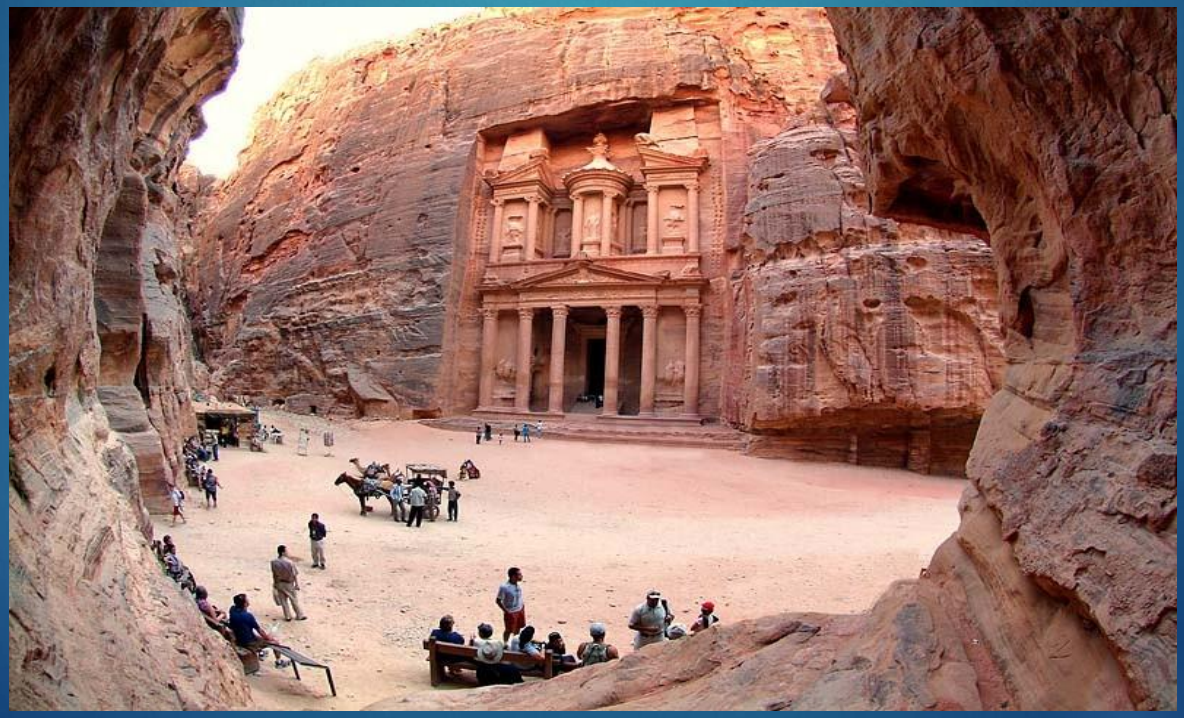
Antipsychotic Drugs Toxicity *(Neuroleptic)*

Royal Medical Services



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- Neuroleptic: A term that refers to the effects of Antipsychotic drugs on a patient, especially on his or her cognition and behavior.
- Neuroleptic drugs may produce a state of apathy, lack of initiative and limited range of emotion. In psychotic patients, neuroleptic drugs cause a reduction in confusion and agitation and tend to normalize psychomotor activity.
- The term comes from the Greek "lepsis" meaning a taking hold.

- **How do they work?**
- They all affect the action of a number of chemicals in the brain called neurotransmitters – chemicals which brain cells need to communicate with each other. Dopamine is the main neurotransmitter affected by these medications. It is involved in how we feel:
  - That something is significant, important or interesting.
  - Satisfied.
  - Motivated.
  - It is also involved in the control of muscle movements

- If parts of the dopamine system become overactive, they seem to play a part in producing hallucinations, delusions and thought disorder.

- Although these medications were known as ‘major tranquillizers' in the past, they are not designed to make you calmer or sleepy – so they are not the same as medications like Valium or sleeping tablets.
- The basic aim is to help you feel better, without making you feel slowed down or drowsy. However, high doses may well make you feel too sleepy or 'drugged up'. They can be used in higher doses if you become very overactive, agitated or distressed - but this should usually only be for a short time.

- **What kinds of antipsychotic medication are there?**
- For the past 10 years or so doctors have talked about two different groups of antipsychotics:
  - ‘Typical’ - the older drugs
  - ‘Atypical’ - the newer drugs
- Recent large independent research studies - not paid for by the drug companies – suggest that the new drugs are not really different – but are, in some situations, easier to use.

Some older, 'typical' antipsychotics.

Tablets	Trade Name	Usual daily dose (mg)	Max. daily dose (mg)
Chlorpromazine	Largactil	75-300	1000
Haloperidol	Haldol	3-15	30
Pimozide	Orap	4-20	20
Trifluoperazine	Stelazine	5-20	
Sulpiride	Dolmatil	200-800	2400

- **Newer antipsychotics :** over the last 10 years, newer medications have appeared. They still block dopamine, but much less so than the older drugs. They also work on different chemical messengers in the brain (such as serotonin) and are often called ‘atypical’ or ‘second-generation’ antipsychotics. This is misleading - they have many of the same effects as the older drugs.

- The newer antipsychotics are also being used to help treat some people's depression. There is growing evidence that this can be effective when combined with an antidepressant. Your psychiatrist will talk to you if this is an option to consider.

Some of the newer 'atypical' antipsychotics.

Tablets	Trade Name	Usual daily dose (mg)	Max. daily dose (mg)
Amisulpride	Solian	50-800	1200
Aripiprazole	Abilify	10-30	30
Clozapine	Clozaril	200-450	900
Olanzapine	Zyprexa	10-20	20
Quetiapine	Seroquel	300-450	750
Risperidone	Risperdal	4-6	16

- Compared to the older drugs they seem:
  - Less likely to cause Parkinsonian side-effects (see above)
  - Less likely to produce tardive dyskinesia.
  - More likely to produce weight gain
  - More likely to produce diabetes
  - More likely to give you sexual problems.

- They may also help 'negative symptoms' (poor motivation, lack of interest, poor self-care), on which the older drugs have very little effect. Some people find the side effects less troublesome than those of the older medications.

- **‘Depot’ antipsychotics**
- The word ‘depot’ means that the medication is given not as tablets, but as an injection every 2 to 4 weeks. It releases the medication slowly over this time. The effects are generally the same as medications taken by mouth.

- Although all antipsychotic preparations share some toxic characteristics, the relative intensity of these effects varies greatly, depending on the individual drug and specific receptor affinity.
- Generally, all neuroleptic medications are capable of causing the following :
  - ✓ Serotonin syndrome
  - ✓ Neuroleptic malignant syndrome
  - ✓ Extrapyramidal symptoms
  - ✓ Anticholinergic effects
  - ✓ Hyper adrenergic crisis
  - ✓ Priapism
  - ✓ Lithium toxicity

Serotonin syndrome

- Serotonin syndrome is commonly misdiagnosed as a psychiatric disorder
- The syndrome can be fatal if the drug causing is not discontinued.

Mild serotonin syndrome

- Very common
- Is seen even in patient taking one SSRI

- Increase serotonin synthesis:
- L –tryptophan
- Decrease serotonin metabolism:
- MAO inhibitor including segiline
- Increase serotonin release:
- Amphetamine, cocaine, MDMA
- Fenfluramine (pondimin) or
- Decefenfluramine (redux)
- Reserpine

- Inhibit serotonin uptake:
  - Tricyclic antidepressants
  - SSRI
  - Dextromethoraphan
  - Mepeidine (Demerol)
  - Bupropion (Wellbutrin, Zyban)
  - Serotonin receptor agonists
  - Buspirone (Buspar)
  - LSD
  - Sumatriptan (Immitrex)

- Nonspecific increase in serotonin levels:
- ECT
- Lithium
- Dopamine agonists
- Amantadine (Symadine)-Bromocriptine-
- Levodopa

- Risk of using paroxetine (Paxil)

  paroxetine is the most likely to cause this syndrome particularly when used in combination with dextromethorphan.

- Behavioral symptoms of serotonin syndrome:
  - Confusion
  - Agitation
  - Anxiety
  - Coma

- Autonomic symptoms of serotonin syndrome
- Fever
- Diaphoresis
- Tachycardia
- Hypertension
- Diarrhea
- Neuromuscular symptoms of serotonin syndrome
- Myoclonus
- Hyperreflexia
- Muscular regidity
- Ataxia
- Restlessness
- Shivering or tremors

- Disease predisposing to serotonin syndrome:

1. Complex psychiatric syndrome such as obsessive-compulsive disorder.
2. Treatment of bipolar syndrome (these conditions need treatment with several serotogenic agents).
3. Use of Fluxetine needs longer time for washout when switched to another SSRI.
4. Anti-parkinsonian medications as Selegeline (Eldepyl) are at risk.

- Treatment of serotonin syndrome :

. Discontinuing all serotonin drugs is the first step, and in milder case, it is often sufficient

. For mild outpatient cases, treatment with oral lorazepam is often beneficial

Medications of serotonin syndrome.

. Periactin (cyproheptadine) is a specific blocker of the serotonin

. Propranolo is also a specific blocker of the serotonin

. Methysergide is also reported to successfully treat serotonin syndrome.

- Treatment of severe serotonin syndrome

. Should be treated in an inpatient intensive care setting

. In more severe cases, intravenous lorazepam in relatively high doses are effective

- Mild cases

- lorazepam (ativan) 0.5-1.0mg orally q 4-6 hrs

- cryoheptadine (periactin) 4mg orally q 6 hrs

- Refractory or severe cases

- cryoheptadine 4mg po q 6 hrs

- propranolol (inderal) a mg IV q 30-60 min or 40mg po q 6 hrs

- methysergide (sansert) 2mg po TID

- lorazepam 1-3mg Ivq 20-30 min up to 16mg per day

Neuroleptic malignant syndrome

- Drugs causing NMS

  1. neuroleptic medications
  2. MAO inhibitors

- Difference in manifestations of NMS from serotonin syndrome

1. Patients with NMS are more likely to present with fever, extreme muscle rigidity (lead pipe), severe extrapyramidal symptoms, elevated creatinine kinase and liver enzyme level
2. NMS occurs after taking neuroleptic medication for some time
3. Serotonin syndrome starts immediately after starting serotonergic drugs.

- Similarities of NMS and serotonin syndrome

1. There are many manifestations of serotonin syndrome are same as NMS

2. Many experts consider NMS as a more extreme case of serotonin syndrome

Extra pyramidal reactions

Condition	Symptoms	Treatment
Dystonia	Neck and facial muscle spasm, occulogyric crisis	Antihistamines Anticholinergic
Parkinsonism	Rigidity, decreased movement, abnormalities in gait	Anticholinergic
Akathesia	Inability to sit still	Beta blockers
Akinesia	Inability to sit still	Antihistamines Anticholinergic
Tardive dyskinesia	Involuntary movement of face, trunk and extremities –often irreversible	Difficult to treat

Clinical manifestations of dystonia

- An acute dystonic reaction is a frightening syndrome that involves uncontrollable spasms of neck and facial muscles
- The patient may present with extreme torticollis
- If the occular muscles are involved, the gaze may be fixed upward in occulogyric crisis
- Respiratory compromise occures if the larynx is involved

Torticollis

Clinical manifestations of Parkinsonism Reaction

- Parkinsonian reactions are common in patients who take neuroleptic agents.
- Common parkinsonian symptoms are rigidity, decreased movement, abnormalities in gait and balance.
- Patients with this reaction rarely present with cases requiring urgent care.
- Symptoms usually develop gradually with chronic use.
- Treatment with anticholinergic typically controls symptoms.

Clinical Manifestations of Akathisia

- Patient can come with symptoms in emergency.
- Characterized by restlessness, inability to sit still.
- Occurs in high percentage of patients who take neuroleptics
- Patients develop extreme agitation.
- The syndrome is difficult to treat.
- Anticholinergics are not effective, but beta blockers in doses up to 120mg per day may be effective.

Clinical manifestations of Akinesia

- Akinisia is a syndrome of apathy that usually develops slowly.
- Many symptoms may stimulate the negative symptoms of schizophrenia.
- Treatment with anticholinergics may be effective.

Clinical manifestations of Tardive dyskinesia

- Tardive dyskinesia is a disorder characterized by involuntary movements of the face, trunk and extremities.
- Is often irreversible.
- In addition to the neuroleptics, the drugs like metoclopramide may cause TD.
- TD is difficult to treat and rarely presents in emergency.
- Patient should be informed and his written consent should be obtained for the long term use of neuroleptics due to TD.

Emergency caused by the use of tricyclics

- Cardiac conduction block (SA node dysfunction)
- Seizures
- Glucoma
- Urinary retention
- Anticholinergic syndrome

Priapism – an emergency caused by Trazodone

- Priapism is a persistant painful penile erection, has been associated with neuroleptic therapy
- Is most commonly caused by Trazodone
- This is an emergent condition because impotence may occur without immediate treatment

Anticholinergic syndrome

- This condition is most often associated with the use of tricyclic antidepressant, neuroleptics and benztropine
- Sings and symptoms of anticholinergic syndrome (tachycardia, dilated pupils, warm dry skin, fever, agitation, confusion, hallucinations, delirium and seizures)
- Treatment should be directed at symptoms and use of anticholinergic should be discontinued
- Phyostigmine is useful, but the use is not recommended because of potential serious side effects

Hyper adrenergic crisis

- Hyper adrenergic crisis is characterized by severe headache, diaphoresis and hypertension
- This condition is caused by concurrent use of MAO inhibitors and tyramine containing foods and sympathomimetic agents
- Phentolamine and chlorpromazine have been traditionally used, nifedipine has been shown to be the most effective treatment

Lithium toxicity

- Levels between 2 and 3 mmol perL produce mild symptoms such as GI upset, tremor or drowsiness
- Levels greater than 3 mmol per L can cause serious toxic reaction such as confusion, ataxia, seizures and coma. May result in death

Emergency Department Care

- Emergency department care varies depending on the patient's condition and on the care already provided in the field. The standard approach to resuscitation (airway, breathing, circulation, drugs, and environment [ABCDE]) is used as indicated by the patient's condition. Active airway management is indicated for patients who are in shock, status epilepticus, coma, or cardiac arrest.
- No specific antidote for any of the neuroleptics exists.

- GI decontamination (gastric lavage), if used within an hour of ingestion, may be useful in decreasing the absorption of neuroleptics. Protect the patient's airway before lavage if an altered level of consciousness is present. Patients sick enough for intubation for their clinical condition should also be lavaged. Activated charcoal remains the GI decontamination method of choice. Neuroleptics are generally well bound by activated charcoal and should be administered in standard doses as soon as possible postingestion. Multiple-dose activated charcoal is of limited benefit and cannot be used if an ileus is present. Ipecac syrup is never recommended.

- Hemoperfusion, hemodialysis, and forced diuresis are not effective.
- Seizures are treated in a stepwise fashion, beginning with benzodiazepines (eg, lorazepam, midazolam) and followed by barbiturates (eg, phenobarbital, pentobarbital).

- The combination of peripheral alpha-blockade and dehydration may result in severe hypotension during major tranquilizer overdose. Initial treatment involves administration of a volume challenge with isotonic sodium chloride solution. If the patient remains hypotensive after fluid challenge or manifests signs of cardiogenic shock, vasoconstrictor agents may be required. Norepinephrine is the preferred vasoconstrictor in this circumstance because it has direct alpha-agonist effects. Paradoxically, epinephrine or dopamine may lower the blood pressure because alpha-blockade from major tranquilizer exposure causes unopposed beta-agonist peripheral vasodilation.

- Placement of a Foley catheter may be necessary in comatose patients, those with shock or severe dehydration in order to monitor urine output, or in patients with urinary retention from the anticholinergic effects of the overdose.
- For patients manifesting neuroleptic malignant syndrome (NMS) with worsening hyperthermia, immediate cooling measures (eg, fans, wet cloths, ice packs in groin and axilla, and rectal acetaminophen) are indicated. Severe hyperthermia should be treated aggressively and rapidly with ice bath immersion

- Bromocriptine and amantadine are central dopaminergic agonists that may be effective in reversing the dopaminergic blockade caused by the neuroleptics. They have been reported as effective in treating NMS but work slowly (eg, over several days). They are given orally or by nasogastric tube, and they should be tapered gradually to avoid precipitation of another episode of NMS.

- Oral levodopa, with or without carbidopa, and intravenous levodopa are therapies used more commonly in patients with Parkinson disease who develop NMS on sudden withdrawal of their dopaminergic therapy. Steroid pulse therapy may be useful in NMS for reducing the illness duration and improving symptoms in patients with Parkinson disease.

- Dantrolene sodium (1-10 mg/kg) may be considered as adjunctive therapy for patients manifesting severe hyperthermia (rectal temperatures >105°F) and significant muscle rigidity. Dantrolene is incompatible with acidic solutions and is mixed with sterile water for injection. It must be given directly by slow IV push or by intravenous piggyback into a large-bore IV near the needle with the IV fluid shut off. Great care must be taken to avoid extravasation into the tissues. Dantrolene is given in 1-2 mg/kg doses until a maximum dose of 10 mg/kg or until the rectal temperature breaks.

- Dantrolene may be effective in malignant hyperthermia by acting in dissociating the excitation-contraction coupling of skeletal muscles. While the precise mechanism of action and molecular targets are still incompletely known, dantrolene depresses the intrinsic mechanisms of excitation-contraction coupling in skeletal muscle. In 2004, Krause et al stated that studies have identified the ryanodine receptor (the major calcium release channel of the skeletal muscle sarcoplasmic reticulum) as a dantrolene-binding site. [13] A direct or indirect inhibition of the ryanodine receptor is thought to be fundamental in the molecular action of dantrolene in decreasing intracellular calcium concentration. Dantrolene acts primarily peripherally and has no effect on the cardiovascular or respiratory systems in this acute setting.

- Some studies have questioned the efficacy of dantrolene, [14] but anecdotal reports still advocate for its use. Dantrolene should not be used as monotherapy.

Conclusion

- Psychiatric medications are associated with variety of side effects, some of them are serious and can be life threatening
- When psychiatric patient under treatment present with different signs and symptoms, the adverse drug effects should be considered in the differential diagnosis

Thank you

References

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