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Effect of Different Psychoactive Substances on Serum Biochemical Parameters

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Background: Psychoactive substances affect mainly central nervous system and brain function causing changes in behavior.
Objectives: The purpose of this study was to determine the effects of different psychoactive substances on serum biochemical parameters.
Patients and Methods: The study included 324 drug dependents, and 69 controls. The patient group was determined according to DSM-IV (The diagnostic and statistical manual of mental disorders, fourth edition) criteria. All patients and control subjects were tested for routine biochemical parameters and urine toxicology parameters for psychoactive substance use. Cases and controls with accompanying diseases like diabetes, cancer, metabolic disorders etc. are excluded from the study. Moreover, an association between urine toxicology results and changes in biochemical parameters was evaluated for statistical significance.
Results: There was a statistically significant difference in the Gamma-Glutamyl Transferase (GGT), uric acid, creatinine, urea, albumin, Aspartate Aminotransferase (AST) medians between the dependent and control groups ($P < 0.05$). We found a statistically significant difference in sodium and albumin levels between the opium-dependent and control groups ($P < 0.05$). In the benzodiazepin dependent group, we found a significant difference in GGT, urea, glucose, sodium, T protein, and AST levels ($P < 0.05$). Moreover, a statistically significant difference was observed in triglyceride and GGT levels between the ethyl glucuronide and control groups ($P < 0.05$).
Conclusions: In psychoactive substance dependents, serum routine biochemistry parameters can be used to predict the need for intensive monitoring and treatment programs.

Keywords: Substance Addiction; Psychoactive Drugs; Biochemistry

1. Background

Psychoactive substances affect mainly central nervous system and brain function causing changes in behavior. Many psychoactive substances have therapeutic function as analgesics or anesthetics and high addiction potential (1). Addiction is a common problem in many countries. In Western countries, synthetic addictives are commonly used on the other hand an opioid consumption is traditionally common in Iran. The effects of different addictives on body systems have been reported; however, there is not enough information about different blood parameters (2).

The effect of some psychoactive substances on commonly observed diseases like coronary artery disease, diabetes mellitus and some psychiatric disorders has been investigated, but effects of long-term use of these substances on endocrine system have not been studied enough (3). Studies have demonstrated controversial results about effects of psychoactive substances on hypothalamic-pituitary axis and thyroid function (4). Psychoactive substances have many different effects on physiologic and neuroendocrine functions in humans (5). It has been demonstrated that endogenous opioids like β-endorphin, enkephalins and opiate receptors influence neuroendocrine regulation (6). Previous studies showed that some psychoactive substances modulate immune function and affect resistance to bacterial, viral and protozoan infections (7, 8).

Monitorization of the psychoactive substance use can be done objectively by urine analysis. Since substance concentrations in urine are higher than blood, urine is the preferred material for determination of substance use. Testing schedules and determination of cut-offs are important for confirmation of the psychoactive substance use (9).

Previous studies demonstrated that more than 50% of abusers consumed mixtures of psychoactive drugs. Co-consumption of cannabinoids, amphetamine and cocaine are observed commonly. Since polydrug abuse is

common worldwide, determination of the effects of only one drug is difficult (10).

Recent studies demonstrated controversial results about the effects of opium on serum electrolytes, lipid markers and glucose metabolism. Defining the real side effects of these psychoactive substances may increase awareness about disadvantages of consumption (11). Studies about the effects of psychoactive substances on different biochemical and hematological parameters were limited in number (2, 12).

2. Objectives

This study was conducted to determine the effects of different psychoactive substances on serum biochemical parameters.

3. Patients and Methods

This study was conducted on 324 patients and 69 controls admitted to Erenkoy Mental Health and Neurology Training and Research Hospital between January 2013 and January 2014. Patients were determined according to the "diagnostic and statistical manual of mental disorders, fourth edition" (DSM IV) criteria and referred to AMATEM clinic for treatment. Table 1 shows the demographic data of patients involved in study.

Levels of toxicology parameters were determined using a HITACHI model 902 automatic analyzer (Hitachi High-Technologies Corporation, Roche Diagnostics) with an enzyme immunoassay (Microgenics CEDIA Fremont, California, USA, for urine toxicology).

After hospitalization, each patient's first urine and blood sample before treatment were taken into account for comparison. Control subjects were selected from applicants for routine control with negative urine toxicology results. Cases and controls with accompanying diseases like diabetes, cancer, metabolic disorders etc. are excluded from the study. Urine samples were tested simultaneously for heroin, cannabinoids, cocain, benzodiazepins, opiates, buprenorfine, amphetamines, extacy and ethyl glucuronide. Routine biochemistry parameters were measured using the architect Ci 4100 (Abbott diagnostics products) automatic biochemistry analyzer. This study was approved by the ethics committee of Erenkoy Mental Health and Neurology Training and Research Hospital.

3.1. Statistical Analysis

SPSS IBM 20.0 software (Chicago, Illinois, USA) was used for statistical analysis. Man-Whitney U tests used for parameters were not normally distributed. P-values < 0.05 were considered as statistically significant.

4. Results

A total of 324 patients (316 males and 8 females) and 69 controls (64 males and 5 females) were involved in this study. The median ages of psychoactive substance users and controls were 26.5 (23 - 34) and 27 (20.5 - 34.5) years, respectively (Table 1).

The concentration of biochemical parameters in the serum of the substance-dependent group was compared to the control group (Table 2). We found a statistically significant difference in Gamma-Glutamyl Transferase (GGT), uric acid, creatinin, urea, albumin, Aspartate Aminotransferase (AST) medians between the patient and control groups ($P < 0.05$).

Forty-six out of 424 addicts tested positive for only opium (cut-off, 300 ng/mL). Several biochemical parameters in the opium-dependent group were compared to the control group (Table 3). There was a statistically significant difference in the serum concentrations of sodium and albumin between the opium-dependent and the control groups ($P < 0.05$).

Moreover, sixty-nine patients were tested positive for only cannabinoids (cut-off, 50 ng/mL). Biochemical parameters did not show any significant difference in the cannabinoid-dependent group compared to the control group ($P > 0.05$). Thirteen out of all addicts were tested positive for only benzodiazepine (cut-off > 300 ng/mL). There was a statistically significant difference in GGT, urea, glucose, sodium, total protein, and AST levels between the benzodiazepine-dependent group and control group ($P < 0.05$).

Also, 12 patients were tested positive for only ethyl glucuronide (cut-off > 500 ng/mL). A statistically significant difference was found in triglyceride and GGT levels between the ethyl glucuronide and control groups ($P < 0.05$). Other patients were tested positive for more than one drug.

Table 1. Demographic Data of Subjects Involved in the Study [a]

Subjects	Dependent Group [b]	Control Group [b]
Gender		
Male	316 (97.5)	64 (92.8)
Female	8 (2.5)	5 (7.2)
Age, y		
< 20	34 (10.5)	14 (20.3)
≥ 20 - < 30	176 (54.3)	27 (39.1)
≥ 30 - < 40	65 (20.1)	21 (30.4)
≥ 40	49 (15.1)	7 (10.1)
Age, y [c]	26.5 (23 - 34)	27 (20.5 - 34.5)

[a] Dependent group involves subjects determined as at least one or more than one type of psychoactive substance users. In the control group urine toxicology results were negative.
[b] Values are presented as No (%).
[c] Median (Quartiles).

Table 2. Comparison of Biochemistry Test Results in Dependent and Control Groups [a,b]

Tests	Dependent Group Median (Quartiles)	Control Group Median (Quartiles)	P Value [c]
CRP, mg/dL	0.34 (0.20 - 0.82)	0.27 (0.09 - 0.64)	0.354
Chloride, mmol/L	101 (99 - 103)	101 (100 - 104)	0.376
Potassium, mmol/L	4.25 (3.92 - 4.50)	4.20 (3.90 - 4.50)	0.952
HDL, mg/dL	35 (41 - 48)	45 (33 - 53)	0.658
Triglyceride, mg/dL	106 (77 - 149)	85 (71 - 114)	0.211
Direct bilirubin, mg/dL	0.21 (0.16 - 0.29)	0.20 (0.15-0.32)	0.847
Total bilirubin, mg/dL	0.53 (0.39 - 0.78)	0.56 (0.40 - 0.90)	0.485
LDH, U/L	186 (161 - 216)	176 (158 - 204)	0.449
GGT, IU/L	25 (18 - 41)	20 (16 - 28)	< 0.001
ALP, U/L	75 (63 - 90)	76 (57-80)	0.262
Uric acid, mg/dL	3.89 (4.58 - 5.40)	5.02 (4.07 - 5.90)	0.047
Creatinine, mg/dL	0.70 (0.80 - 0.90)	0.80 (0.75 - 0.90)	0.019
Urea, mg/dL	25 (20 - 28)	26 (22 - 30)	0.034
Glucose, mg/dL	90 (83 - 100)	90 (85 - 97)	0.798
Sodium, mmol/L	140 (139 - 141)	140 (139 - 141)	0.845
LDL, mg/dL	101 (79 - 122)	99 (96 - 111)	0.812
Cholesterol, mg/dL	166 (140 - 194)	167 (144 - 174)	0.508
Albumin, g/dL	4.3 (4.00 - 4.60)	4.51 (4.21 - 4.87)	< 0.001
Protein, g/dL	7.2 (6.80 - 7.57)	7.40 (6.97 - 7.52)	0.519
ALT, U/L	18 (13 - 32)	17 (14 - 24)	0.214
AST, U/L	20 (15 - 28)	17 (15 - 20)	0.002
Magnesium, mg/dL	2.08 (1.95-2.22)	2.0 (1.94-2.22)	0.831
Folate, ng/mL	4.75 (3.77 - 6.40)	6.10 (4.30 - 9.20)	0.278
Calcium, mg/dL	9.49 (9.21 - 9.83)	9.56 (8.71 - 9.88)	0.780

[a] Abbreviations: ALP, Alkaline Phosphatase; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; CRP, C-Reactive Protein; GGT, Gamma-Glutamyl Transferase; HDL, High Density Lipoprotein; LDH, Lactate Dehydrogenase; and LDL, Low Density Lipoprotein.
[b] Quartiles (25 and 75 percentiles).
[c] P-values < 0.05 were considered as statistically significant.

5. Discussion

Clinical observations demonstrated that adverse effects of psychoactive substances were associated with the addiction period and route of administration. The psychoactive substance use more than 2 years causes more profound effects. Psychoactive substance users commonly have nutritional problems since they spend their money largely for drugs (13). Coexistence of psychiatric disorders in drug addicts is also important since some psychiatric disorders may cause loss of appetite and poor nutritional status and changes in biochemical parameters (14).

Clinical studies showed that long-term use of opium and heroin can affect serum glucose, potassium, calcium, uric acid and cholesterol levels (12). In our study, we found a significant difference in GGT, uric acid, creatinine, urea, albumin, and AST medians between the dependent and control groups ($P < 0.05$).

Studies about the effects of opium addiction on blood glucose showed that the opium-dependence decreased fasting blood glucose temporarily without any effect on Hemoglobin A1c (15). We found a statistically significant decrease in glucose levels only in patients tested positive for benzodiazepine ($P < 0.05$). Some psychoactive substances may affect gluconeogenesis so that blood glucose levels may decrease, especially in cases with poor nutrition.

Some people believe that psychoactive substances like opium can have beneficial effects on blood lipid profile and cardiovascular disease, but clinical observations demonstrated that opium can increase risk of atherosclerotic plaque formation and adversely affect lipid profile in animal models (16). We found a statistically significant increase in triglyceride levels in ethylglucuronide group ($P < 0.05$). In our study, we did not found statistically significant difference in total cholesterol, low density lipoprotein (LDL), and high density lipoprotein (HDL) levels between dependent and control groups ($P > 0.05$). Cardiovascular side effects of some psychoactive substances may not be attributed to changes in lipid profile. There is a need to conduct a prospective study with the larger sample size for the prevalence of the cardiovascular disease.

Table 3. Comparison of Serum Biochemistry Parameters in all Groups According to Medians

Tests	Control Group Median (Quartiles) [a]	Opiate Group Median (Quartiles) [b]	Cannabinoid Group Median (Quartiles) [a]	Benzodiazepin Group Median (Quartiles) [c]	Glucuronide Group Median (Quartiles) [d]
CRP, mg/dL	0.27 (0.09 - 0.64)	0.41 (0.15 - 0.93)	0.20 (0.11 - 0.47)	0.26 (0.13 - 0.60)	0.28 (0.10-0.38)
Clor, mmol/L	101 (100 - 104)	100 (99 - 102)	100 (99 - 104)	101 (100 - 102)	102 (99-104)
Potassium, mmol/L	4.2 (3.9 - 4.5)	4.4 (4 - 4.6)	4.4 (4.3 - 4.7)	4.2 (4.1 - 4.5)	4.1 (3.8-4.5)
HDL, mg/dL	45 (33 - 53)	42 (35 - 50)	36 (32 - 44)	41 (33 - 47)	44 (33-52)
Triglyceride, mg/dL	85 (71 - 114)	104 (71 - 124)	125 (90 - 172)	130 (105 - 151)	138 (90-207) [e]
Direct bilirubin, mg/dL	0.20 (0.15 - 0.32)	0.21 (0.17 - 0.30)	0.27 (0.22 - 0.34)	0.20 (0.17 - 0.30)	0.24 (0.12-0.34)
Total bilirubin, mg/dL	0.56 (0.40 - 0.90)	0.53 (0.39 - 0.74)	0.85 (0.54 - 1.05)	0.53 (0.40 - 0.80)	0.61 (0.33-1.06)
LDH, U/L	176 (158 - 204)	178 (158 - 200)	152 (139 - 195)	178 (156 - 191)	163 (141 - 205)
GGT, IU/L	20 (16 - 28)	25 (18 - 37)	17 (14 - 26)	32 (21 - 64) [f]	37 (25 - 50) [f]
ALP, U/L	76 (57 - 80)	76 (60 - 98)	68 (60 - 87)	77 (64 - 88)	79 (70 - 93)
Uric acid, mg/dL	5.05 (4.15 - 5.90)	4.55 (3.63 - 5.24)	4.35 (4.12 - 5.60)	5.24 (3.90 - 6.32)	6.12 (4.93 - 6.47)
Creatinine, mg/dL	0.80 (0.75 - 0.90)	0.80 (0.78 - 0.83)	0.90 (0.70 - 1.00)	0.80 (0.80 - 0.90)	0.80 (0.80 - 0.90)
Ure, mg/dL	26 (22 - 30)	24 (22 - 29)	27 (25 - 28)	22 (19 - 27) [e]	25 (21 - 27)
Glucose, mg/dL	90 (85 - 97)	88 (84 - 99)	91 (82 - 94)	83 (78 - 88) [f]	95 (85 - 102)
Sodium, mmol/L	140 (139 - 141)	141 (139 - 142) [e]	140 (138 - 142)	141 (140 - 143) [f]	140 (138 - 142)
LDL, mg/dL	99 (96 - 111)	108 (88 - 121)	121 (83 - 140)	102 (87 - 138)	117 (81 - 144)
Cholesterol, mg/dL	167 (144 - 174)	165 (140 - 184)	189 (138 - 206)	170 (150 - 206)	181 (153 - 210)
Albumin, g/dL	4.5 (4.2 - 4.9)	4.3 (4 - 4.5) [f]	4.5 (4.4 - 4.7)	4.2 (3.9 - 4.7)	4.3 (3.8 - 4.8)
Protein, g/dL	7.4 (6.9 - 7.5)	7.0 (6.7 - 7.5)	6.9 (6.8 - 7.3)	6.8 (6.5 - 7.0) [f]	7.2 (6.5 - 7.4)
ALT, U/L	17 (14 - 24)	201 (12 - 40)	22 (13 - 37)	18 (16 - 40)	15 (12 - 24)
AST, U/L	17 (15 - 20)	19 (15 - 30)	16 (15 - 35)	22 (17 - 28) [f]	18 (15 - 26)
Magnesium, mg/dL	2.0 (1.94 - 2.22)	2.12 (2.05 - 2.21)	2.12 (2.03 - 2.41)	2.04 (1.99 - 2.15)	2.20 (2.07 - 2.30)
Calcium, mg/dL	9.56 (8.71 - 9.88)	9.76 (9.45 - 10.12)	9.2 (9.2 - 9.2)	9.63 (9.48 - 9.84)	9.48 (8.70 - 9.54)

[a] n = 69.
[b] n = 46.
[c] n = 13.
[d] n = 12.
[e] $P < 0.05$.
[f] $P < 0.01$.

Another study, which was performed on opium addicts showed that serum adiponectin levels were decreased but no significant change was observed in serum leptin levels. It was also indicated in previous studies that a decrease in adiponectin levels can be associated with an increased risk of metabolic disorders like insulin resistance and cardiovascular disease since it has known antidiabetic and antiatherogenic effects (17).

Coexistance of several types of infections like hepatitis may affect nutritional status. Addicts usually prefer carbohydrates instead of animal proteins. Changes in nutritional patterns may also be related with changes in albumin levels in these patients (18). We found a statistically significant difference in albumin levels between the drug-dependant and control groups. In our study, the amount of total protein showed a significant difference only in the benzodiazepine dependent group ($P < 0.05$). Since in our study, patients with significant derangements were referred to specialized medical centers for further assessment and excluded from the study, changes in their albumin levels may not be due to viral infections or metabolic disorders.

In a previous study, it has been demonstrated that morphine consumption for long period in animal models increases uric acid and creatinine levels (19). We found a statistically significant decrease in uric acid and creatinine levels in the dependant group compared to the control group ($P < 0.05$). Poor living conditions and nutritional factors like low protein intake may likely to contribute to changes in biochemical parameters in psychoactive substance users.

Opioids have effects on kidney, central nervous system and other organs. These effects on renal system include changes in urinary output and urinary sodium excretion (20). Divsalar et al. showed that a sodium level in the heroin-dependent group did not change; however, it was significantly high in the ex-heroin dependent group compared to the control group. However, no significance difference was found in potassium and calcium levels between the ex-heroin dependent and control groups (14).

We found that the concentration of sodium in the serum of the opium-dependent and benzodiazepine dependent groups was significantly increased compared to the control group ($P < 0.05$). No statistically significant difference was observed in calcium levels between the dependent and control groups ($P > 0.05$).

Routine biochemistry, and hematology parameters, and vitamin, and mineral levels are affected by nutritional factors. Nutritional status of addicted patients involved in treatment programs was changed after the treatment. Determining the differences in biochemical parameters, vitamin and mineral levels between addicts and healthy subjects may help to define individuals at nutritional risk and provide these patients with the corrective nutritional programs (18).

In this study we tried to describe the extent of changes in various blood parameters due to psychoactive drug use. Previous literature has revealed effects of some psychoactive substances on serum biochemical parameters. Our study involves a range of psychoactive substances like heroin, cannabinoids, cocaine, benzodiazepine, opiate, buprenorphine, amphetamine, extacy, ethyl glucuronide and their potential effects on many biochemical parameters. Raising awareness about potential adverse effects of psychoactive substances may warn those using these substances for the first time. Health problems associated with physiological side effects of these substances may increase economic burden on health care resources. Therefore, in psychoactive substance users defining the real need for intensive monitoring and treatment programs are extremely important.

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Authors' Contributions

Designing, and drafting of the manuscript: Dilek Beker Sanli; gathering data: Rabia Bilici, Ozgur Suner, and Serhat Citak; analyzing the data: Fezan Sahin Mutlu; interpretation of results, and preparation of tables: Kazim Kartkaya. All authors read and approved the final manuscript.

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