CHAPTER - V

LITERATURE ON DRUGS INVESTIGATED

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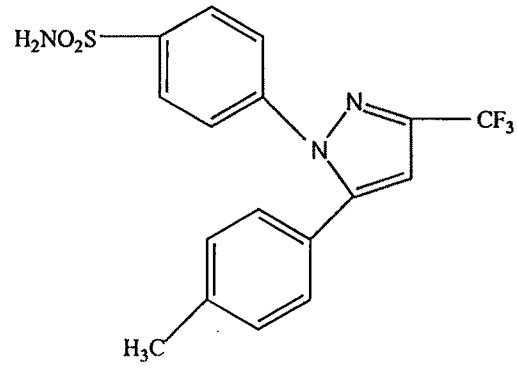
CELECOXIB

Celecoxib is a nonsteroidal anti- inflammatory drug that exhibits anti inflammatory, analgesic, and antipyretic activities in human and animal models. Celecoxib is used treat pain or inflammation caused by many conditions such as arthritis, ankylosing spondylitis, and menstrual pain. It is also used as an adjunct to standard therapy in the treatment of Primary Dysmenorrhea (PD) hereditary polyps in the colon.

Celecoxib is chemically[1] designated as 4-[5-(4-methylphenyl)-3-(trifluromethyl)-1H-pyrazole-1-yl] benzenesulfonamide and is a diaryl substituted pyrazole.

The chemical structure is as follows:



Celecoxib is available in oral dosage forms (capsules/tablets) containing either 50 mg, 100 mg, 200 mg, or 400 mg of celecoxib.

The empirical formula is $C_{17}H_{14}F_3N_3O_2S$, Molecular Weight: 381.38

Physicochemical properties[1]:

Description: White to off-white crystalline powder

Solubility : poorly soluble in water

Melting point: 155 – 170^{0}C

Indications[2,3]

Celecoxib is used to treat pain or inflammation caused by many conditions such as arthritis, ankylosing spondylitis, and menstrual pain. It is also used as an adjunct to standard therapy in the treatment of Primary Dysmenorrhea (PD) hereditary polyps in the colon.

Mechanism of Action

Celecoxib is a nonsteroidal anti- inflammatory drug that exhibits anti inflammatory, analgesic, and antipyretic activities in human and animal models. The mechanism of action of celecoxib is believed to be due to inhibition of prostaglandin synthesis, primarily via inhibition of cyclooxygenase (COX-2), and at therapeutic concentrations in humans. In animal colon tumor models, celecoxib reduces the incidence and multiplicity of tumors.

Pharmacokinetics[4]

Absorption: Peak plasma levels of celecoxib occur approximately 3 h after an oral dose. Under fasting condition both peak plasma levels (C_{max}) and area under curve (AUC) are roughly dose proportional upto 200 mg; at higher dose there are less than proportional increase in C_{max} and AUC. Absolute bioavailability studies have

not been conducted. With multiple dosing , study state conditions are reached on or before Day 5.

Food effects: when celecoxib capsules were taken with a high fat meal, peak plasma levels were delayed for about 1-2 h with an increase in total absorption (AUC) of 10% to 20%. Under fasting conditions, at doses above 200 mg, there is less than a proportional increase in C_{max} and AUC, which is thought due to the low solubility of the drug in aqueous media.

Distribution: In healthy subjects, celecoxib id highly protein bound (~97%) within the clinical dose range. *In vitro* studies indicate that celecoxib binds primarily to albumin and, to a lesser extent, α_1- acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400 L, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells.

Metabolism: Celecoxib metabolism is primarily mediated via the cytochrome P-450 iso enzyme CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in plasma. These metabolites are inactive as COX-1 or COX-2 inhibitors.

Excretion: celecoxib is eliminated predominately by hepatic metabolism with little (< 3%) unchanged drug recovered in the urine and feces. Following a single oral dose of radio labeled drug, approximately 57% of the dose was excreted in the feces and 27% was ecreted into the urine. The primary metabolite in both urine and feces was the carboxylic acid metabolite (73% of dose) with low amounts of

glucuronide also appearing in the urine. It appears that the low solubility of the drug prolongs the absorption process making terminal half-life ($t_{1/2}$) determinations more variable. The effective half life is approximately 11 h under fasted conditions. The apparent plasma clearance (CL/F) is about 500 ml/min.

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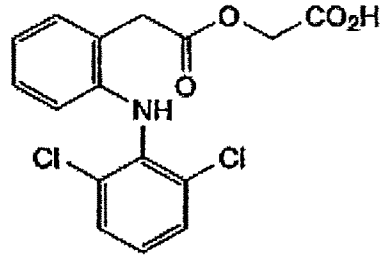
ACECLOFENAC



Aceclofenac

Chemically aceclofenac is [2,[(2,6-dichlorophenyl) amino] phenyl acetooxy acetic acid.

Molecular formula : $C_{16}H_{13}C_{l2}NO_4$

Molecular weight : 354.19

Melting point : 150 – 155°C

UV max : 275 nm

Properties

Aceclofenac is a white or almost white crystalline powder. Practically insoluble in water, freely soluble in acetone, soluble in alcohol. Aceclofenac is an orally administered non-steroidal analgesic and anti-inflammatory agent[1-3] with a good gastrointestinal tolerability profile[4-11]. It is official in B.P.[3] Aceclofenac is used in the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and scapulhumeral periarthritis[12]. It is also indicated for pains of various etiologies, such as musculoskeletal pain, dental pain or post surgical pain[13].

The mode of action of aceclofenac is largely based on the inhibition of prostaglandin synthesis. Aceclofenac is a potent inhibitor of the enzyme cyclooxygenase (selectivity cox-2 being evident)[14-15] which is involved in the production of prostaglandins, believed that they mediate may of symptoms of inflammation such as oedema and pain.

Pharmacokinetics

Absorption

Aceclofenac is rapidly and completely absorbed after oral administration. Peak plasma concentrations are reached 1.0 to 3.0 hours following ingestion. The presence of food does alter the extent of absorption of aceclofenac but the absorption rate is reduced.

Distribution

Aceclofenac is highly protein bound (> 99.7%). The plasma concentration of aceclofenac was approximately twice that in synovial fluid after multiple doses of the drug in-patient with knee pain and synovial fluid effusion. The volume of distribution is approximately 30 L.

Elimination

Renal excretion is the main route of elimination of aceclofenac with 70-80% of an administered dose found in the urine, 20% is excreted in the feaces mainly as conjugated hydroxyl metabolites. The mean plasma elimination half-life is 4.0-4.3 hours. Clearance is estimated to be 5 litres per hour. Aceclofenac is metabolized to a major metabolite, 4-hydroxy aceclofenac, and to a number of other metabolites including 5-hydroxy aceclofenac, 4-hydroxy diclofenac, diclofenac and 5-hydroxy diclofenac.

Dosage and Administration

The usual dose of aceclofenac is 100 mg given twice daily by mouth, one tablet in the morning and one in the evening can be taken before or after food. There is no evidence that the dose of aceclofenac needs to be modified in patient with mild renal impairment but as with other NSAIDs caution should be exercised.

Elderly: Generally no dose reduction necessary.

Children: Safety and efficacy not established.

Hepatic insufficiency : Mild to moderate, 100 mg daily, severe – not recommended.

Renal insufficiency : Mild-treat with caution.

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