Lecture Notes: Session 7 - Anticonvulsants: Barbiturates, Hydantoins, and Oxazolidine Diones

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Introduction

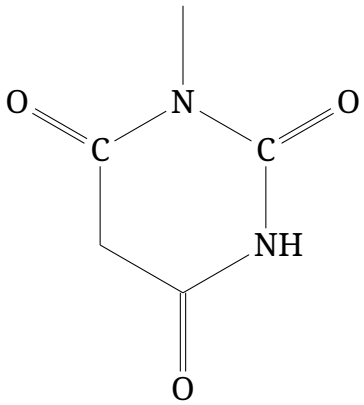
This lecture focuses on anticonvulsants, specifically barbiturates (Phenobarbitone, Methabarbital), hydantoins (Phenytoin, Mephenytoin, Ethotoin), and oxazolidine diones (Trimethadione, Paramethadione). Anticonvulsants are used to manage epilepsy by stabilizing neuronal excitability. The session explores their chemical structures, structure-activity relationships (SAR), mechanisms of action, and clinical applications, emphasizing their role in treating various seizure types.

1 Barbiturates

Barbiturates are derivatives of barbituric acid, acting as central nervous system (CNS) depressants with anticonvulsant properties. They enhance $GABA_A$ receptor activity, increasing chloride ion influx to hyperpolarize neurons, and may inhibit glutamate-mediated excitation.

1.1 Phenobarbitone (Phenobarbital)

Chemical Structure: 5-Ethyl-5-phenylbarbituric acid.



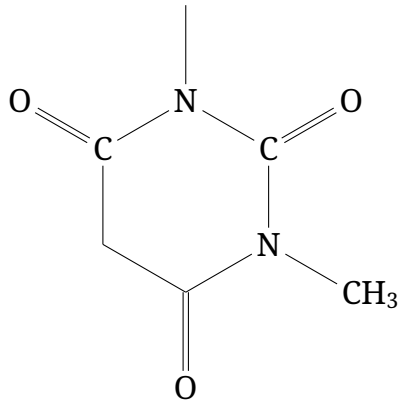
Pharmacological Properties:

- *Mechanism:* Prolongs $GABA_A$ receptor chloride channel opening, enhancing inhibitory neurotransmission. Also inhibits voltage-gated sodium channels, reducing neuronal excitability.
- *Pharmacokinetics:* Long half-life (70–100 hours), metabolized via hepatic hydroxylation and glucuronidation. Induces CYP450 enzymes, affecting drug interactions.
- *Clinical Use:* Generalized tonic-clonic seizures, partial seizures, neonatal seizures. Also used as a sedative in specific cases.

SAR Notes: The 5-phenyl group increases anticonvulsant potency compared to dialkyl substitutions. The 5-ethyl group balances lipophilicity for CNS penetration.

1.2 Methabarbital

Chemical Structure: 5,5-Diethyl-1-methylbarbituric acid.



Pharmacological Properties:

- *Mechanism:* Similar to Phenobarbitone, enhances $GABA_A$ receptor activity and modulates sodium channels.
- *Pharmacokinetics:* Long-acting (half-life 20–40 hours), metabolized to barbital, which is excreted renally.
- *Clinical Use:* Generalized and partial seizures, though less commonly used due to availability of safer alternatives.

SAR Notes: N-methylation at position 1 increases lipophilicity, enhancing CNS penetration but slightly reducing potency compared to Phenobarbitone.

1.3 SAR of Barbiturates

- **5,5-Disubstitution:** Two substituents (alkyl or aryl) at position 5 are critical for activity. Aryl groups (e.g., phenyl in Phenobarbitone) enhance anticonvulsant effects.
- **N-Substitution:** Alkylation (e.g., methyl in Methabarbital) increases lipophilicity, affecting onset and duration.

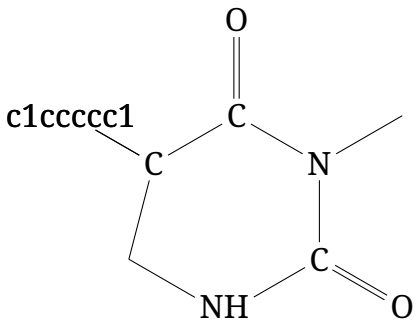
- **C2/C4/C6 Oxygen:** Keto groups facilitate hydrogen bonding with $GABA_A$ receptors.
- **Lipophilicity:** Balanced lipophilicity is key for CNS penetration; excessive lipophilicity shortens duration.
- **Ionization:** Barbiturates are weak acids (pKa 7.6–8.0); ionization affects solubility and distribution.

2 Hydantoins

Hydantoins are cyclic ureides with potent anticonvulsant activity, primarily acting by stabilizing voltage-gated sodium channels in their inactive state, reducing repetitive neuronal firing.

2.1 Phenytoin

Chemical Structure: 5,5-Diphenylhydantoin.



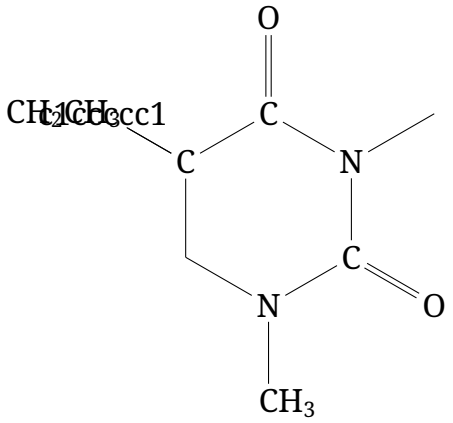
Pharmacological Properties:

- *Mechanism:* Blocks voltage-gated sodium channels, preventing high-frequency neuronal firing. Minimal effect on GABA receptors.
- *Pharmacokinetics:* Non-linear pharmacokinetics, half-life 7–42 hours (dose-dependent), metabolized via hepatic CYP2C9/2C19. Induces CYP450 enzymes.
- *Clinical Use:* Generalized tonic-clonic seizures, partial seizures, status epilepticus (intravenous).

SAR Notes: The 5,5-diphenyl groups enhance sodium channel binding and lipophilicity, critical for activity. Lack of N-substitution maintains potency.

2.2 Mephenytoin

Chemical Structure: 5-Ethyl-5-phenyl-3-methylhydantoin.



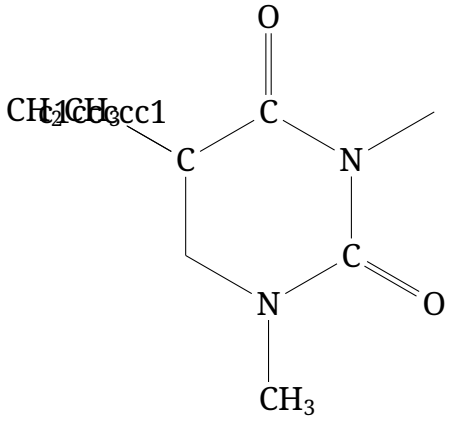
Pharmacological Properties:

- *Mechanism:* Similar to Phenytoin, inhibits sodium channels. Active metabolite (nirvanol) contributes to efficacy.
- *Pharmacokinetics:* Half-life 12–30 hours, metabolized to nirvanol, which has a longer half-life.
- *Clinical Use:* Partial and generalized seizures (less common due to toxicity risks).

SAR Notes: N-methylation and 5-ethyl substitution reduce potency compared to Phenytoin but improve solubility.

2.3 Ethotoin

Chemical Structure: 5-Ethyl-5-phenyl-3-methylhydantoin.



Pharmacological Properties:

- *Mechanism:* Sodium channel blockade, similar to Phenytoin, but less potent.
- *Pharmacokinetics:* Short half-life (3–9 hours), metabolized hepatically.
- *Clinical Use:* Partial seizures, though rarely used due to lower efficacy.

SAR Notes: Similar to Mephenytoin, but structural variations (e.g., ethyl vs. phenyl) reduce potency.

2.4 SAR of Hydantoins

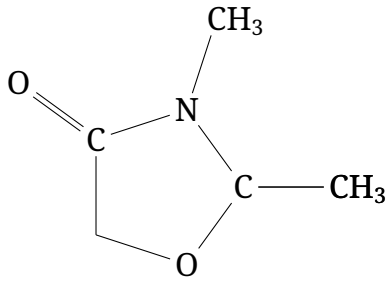
- **5,5-Disubstitution:** Two aryl or alkyl-aryl groups (e.g., diphenyl in Phenytoin) are optimal for sodium channel binding.
- **N-Substitution:** Methylation at N3 (e.g., Mephenytoin, Ethotoin) increases solubility but may reduce potency.
- **C2/C4 Carbonyls:** Essential for receptor interaction and stability.
- **Lipophilicity:** Aryl groups enhance CNS penetration; excessive alkyl substitution may reduce activity.

3 Oxazolidine Diones

Oxazolidine diones are used primarily for absence (petit mal) seizures, acting by inhibiting T-type calcium channels in the thalamus, reducing synchronized neuronal firing.

3.1 Trimethadione

Chemical Structure: 3,5,5-Trimethyloxazolidine-2,4-dione.



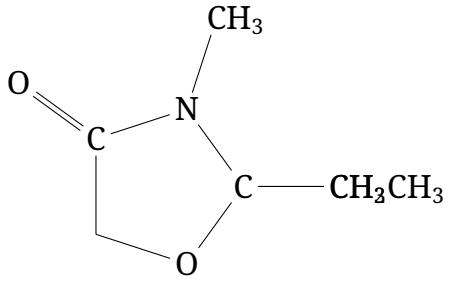
Pharmacological Properties:

- *Mechanism:* Inhibits T-type calcium channels, reducing thalamic burst firing associated with absence seizures.
- *Pharmacokinetics:* Half-life 16–24 hours, metabolized to dimethadione (active metabolite, half-life 6–13 days).
- *Clinical Use:* Absence seizures (rarely used due to toxicity and availability of safer drugs like ethosuximide).

SAR Notes: The 3,5,5-trimethyl groups enhance lipophilicity and receptor binding, critical for activity.

3.2 Paramethadione

Chemical Structure: 5-Ethyl-5-methyl-3-methyloxazolidine-2,4-dione.



Pharmacological Properties:

- *Mechanism:* Similar to Trimethadione, inhibits T-type calcium channels.
- *Pharmacokinetics:* Half-life 12–24 hours, metabolized to active derivatives.
- *Clinical Use:* Absence seizures (less common due to toxicity).

SAR Notes: The 5-ethyl group slightly increases lipophilicity compared to Trimethadione, but clinical use is limited by side effects.

3.3 SAR of Oxazolidine Diones

- **3,5-Substitution:** Methyl or ethyl groups at positions 3 and 5 enhance lipophilicity and receptor affinity.
- **2,4-Dione Core:** Essential for T-type calcium channel inhibition.
- **Lipophilicity:** Balanced alkyl substitution ensures CNS penetration without excessive toxicity.

4 Clinical Considerations

- **Barbiturates:** Phenobarbitone is preferred for generalized seizures but has significant side effects (sedation, enzyme induction). Methabarbital is less potent.
- **Hydantoins:** Phenytoin is a cornerstone for partial and tonic-clonic seizures but requires monitoring due to non-linear pharmacokinetics and gingival hyperplasia. Mephenytoin and Ethotoin are less effective.
- **Oxazolidine Diones:** Trimethadione and Paramethadione are effective for absence seizures but are rarely used due to hepatotoxicity and availability of safer alternatives.

5 Key Learning Points

- Barbiturates (Phenobarbitone, Methabarbital) enhance $GABA_A$ activity and modulate sodium channels, with SAR driven by 5,5-disubstitution.

- Hydantoins (Phenytoin, Mephenytoin, Ethotoin) target sodium channels, with diphenyl groups optimizing potency.
- Oxazolidine diones (Trimethadione, Paramethadione) inhibit T-type calcium channels, effective for absence seizures.
- SAR guides the design of anticonvulsants with improved efficacy and reduced toxicity.