2.1 Tolfenamic Acid

(British Pharmacopoeia, 2010; EMEA, 1997; EMC Medicine, 2010; Pederson SB, 1994)

Tolfenamic Acid is a Non-steroidal anti-inflammatory drug belonging to the fenamate group. The molecule was originally developed over 40 years ago for use in human medicine. Recently it is also developed for use in veterinary formulations (EMEA, 1997). It is Cyclo-oxygenase inhibitor; with analgesic; anti-inflammatory action. It is commonly used in the treatment of acute attacks of migraine.

**Physico-chemical Properties**

- **Appearance**: White or slightly yellow, crystalline powder.
- **Chemical Name**: 2-[(3-Chloro-2-methylphenyl) amino] benzoic acid.
- **Chemical Structure**:  
  ![Structure of Tolfenamic Acid](image)
  
  **Figure 2.1**: Structure of Tolfenamic Acid
- **Molecular Weight**: 261.7
- **Molecular Formula**: C_{14}H_{12}ClNO_{2}
- **Melting Point**: About 213 °C.
- **Solubility**: Practically insoluble in water, soluble in
dimethylformamide,
Sparingly soluble in ethanol and in methylene chloride.
It dissolves in dilute solutions of alkali hydroxides.

**Pharmacological Properties**

**Pharmacodynamics**
Tolfenamic acid is basically inhibiting the prostaglandin synthesis and leukotriene synthesis. It is having NSAIDs with anti-inflammatory, analgesic, and antipyretic effects.

**Pharmacokinetics**

**Absorption**
Absorption of Tolfenamic acid is quickly and almost completely absorbed after oral administration. Peak plasma concentration of Tolfenamic acid is approx 60-90 minutes after oral administration. Relative Bioavailability of Tolfenamic acid is approx 85%.

**Distribution**

- Protein-binding : 99%.
- Plasma half-life : 2 hr. Distributed into breast milk.

**Metabolism**
Tolfenamic acid is metabolized in the liver. Tolfenamic acid is metabolized by hydroxylation and subsequent conjugation of metabolites. Hepatic first pass metabolism is as low as 15%.

**Excretion**
More than 90% Tolfenamic acid excreted in urine and faeces. About 90% of a given dose of Tolfenamic acid is excreted in the urine as glucuronic acid conjugates, and about 10% is excreted in the faeces. Tolfenamic Acid undergoes enter hepatic circulation.

**Therapeutic Indication**
NSAIDs with anti-inflammatory, analgesic, and antipyretic effects.
**Posology and Method of Administration**

Method : Oral, to be taken preferably with or after food.
Symptom : Acute migraine attacks
Dosage : 100-200 mg thrice a day
Precaution : Undesirable effects may be minimized by using the lowest effective dose

**Innovator Details**

Name of Innovator : Clotam Rapid™
Generic Name : Tolfenamic acid 200 mg
Dosage Form : Tablet
Manufactured by : Galen Limited Ireland, UK
List of Excipients : Maize starch; Sodium starch glycolate (Type A); Macrogol 6000; Alginic acid; Cellulose, microcrystalline; Croscarmellose sodium; Silica, colloidal anhydrous; Sodium stearyl fumarate.

**Details of Available Formulation in India**

Name of Product : Clotan™
Generic Name : Tolfenamic acid 200 mg
Dosage Form : Capsules
Manufactured by : Elder Pharmaceuticals Limited, India
2.2 Paracetamol

(British Pharmacopoeia, 2010; Indian Pharmacopoeia, 2010; European Pharmacopoeia, 2010; EMC Medicine, 2010; Stricker BHC, 1985; Graham GG et. Al, 2005)

Painkilling properties of paracetamol were accidently discovered about 100 years ago in 1893. Paracetamol was first marketed in the United States in 1953 by Sterling Drug, a global pharmaceutical company in the United States, which promoted it as preferable to aspirin as it was safe to take for children and ulcer patients.

Physico-chemical Properties

Appearance : White or almost white, crystalline powder
Chemical Name : N-(4-Hydroxyphenyl) acetamide
Molecular Weight : 151.2
Molecular Formula : C₈H₉NO₂

Chemical Structure :

![Figure 2.2: Structure of Paracetamol](image)

Melting Point : 168 °C to 172 °C.
Solubility : Sparingly soluble in water,
Freely soluble in alcohol,
Very slightly soluble in methylene chloride.

Pharmacological Properties

Pharmacodynamics

Analgesic
Paracetamol may act predominantly by inhibiting prostaglandin synthesis in the central nervous system (CNS) and to a lesser extent, through a peripheral action by blocking pain-impulse generation.

Antipyretic
Paracetamol probably produces antipyresis by acting centrally on the hypothalamic heat-regulation centre to produce peripheral vasodilatation resulting in increased blood flow through the skin, sweating and heat loss.

Pharmacokinetics

Absorption
Paracetamol is readily absorbed from the gastro-intestinal tract with peak plasma concentrations occurring about 30 minutes to 2 hours after ingestion.

Distribution
Present in most body tissues; crosses the placenta and enters the breast milk. Protein binding: 8-43% (at toxic doses).

Metabolism
It is metabolized in the liver and excreted in the urine mainly as the glucuronide and sulphate conjugates.

Excretion
Less than 5% is excreted as unchanged paracetamol. The elimination half-life varies from about 1 to 4 hours. Plasma half-life: 2.7 hr (adults); 1.5-2 hr (infants and children); 3.5 hr (neonates).

**Therapeutic Indication and Dosage**

**Therapeutic Uses**

- Headache
- Muscular aches
- Backache
- minor pain of arthritis
- Common cold
- Toothache
- Temporarily reduces fever

**Route of Administration**

Oral

**Symptoms**

Mild to moderate pain and fever

**Dosage**

Adult: 0.5-1 g 4-6 hrly as necessary. Max: 4 g daily.

Neonate: >32 wk post menstrual age: 20 mg/kg as a single dose then 10-15 mg/kg 6-8 hrly (max 60 mg/kg daily in divided doses).

Child: 1-3 mth: 30 mg 8 hrly (max 60 mg/kg daily in divided doses);

  - 3 mth-1 yr: 60-120 mg 4-6 hrly (max 4 doses in 24 hr);
  - 1-5 yr: 120-250 mg 4-6 hrly (max 4 doses in 24 hr);

**Innovator Details**

Name of Innovator: Tylenol

Generic Name: Acetaminophen
<table>
<thead>
<tr>
<th>Dosage Form</th>
<th>Tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufactured by</td>
<td>Macneil Healthcare LLC, USA</td>
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<tr>
<td>List of Excipients</td>
<td>Corn starch; Powder Cellulose, Sodium starch glycolate (Type A); Potato, Magnesium Stearate.</td>
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