Neuroleptic-Induced Extrapyramidal Symptoms

LIZA S. PAPPACHAN

Lecturer, M.Sc. (Mental Health Nursing)
C/o Manopchar Hospital,
Mana Basti, Raipur, Chhattisgarh

Abstract

The present study aimed to assess the knowledge of different types of neuroleptics, which are antipsychotic medication used in mental illness and to know about different types of extrapyramidal side effects (drug reaction), their symptoms, diagnosis and treatments.

Keywords: Extrapyramidal symptoms; Neuroleptics; Acute dystonia, Parkinsonism; Akathisia; Tardive dyskinesia; Neuroleptic malignant syndrome.

Introduction

Neuroleptics are antipsychotic medications used in the treatment of mental illness - primarily schizophrenia. Some neuroleptics have also been used to treat certain digestive disorders associated with diabetes and full or partial stomach paralysis (gastroparesis).[1]

These medications operated by blocking receptors in the dopamine pathway of the brain, which controls voluntary muscles and certain emotional response mechanisms (known as the nigrostriatal pathway). While neuroleptics are designed to target specific dopamine receptors and relieve patients of certain conditions, side effects from using them may include symptoms associated with tardive dyskinesia and other movement disorders.[1]

Types of Neuroleptics

Many neuroleptic medications have been developed throughout the past 60 years, but all of these fall into three broad categories, including:[1]

Typical: These are the earliest neuroleptic drugs, dating from the early 2950s. Typical neuroleptics are strongly associated with the development of tardive dyskinesia symptoms. Some of these medications have been "first generation."

Atypical: The "second generation" of neuroleptics were developed between the early 2960s and the 2980s. Although these drugs are also known to cause symptoms of tardive dyskinesia, such symptoms may take longer to develop.

*Third Generation:*These medications are the latest to be developed and still carry the risk of causing dyskinesia. Since these are the newest medications available (developed since 2002), they are also the most costly.

Corresponding author: Mrs. Liza S. Pappachan, Lecturer, M.Sc. (Mental Health Nursing), C/o Manopchar Hospital, Mana Basti, Raipur, Chhattisgarh.

E-mail: liza_hiradhar@yahoo.com

(Received on 06.04.2013, Accepted on 30.04.2013)

Extrapyramidal symptoms

Extrapyramidal side effects are type of drug reaction that occurs due to interactions with the extrapyramidal system in our body. There are two broad categories of motor neural pathways in our body.

One is Pyramidal system (Tracts originating from motor cortex and innervating skeletal muscles) and other is Extrapyramidal system (Pathways other than pyramidal system which affects motor movements).

Most antipsychotic drugs affect this extrapyramidal system due to their dopamine blocking properties. Therefore, they cause extrapyramidal side effects. Older or typical antipsychotics are notorious for this side effect.

What are the symptoms of extrapyramidal side effects?

Box: 1

Common Dystonias
• Torticollis (lateral neck rotation) • Retrocollis (neck extension) • Limb torsion • Forced jaw closing (trismus) or opening • Tongue protrusion • Opisthotonus (extension of head, neck, and paraspinal muscles in an arch) • Occulogyric crisis (forceful eye deviation).

1. Acute Dystonia
2. Parkinsonism
3. Akathisia
4. Tardive Dyskinesia
5. Neuroleptic Malignant Syndrome

Acute dystonia

Long-lasting contraction or spasm of musculature develops secondary to the use of antipsychotic medication.[2]

Acute dystonia typically subsides spontaneously within hours after onset.

Dystonia usually emerge within 0–7 days of starting antipsychotics therapy.

Pathophysiology

Abnormalities in dopamine–acetylcholine balance - (cholinergic antagonists and dopaminergic agonists improve the dystonia in many patients).[2]

A relative norepinephrine hyperactivity may be caused by dopaminergic blockade (as occurs in drug-induced dystonia) or from enhanced release of norepinephrine (in idiopathic torsion dystonia).

Epidemiology

2 to 12% patients on conventional antipsychotic medications develop dystonia.

Risk factors include

- If the patient is on high-potency conventional antipsychotics, e.g. Haloperidol
- If the patient is of young age, male sex, and had a prior dystonic reaction.

Clinical features

- Abnormal positioning of the head and neck in relation to the body (e.g., retrocollis, torticollis).
- Spasms of the jaw muscles (trismus, gaping, grimacing).
- Impaired swallowing (dysphagia).
- Thickened or slurred speech due to hypertonic or enlarged tongue (Macroglossia) tongue protrusion or tongue dysfunction.
- Eyes deviated up, down, or sideward (occulogyric crisis).
- Abnormal positioning of the distal limbs or trunk.

Treatment

Standard treatment is anticholinergic agent-equivalent of 2 mg of benztropine or 50 mg of diphenhydramine/promethazine.[2]

In case of laryngeal or pharyngeal dystonias

with airway compromise, repeated dosing of medication should occur at shorter intervals until resolution is achieved.[2]

Parkinsonism

A condition characterized by Parkinsonian signs or symptoms (resting tremor, muscle rigidity, and bradykinesia/akinesia) that develop in association with the use of an antipsychotic medication.[2]

Most commonly associated with use of Dopamine Receptor Antagonists.

Pathophysiology

No specific, standard criteria exist for the neuropathologic diagnosis of Parkinson disease, as the specificity and sensitivity of its characteristic findings have not been clearly established. However, the following are the 2 major neuropathologic findings in Parkinson disease:

- Loss of pigmented dopaminergic neurons of the substantia nigra pars compacta
- The presence of Lewy bodies and Lewy neurites

The loss of dopamine neurons occurs most prominently in the ventral lateral substantia nigra. Approximately 60-80% of dopaminergic neurons are lost before the motor signs of Parkinson disease emerge.

Epidemiology

5 to 90%, depending on the use of first-generation antipsychotic.[2]

The *prevalence* (proportion in a population at a given time) of Parkinson disease is about 0.3% of the whole population in industrialized countries. Parkinson disease is more common in the elderly and prevalence rises from 1% in those over 60 years of age to 4% of the population over 80.[3]

Clinical features include

- Parkinsonian tremor (i.e., a coarse, rhythmic, resting tremor with a frequency between 3 and 6 cycles per second, affecting the limbs, head, mouth, or tongue).
- Parkinsonian muscular rigidity (i.e., cogwheel rigidity or continuous "lead-pipe" rigidity).
- Akinesia (i.e., a decrease in spontaneous facial expressions, gestures, speech, or body movements)

Differential diagnosis includes

- Major depressive disorder
- Catatonia
- Negative symptoms of schizophrenia

Treatment

- Milder cases do not require treatment.
- Decrease the dose of antipsychotic to the lowest effective dose for the patient.
- Administer low dose anticholinergic - benztropine/trihexyphenidyl.
- Treat with atypical antipsychotics.

Akathisia ("inability to sit")

Definition: "A subjective feeling of restlessness and an intensely unpleasant need to move occurring secondary to antipsychotic treatment".[1,2]

Usually emerge with in 7–24 days of starting antipsychotics therapy.

Pathophysiology

The pathophysiology of Akathisia may involve dopamine, acetylcholine, ã-aminobutyric acid (GABA), norepinephrine, serotonin, and neuropeptides. Dopamine antagonism impacts various neurotransmitters and directly correlates with EPS. For example, dopamine antagonism may affect GABA in the pallidus or norepinephrine in the locus ceruleus.[4]

Epidemiology

Occurs in 20–75% of patients treated with conventional agents.

Clinical features

- Subjective complaints of restlessness
- Fidgety movements or swinging of the legs
- Rocking from foot to foot while standing
- Pacing to relieve restlessness

Inability to sit or stand for at least several minutes

Differential Diagnosis

Primary psychiatric disorders presenting with agitation, such as depression, mania, anxiety, schizophrenia, dementia, delirium, substance intoxication/withdrawal, and attention-deficit/hyperactivity disorder.[2,5]

Restless legs syndrome (RLS)

Treatment

- Beta-blocker propranolol - often considered first-line treatment
- Benzodiazepines - clonazepam and Lorazepam[6,7]
- Anticholinergic agents – benztropine[6,7]

Tardive Dyskinesia

Definition: A syndrome consisting of abnormal, involuntary, choreoathetoid movements typically involve the mouth, face, limbs, and trunk caused by long-term treatment with antipsychotic medication.[8,9]

Pathophysiology[2,5]

Although the pathophysiology of Tardive Dyskinesia is not well understood, it is hypothesized that central dopamine blockade plays a role in the pathogenesis of this condition. It is also hypothesized that acute movement disorders result, in part, from the blockade of dopamine receptors by dopamine antagonists.[10]

Several mechanisms have been proposed by which Tardive Dyskinesia may develop, including the following:

- Striatal dopamine receptor supersensitivity may be responsible
- Chronic dopamine blockade may result in upregulation of dopamine receptor responsiveness
- Compensatory supersensitivity of dopamine receptors may develop after long-term blockade; long-term blockade of dopamine D_2 receptors in the basal ganglia by dopamine D_2 antagonists (eg, neuroleptics) may produce Tardive Dyskinesia.
- When dopamine D_2 -receptor blockade is reduced (even slightly), an exaggerated response of the postsynaptic dopamine D_2 -receptor (even to low concentrations of dopamine) may result
- Striatal disinhibition of the thalamocortical pathway from imbalance of D_1 and D_2 receptors may be involved
- Neurodegeneration secondary to lipid peroxidation or excitotoxic mechanisms may be responsible

Epidemiology (after starting antipsychotics)

- 5% after 2 year
- 28.5% after 4 years
- 40% after 8 years

Clinical Features

- Involuntary movements of the tongue, jaw, trunk, or extremities have developed in association with the use of neuroleptic medication.[8,9]
- Choreiform movements (i.e., rapid, jerky, nonrepetitive).[8,9]
- Athetoid movements (i.e., slow, sinuous, continual).[8,9,]

- Rhythmic movements (i.e., stereotypies).[8,9]

Differential Diagnosis

- Sydenham's chorea
- Huntington's disease
- Conversion disorder and malingering
- Hyperthyroidism

Complications

- Emotional distress
- Dental problems
- Respiratory alkalosis

Treatment

- Atypical antipsychotics may improve the condition
- Clozapine may be effective in reducing Tardive Dyskinesia in patients with existing Tardive Dyskinesia.
- Vitamin E (alpha-tocopherol), a free-radical scavenger, has been reported to improve symptoms of tardive dyskinesia.[11]
- Abnormal Involuntary Movement Scale (AIMS) may be used to monitor progress of the treatment.[6,7]

Neuroleptic Malignant Syndrome

"Neuroleptic malignant syndrome is a life-threatening, neurological disorder most often caused by an adverse reaction to neuroleptic or antipsychotic drugs. Symptoms include high fever, sweating, unstable blood pressure, stupor, muscular rigidity, and autonomic dysfunction."[3]

Causes

All classes of neuroleptics (dopamine D2-receptor antagonists) are associated with Neuroleptic malignant syndrome, and dopamine receptor blockade is considered the cause of Neuroleptic malignant syndrome.

Blockade of dopamine in the striatum can cause rigidity, tremor, and rhabdomyolysis.

Blockade of dopamine in the hypothalamus can cause impaired temperature regulation and hyperthermia.

This theory does not explain why only some patients develop Neuroleptic malignant syndrome. It also does not explain why patients rechallenged with neuroleptics do not always redevelop Neuroleptic malignant syndrome.[8,9]

Neuroleptic malignant syndrome is usually caused by Neuroleptic Drug use, and a wide range of drugs can result in Neuroleptic malignant syndrome.[2]

Pathophysiology

The mechanism is thought to depend on decreased levels of dopamine activity due to:

- Dopamine receptor blockade
- Genetically reduced function of dopamine receptor D_2

Symptoms overview

- Increased body temperature >38°C (>100.4°F) in Neuroleptic malignant syndrome.
- Confused or altered consciousness
- Diaphoresis "sweat shock"
- Rigid muscles
- Autonomic imbalance

Epidemiology

The incidence of Neuroleptic malignant syndrome is between 0.2%–3.23percent.[2,7]

Male: female ratio is 2:2.[2]

Treatment

Stop causative agent: Neuroleptic malignant syndrome is a medical emergency, and can lead to death if untreated. The first step is to stop neuroleptic drugs and treat the hyperthermia aggressively, such as with cooling blankets or

ice packs to the axillae and groin.[12]

Supportive care: Supportive care in an intensive care unit capable of circulatory and ventilatory support is crucial.[12]

Complications are common and severe, even fatal. These include:[3]

- Dehydration
- Electrolyte imbalance
- Acute renal failure associated with rhabdomyolysis
- Cardiac arrhythmias including torsades de pointes and cardiac arrest
- Myocardial infarction
- Cardiomyopathy
- Respiratory failure from chest wall rigidity, aspiration pneumonia, pulmonary embolism
- Deep venous thrombophlebitis
- Thrombocytopenia
- Disseminated intravascular coagulation
- Deep venous thrombosis
- Seizures from hyperthermia and metabolic derangements
- Hepatic failure
- Sepsis

Medical therapy

Dantrolene is a direct-acting skeletal muscle relaxant and is effective in treating malignant hyperthermia.[6,7]

Bromocriptine, a dopamine agonist, is prescribed to restore lost dopaminergic tone.

Amantadine has dopaminergic and anticholinergic effects and is used as an alternative to bromocriptine.[8,9]

Other medications used with anecdotal success include levodopa , apomorphine , carbamazepine , and benzodiazepines (lorazepam or clonazepam).[8,9,12]

Prognosis

Most episodes resolve within two weeks. Reported mean recovery times are 7 to 22 days.[7]

Scales & Instruments

Simpson-Angus Rating Scale for Extra-pyramidal Side Effects[9]

The Simpson-Angus scale was developed to monitor the effects of antipsychotic drugs.

It has 20 items, each of which is rated on an item-specific, five-point severity scale ranging from 0 to 4.

Scores are reported as the mean on all 20 items, with 0.3 considered the upper limit of normal.

It is focused on parkinsonian symptoms - rigidity, bincludes one akathisia item.

It can be administered by trained lay raters.

Good psychometric properties have been reported.

Abnormal Involuntary Movement Scale (AIMS)

The Abnormal Involuntary Movement Scale (AIMS) is a rating scale that was designed in the 1970s to measure involuntary movements known as tardive dyskinesia (TD). Tardive dyskinesia is a disorder that sometimes develops as a side effect of long-term treatment with neuroleptic (antipsychotic) medications.

Developed to measure dyskinetic symptoms in patients taking antipsychotic drugs.[7]

22 items, on five-point severity scale ranging from 0 to 4.

Total scores are not generally reported. Instead, changes in global severity and individual areas can be monitored over time.

Ten items cover the movements themselves, divided into sections rating global severity and those related to specific body regions; two items concern dental factors that can complicate the diagnosis of dyskinesia.

In the presence of extended neuroleptic exposure and the absence of other conditions causing dyskinesia, mild dyskinetic movements in two areas or moderate movements in one area suggest a diagnosis of tardive dyskinesia.

The scale can be administered by trained raters.

It can be completed in less than 20 minutes.

Good psychometric properties have been reported.

References

1. http://www.tardivedyskinesia.com/causes/neuroleptics.php.
2. Miyamoto S, Merrill DB, Lieberman JA, Fleischacker WW, Marder SR. Antipsychotic Drugs. In Psychiatry, Third Edition. Edrs. Allan Tasman, Jerald Kay, Jeffrey A. Lieberman, Michael B. First and Mario Maj. John Wiley & Sons Ltd; 2008.
3. http://en.wikipedia.org/wiki/Parkinson%27s_disease#Pathophysiology
4. http://www.cnsspectrums.com/aspx/articledetail.aspx?articleid=1262
5. Theodore I Benzer, MD, PhD. Neuroleptic Malignant Syndrome. *Emedicine.* 2005.
6. Daniel DG, Igan MF, Wolf SS. Neuropsychiatric Aspects of Movement Disorders. In Comprehensive Textbook of Psychiatry, Vol 7, Kaplan HI and Saddock BJ (eds). Baltimore, MD, USA: Williams & Wilkins; 2012.
7. http://www.uptodate.com/contents/neuroleptic-malignant-syndrome#H4
8. Buckley PF, Hutchinson M. Neuroleptic malignant syndrome. *J Neurol Neurosurg Psychiatr*. 2995; 58(3): 272–3. doi:20.2236/jnnp.58.3.272. PMC 2073359. PMID 7897404.
9. http://www.minddisorders.com/A-Br/Abnormal-Involuntary-Movement-Scale.html
10. http://emedicine.medscape.com/article/1151826-overview#aw2aab6b3
11. http://ajp.psychiatryonline.org/article.aspx?Volume=149&page=773&journalID=13
12. http://en.wikipedia.org/wiki/Neuroleptic_malignant_syndrome