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RESEARCH ARTICLE

A REVIEW OF HALOPERIDOL INDUCED NEUROLOGICAL COMPLICATIONS.

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Abstract

Haloperidol is a known antipsychotic that is administered in the treatment of neurological conditions such as hallucinations, mild to severe psychosis, agitated schizophrenia and other conditions related to mental impairment. As with most drugs, it possesses adverse effects seen in the use of most antipsychotics such as extrapyramidal symptoms or accidental haloperidol symptoms (some of which include tremors, dystonia, and myoclonus disorders), and other neurological complications such as seizures, parkinson's disease, obsessive compulsive symptoms (OCS) and neuroleptic malignant syndrome (NMS). This review consists of a base study of a seizure case (which occurred as a result of accidental haloperidol poisoning), and a compilation of examined cases which detail the neurological complications associated with the use of haloperidol and antipsychotics in general, such as laryngeal dystonia, rhabdomyolysis associated seizures, etc.

Introduction:-

Haloperidol is a butyrophenone derivative antipsychotic agent that is applied in the treatment of hyperactivity, schizophrenia, mania, agitation, acute psychosis, delirium, hallucinations, tourette syndrome as well as the symptoms of these diseases such as nausea and vomiting. It works by blocking the D1 and D2 receptors at the mesolimbic and mesocortical region of the brain. Most of the administered drug is metabolized through the liver and the excess of the drug is eliminated through the urine. The concentration of haloperidol in brain tissue is a lot higher when compared to blood levels, and it is slowly eliminated from brain tissue, which is probably why a gradual disappearance of adverse effects when the medication is stopped is observed. When administered orally, its bioavailability ranges from 60 to 70 percent but it is 100 percent when administered intravenously. The half life of haloperidol is 18 to 21 hours and its common side effects are extrapyramidal symptoms like akathisia, tardive dystonia, dystonic reactions, tremors, muscle spasms, rigidity, convulsions and anticholinergic effects. Haloperidol induced anticholinergic effects include dry mouth, diaphoresis, urinary retention, blurred vision. Other common side effects caused by haloperidol include neuroleptic malignant syndrome, parkinsonism, seizures and erectile dysfunction. Haloperidol is contraindicated in parkinson's disease, akathisia, spasticity disorders, CNS depression, dementia, progressive supranuclear palsy. Common symptoms associated with its overdose include drowsiness, hypotension or hypertension, tremors, hypothermia, ventricular arrhythmias and in severe cases, coma.

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The review shows different neurological complications of haloperidol, apart from the case study of accidental haloperidol poisoning. It also refers to other manifestations such as the case of drug induced dystonia as a result of antipsychotics (haloperidol) administered for sedation. Parkinsonism, associated with the blockage of dopaminergic D2 and serotonergic 5-HT2A receptors induced by antipsychotics (haloperidol), may occur with extrapyramidal side effects. Myoclonus with other acute or chronic movement disorders is associated with the cortex, basal ganglia and brain stem and is observed as the blockage of dopamine receptors at the striated pathways, induced by the action of haloperidol. The complex relationship between antipsychotics (haloperidol) and neuroleptic malignant syndrome (NMS) is also observed due to the presence of hypothermia, muscle rigidity, altered mental status an autonomic dysfunction. The presence of obsessive compulsive symptoms (OCS) is also observed due to the administration of antipsychotics, although the incidence potential of obsessive compulsive symptoms in patients may vary based on the specificity of antipsychotic administered, in this case clozapine and haloperidol. Apart from neurological complications, haloperidol affects other areas of the human anatomy and physiology, as it induces cardiac side effects such as tachycardia, hypotension, cardiac arrhythmias, QT interval prolongation and torsade de points.

Haloperidol overdose or accidental poisoning can be therapeutically managed by intensive care with a primary aim to stabilize the body's vital functions. Gastric lavage or emesis is carried out if its detected early in the case of oral overdose/poisoning. Bromocriptine and ropinirole can be administered in cases of intense complications seen in serious overdose. They act as dopamine receptor antagonists thereby reducing the extrapyramidal effects. Haloperidol overdose if not detected early or treated appropriately can produce dire repercussions. In cases of withdrawal, a gradual process is recommended due to the acute symptoms associated with withdrawal like restlessness, muscle pain, nausea, vomiting and insomnia.

Case Report

A 3 year old male child with body weight (10kg) was brought into the hospital with a chief complaint of fever since 2 days, and one episode of seizure. The child was dull and drowsy and his physiological and laboratory examinations revealed in the table below.

EXAMINATIONS	VALUES
BP	80/60mmHg
PULSE RATE	126bpm
RESPIRATORY RATE	26 b/min
WBC	11800/mL
HB	8.1g/dl
PH COUNT	3.6
ESR	30mm/h
CRP LITRES	5.3mg/L
S, SODIUM	141
S. POTASSIUM	38
S.CHLORINE	102
S. CALCIUM	5

The patient was provisionally diagnosed with occulogyric crisis with encephalopathy. Accidental ingestion of haloperidol was suspected and the label of the medicine indicated the dosage as 5mg. Based on the laboratory findings and the symptoms presented, the child was diagnosed with haloperidol induced seizures, and gastric lavage was done to remove the ingested drug. The patient was given IV fluids and antibiotics. Seizure related activity was observed on the 2nd day of hospitalization. Intravenous fosphenytoin 4ml + 20ml NS was started. The patient became gradually asymptomatic and started accepting feeds. He was subsequently discharged with multivitamin drops.

A Concise Review Of Haloperidol Induced Neurological Disorders

REFERENCE	**5**	**6**	**7**	**8**	**9**	**10**	**14**	**15**
AGE	6 years	2 years	75 years	33 years	12 years	83 years	48 years	37 years
SEX	Female	Female	Male	Male	Male	Male	Male	Male
SYMPTOMS	Altered sensation, persistent	Seizures, abnormal neck	Primary generalized tonic	Parkinson like symptoms,	Eye deviation, hypertoni	Myoclonus jerks in limbs,	Raised BP. Altered	Obsessive Compul

	vomiting, febrile.	movements.	clonic seizures lasting for 2-5 minutes, post-ictal confusion and weakness.	rigidity of movement, slowness in movement, increased salivation.	a. Left deviation of lip, jaw swinging, torticollis, hypertonia of limb.	trunks, observed after 2 days use of haloperidol.	consciousness, Muscle rigidity, hyperthermia.	sive symptoms.
TREATMENT	Promethazine hydrochloride (0.1mg/kg), Trihexyphenidyl (2mg/dose TID).	Fosphenytoin (5mg), Promethazine (0.1mg/kg), Trihexyphenidyl (2mg/TID).	Haloperidol discontinued.	Patient was advised to stop haloperidol and replace it with promethazine, olanzapine, risperidone, trihexyphenidyl HCL with vitamin D supplement.	Patient treated with IV hydroxyzine.	Haloperidol was stopped, and clonazepam 0.5mg BID was introduced.	Haloperidol was discontinued, and dantrolene sodium 9mg IV and bromocriptine 5mg TID was used.	Haloperidol was replaced with olanzapine (7.5mg) BD
PROGNOSIS	Patient regained consciousness and was asymptomatic.	Patient was asymptomatic and discharged with multivitamin drops.	No further seizure activity.	After a month of regimen changing, extrapyramidal symptoms decreased.	The patient was asymptomatic and discharged.	Myoclonus jerks decreased after 2 days then after clonazepam was also discontinued.	After 7 days of drugs, fever, muscle rigidity decreased.	Symptoms gradually decreased.
DOSE	5mg	2-5mg	2mg every 6 hours	5mg TID	4.5mg	1mg TID	5mg every 6 hours. 60mg daily over the course of 5 days.	7.5mg BD

Discussion:-

The factors responsible for determining the risk of provocation of seizure by antipsychotic drug therapy include Drug dosage, Plasma concentration, Intrinsic convulsant potential of a drug, Patient related factors (epilepsy, reduced drug elimination, neurologic abnormality, etc), and Factors influencing CNS levels. Among 1st generation antipsychotic, chloropramazine has the greatest risk for the induction of seizures. In 2nd generation antipsychotic however, clozapine is noted for having the greatest risk. Incidence of seizures is more prevalent in patients with

antipsychotics as compared to patients that are not on antipsychotic medication. 2nd generation antipsychotics are usually associated with a higher risk of seizures as compared to the 1st generation antipsychotics. Haloperidol being a butyrophenone acts by inhibiting dopamine mediated neurotransmission in the cerebrum and basal ganglia. An adverse effect of this pharmacological action would be the initiation of an imbalance in the glutamatergic signaling (excitatory) and GABAergic signaling (inhibitory) of the synapses which is what constitutes as the cause of a seizure activity. Seizures are a very common adverse neurological complication of haloperidol poisoning. Extrapyramidal side effects occur mostly due to the presence of an active metabolite, which is rarely the case in intravenous administrations as compared to intramuscular administrations.

The metabolism of haloperidol mostly occurs through glucuronidation and ketone reduction. Enzymes such as cytochrome p450 is paramount (CYP3A4 particularly), as well as CYP2D6. Haloperidol concentrations are determined by the actions of these enzymes, as a decrease in CYP2D6 enzyme activity may elevate the concentration levels. Also, haloperidol plasma concentrations may be influenced by the action of these inhibitory enzymes, some of which include CYP3A4 inhibitors (Azoles), CYP2D6 inhibitors (Quinidine, Sertaline), combined CYP3A4 and CYP2D6 inhibitors (Fluoxetine) and miscellaneous mechanisms (Buspirone). The consequence of increased haloperidol plasma concentrations is evident in the presence of adverse effects, some of which are discussed in this study. Similarly, the decrease in the plasma concentration of haloperidol is facilitated by its co-administration with strong enzyme inducers of CYP3A4. This is seen in interactions with drugs such as carbamazepine, phenobarbitol, phenytoin, rifampicin, etc. During drug combinations such as these, it is advised that the patients are monitored properly, as well as the dosage intervals.

Removal of the CYP3A4 inducer, leads to the subsequent increase in the concentration of haloperidol. Therefore, adjusting the dosage as well as the interval based on administration is advised. Haloperidol also plays a major role in the augmentation of CNS depressants (opiates, hypnotics). It possesses an increased CNS effect on combination with methyldopa and it impairs the antiparkinsonism action of levodopa. It antagonizes the action of sympathomimetic agents and consequently reduces the action of adrenergic blocking agents, By negating the action of TCA; it potentially leads to increased TCA toxicity. Haloperidol is present in the plasma and urine of breast fed newborns of mothers that are treated with it, therefore, nursing of infants while undergoing treatment is ill advised. It is also not advisable to dispense during 3rd trimester of pregnancy due to the risk of developing extrapyramidal neurological complications.

Apart from the occurrence of seizures, other neurological complications influenced by the action of haloperidol based on the review include extrapyramidal symptoms (consisting of symptoms such as restricted mobility, slurred speeches, and generalized weakness), which manifests as laryngeal dystonia (after 1-5 days of initiation), characterized by respiratory distress and hypoxia as well as myoclonus symptoms which occur as infrequent muscle twitches and jerks. Extrapyramidal symptoms based on antipsychotics, occurs due to the blockage of D2 receptors in the nigostriatal pathway. Tardive dyskinesia, (characterized by involuntary movements of the limbs), also occurs as well as motor restlessness and parkinson's disease which occurs after 1-4 weeks of drug initiation and is characterized by rigidity and slowness in movement as well as increased salivation. Neuroleptic Malignant Syndrome (NMS) is a serious neurologic condition that arises from an unusual or peculiar reaction to an antipsychotic, in this case, Haloperidol. Recovery from NMS based on haloperidol use is a likely outcome, especially in females. Death, however is also considered an outcome by gastrointestinal/ulcer bleeding or by necrotizing enteritis. Haloperidol, being a potent non-selective dopamine receptor antagonist, has a role in the withdrawal of dopaminergic agents that acts as a secondary cause in the manifestation of NMS. In this study, it is characterized by the occurrence of altered consciousness, increased BP, muscle rigidity, and hyperthermia with profuse diaphoresis, as well as elevated serum creatinine phosphokinase and rhabdomyolysis. Obsessive compulsive symptoms can manifest in its symptoms as a complication of haloperidol, and upon replacement, the symptoms are abated.

Conclusion:-

Haloperidol is an antipsychotic usually prescribed to treat neurological conditions such as schizophrenia, tics in tourette syndrome, derilium, hallucinations, acute psychotics, etc. Other antipsychotics can also be used in place of haloperidol as it has been shown to reduce extrapyramidal symptoms. Research has reported gross adverse effect, on the combination of haloperidol and lithium such as tardive dyskinesia, lethargy, leukocytosis, neuroleptic malignant syndrome, coma and irreversible brain damage. Also, haloperidol has been noted to obtrude with the action of coumarin anticoagulant in an antagonistic manner.

Apart from neurological (nervous system) disorders, haloperidol leads to endocrine disorders (hormonal), vascular disorders (hypotension), reproductive disorders (dysmenorrheal, menstrual disorders) and cardiovascular disorders (ventricular arrhythmia). Adverse reactions associated with the nervous system upon haloperidol use based on NMS are notably convulsions and headache. Extensive research is still being done to determine the full impact and pharmacokinetic action of haloperidol, especially in its influence on renal or hepatic impairment. Reported cases of sudden death in psychiatric patients receiving haloperidol, is rare, although elderly patients are at an increased risk. Observational studies have also shown a potential risk of cerebrovascular adverse event with some atypical antipsychotics.

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None.

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