey. 28 patients (46.67%) reported this mode of infection. All subjects completed the previously validated questionnaire. Laboratory tests results were obtained from patient medical history records, all patients consent to access their data.

Frequency of the following symptoms was analyzed: diarrhea, nausea and vomiting, heartburn, abdominal pain, bloating, loss of appetite, impaired taste, constipation, body weight changes, the lipodystrophy syndrome and lipoatrophy, cough, nasal congestion, joints and muscles pain, skin changes, hair loss, sensory disorders, pain, dizziness, impaired vision or hearing, abstract and disturbing dreams, weakness, impaired memory and concentration, nervousness, libido disorders, depression, allergic reaction to the drug. The following laboratory results were taken under consideration: red blood cells count, platelets count, hemoglobin level, hematocrit, mean corpuscular volume, alanine aminotransferase and aspartate aminotransferase activity, bilirubin, glucose, creatinine, cholesterol and triglycerides, urine proteine concentration, as well as glomerular filtration rate.

To assess the incidence of adverse effects, their severity and the consequences for the health and lives of patients scoring scale was constructed. Symptoms were divided into 4 groups. The first group included symptoms that occurred sporadically, with low intensity (1 point). The second group: symptoms occurring often impeding the everyday functioning (4 points). The third: symptoms causing necessity of cART change or inclusion of other drugs (7 points). The fourth: adverse events that were life threatening or required patient hospitalization (10 points).

After evaluating all reported or observed adverse reactions scored points were totaled and divided by the possible to obtain number of points. The result was named "adverse event quality ratio" (AEQR). These proceedings resulted from the inability to evaluate all parameters. As shown in Table 1 categorization of patients was carried out.

This tool allows a statistical calculation not only of specific adverse events, but also their impact on patient quality of life. Also it made it possible to answer the question of whether and how methadone therapy affects the incidence of adverse effects of cART.

The final stage of the study was to perform statistical calculations using the χ^2 test of high reliability. Statistically significant were considered differences values equal to or less than 0.05.

3. Results

The average length of treatment of HIV patients was 5.65 ± 3.97 years. Most patients (45%) were receiving ARV for less than four years. Characteristic of patients due to the treatment time are shown in Table 2.

The main objective of this study was to determine the incidence of adverse effects of cART and to assess the impact of the substitution therapy with methadone on cART. In addition, the effect of cART treatment duration and route of HIV infection on the occurrence of ADRs was studied.

Based on the statistical analysis significant differences in the incidence of the following adverse effects was found:

1. Loss of appetite. It has been found that taking cART with methadone increases the incidence of loss of appetite ($p = 0.02$), this symptom was observed in 52.38% of patients taking methadone and 23.08% of those treated only with antiretrovirals.
2. Constipation. Methadone therapy used together with cART increased risk of constipation ($p < 0.001$). They occurred in 38.1% of patients treated with methadone and in only 2.56% of the remaining patients.
3. There was a statistically significant increase in the incidence of cough ($p < 0.01$), and rhinitis ($p = 0.04$) in patients receiving additional methadone (23.81%) compared to the control group (2.56%).
4. In patients treated with antiretroviral therapy and using methadone muscle pain and weakness of their strength were more common compared to not addicted subjects (47.62% vs. 10.26%, $p = 0.001$).
5. Impaired vision. Patients treated with methadone had statistically significantly frequently impaired vision and hearing ($p = 0.03$). About 33.33% of patients treated with methadone and ARV complained for mentioned above symptoms compared to only 10.26% of the treated with ARV.
6. Insomnia. Problems with sleeping declared 55.14% of patients in methadone program with antiretroviral treatment. Among patients outside the program, 15.38% complained of insomnia ($p < 0.001$).
7. Problems with potency, and erectile dysfunction – symptoms such were reported by 38.1% of patients infected with HIV in MP, while the proportion in the second group was 7.68% ($p = 0.004$).
8. The percentage of subjects with abnormal hemoglobin was statistically significantly higher ($p < 0.01$) in the group of patients treated with methadone (47.62%) compared to the control group (12.82%).

There were no statistically significantly differences in patients taking methadone and antiretroviral drugs compared to those treated only with HIV infection following symptoms: diarrhea, nausea and vomiting, heartburn, abdominal pain, bloating, impaired taste, body weight changes, the lipodystrophy syndrome and lipoatrophy, skin changes, hair loss, sensory disorders, pain, dizziness, abstract and disturbing dreams, weakness, impaired memory and concentration, nervousness, depression, allergic reaction to the drug, headache, weakness, red blood cells count, platelets count, hematocrit, mean corpuscular volume, alanine aminotransferase and aspartate aminotransferase activity, bilirubin, glucose, creatinine, cholesterol and triglycerides, urine proteine concentration, as well as glomerular filtration rate.

Moreover, the concomitant use of methadone with cART significantly affects the incidence and severity of adverse effects of ARV drugs ($p < 0.001$). The percentage distribution of patients in the group defining the severity of adverse reactions in patients being in methadone program and control group is shown in Table 3.