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Role of dichlorphenamide in management of periodic paralysis - A review

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1. INTRODUCTION:-

Periodic Paralysis (PP) is a rare group of hereditary neuromuscular disorders in which the patient experiences repeated episodes of temporary muscle weakness or complete paralysis. These attacks happen because of abnormal ion movement (especially potassium and sodium) inside muscle cells. When these ions do not move normally through their channels, muscle fibers cannot contract properly. This results in weak, floppy muscles or complete inability to move during an episode.

Periodic Paralysis mainly affects skeletal muscles (like arms, legs and trunk muscles). These episodes usually begin in childhood or teenage years and can continue throughout adult life. During an attack, a person may not be able to walk, lift, or hold objects normally. Some attacks last only a few minutes but others may last for hours. Between attacks, the person may appear normal, but repeated attacks can eventually cause permanent muscle weakness.

It is important to understand PP early because with proper lifestyle modification, trigger avoidance, and correct medicines, the frequency and severity of attacks can be reduced. With education, monitoring and supportive management, most patients can live an active and stable life.

2.CAUSES:-

Periodic Paralysis mainly occurs due to defects in the ion channels present in muscle cell membranes. These ion channels are responsible for the movement of sodium (Na^+), potassium (K^+), and calcium (Ca^{2+}) ions in and out of the muscle cells. These ions are essential for generating electrical signals that allow the muscle to contract and relax normally.

When a genetic mutation changes the structure or functioning of these channels, ions cannot move properly and muscle cells become electrically unstable. During certain situations (like high carb meal, rest after exercise, stress), this imbalance suddenly increases and causes the muscle to temporarily become non-functional, leading to paralysis episodes.

Main causes include:

1. Genetic mutations in SCN4A, CACNA1S, KCNJ2, and other ion channel genes.

2. Abnormal ion movement → especially potassium shift inside/outside muscle fibers.

3. Autosomal dominant inheritance → one mutated parent gene can pass the condition to children.

4. Thyroid dysfunction (in Thyrotoxic PP) due to excessive thyroid hormones influencing K^+ handling.

5. Lifestyle/environment triggers which worsen ion imbalance.

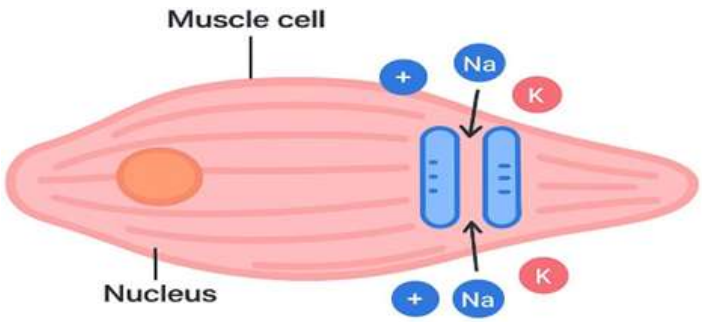

Figure 1: Ion Channel Malfunction in Muscle Cell

2.SYMPTOMS:-

The symptoms of Periodic Paralysis vary from person to person, but the main symptoms are related to sudden weakness due to ion imbalance.

Common symptoms include:

- Sudden episodes of severe muscle weakness, especially in arms and legs.
- Difficulty standing up, walking, climbing stairs or holding objects.
- Attacks may happen after waking up in the morning, after exercise, after eating high carbohydrate meals, emotional stress, or sudden temperature change.
- Some people feel a heavy feeling, numbness, light tingling or stiffness before an attack begins. The is known as a " warning" or a prodromal symptom.
- During severe attacks, a person may not be able to move limbs at all.
- Breathing muscles and throat muscles can rarely be involved, which is a medical emergency.
- Repeated attacks for many years can slowly lead to permanent muscle weakness even between episodes (progressive myopathy).
- Symptoms usually develop gradually over many years. That is why early diagnosis and treatment are important to prevent long term disability.

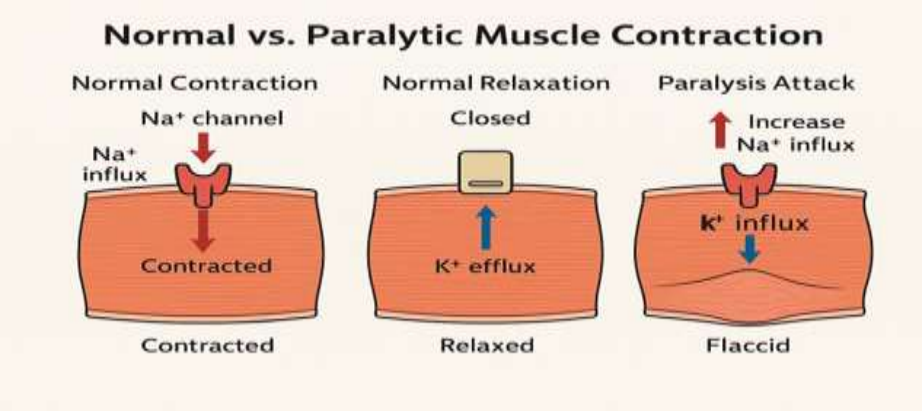

Figure 2: normal vs contraction vs attack condition in muscle

3.TYPES OF PERIODIC PARALYSIS:-

There are four major clinically recognized forms of Periodic Paralysis. They are classified based on potassium level changes in blood during attacks and based on underlying associated causes.

1) HypoPP (Hypokalemic Periodic Paralysis):-

- Serum potassium drops low during attacks.
- Triggered by carbohydrate heavy meals, stress, and rest after intense exercise.
- Caused commonly by mutations in CACNA1S and SCN4A genes.
- Mostly occurs in adolescence or early adulthood.
- Mild weakness between attacks may slowly become permanent over time.

2) HyperPP (Hyperkalemic Periodic Paralysis):-

- Serum potassium becomes high during attacks.
- Triggered by fasting, potassium rich foods, cold exposure, or rest after exercise.
- Episodes tend to be shorter but more frequent.
- Mutations usually in SCN4A gene.

3) ATS (Andersen–Tawil Syndrome):-

- Includes triad: periodic paralysis + cardiac arrhythmias + skeletal bone abnormalities.
- Potassium may be normal, low, or high during attacks.
- Characteristic ECG changes present.
- Caused by mutation in KCNJ2 gene.

4) TPP (Thyrotoxic Periodic Paralysis):-

- Occurs due to hyperthyroidism (thyroid hormone excess).
- Seen frequently in young adult males (but can occur in females).
- Potassium becomes low during attacks.
- Treatment mainly focuses on correction of thyroid function.

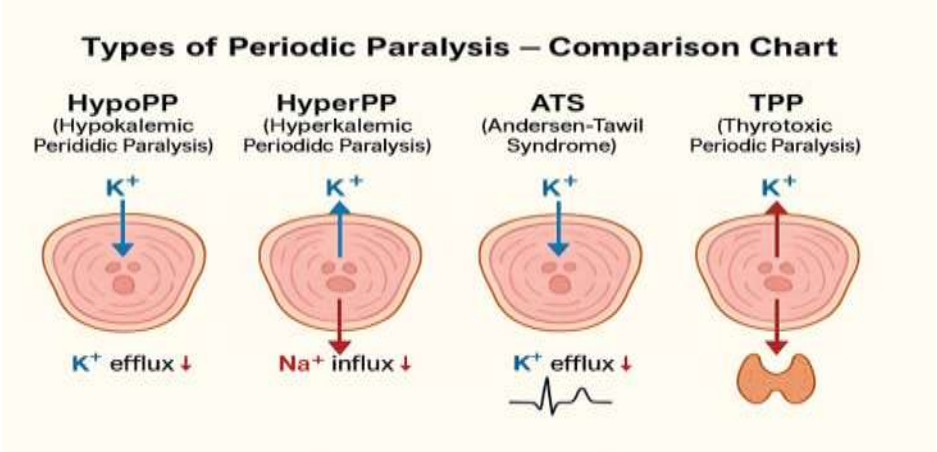

Figure3: comparison of periodic paralysis types

4.DIAGNOSIS:-

Diagnosis of Periodic Paralysis requires a combination of clinical observation, patient history, laboratory tests, and specialized investigations. This disorder is often misdiagnosed for many years because symptoms appear episodic and patients look normal between attacks. A good diagnosis depends heavily on understanding the pattern of weakness and identifying triggers.

Important diagnostic approaches:

1. Detailed medical history:

Doctor asks about frequency, pattern, triggers, and duration of episodes. Information like “episodes occur after eating rice or sweets” is extremely important.

2. Blood potassium levels:

Potassium (K^+) levels must be checked during the attack because between attacks potassium may be normal.

HypoPP → low potassium during attack

HyperPP → high potassium during attack

3. Electromyography (EMG):

EMG helps observe muscle electrical pattern. Certain characteristic EMG changes occur in Periodic Paralysis patients.

4. Genetic testing:

Most accurate method for confirming the exact type. Detects mutation in CACNA1S, SCN4A, or KCNJ2 genes.

5. Thyroid function tests:

This helps detect Thyrotoxic PP (hyperthyroidism induced).

6. ECG (Electrocardiogram):

Very useful especially in ATS type where heart rhythm abnormalities occur.

Correct diagnosis prevents wrong treatment and reduces future risk of permanent muscle damage.

5. RISK FACTORS :-

There are certain factors that increase the chance of having episodes or developing more severe forms of Periodic Paralysis.

Major Risk Factors include:

Genetic family history → close family members with PP increases risk significantly.

Dietary triggers → high carbohydrate food, sweets, rice meals, large sudden potash intake (banana, coconut water etc.).

Physical triggers → vigorous exercise followed by sudden rest period.

Environmental triggers → sudden cold exposure increases attack chance.

Hormonal issues → especially Hyperthyroidism (TPP type).

Stress and emotional instability → causes hormonal and adrenergic fluctuations which disturb ion homeostasis.

Certain medications → diuretics, insulin doses, steroids etc. can cause rapid potassium shifts.

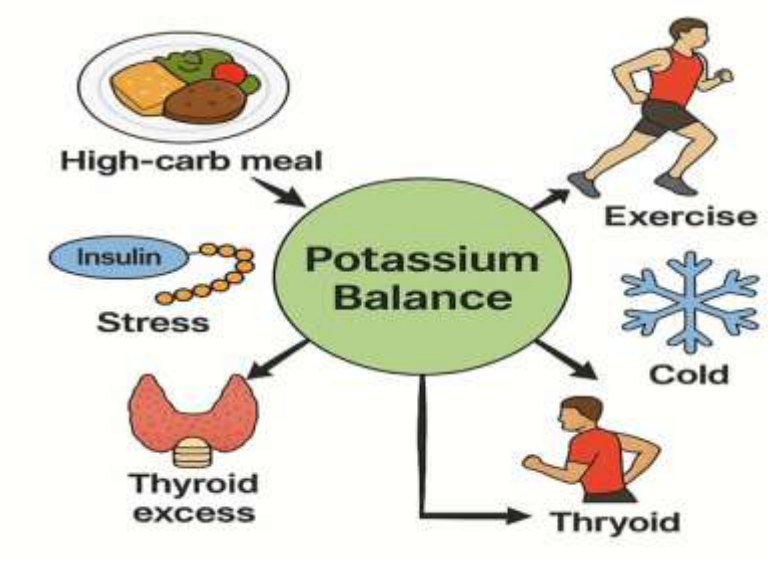

Figure 4: potassium balance trigger.

6.AGE GROUP AFFECTED:-

Periodic Paralysis usually begins in childhood or teenage years. Most patients start experiencing first episodes between the age of 10–20 years. This early onset is because the disorder is genetically determined and begins expressing itself when skeletal muscle demand and metabolic fluctuations increase during puberty growth phase.

Symptoms may continue throughout adult life. In some people, the frequency of attacks may reduce with increasing age, but long years of repeated attacks may result in permanent muscle weakness in older age.

Thyrotoxic PP commonly appears in the 20–40 year age group, especially in males with hyperthyroidism.

Overall, both males and females can be affected depending on the type, but thyroid related PP shows slight gender dominance patterns.

7. TREATMENT :-

Treatment for Periodic Paralysis focuses on preventing attacks, controlling triggers, correcting potassium imbalance, and protecting muscles long term.

General Management Strategies:

- Identify and avoid personal triggers (example: too much sugar, fasting, heavy exercise then rest).
- Maintain a stable daily diet with balanced potassium and carbohydrates.
- Have regular moderate-controlled exercise instead of sudden intense activity.
- Reduce emotional stress and ensure regular sleep because lack of rest can trigger attacks.

Acute Attack Management:

HypoPP → Potassium replacement under medical supervision.

HyperPP → Mild exercise and intake of carbohydrates may help lower serum potassium.

Long Term Treatment Goals:

- Provide membrane stabilization therapy
- Prevent progressive muscle damage
- Maintain normal potassium regulation

Pharmacological Approach:

Certain medications modify ion channel activity inside muscle fibers to reduce sudden abnormal ionic shifts. This reduces number and severity of attacks.

8. DRUGS USED IN TREATMENT:-

Drug therapy in Periodic Paralysis is mainly aimed at stabilizing muscle cell ion channels and maintaining a stable potassium balance. Pharmacological treatment reduces the frequency, severity and intensity of paralysis episodes.

1) Acetazolamide:

- Drug class: Carbonic Anhydrase Inhibitor.
- Use: Reduces frequency of attacks in both HypoPP and HyperPP.
- Mechanism: Causes mild metabolic acidosis → stabilizes sodium/calcium channels → prevents sudden muscle membrane depolarization.
- Side Effects: tingling, metallic taste, frequent urination, fatigue.
- Precaution: used carefully in kidney patients.

2) Dichlorphenamide:

- FDA approved drug for both HypoPP and HyperPP.
- Use: reduces attack severity and improves quality of life in chronic cases.
- Mechanism: controls ion flow across skeletal muscle cells.
- Side Effects: dizziness, confusion, mild cognitive slowing.
- Advantage: works even in some patients resistant to acetazolamide.

3) Potassium Supplements:

- Type: oral potassium chloride commonly used.
- Indication: Hypokalemic PP only (to increase low potassium during attacks).
- Precaution: overdosing can cause dangerous hyperkalemia so must be monitored medically.

4) Beta Blockers (Propranolol):

Indication: Thyrotoxic PP (caused by hyperthyroidism).

Use: control adrenergic symptoms, stabilize heart rate, reduce muscle weakness from thyroid excess.

5) Carbonic Anhydrase Inhibitors (general):

This whole class (acetazolamide, dichlorphenamide) is overall the most reliable drug therapy category for both major PP types.

9.PATHOPHYSIOLOGY AND ION CHANNEL INVOLVEMENT:-

Periodic Paralysis occurs mainly because of changes in ion channels that control the movement of sodium, potassium, and calcium in muscle cells. These changes disturb normal muscle contraction and relaxation. Dichlorphenamide helps by changing the acid-base level (pH) inside cells, which keeps the channels more stable and prevents extreme potassium movement that causes weakness.

10.ROLE OF DICHLORPHENAMIDE:-

Mechanism of Action:

Dichlorphenamide blocks the enzyme carbonic anhydrase. This causes a slight metabolic acidosis that helps muscles remain active by balancing the ions inside and outside the cells. Because of this, the number and intensity of weakness episodes decrease.

Clinical Effectiveness:

Clinical trials have proved dichlorphenamide effective in both Hypo PP and Hyper PP. Studies done by Statland and colleagues (2018) and Sansone et al. (2016) showed fewer attacks and better quality of life for patients using this medicine. It is also approved by the U.S. FDA for treating primary Periodic Paralysis.

Dosage and Administration:

The typical starting amount is 50mg taken two time a day, but this can be adjusted based on the patient's situation and the doctor's recommendation. It must always be used with a doctor's guidance

Adverse Effects:

Some common side effects include tiredness, tingling, mild dizziness, or stomach discomfort. Rarely, it can cause kidney stones or electrolyte imbalance. Regular follow-up and blood tests are advised during treatment.

Feature	**dichlorphenamide**	**Acetazolamide**	**Potassium supplement**
Mechanism	Carbonic anhydrase inhibitor	Carbonic anhydrase inhibitor	Restores potassium directly
Duration	Long action	Short acting	Short acting
Indication	Works in both hypo PP & hyper PP	Mainly hypo PP	Hypo PP only
Major advantage	Fewer attacks ,better control	May not work in all patients	Only short-term relief
Limitation	High cost, limited access	Cross-sensitivity, variable effect	Needs frequent dosing

11.COMPARISON WITH OTHER DRUGS:-

12.LIMITATION:-

• Drug is expensive compared to older medicines.

• Not available easily in every country.

• Some patients do not respond due to genetic differences.

• Requires monitoring of acid-base balance and kidney function during therapy.

13.FUTURE PROSPECTS:-

• Development of sustained-release or targeted forms for stable blood levels.

• Genetic testing to identify which patients respond best.

• Combining drug therapy with mobile-based monitoring to predict attacks early.

• More research on safety for long-term and elderly use.

14. PREFORMULATION STUDIES OF DICHLORPHENAMIDE:-

Pre-formulation studies are the fundamental step in the development of any pharmaceutical dosage form. These studies aim to investigate the physicochemical properties of a drug substance to ensure stability, compatibility, and suitability for formulation. Understanding the pre-formulation characteristics of Dichlorphenamide is

essential for optimizing its performance and ensuring therapeutic effectiveness in the management of Periodic Paralysis.

Dichlorphenamide is a white, crystalline, odorless powder with a slightly bitter taste. It is slightly soluble in water but freely soluble in organic solvents such as ethanol and acetone. The drug shows a melting point in the range of 265–268°C, indicating good purity and thermal stability. It has a moderate lipophilicity with a partition coefficient (log P ≈ 1.2) and an acidic pKa value of about 8.0, which influence its solubility and ionization at physiological pH.

Major pre-formulation tests performed for Dichlorphenamide include:-

- Organoleptic properties: Color, odor, and texture to confirm physical identity.
- Solubility studies: Evaluation in various solvents and pH conditions to determine solubility behavior.
- Melting point and thermal analysis: Performed using DSC to assess purity and stability.
- pKa and partition coefficient determination: To predict ionization and absorption potential.
- Hygroscopicity and moisture content: Measured by loss-on-drying to assess storage stability.
- Micromeritic properties: Bulk density, tapped density, and angle of repose to evaluate flow and compressibility.
- Drug–excipient compatibility: Tested by FTIR and DSC to detect any possible interactions.
- Stability studies: Conducted under accelerated temperature and humidity to ensure chemical and physical stability.

15.RESULTS:-

The results of reviewed studies showed that Dichlorphenamide is a stable, crystalline compound with suitable physicochemical properties for oral administration. It demonstrated good thermal stability with a melting point in the range of 265–268°C and moderate lipophilicity, indicated by a partition coefficient (log P ≈ 1.2). The drug is slightly soluble in water but soluble in organic solvents such as ethanol and acetone.

Pre-formulation investigations reported no significant interaction between Dichlorphenamide and commonly used excipients. The drug remained stable under normal storage conditions and showed acceptable flow and compressibility characteristics. These findings confirm that Dichlorphenamide is physically and chemically suitable for use in oral dosage forms and supports its effective role in the management of Periodic Paralysis.

16.CONCLUSION:-

Dichlorphenamide is an effective therapeutic agent for managing both hypokalemic and hyperkalemic forms of Periodic Paralysis. By inhibiting carbonic anhydrase, it helps maintain ionic balance in muscle cells and reduces the frequency of paralysis episodes. Clinical evidence supports its efficacy and safety compared to older drugs like acetazolamide.

Although cost and limited availability remain challenges, its consistent results and tolerability make Dichlorphenamide a valuable option for long-term management of Periodic Paralysis..

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