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The Biochemical, Cognitive, and Psychiatric effects of Anticholinergics Benzhexol Hydrochloride and Biperiden Hydrochloride in Schizophrenic Patients

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Abstract: It is estimated that 45 million people suffer from schizophrenia around the world; it is among the top ten leading causes of disability. By 2050, this number will have grown to approximately 71 million people. Mental illnesses contribute more to the global burden of disease than all cancers combined. The present study has been planned to evaluate the effect of anticholinergic parkinol (benzhexol hydrochloride) and akineton (biperiden hydrochloride) on erythrocyte acetyl cholinesterase (AChE) activity and serum activities of gamma-glutamyl transferase (GGT), alanine transaminase (ALT), aspartate transaminase (AST), and alkaline phosphatase (ALP) in schizophrenic patients treated with haloperidol, and also to study the effect of the previously mentioned two anticholinergics on both the cognitive functions and psychiatric symptoms in such patients. The study was carried out on 30 male schizophrenic patients who were divided into two main groups (group 1 and group 2) each of 15 patients of comparable age. The present results revealed that the total score of (PANSS) showed a significant decrease in all studied groups. The total score of (MMSE) showed a significant increase in all studied groups. The AChE activity did not show any significant difference in all comparisons in all studied groups. In our study, there was a significant elevation of serum GGT, ALT, AST and ALP levels in some groups of treated patients as compared to pretreatment groups. The results obtained in our study showed a significant increase in serum GGT, ALT, AST, and ALP levels in groups treated with either (haloperidol+benzhexol hydrochloride) or (haloperidol+biperiden hydrochloride) as compared to the corresponding levels in groups treated with haloperidol only, respectively. From all results we can concluded that the biochemical parameters used in this study are useful in detecting any side effects of antipsychotic and anticholinergic drugs on liver functions. The treatment with (haloperidol+benzhexol hydrochloride) and (haloperidol+biperiden hydrochloride) are effective in decreasing the positive and negative symptoms of schizophrenia.

INTRODUCTION

Schizophrenia is a psychiatric diagnosis that describes a mental disorder characterized by impairments in the perception or expression of reality and by significant social or occupational dysfunction. A person experiencing schizophrenia is typically characterized as demonstrating disorganized thinking, and as experiencing delusions or auditory hallucinations(1).

The report from the WHO on the diagnosis of schizophrenia according to the

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International Classification of Diseases Revision Ten (ICD-10) stated that no strictly pathogenic symptoms can be identified, and it is useful to divide the various symptoms of schizophrenia into groups that have special importance for diagnosis and often occur together[2].

It is estimated that 45 million people suffer from schizophrenia around the world[3]; it is among the top ten leading causes of disability. No population is free of schizophrenia. By 2050, this number will have grown to approximately 71 million people[4]. Mental illnesses contribute more to the global burden of disease than all cancers combined[5].

The prevalence of schizophrenia is much greater in densely populated, large, urban areas of industrialized countries[6,7]. There is a strong evidence that using certain drugs can trigger either the onset or relapse of schizophrenia in some people[8]. Some of these drugs are amphetamines, hallucinogens, and cannabis[9].

The antipsychotic drugs are a chemically diverse group of heterocyclic compounds, which ameliorate many symptoms of schizophrenia[10]. The side effects of antipsychotic drugs have always been a major concern for clinicians and the appreciation of the importance in the treatment of schizophrenia has increased steadily over the years[11]. Most conventional antipsychotic drugs have central nervous system effects, particularly extrapyramidal symptoms (EPS), hypotension, changes in liver function, antiadrenergic side effects, sexual dysfunction, and weight gain[12]. The effect of conventional antipsychotic is presumed to be associated with dopamine D2-receptor blockade[13], that cause extrapyramidal side effects[14]. One explanation of extrapyramidal disorders is an imbalance between dopaminergic and cholinergic systems in the brain[15]. Antipsychotics (e.g., haloperidol) induced pseudo-parkinsonism that has the same clinical appearance as

idiopathic parkinsonism. Symptoms generally appear within the first three months[16].

Benzhexol hydrochloride (Parkinol) and biperiden hydrochloride (Akineton) are anticholinergic drugs which are used for the treatment of extrapyramidal side effects induced by antipsychotics[17,18]. Acetylcholine (Ach) has an important function in the cholinergic system where it acts as a transmitter of impulses on the cholinergic synapses[19].The cholinergic system is one of the most important modualtory neurotransmitter systems in the brain[20,21].

Cholinesterase (ChE), which is an enzyme, breaks acetylcholine down into choline and acetate and the most significant action of the ChEs physiologically is the hydrolysis of Ach to choline and acetic acid[22].

There have been relatively few studies of the cholinergic system, although there is increasing evidence that the activity of the cholinergic system is abnormal in certain psychiatric illnesses[23]. There are a number of studies implicating a role of cholinergic neurons in schizophrenia. Although the obvious pathology of cholinergic system as seen in Alzheimer's disease is absent from the brains of schizophrenic patients[24], a correlation has been found at post mortem examination between decreases in brain choline acetyl transferase levels and the severity of ante mortem cognitive impairments. Therefore, subtle changes in cholinergic function may contribute to the cognitive impairment associated with schizophrenia[25].

Neuroleptics are known to induce asymptomatic alterations of liver function. Treatment with haloperidol is associated with a high incidence of extrapyramidal effects and changes in liver function. Liver enzymes frequently determined in clinical practice include alanine transaminase (ALT), aspartate transaminase (AST), and gamma-glutamyl transferase (GGT). In

general, consequences of drug metabolism are thought to be the most important causes of drug-induced elevation of liver enzyme levels[26].

The aim of this work is to study the effect of anticholinergics parkinol (benzhexol hydrochloride) and akineton (biperiden hydrochloride) on the biochemical parameters: true cholinesterase, gamma glutamyl transferase, alkaline phosphatase, alanine transaminase, and aspartate transaminase in schizophrenic patients treated with haloperidol. Also, to study the effect of the previous mentioned two anticholinergics on both the cognitive function and the psychiatric symptoms in schizophrenic patients treated with haloperidol.

MATERIAL and METHODS

The study was carried out on 30 male schizophrenic patients who were divided into two main groups (group 1 and group 2) each of 15 patients of comparable age. Group (1) was noted (group 1a, group 1b, group 1c) and group (2) was noted (group 2a, group 2b, group 2c). Groups (1a) and (2a) were pretreatment groups: groups (1b) and (2b) were treated with either (haloperidol + benzhexol hydrochloride) or (haloperidol + biperiden hydrochloride), respectively. Both groups (1c) and (2c) were treated with haloperidol only. The dose of haloperidol was (5-20 mg/day) and the dose of benzhexol hydrochloride and biperiden hydrochloride was (2-6 mg/day).

All patients were subjected to the following: 1-Socio demographic status, medical, and psychiatric assessments, 2-psychometric assessment: using Scale for assessment of negative symptoms (SANS) and positive symptoms (SAPS) of schizophrenia[27]. and Mini Mental State Examination (MMSE) for assessment of cognitive function[28]. 3-Determination of acetyl cholinesterase (true cholinesterase) activity in red blood cells[29]. Serum Gamma glutamyl transferase activity using GGT Kit from Biosystem[30], alanine transaminase,

aspartate transaminase activities in serum using ALT and AST Kit from Biosystem[31,32] and alkaline phosphatase activity in serum using ALP Kit from Human[33].

Statistical analyses were performed using the SPSS version 9. Repeated measurement ANOVA was used to compare the means of the different studied groups. Correlation between variables of all groups was also studied.

RESULTS

Statistical analyses of total score of the positive and negative symptoms scale (PANSS) are shown in Table (1). There was a significant decrease (P=0.001) in the total score on (PANSS) in groups (1b) and (1c) as compared to the corresponding values in group (1a) and in group (1b) as compared to (1c) (P1=0.001) and in groups (2b) and (2c) as compared to group (2a) (P=0.001) and in group (2b) as compared to group (2c) (P1=0.001). The results of total score of the Mini-Mental state examination (MMSE) are illustrated in table (2). There was a significant increase (P=0.001) in the total score of (MMSE) in groups (1b) and (1c) as compared to the corresponding values in group (1a) and in groups (2b) and (2c) (P=0.001) as compared to group (2a) and in group (2c) as compared to group (2b) (P1=0.001).

The results of the erythrocyte acetyl cholinesterase activity (AChE) are shown in Table (3). They indicated that the enzyme activity level didn't show any significant difference in all studied groups.

The results of serum GGT activity are shown in Table (4). Statistically there were significant increases (P=0.0001, 0.002) in the enzyme activity in groups (1b) and (1c) as compared to the corresponding levels in group (1a) and also in group (1b) as compared to group (1c) (P1=0.0001).There was also a significant increase (P=0.0001, 0.039) in the enzyme activity in groups (2b) and (2c) as compared to the corresponding levels in group (2a), and also in group (2b) as compared to group (2c) (P1=0.0001).

The results of serum ALT activity are shown in Table (5). There was a significant increase (P=0.0001, 0.006) in the enzyme activity in groups (1b) and (1c) as compared to the corresponding levels in group (1a), and also in group (1b) as compared to group (1c) (P1=0.001). Also there was a significant increase (P=0.0001) in the enzyme activity in group (2b) as compared to the corresponding levels in group (2a) and also in group (2b) as compared to group (2c) (P1=0.0001).

The results of serum AST activity are shown in Table (6).There was a significant increase (P=0.0001) in the enzyme activity in group (1b) as compared to the corresponding levels in group (1a), and also in group (1b) when compared to group (1c) (P1=0.0001).There was a significant increase (P=0.0001)in the enzyme activity in group (2b) when compared to the corresponding levels in group (2a), and also in group (2b) when compared to group (2c) (P1=0.0001).

The results of serum ALP activity are shown in Table (7).There was a significant increase (P=0.0001) in the enzyme activity in group (1b) as compared to the corresponding levels in group (1a), and also in group (1b) when compared to group (1c) (P1=0.001).There was a significant increase (P=0.0001,0.023) in the enzyme activity in groups (2b) and (2c) as compared to the corresponding levels in group (2a), and also in group (2b) when compared to group (2c) (P1=0.0001).

Correlation between the different parameters in all studied groups are shown in Table (8). The level of GGT was significantly positively correlated with the level of ALT, AST, and ALP. Also a significant positive correlation has been observed between ALT and each of AST and ALT. The level of AST was found to be significantly positively correlated with ALP.

DISCUSSION

Schizophrenia is the most persistent and disabling of the major mental illnesses. It

usually attacks people between the ages of 16 and 30, as they are beginning to realize their potential. It affects approximately one in 100 people worldwide, affecting men and women almost equally. While it is treatable in many cases, there is as yet no cure for schizophrenia.[34]

The decrease in the total score (PANSS) in groups (1b,1c) and (2b,2c) as compared to groups (1a) and (2a), respectively, is in agreement with several studies which showed that, haloperidol was so effective in treatment of positive and negative symptoms of schizophrenia. Also the decrease in the total score of (PANSS) in groups (1b) and (2b) in comparison to groups (1c) and (2c), respectively, can be explained by the increase of the motor retardation and spontaneous speech score of the (PANSS) items after stoppage of benzhexol hydrochloride or biperiden hydrochloride and using haloperidol only which causes such side effect. This is in agreement with other studies which reported that haloperidol elicits significant EPS and may also result in selective impairments in cognitive function, e.g., processing speed, motor skill, and procedural learning as a consequence of D2 receptor blockade in dorsal striatum[35,36].

The significant increase in the total score of (MMSE) in groups (1b,1c) and (2b,2c) as compared to groups (1a) and (2a), respectively, is in agreement with the study of Richard and his associates who reported that, the improvement of the cognitive function on (MMSE) may be attributed to the improvement of the psychotic symptoms with haloperidol[37].

The significant increase in the total score of (MMSE) in group (2c) as compared to group (2b) may be due to the improvement of cognitive function with haloperidol which becomes more evident after stoppage of the treatment with biperiden. This is in accordance with many studies which showed that anticholinergic medication used to treat EPS, can also

impair cognitive processes related to learning and memory[38,39]. But this was not happened in case of benzhexol treated group which is in agreement with other study which stated that anticholinergic medication used to control emergent EPS have benign cognitive profiles that do not interfere with normal cognitive processes[40].

Results of the present work are in accordance with the results of Donino and Krause who reported that there is not any change in the levels of red blood cell acetylcholinesterase in schizophrenic patients who were treated with haloperidol[41].These results are also supported by those of Korenovsky and his associates who found that haloperidol did not significantly alter erythrocyte acetylcholinesterase levels in rats[42]. Shih and co-workers reported that administration of benzhexol hydrochloride or biperiden hydrochloride alone did not affect the base-line CHE activity[43]. The relation between some neuroleptic drugs and anticholinesterase activity has been previously described in different extrapyramidal situations[44,45]. Some drugs that are potent antipsychotic agents such as haloperidol have low cholinesterase inhibitory actions[46].

The increase of GGT activity in our study in groups (1b), (1c), (2b), and (2c) is in accordance with the study of Hubertus and his associates which showed that serum GGT activity was increased in patients who were treated with antipsychotic drugs[47]. It also showed the possibility that GGT is to some extent induced by haloperidol itself[48].

In our study the increase of ALT activities in the groups (1b), (1c) and (2b) and the increase of AST activities in groups (1b) and (2b) are in accordance with the results of several studies. They showed that transaminase enzyme levels increase during treatment with haloperidol and other neuroleptics and usually return to normal[49]. Green *et al*., study revealed that ALT and AST levels were found to be higher in

patients treated with haloperidol[50].This increase in these enzyme activities may be attributed to the fact that many medications produce hepatic injury by competitively interfering with cellular metabolism[51]. Our results showed a significant positive correlation between ALT and AST activity levels.

The high levels of ALP activity in the studied groups are in agreement with that reported by Moradpour and co-workers who showed that the treatment by conventional antipsychotic drugs was characterized by high ALP levels[52].

In our study, there was a significant elevation of serum GGT, ALT, AST and ALP levels in some groups of treated patients as compared to pretreatment groups. This increase in the enzymes activities may be attributed to drug metabolism and side effects of halopereidol, benzhexol hydrochloride, and biperiden hydrochloride[47,53,54].

The results obtained in our study showed a significant increase in serum GGT, ALT, AST, and ALP levels in groups treated with either (haloperidol + benzhexol hydrochloride) or (haloperidol + biperiden hydrochloride) as compared to the corresponding levels in groups treated with haloperidol only, respectively. This increase in the enzyme activities may be attributed to the coadministration of (haloperidol + benzhexol hydrochloride) or (haloperidol + biperiden hydrochloride. These anticholinergic drugs produced an increase in the enzymes activities than haloperidol alone, therefore, we can suggest that GGT, ALT, AST, and ALP may be considered as clinically useful markers for the drug-drug interaction. This means that both benzhexol hydrochloride and biperiden hydrochloride increased the side effects of haloperidol[55]. In this study, the results showed no significant difference in all enzyme activities in group (1b) as compared to the corresponding levels in group (2b). This

means that benzhexol hydrochloride has the same action as biperiden hydrochloride on all enzyme activities. This action is not extraordinary, since there is a similarity in the chemical structure of the two studied drugs.

Conclusively, the biochemical parameters used in this study, are useful in detecting any side effect of antipsychotic and anticholinergic drugs on liver functions. GGT, ALT, AST, and ALP activities can be useful for diagnosis of liver disease in individuals treated with haloperidol, benzhexol hydrochloride or biperiden hydrochloride. They are also widely available and relatively inexpensive.

Treatment with (haloperidol +benzhexol hydrochloride) and (haloperidol + biperiden hydrochloride) are more effective in decreasing the positive and negative symptoms of schizophrenia, than treatment with haloperidol only.

Table (1): Statistical analyses of total score of the positive and negative symptoms scale (PANSS) for Schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	**Halo.+Benz. group (1b)**	**Halo. group(1c)**	**Pretreat. group (2a)**	**Halo. + BPR group (2b)**	**Halo. group(2c)**
Mean	115.5	35.6	37.9	121.3	36.5	38.9
± S.E.M.	5.33	1.07	1.12	4.53	1.23	1.20
M_1	-79.9			-84.8		
M_2	→ -77.6 ←			→ -82.4 ←		
M_3	2.3			2.4		
M_4	→ -0.9 ←					
M_5	→ -1.0 ←					
p		0.001*	0.001*		0.001*	0.001*
p_1		0.001*			0.001*	
P_2		0.573				
P_3			0.521			

M_1: Mean difference between groups (1b) and (1a) or between (2b) and (2a).
M_2: Mean difference between groups (1c) and (1a) or between (2c) and (2a).
M_3: Mean difference between groups (1c) and (1b) or between (2c) and (2b).
M_4: Mean difference between groups (1b) and (2b).
M_5: Mean difference between groups (1c) and (2c).
P : Values compared to group (1a) or group (2a).
p_1 : Values compared to group (1c) or group (2c).
p_2 : Values compared to group (2b).
p_3 : Values compared to group (2c).
p* < 0.05 was considered significant.
Number of patients in each group = 15
Pretreat : Pretreatment **Halo. :** Haloperidol.
Benz. : Benzhexol hydrochloride. **BPR :** Biperiden hydrochloride.

Table (2): Statistical analyses of total score of the mini-mental state examination (MMSE) for Schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	Halo.+Benz. group (1b)	Halo. group(1c)	Pretreat. group (2a)	Halo. + BPR group (2b)	Halo. group(2c)
Mean	25.4	27.7	28.7	24.9	27.7	28.8
± S.E.M.	0.35	0.45	0.45	0.27	0.37	0.40
M_1	2.3			2.8		
M_2	→ 3.3 ←			→ 3.9 ←		
M_3	1			1.1		
M_4	→ 0.0 ←					
M_5	→ -0.1 ←					
p		0.001*	0.001*		0.001*	0.001*
p_1		0.090				0.001*
P_2		1.000				
P_3			0.828			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
p* < 0.05 was considered significant.
Number of patients in each group = 15

Table (3): Statistical analyses of erythrocyte acetyl cholinesterase activity (moles/min/RBC × 10^{-16}) in schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	Halo.+Benz. group (1b)	Halo. group(1c)	Pretreat. group (2a)	Halo. + BPR group (2b)	Halo. group(2c)
Mean	14.05	14.50	14.76	15.20	15.29	15.61
± S.E.M.	0.69	0.72	0.64	0.50	0.55	0.58
M_1	0.45			0.09		
M_2	→ 0.71 ←			→ 0.41 ←		
M_3	0.26			0.32		
M_4	→ 0.79 ←					
M_5	→ 0.85 ←					
p		0.516	0.229		1.000	0.470
p_1		0.925			0.326	
P_2		0.666				
P_3			0.660			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
Number of patients in each group = 15

Table (4): Statistical analyses of gamma glutamyl transferase activity (U/L) in serum of schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	**Halo.+Benz. group (1b)**	**Halo. group(1c)**	**Pretreat. group (2a)**	**Halo. + BPR group (2b)**	**Halo. group(2c)**
Mean	28.2	46.9	32.3	30.9	51.4	34.3
± S.E.M.	2.74	3.3	2.93	2.61	2.83	2.55
M_1	18.7			20.5		
M_2	→ 4.1 ←			→ 3.4 ←		
M_3	14.6			17.1		
M_4	→ 4.5 ←					
M_5	→ 2.0 ←					
p		0.0001*	0.002*		0.0001*	0.039*
p_1		0.0001*			0.0001*	
P_2		0.306				
P_3			0.610			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
p* < 0.05 was considered significant.
Number of patients in each group = 15

Table (5): Statistical analyses of alanine transaminase activity (U/L) in serum of schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	**Halo.+Benz. group (1b)**	**Halo. group(1c)**	**Pretreat. group (2a)**	**Halo. + BPR group (2b)**	**Halo. group(2c)**
Mean	29.5	38	32.7	28	38	30.3
± S.E.M.	1.6	1.93	1.61	2.15	2.92	2.36
M_1	8.5			10		
M_2	→ 3.2 ←			→ 2.3 ←		
M_3	5.3			7.7		
M_4	→ 0.0 ←					
M_5	→ -2.4 ←					
p		0.0001*	0.006*		0.0001*	0.120
p_1		0.001*			0.0001*	
P_2		1.000				
P_3			0.408			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
p* < 0.05 was considered significant.
Number of patients in each group = 15

Table (6): Statistical analyses of aspartate transaminase activity (U/L) in serum of schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	Halo.+Benz. group (1b)	Halo. group(1c)	Pretreat. group (2a)	Halo. + BPR group (2b)	Halo. group(2c)
Mean	26.0	34.5	28.1	24.3	35.7	27.1
± S.E.M.	2.08	2.59	2.28	2.50	2.91	2.57
M_1	8.5			11.4		
M_2	→ 3.1 ←			→ 2.8 ←		
M_3	6.4			8.6		
M_4	→ 1.2 ←					
M_5	→ -1.0 ←					
p		0.0001*	0.170		0.0001*	0.083
p_1		0.0001*			0.0001*	
P_2		0.706				
P_3			0.773			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
p* < 0.05 was considered significant.
Number of patients in each group = 15

Table (7): Statistical analyses of alkaline phosphatase activity (U/L) in serum of schizophrenic patients before and after treatment.

	Group (1) (n = 15)			Group (2) (n = 15)		
	Pretreat. group (1a)	Halo.+Benz. group (1b)	Halo. group(1c)	Pretreat. group (2a)	Halo. + BPR group (2b)	Halo. group(2c)
Mean	165.8	203.6	168.4	171.3	222.3	184.1
± S.E.M.	8.85	9.34	8.55	7.17	8.90	6.64
M_1	37.8			51		
M_2	→ 2.6 ←			→ 12.8 ←		
M_3	35.2			38.2		
M_4	→ 18.7 ←					
M_5	→ 15.7 ←					
p		0.0001*	1.000		0.0001*	0.023*
p_1		0.001*			0.0001*	
P_2		0.156				
P_3			0.157			

M_1, M_2, M_3, M_4, M_5, P, P_1, P_2, and P_3 as represented in Table (1)
p* < 0.05 was considered significant.
Number of patients in each group = 15

Table (8): Correlation between all biochemical parameters in all studied groups.

	AChE	GGT	ALT	AST	ALP
AChE		0.120	-0.152	-0.123	-0.102
GGT			0.427**	0.609**	0.433**
ALT				0.802**	0.585**
AST					0.534**
ALP					

- The values are statistically significant at r > 0.30.

** Significant correlations (p < 0.01).

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