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HALOPERIDOL LEADS TO TORSE DE POINTES IN SCHIZOPHRENIC POOL

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ABSTRACT

Schizophrenia is a mental disorder characterized by diminishing of emotions, intelligence, social isolation, speech confusion, behavioral misconceptions and hallucinations. Intravenous (IV) haloperidol is effective and safe for the tranquility of the patients to be freed from numerous hazardous circulatory & anticholinergic side effects of the anti-schizophrenics drugs. In patients with schizophrenia, haloperidol is better choice than atypical schizophrenic drugs for improvement in symptoms but increases the rates of parkinson's disease, akathisia, and acute dystonias substantially. The dose dependent side effects like hyperlipidemia and torese de point (prolongation of QT interval) are the worst side effect of haloperidol, which is the major cause of death in schizophrenic patients. Typical anti-schizophrenic drugs are as potent as atypical schizophrenic drugs and if used in proper dosage as recommended by physicians' patients can live a progressive life. Furthermore, there should be provision of healthy environment to schizophrenic patients, so they become helpful to society.

KEYWORDS: Haloperidol, Schizophrenia, QT interval, Hyperlipidemia, Torese de point.

INTRODUCTION

Schizophrenia is a mental disorder characterized by diminishing of emotions, intelligence, social isolation, speech confusion, behavioral misconceptions and hallucinations. Schizophrenics may also feel and see things that are not there. The schizophrenic individual may speak in ways which are hard to comprehend. Sometimes the speech is beyond understanding. Schizophrenia has usually been observed as a chronic disease with suspicious outlook.[1-3] Lack of knowledge regarding disorder like schizophrenia can cause negative effect in diagnosis and treatment of schizophrenia. Many personality deficiencies were found in schizophrenic patients, which may be neutrally based, and therefore important when treating patients.[4] But there can be some problems that might rise with respect to the understanding, diagnosis, and treatment of aged schizophrenic patient. Some patients having clinical symptoms like schizophrenia but having no deterioration, delusions or hallucination. These patients are psychoneurotic form of schizophrenia. They are prone to become schizophrenic in future depending upon the environmental, socioeconomic factors.[5] Moreover, critical gaps exist in clinical services for this population. The epidemiology of schizophrenia with reference to the age and spread of schizophrenia in elderly people which relates to physical health, socioeconomic aspect and its method of evaluation.[6, 7]

GENETICAL EXPLANATION

The hereditary models shows the spread of schizophrenia consist of the multi-factorial threshold and single locus threshold models.[8] The single major locus model is not enough to forecast the occurrence in four classes of relatives of schizophrenic (monozygotic, co-twins, dizygotic and parents). The development and use of strict, dependable diagnostic criteria, together with family, twins and adoption paradigms, shows the importance of genetic factors in familial basis of the schizophrenia.[9] The heredity transmission is significant in diagnosis of schizophrenia. The heritability estimation for diagnosis was comparable. Residual twin similarity was statistically important which cannot explain the effects of genetic supremacy. The results can be similar to those of an earlier analysis based upon a similar data set.[10]

The restructuring of human brain function takes place during puberty. The rate of brain metabolism and quantity of deep sleep descend sharply. A defect in this maturation process may underlie those cases of schizophrenia that appeared during puberty.[11] The

neuro-imaging and postmortem studies of schizophrenic patients show changes in the brain development and a decrease of neuritic processes somewhat less then neuronal or glial cell bodies. These are the significant aspects of schizophrenia, with its short and long term course and distinctive symptoms.[12] The heredity and environmental influence are the major cause of schizophrenia. The change in behavior appears at some stage, in childhood and during puberty.[13] Schizophrenia is a disorder with irregular phenotypic form and is weakly understood. A diverse combination of genes and alleles plays key role in the development of this disorder. Genotypes remaining clinically unexpressed.[14] Schizophrenia occurs in various populations at similar rates.[15] There is a complete proof present which shows that phenotype allocate a common genetic etiology with schizophrenia. Earlier reports about the disorder explains the continuity between adult and early onset of disorder and the presence of neuro-cognitive, neuro-logical, neuro-anatomical defects in both adults and in early childhood patients with schizophrenia.[16, 17]

DOPAMINE

The brain is a complicated structure. Dopamine, one of the chemical messengers, has been a base of much investigation. Initially there was uncertainty, as dopamine itself is a predecessor for other neurotransmitters. The Carlsson conducted further experiments in 1957, was dopamine acknowledged as a neurotransmitter in its own right, leading to its link in treating disorders like Schizophrenia and Parkinson's disease.[18, 19]

RECEPTOR PHARMACOLOGY

The over excitation of D_2 receptor causes schizophrenia and dysfunction in NMDA receptor. Glutamate/ dopamine both and relations between dopamine/ glutamate may be applicable to schizophrenia management and pathophysiology. The alterations in dopamine might aggravate glutamate transmission deficits.[20] The new drugs used (5-HT)-receptor-based mechanisms play an important role in treating the schizophrenia with lesser extra-pyramidal side effects in comparison to typical antipsychotic drugs such as haloperidol.[21, 22]

INFECTIONS INDUCED SCHIZOPHRENIA

The link between infections caused by influenza, T. gondii, HSV-2, exposure during pregnancy and schizophrenia disorder in offspring. Both pro-inflammatory cytokines and infection linked to fetal hypoxia, which has been associated with schizophrenia and many of the brain abnormalities linked to the disorder.[23] Maternal cytokines plays a key role in development of schizophrenia. In late pregnancy in relation to development of adult schizophrenia was studied. Considerable differences were found in serum levels of IL-1, IL-2, IL-6 & IL-8. These facts support earlier investigations which explained that the high levels of cytokines in pregnancy are a risk factor for schizophrenia.[24] Prenatal infection is the major risk factor which increased specificity through phase-specific distorted gene expression now both toughen and alter the neuro-developmental theory of schizophrenia.[25] Acute *T. gondii* infection may also produce psychotic symptoms similar to schizophrenia. A total of 19 studies of *T. gondii* in schizophrenic and other brain disorder; 18 showed, a higher proportion of antibodies in the affected persons.[26] The parental influenza exposures increase the risk of schizophrenia. The possibility of schizophrenia was improved 7-fold for influenza coverage during the first trimester. No threat of schizophrenia was establish second or third trimester.[27] Rubella-exposed focuses designed to progress schizophrenia as matched with control subjects. It was found that Rubella-exposed schizophrenic cases demonstrated a decline in IQ compared with rubella exposed control subjects.[28] Complications in pregnancy like pre-eclampsia, diabetes, bleeding, and rhesus incompatibility. Population-based studies showed that the three groups of complications were considerably linked with schizophrenia.[29]

Neuro-development models of schizophrenia shows the outline of illness. There is a great diversity in models. With 80% around non-genetic factors impairing development must also be part of the model, schizophrenia chromosomal abnormality and susceptible genes, particularly evaluated for schizophrenia. (ie *GAD1*, 22q11DS) are accountable for premorbid neurological abnormalities.

In patients with schizophrenia, there is glut of victimizing experiences, which occurred during childhood.[30] Comparison has been done with general population. Schizophrenics and their family were seen separately to set up the rate of certain kinds of catastrophe and changes in life, the thirteen weeks before onset. Marked difference has been found between the two groups. Long-term nervousness at home seems to increase the likelihood of patients becoming disturbed after such changes.[31] Neuro-developmental disorders are marked by cognitive deficits. The results showed that schizophrenia is evident by sizable cognitive discrepancies, and schizophrenic signs, and the initial experience of ailment is marked by decline.[32]

Inheritance theory of schizophrenia postulated by David Horrobin to back his theory of the nutritional causes of schizophrenia explained that schizophrenia not only caused by inadequate nutrition but genetic makeup also plays a key role in exposing the schizophrenia.[33] Bio-psychosocial model and stress-diathesis model of schizophrenia are new kind of models for studying schizophrenia combining the biological and social factors responsible for development or triggering the schizophrenia.[34] The stress-diathesis model relates predisposition of persons and stressors causing schizophrenia.[35] Stress free environment, and life with opportunities where the people with schizophrenic people, provide rehabilitation condition and put better

effect on these patients.[36] The death rate in schizophrenic patients in accidents are 28% and 12% to is due to suicide.[37]

The symptoms of schizophrenia in childhood show severity as compared to schizophrenia in adults. Maternal obstetric complications are the major cause of childhood onset of schizophrenia.[38] The weather and month have an important role in the progression of schizophrenia according to various studies showing a 5–8% winter–spring excess of births for schizophrenics and manic/bipolar disorder in (December–March).[39] Morphological state of the brain shows that the size of the brain gets reduced and morphology and molecular composition changed in different areas of the brain like glial population, dorsolateral prefrontal cortex, and hippocampal areas. These finding might lead us to the generation of another hypothesis about schizophrenia.[40] There is not much difference present between the schizophrenic and healthy individuals in subcortical volumes apart from for lower thalamic volume. In schizophrenic group, volumes did not associate with intensity of negative symptoms, but higher capacities in both the thalamus and the putamen were linked with added positive symptoms. Increase in subcortical volumes slightly interrelated with more severity of both negative and positive symptoms. Higher subcortical volumes in schizophrenic patients seem to be drug-induced hypertrophy. This hypertrophy may possibly reveal structural changes to receptor blockade and effects of anti-schizophrenic drug treatment.[41]

HALOPERIDOL

Intravenous (IV) haloperidol is effective and safe for the tranquility of the patients to be freed from numerous hazardous circulatory & anticholinergic side effects of the anti-schizophrenics drugs. There is a report of schizophrenics who established lengthening of the Q-T interval through management with IV haloperidol.[42]

The normal life probability is 76-80 years in females, 72 years in male in Europe. whereas the matching figure is 61 years, with schizophrenia 65 in females, 57 years in males. The patients with schizophrenia are ten to 20% have suicidal tendency than general population, more than two thirds of schizophrenics, die of coronary heart disease (CHD) compared to almost one-half in the general population, The risk elements for death in schizophrenics are smoking, dyslipidemia, obesity, diabetes, insulin resistance and hypertension.[43]

Haloperidol exerts its antipsychotic effect most likely through potent blockade of central dopamine receptors and marked rigidity linked with haloperidol administration. Haloperidol was well tolerated in the euthyroid state may also cause hypotension.[44, 45]

The extrapyramidal motor disturbance is major cause of dysphagia in schizophrenics. The complication with dysphagia starts with the loss of weight and aspiration after the treatment with haloperidol. Neuroleptic malignant syndrome are most fatal complication, which is characterized by dyspnea, dysphagia, skeletal muscle rigidity and extreme hyperthermia.[46-48]

Tranquillizers may cause severe dysphagia. Patients taking haloperidol are observed regularly while swallowing is suggest as a useful addition to clinical examination of these patients.[49, 50] Another major side effect of anti-schizophrenic drugs is extrapyramidal symptoms that can affect swallowing, Swallowing through oral and pharyngeal phases get disturbed. Drug induced dysphagia may easily be reversed as compared to the other cause of dysphagia.[51]

The mortality rate in patients taking typical antipsychotic is higher than the patients taking atypical antipsychotic medication acutely ill with pneumonia. The mortality rates for patients taking atypical and typical antipsychotic shows unmeasured severity of illness regardless of the use of antipsychotic medication. The dopamine blocker use may be a substantial risk of breast carcinoma. these outcomes should be on the top for further research but not to alter the treatment strategies.[52]

HALOPERIDOL EFFECTS ON LIPID PROFILE

The typical and atypical anti-schizophrenic drugs may alter the lipid profile in patients with schizophrenia in comparison to atypical anti-schizophrenic drugs, experience with olanzapine and, somewhat less to clozapine is linked with amplified risk of hyperlipidemia, but hyper-lipidimic effects of typical anti-schizophrenic drugs cannot be ruled out among people with schizophrenia. Haloperidol involved in producing oxidative cell injury and oxidative stress in the brain.[53]

The FDA has approved the use of anti-schizophrenic drugs in some children and adolescents with emotional and behavioral disorders. There is twofold to fivefold increase in the antipsychotic medications usage in preschool children, regardless of information on their long-term side effects and associated diseases. The diseases associated with the schizophrenia play a key role in mortality and morbidity. Patients with old age are most likely to have comorbid disorders. Co morbidity due to the use of haloperidol causing anti cholinergic effects.[54] Schizophrenics are at risks of cardiac arrest, serious ventricular arrhythmia. It is believed that cardiac diseases in schizophrenics are due to free radicals and related reactants. The haloperidol might also be involve in the induction of oxidative stress.[55]

Fasting blood glucose and serum cholesterol levels were recorded at baseline and subsequently repeated at 02nd week, 06th week and 08th week of treatment. All the blood samples were taken as a fasting sample. Hyperglycemia and hypercholesterolemia were found in patients having olanzapine treatment as compared to risperidone and haloperidol in the study population but

still the typical anti-psychotic medication produce their effects which might be different in long term and short term uses as well as vary with patient to patient.[56] The FDA has approved the use of anti-schizophrenic drugs in some children and adolescents with emotional and behavioral disorders. There is twofold to fivefold increase in the antipsychotic medications usage in preschool children, regardless of information on their long-term side effects and associated diseases. The diseases associated with the schizophrenia play a key role in mortality and morbidity. Patients with old age are most likely to have comorbid disorders. Co morbidity due to the use of haloperidol causing anti cholinergic effects.[54] Schizophrenics are at risks of cardiac arrest, serious ventricular arrhythmia. It is believed that cardiac diseases in schizophrenics are due to free radicals and related reactants. The haloperidol might also be involve in the induction of oxidative stress.[55]

HALOPERIDOL & QT INTERVAL

Haloperidol responsible for prolonged QT preceded the torsade de pointes episode and is the major causes of ventricular arrhythmias in old age women. Overdose of haloperidol and orphenadrine causes QT elongation and life threatening incidents of torsades de pointes. The haloperidol is the most likely cause of the torsades de pointes.[57] Haloperidol, used in the treatment of schizophrenia is modestly cardio toxic. Numerous cases of torsade de pointes testified in link with haloperidol oral use. Torsades de Pointes (TDP) is a potentially dangerous ventricular arrhythmia by haloperidol. Oral, but not intravenous, haloperidol has been generally associated with this arrhythmia.[58] IV haloperidol is the drug with excellent controlling of agitated delirium in extremely ill patients with cardiac problems in many hospitals. The previous researches have suggested that high-dose of IV haloperidol showed no side effects in these patients. On the other hand, some reports of substantial QT elongation and torsade de pointes as problems of high-dose of IV haloperidol therapy outcome. There is definite involvement of haloperidol induced QT prolongation. The main cause of death among patients with schizophrenia is CHD due to adverse risk factor profile.[43]

Ventricular arrhythmias and Torsade de pointes related to the increase of the QT interval have upraised concerns about the use of anti-schizophrenic drugs and cardiac side effects.[59] Torse de pointe and sudden death have been diagnosed in schizophrenic patients using haloperidol and to a much lesser ratio in schizophrenics using atypical antipsychotics.[60, 61] Patients using typical anti-psychotic medication greater than a "thioridazine-equivalent" dose of 100 mg, may have a 2.4-fold increased risk of sudden cardiac death.[62] To compare the rates of cardiovascular dealings, onset and death in diabetic patients with schizophrenia and prescribed antipsychotic drugs with inhabitants of similar sex, age, and health plan membership.[63] There is an urgent need to determine whether the high death rates in schizophrenics is attributable to the disorder or the use of antipsychotic medication.[64]

The haloperidol can also encourage ventricular arrhythmias. There is involvement of several duplicated cardiac K^+ channels, comprising the human ether-a-go-go linked gene (HERG) channels, in *Xenopus*oocytes and verified them for haloperidol sensitivity. The mechanism of haloperidol block includes binding to inactivated (HERG) channels.[65] The existing data concerning increasing dose of IV haloperidol of <2 mg can carefully be administer without electro-cardiographic observation in patients without associated risk factors.[66] Cardiovascular adverse effects from anti-schizophrenic drugs like haloperidol including tachycardia, postural hypotension, α1-adrenoceptor blockade, blockade of calmodulin, sodium and calcium channels and α_2-adrenoceptors in CNS are common. Blockade of cardiac potassium channels such as HERG are related for the development of arrhythmias and sudden.[67] Although sudden unexpected death occurs almost twice as often in populations treated with anti-schizophrenic drugs. Anti-schizophrenic drugs including haloperidol cause torsade de pointes and sudden death. To date, all anti-schizophrenic drugs have the potential for serious adverse events.[59]

Orthostatic hypotension develops in 10-30% of the aged patients. Generally, a number of factors involve, of which autonomic dysfunction showed a significant part in aged people. Haloperidol very often induced orthostatic hypotension which is more remarkable in old aged patients.[68] Twenty male psychiatric inpatients were put into two groups and received high & low dose of haloperidol using neuro-leptization technique. A six-day after looking were followed. The two groups were better at one hour, one day, and seven days after the intake of haloperidol, none of the two groups differed in the degree or rapidity of symptoms aggravation. however, the outcomes of the research do not give support for the administration of high doses of haloperidol to acutely psychotic schizophrenics with relatively good prognoses.[69]

The neuroleptic malignant syndrome (NMS) is a dangerous outcome of treatment with potent anti-schizophrenic drugs. Better knowledge and understanding of anti-schizophrenic drug pharmacology will produce more effective means of prevention and treatment.[70] Mortality in schziophrenics often occurs, but complete retrieval can only be achieved with proper management. Classic features of neuroleptic malignant syndrome appeared upon stopping the use of anti-parkinsonian drugs. Manifestations of neuroleptic malignant syndrome accredited to dopamine receptor blockade in striatum, increasing thermogenesis, impairing heat degeneracy in hypothalamus,[71]

The tachycardia linked to treatment with haloperidol in conventional doses. The QT interval elongates and

shortened when haloperidol removed from course of therapy resulting in disappearing of torsades de pointes bursts.[72] Though the IV haloperidol is an effective for the treatment of agitation, prolonged QT interval has been a problem. In emergency state, clinicians cannot ignore patients in which torsade de pointes is susceptible, like those with genetics of ion channel disorders. Therefore, clinicians should be aware of the link between iv haloperidol administration and prolongation of QT interval.[73]

Patient's taking moderate doses of anti-schizophrenic drugs having the risk of unexpected cardiac death. Although the study data cannot demonstrate causality, they suggest that adverse cardiac effects of anti-schizophrenic drug should be apply in clinical practice, particularly for patients with cardiovascular disease.[62]

The effect of oral haloperidol and nicotine intake in patient's measures of desire and smoking fulfillment were compared. Patients using haloperidol smoked more significantly more, as nicotine levels was measured. The haloperidol might increase the nicotine craving.[74] Individuals with schizophrenic disorder have extreme illness due to respiratory, infectious diseases, substance abuse, smoking, diabetes mellitus, obesity and cardiovascular diseases. Schizophrenics have high risk factors for CVD. The use of anti-schizophrenic drugs result in excessive weight gain adds other complications like diabetes and coronary disease incidence.[75]

Users of typical antipsychotics like haloperidol had a fivefold higher risk of myocardial infarction than the control subjects. The antipsychotic drugs like haloperidol may involve in the prevalence of type II diabetes mellitus.[76, 77] Haloperidol can induce cardiovascular and metabolic diorders like dyslipidemia, obesity, hyperglycemia that are linked with an increased risk of type II diabetes mellitus and cardiovascular disease. In children especially these anti-schizophrenic drugs cause orexigenic effects. Death rates in schizophrenics are two to three times higher than that of the common population. The symptoms of schizophrenia and death particularly from suicide can be reduced by the proper use of the neuroleptic drugs. Though, conventional drugs are linked with extrapyramidal symptoms and other, often unbearable side effects.[78]

In schizophrenic patients with 50% structurally normal hearts, sudden death is the most awful manifestation of disease. A merging methodology of heart examinations with review of history will be effective in elucidating potential Sschizophrenic mechanisms in 57% of cases.[79] Weight gain is relevant and clearly linked with olanzapine, and to less extent, with risperidone and haloperidol. Because of the short duration of treatment data for quetiapine were not conclusive.[80] Anti-schizophrenic drugs involved in QT prolongation depending upon the dosing manner. Risks are considerably higher for haloperidol, thioridazine and doperidol. Drug induced arrhythmias may therefore confer an increased risk.[81]

CONCLUSION

In patients with schizophrenia, haloperidol is better choice than atypical schizophrenic drugs for improvement in symptoms but increases the rates of parkinson's disease, akathisia, and acute dystonias substantially. The dose dependent side effects like hyperlipidemia and torese de point (prolongation of QT interval) are the worst side effect of haloperidol, which is the major cause of death in schizophrenic patients. Typical anti-schizophrenic drugs are as potent as atypical schizophrenic drugs and if used in proper dosage as recommended by physicians' patients can live a progressive life. Furthermore, there should be provision of healthy environment to schizophrenic patients, so they become helpful to society.

CONFLICT OF INTEREST

No conflict of interest associated with this work.

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