THE NORTHERN HOSPITAL

PHENYTOIN

James Dean in Times Square, New York City, Photographed by Dennis Stock, 1955

See the way he walks down the street
Watch the way he shuffles his feet
My, he holds his head up high
When he goes walking by
He's my guy

When he holds my hand, I'm so proud
'Cause he's not just one of the crowd
Why is he always the one
To try the things they've never done?
And just because of that, they say:

He's a rebel and he'll never ever be any good
He's a rebel 'cause he never ever does what he should
But just because he doesn't do what everybody else does,
That's no reason why I can't give him all my love

He's always good to me,
Always treats me tenderly
'Cause he's not a rebel, no no no
He's not a rebel, no no no, to me

If they don't like him that way,
They won't like me, I'm sure, today
And I'll be standing right by his side when they say:

He's a rebel and he'll never ever be any good
He's a rebel 'cause he never ever does what he should
But just because he doesn't do what everybody else does,
That's no reason why we can't share love

He's always good to me
Good to him, I try to be
'Cause he's not a rebel, no no no
He's not a rebel, no no no, to me
Oh! (he's not a rebel, no no no)
He's not a rebel, no no no to me

"He's a Rebel", The Crystals, written by Gene Pitney, 1962.

Phenytoin is not just one of the crowd! Nobody likes it because of its pharmacokinetic profile - it simply doesn't do what everybody else does! But that's no reason why we still can't love it - it's always been good to us - at least in seizure emergencies – it's not a rebel, no, no, no! - it just needs a little more understanding when it comes to dosing!

PHENYTOIN

Introduction

Phenytoin is an anti-convulsant agent.

It is also classified as a class Ib anti-arrhythmic agent, though it is no longer (or very rarely) used in clinical practice for this indication.

For phenytoin overdose see separate document

Chemistry

Phenytoin sodium is a hydantoin derivative anticonvulsant.

It is related to the barbiturates in chemical structure.

Preparation

- Tablets/ capsules:
  - ♥ 30mg, 50mg, 100 mg, 200mg.
- Liquid:
  - ♥ Paediatric suspension 30mg/5ml
- Ampoules:
  - ♥ 100mg/2ml of phenytoin sodium
  - ♥ 250mg/5mL of phenytoin sodium

Mechanism of Action

Phenytoin inhibits the spread of seizure activity in the motor cortex.

Epileptic seizures are thought to occur through the development of excessive central excitability due to post-tetanic potentiation, which is blocked by phenytoin.

The primary target of phenytoin appears to be **sodium channels in depolarising neurones**, where phenytoin binds and blocks sodium influx, reducing neuronal excitability and the spread of electrical activity characteristic of epileptic seizures.

It is also classified as a class Ib anti-arrhythmic agent.

Pharmacokinetics

Absorption:

- Phenytoin can be given orally or IV:
- The following routes of administration are **not** recommended:
    - ♥ IM injection is **not** recommended (due to local tissue reactions and very slow absorption).
    - ♥ SC Injection is **not** recommended (due to local tissue damage).
    - ♥ Endotracheal route is not recommended

Distribution:

- Phenytoin is about 90% protein bound.

Metabolism and excretion:

- The liver is the principle site of biotransformation of phenytoin. Most of the drug is excreted in the bile as inactive metabolites.

  Patients with impaired liver function, elderly patients, or those who are gravely ill may show early signs of toxicity.

  A small percentage of individuals who have been treated with phenytoin have been shown to metabolize the drug slowly. Slow metabolism may be due to limited enzyme availability and lack of induction; it appears to be genetically determined. [4]

  The plasma half-life is normally from 10 to 15 hours. Because phenytoin exhibits saturable or dose dependent pharmacokinetics, the apparent half-life of phenytoin can change appreciably with dose and serum concentration

  Conventionally, with drugs following linear kinetics the half-life is used to determine the dose rate, drug accumulation and the time to reach steady state. Phenytoin, however, demonstrates **nonlinear** kinetics and the half-life is affected by the saturation of metabolic pathways. As metabolism becomes saturated with dose increases, the kinetics progressively change from first-order to zero-order kinetics and the apparent elimination half-life becomes longer. A small change in the dose can therefore cause a large change in the steady-state plasma concentration.

  This results in considerable interpatient and intrapatient variability in phenytoin pharmacokinetics. As a consequence the clinical relevance of reported phenytoin

half-life values are limited and cannot be used in the conventional manner to estimate dosage regimens. [3]

Blood levels

- Therapeutic phenytoin levels are **40 - 80 micromol/L.**

Note that a small change in dosage may result in a disproportionately large change in phenytoin concentration because of saturation of its hepatic metabolism.

The dose can be increased by 100 mg daily if total plasma phenytoin concentration is 5 mg/L or less, but by no more than 30 mg daily if concentration is higher.

Indications

Indications include:

Anticonvulsant:

- Seizure prophylaxis:
  - ♥ Note however that phenytoin is **not** effective for absence (petit mal) seizures.
- Seizure treatment:
  - ♥ IV usually as a second line agent, following the use of benzodiazepines.

Contraindications/ Precautions

These include:

- A-V block/ bradyarrhythmias.
- Known hypersensitivity
- Hypotension (relative)

Pregnancy

Phenytoin is a category D drug with respect to pregnancy.

Category D drugs are those drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Specialized texts should be consulted for further details

Adverse Effects

1. Hypotension
    - May occur if given too rapidly IV.
2. Cardiotoxic reactions:
    - Myocardial depression.
    - Conduction delays
3. Local tissue reactions:
    - On extravasation thrombophlebitis can occur, (phenytoin is quite alkaline).
4. Neurotoxicity:
    - With toxic levels: nystagmus, ataxia, slurred speech, decreased coordination and mental confusion may occur.
5. GIT:
    - Nausea, vomiting, constipation, toxic hepatitis.
6. Dermatological reactions:
    - The most serious of which is **Stevens-Johnson Syndrome.**
7. Gingival hypertrophy, may occur with long term oral use.
8. Abrupt withdrawal:
    - Abrupt withdrawal of oral maintenance phenytoin in epileptic patients may precipitate status epilepticus.

      When, in the judgment of the clinician, the need for dosage reduction, discontinuation, or substitution of alternative antiepileptic medication arises, this should be done gradually.

      However, in the event of an allergic or hypersensitivity reaction, rapid substitution of alternative therapy may be unavoidable. [4]
9. Porphyria:
    - Phenytoin may exacerbate this condition.

Dosing

- Oral administration:

  - ♥ Standard oral dosing is around **300 mg orally,** daily, (with a maximum dose of around **600 mg per day**).

    Note that the phenytoin dose is adjusted to obtain plasma concentrations in the reference range (40 to 80 micromol/L or 10 to 20 mg/L) provided the dose is tolerated.

    Because the elimination of phenytoin approaches saturation at plasma concentrations above **40 micromol/L** (or 10 mg/L), small dose changes can produce disproportionately large changes in drug concentrations (and drug effect) and lead to clinical toxicity or loss of seizure control.

    In general dose adjustments should not exceed 50 mg daily.

- IV administration:

  - ♥ Standard loading dose is: **15 mg (- up to 20 mg) / kg IV:**

    A 70 kg adult, usually therefore will have a 15 mg/kg loading dose of approximately **1 gram over 20 minutes.**

    Maximum dose is generally taken as 1.5 grams. [4]

    Give IV by **slow** bolus injection

    Rate must **not exceed 50mg/min,** (and for children and neonates not exceeding 3mg/kg/min to a maximum of 50 mg). [4]

    Rates should also be reduced in the elderly or those with cardiovascular disease.

    Inject into a large vein through a large-gauge needle or IV catheter.

    Dilute with small volume (100 mls) sodium chloride 0.9% to avoid venous irritation from the alkalinity of the solution. (It is not compatible with any other type of fluid)

References

1. eTG - July 2013

2. Australian Medicines Handbook, October 2013

3. MIMs October 2013.

4. Paul Young, Critical Care Drug Manual, Wellington Hospital Intensive Care Unit, 2010.

Dr J. Hayes
December 2013.