CHAPTER 2

: DRUGS USED IN STUDY
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2.1 Nimesulide

Nimesulide is a selective Cox-2 inhibitor used in a variety of inflammatory, pain and fever states. It is a sulfonamide compound. Its structure is as follows:

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O
HN
S
O
O
O

N
O^+
O^-
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Nimesulide is absorbed rapidly and extensively when administered through oral route. The mean peak concentration ($C_{\text{max}}$) of 2.86 to 6.5 were achieved within 1.22 to 2.75 hr. Nimesulide is rapidly distributed and has an apparent volume of distribution ranging between 0.18 and 0.39 L/kg. It is extensively bound to plasma protein; the unbound fraction in plasma was 1%. The estimated mean terminal elimination half-life varied from 1.80 to 4.73 hr. Nimesulide is largely eliminated via metabolic transformation and the principal metabolite is the 4'-hydroxy derivative. The total plasma clearance of nimesulide was 31.02 to 106.16 ml/hr/Kg, reflecting almost exclusive metabolic clearance\(^1\). Nimesulide causes very little adverse side effects in gastrointestinal tract\(^2\).
therapeutic concentration, the binding of nimesulide was unaffected by warfarin, cefoperazone, furosemide, glibenclamide, nimesulide.

2.2 Lamivudine

Lamivudin, the negative enantiomer of 2'-deoxy-3'-thiacytidine, a dideoxynucleoside analogue used in combination with other agents in the treatment of human immunodeficiency virus type 1 (HIV – 1) infection and as monotherapy in treatment of hepatitis B virus (HBV) infection. The structure of lamivudine is as follows,

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{N} \\
\text{N} & \quad \text{O} \\
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{H}
\end{align*}
\]

Lamivudin undergoes anabolic phosphorylation by intercellular kinases to form lamivudin – 5'- triphosphate, the active anabolite which prevents HIV – 1 and HBV replication by competitively inhibiting viral reverse transcriptase and terminating proviral DNA chain extension.

The drug is rapidly absorbed after oral administration, with maximum serum concentration usually attained between 0.5 - 1.5 hr after the dose. The absolute bioavailability is approximately 1.3 L/kg following i.v. administration. The plasma t\text{½} averages about 9 hr and approximately 70 % of the dose is excreted unchanged in the urine. About 5 % is metabolized to an inactive trans–sulfoxide metabolite. The CSF to plasma AUC ratio is 0.15. In HBV – infected children, doses of 3 mg /Kg per day provide plasma exposure and trough plasma levels comparable to dose in adults receiving 10 mg daily. Systemic clearance following single i.v. doses average 20 to 25 L/hr. The plasma protein binding of lamivudin is less than 36 %. Drug interaction studies have shown that trimethoprim increases the AUC and decreases the renal clearance of lamivudine.
2.3 Lamotrigine

Lamotrigine is a phenyltriazine derivative. It is utilized as an antiseizure drug. This new antiepileptic drug is chemically unrelated to any established drugs in use. The chemical structure is

![Chemical structure of Lamotrigine](image)

Lamotrigine suppresses tonic hind limb extension in the maximal electroshock model and partial and secondarily generalized seizures in the kindling model but does not inhibit clonic motor seizures induced by phenylenetrazol.

Lamotrigine is rapidly absorbed, reaching peak concentration within about 3 hrs post dose. Bioavailability of the oral formulation is about 98 %. The area under the plasma concentration time curve indicates dose-linear pharmacokinetics. The plasma half-life of a single dose is 24 to 35 hr. The concentration of lamotrigine in the brain is similar to the total concentration in the plasma.

Lamotrigine exhibits first-order linear kinetics during long-term administration. 43 to 87% of a dose is recovered in the urine, predominantly as glucuronide metabolites. Administration of enzyme inducing antiepileptic drugs such as phenytoin, phenobarbitone or carbamazepine reduce the half life of lamotrigine to mean values of 13.5 to 15 hr where as valproic acid increases the half life of the drug. The degree of plasma protein binding of lamotrigine is 56 %. The oral bioavailability of lamotrigine is unaffected by food and there is no first pass metabolism. The volume of distribution is between 1.25 and 1.47 L/kg.
Clinical trails demonstrated no evidence of auto induction or saturable metabolism\(^9\). Patients with already administered hepatic enzyme inducing drug (such as carbamazepine, phenytoin, phenobarbitol or primidone) should start with 50 mg per day for 2 weeks. The dose is increased to 50 mg twice daily for 2 week and then increased in increments of 100 mg/day each week up to a maintenance dose of 300 to 500 mg/day divided in two doses\(^10\).

### 2.4 Diclofenac sodium

Diclofenac sodium is a synthetic, nonsteroidal anti inflammatory and analgesic compound. Its molecular formula is \(\text{C}_{14}\text{H}_{10}\text{Cl}_{2}\text{NO}_{2}\text{Na}\) and molecular weight is 318.13. Chemically it is known by different names a) 2 – [(2,6-Dichlorophenyl) amino] benzene acetic acid mono sodium salt, b) [ 0-(2,6-dichloroanilino) phenyl ] acetic acid sodium salt and c) sodium [0-((2,6- dichlorophenyl)amino)phenyl acetate.

The structure of diclofenac sodium is given below

![Diclofenac Sodium Structure](image)

Diclofenac sodium is completely absorbed from the gastrointestinal tract after oral administration. The half-life of diclofenac sodium is 2 hr, and mean peak plasma concentration of 1.9 \(\mu\text{g}/\text{ml}\) is reached 2 hr after a single dose of 75 mg\(^11\). The drug is highly bound to human serum protein to the extent of 99.5%, of which not less than 99% is bound to serum albumin fraction. But it does not
modify the binding of Warfarin, acenocumarol, prednisolone and salicylic acid to proteins\textsuperscript{12}.

Diclofenac is metabolized in the liver by a cytochrome P450 isozyme of the CYP2C subfamily to 4-hydroxy diclofenac, the principal metabolite and other hydroxylated form\textsuperscript{11}. Diclofenac is widely used as a therapeutic agent against rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, and acute gouty arthritis.
REFERENCES: