CHAPTER 2

DRUG PROFILE

2.1. Celecoxib

Celecoxib is a non-steroidal anti-inflammatory drug (NSAID) and the first specific inhibitor of cycloxygenase-2 (COX-2) to be approved by the United States Food and Drug Administration (US FDA), in 1998 [Davies et al., 2000]. In comparison to newer COX-2 inhibitors like, rofecoxib, valdecoxib, etoricoxib, etc, celecoxib has been reported to have minimum adverse effect [Micromedex, 2002].

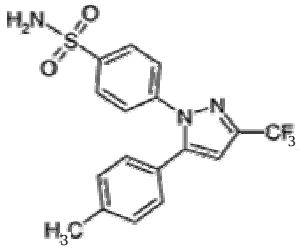
2.1.1. Chemistry

Name : Celecoxib

Chemical name : 4-[5-(4-methylphenyl)-3-trifluoromethyl-1H-pyrazol-1-yl] benzene sulphonamide

Molecular formula : $C_{17}H_{14}F_3N_30_2S$

Chemical structure :



Molecular weight : 381.38

Chemical Class : Fluorinated benzenesulfonamide derivative

Therapeutic Class : Anti-inflammatory, analgesic, and antipyretic

Description : Odourless, white to off-white crystalline powder

Melting point : 157 - 158 ºC

Solubility : Reported aqueous solubility at pH < 9 (5 - 40 °C) is 3-7 µg/ml and at pH 12 (40 °C) is 0.8 mg/ml. It is soluble in methanol and chloroform with a solubility of 111 mg/ml in alcohol at room temperature. It is highly soluble in acetonitrile.

pK_a : 11.1

log P : 3.683

2.1.2. Official methods of analysis

Celecoxib is not official in any of the Pharmacopoeia, but nine chromatographic techniques and one UV spectrophotometric method for the analysis of celecoxib in pure form, in pharmaceutical formulations and biological fluid, are reported in peer-reviewed journals. The reported methods have been discussed in Chapter 3 of this thesis. However, in the present thesis, an in-house developed and validated UV-visible spectrophotometric method was used for the analysis of celecoxib in pure form, in designed formulations and in various in vitro studies. The method has been described in detail in Chapter 3.

2.1.3. Therapeutic indications and dose

Acute pain: In case of pain associated with postorthopedic surgery, post dental surgery and primary dysmenorrhea, 400 mg should be given initially with one additional dose of 200 mg as needed on day 1, and then 200 mg twice daily as needed on subsequent days. In case of normal dental pain, single dose of 100 mg (although use of a selective COX-2 inhibitor is not warranted) to be given [Searle/ Pfizer, 2005].

Ankylosing spondylitis: For the treatment of axial pain, inflammation, and morning stiffness associated with ankylosing spondylitis, 100 mg twice daily has been effective.

Arthritis: For long term treatment of chronic osteoarthritis, a daily single or divided dose of 200 mg is prescribed. In case of rheumatoid arthritis, 100 or 200 mg is prescribed twice daily [Searle/ Pfizer, 2005].

Chemoprevention of various cancers: Preclinical studies suggest that celecoxib is efficacious in tumor prevention and at slowing tumor growth as a monotherapy. Its antiangiogenic activity and safety profile make in an ideal add-on with current standard cytotoxic therapies including cisplatin-11, 5-fluorouracil and radiation therapy [Nishimura et al., 2000; Wang et al., 2002; Zweifel et al., 2002; Wang et al., 2003].

Familial adenomatous polyposis: Celecoxib is approved as a secondary treatment among patients with familial adenomatous polyposis at a dose of 400 mg twice daily, to be taken with food [Roy, 2002; Phillips et al., 2002; Searle/ Pfizer, 2005].

Neuroprotective effect: COX-2 inhibition is reported to be effective in reducing cognitive impairments in patients receiving electro convulsive treatment, as in case of Alzheimer's disease [Aisen and Davis, 1994; Devanand et al., 1994; Rao et al., 2002].

Postcoital contraception: Celecoxib because of its COX-2 specificity and good gastric safety profile is reported to have a potential role in non-hormonal postcoital contraception [Sookvanichsilp and Pulbutr, 2002].

In case of hepatic insufficiency (moderate hepatic impairment; Child-Pugh Class II), a dose equivalent to 50 % of normal adult dose is recommended. Celecoxib is not recommended for patients with severe hepatic impairment. For patients who weigh less than 50 kg, the lowest recommended dose is used to initiate therapy.

2.1.4. Mechanism of action

Celecoxib is a highly selective inhibitor of enzyme cyclooxygenase-2 (COX-2). COX-2 is induced in response to inflammatory stimuli, which leads to the synthesis and accumulation of inflammatory prostanoids (prostaglandin E2) causing inflammation, oedema and pain. Celecoxib acts as an anti-inflammatory, analgesic and antipyretic agent by blocking the production of prostaglandin E2 via COX-2 inhibition. Traditional NSAIDs inhibit both COX-1 and COX-2. As COX-1 is the constitutive isoform of the enzyme and is present in most cell types; its inhibition is responsible for adverse activity of conventional NSAIDs [Davies et al., 2000]. Celecoxib is approximately 10-20 times more selective for COX-2 inhibition over COX-1 and this selctivity is considerably better than other NSAIDs like, etodolac, meloxicam, and nabumetone. In theory, this specificity allows celecoxib and other COX-2 inhibitors to reduce inflammation (and pain) while minimizing gastrointestinal adverse drug reactions (e.g. stomach ulcers) that are common with non-selective NSAIDs. It also means that it has a reduced effect on platelet aggregation compared to traditional NSAIDs [Cryer and Feldman, 1998; Bolten, 1998; Davies et al., 2000; Silverstein et al., 2000; Wolfe et al., 2002; Laine et al., 2002].

2.1.5. Clinical pharmacology

2.1.5.1. Pharmacokinetics

After oral dosing, peak plasma levels (C_{max}) of celecoxib occur approximately 2-3 h after an oral dose under fasting conditions. C_{max} of approximately 800 ng/ml and 950 ng/ml have been observed after single 200 mg doses in healthy fasting European and Japanese subjects respectively. Both C_{max} and AUC (area under the plasma concentration-time curve) are roughly dose proportional across the clinical dose range of 100-200 mg [AHFS, 2001].

In situ experiments conducted on dogs suggested that celecoxib has high permeability with good absorption throughout the GIT and that dissolution may be a rate limiting factor for absorption from solid dosage forms. In humans, lower dose and longer GI residence time may promote the opportunity for absorption of poorly soluble drug such as celecoxib that can be absorbed throughout the GIT [Paulson et al., 2001]. On oral administration of

200 mg of celecoxib along with high fat meal the absorption was delayed (T_{max}, time to attain C_{max} of about 4 h) but bioavailability was increased by about 10-20 % [Paulson et al., 2001].

In healthy subjects, celecoxib is highly protein bound (~ 97 %). In vitro studies indicate that celecoxib binds primarily to albumin and to a lesser extent, to alpha-1-acid glycoprotein. The apparent volume of distribution at steady state (V_{ss}/F) is approximately 400-500 L/70 kg in young healthy adults after a single 200 mg dose, suggesting extensive distribution into the tissues. Celecoxib is not preferentially bound to red blood cells. Pre-clinical studies indicate that the drug crosses the blood-brain barrier [Paulson et al., 2001].

Celecoxib is metabolized in the liver by hydroxylation, oxidation and some glucuronidation. In vitro and in vivo studies indicate that metabolism is mainly by cytochrome P450 CYP2C9. Three metabolites, a primary alcohol, the corresponding carboxylic acid and its glucuronide conjugate, have been identified in human plasma. These metabolites are inactive as COX-1 or COX-2 inhibitor [Paulson et al., 2001].

Celecoxib is eliminated predominantly by hepatic metabolism with little (<3 %) unchanged drug recovered in the urine and feces. Effective half-life is approximately 11 hours under fasted conditions. After multiple dosing, elimination half life is 8-12 hours and the rate of clearance i.e. apparent plasma clearance (CL/F) is about 500 ml/min. Multiple, dosing steady state plasma concentration is reached within 5 days of continuous administration [AHFS, 2001].

Summary of single dose (200 mg) disposition kinetics of celecoxib in healthy subjects under fasting conditions (n=36, 19-52 yrs of age) is presented in Table 2.1. The mean inter-subject variability of the main pharmacokinetic parameters (AUC, C_{max}, elimination half-life) is about 30 %.

Table 2.1: Pharmacokinetic data of celecoxib in human subjects

C_{max} (ng/ml)	T_{max} (h)	$t_{1/2}$ (h)	V_{ss}/F (L)	CL/F (L/h)
705 (38) [a]	2.8(37) [a]	11.2(31) [a]	429(34) [a]	27.7(28) [a]

[a]: Data in parenthesis indicate % CV (coefficient of variation); C_{max}= maximum plasma concentration; T_{max}= time to attain C_{max}; $t_{1/2}$= elimination half-life; V_{ss}/F= apparent volume of distribution at steady state; CL/F= apparent plasma clearance.

2.1.5.2. Special populations

Celecoxib has been found to show erratic pharmacokinetics in following classes of patient or population group [AHFS, 2001].

P450 2C9 per-oral metabolizers: To these patients, celecoxib should be administered with caution as they may have abnormally high plasma levels due to reduced metabolic clearance.

Elderly population: At steady state, elderly subjects (over 65 years) have 40 % higher C_{max} and 50 % higher AUC compared to younger subjects. This is a predominantly weight-related rather than age-related change. Celecoxib levels are found to be higher in lower weight individuals and consequently higher in the elderly population who are generally of lower mean weight than the younger population. Due to their lower body weights, elderly females show higher C_{max} and AUC than those for elderly males.

Race: Meta-analysis of pharmacokinetic studies has suggested an approximately 40 % higher AUC of celecoxib in Blacks compared to Caucasians. The cause and clinical significance of this finding is unknown.

Hepatic impairment: Pharmacokinetic study in subjects with mild (Child-Pugh Class I) and moderate (Child-Pugh Class II) hepatic impairment has shown that steady-state celecoxib AUC is increased by about 40 % and 180 % than that of healthy control subjects respectively.

Renal impairment: Celecoxib AUC was approximately 40 % lower in patients with chronic renal insufficiency, having glomerular filtration rate (GFR) of 35-60 ml/min/1.73m^2, than that seen in subjects with normal renal function. In elderly subjects with age related reductions in GFR (mean GFR > 65ml/min/1.73m^2), celecoxib pharmacokinetics were comparable to those seen in patients with normal renal function [Schwartz et al., 2002]. Patients with severe renal insufficiency have not been studied and celecoxib's use is not recommended in these patients.

2.1.5.3. Drug interactions

Concomitant use of celecoxib with aspirin or other NSAIDs (e.g. ibuprofen, naproxen, etc.) may increase the occurrence of stomach and intestinal ulcers. Celecoxib metabolism is predominantly mediated via cytochrome P450 2C9 in the liver. Therefore, significant interactions may occur when celecoxib is administered together with drugs that inhibit P450 2C9. In vitro studies indicate that celecoxib is an inhibitor of cytochrome P450 2D6. Therefore, there is a potential for an in vivo drug interaction with drugs that are metabolized by P450 2D6. Co-administration of celecoxib with aluminum and magnesium containing antacid results in reduction in plasma celecoxib concentrations with a decrease of 37 % in C_{max} and 10 % in AUC. Other drugs reported to interact with celecoxib include ACE

inhibitors, diltiazem, fluconazole lithium, loop diuretics and thiazide diuretics [Searle/ Pfizer, 2005].

2.1.6. Contraindications

Celecoxib is contraindicated in patients with hypersensitivity to celecoxib; documented allergic-type reaction to sulfonamides; urticaria, asthma, or allergic reactions to aspirin or other NSAIDs; advanced renal impairment; and severe hepatic impairment [Searle/ Pfizer, 2005].

2.1.7. Precautions

No clinical data on exposed pregnancies are available for celecoxib, but studies in pregnant Wistar rats have shown reproductive toxicity (anti-implantation effect) on use of celecoxib. Studies in rats show that celecoxib is excreted in milk at concentrations similar to those in plasma. It is recommended to be taken during pregnancy or while breastfeeding only after consulting the doctor and to be totally avoided during last trimester of pregnancy due to possible premature closure of ductus arteriosus [Sookvanichsilp and Pulbutr, 2002].

Caution should also be exercised when administering celecoxib to patients with history of liver/ renal dysfunction; hypertension/ cardiac conditions aggravated by fluid retention and oedema; and GI ulceration, bleeding, or perforation [Searle/ Pfizer, 2005].

2.1.8. Adverse reactions

Hematologic effects: Anemia and thrombosis, in lower extremity and pulmonary sites, have been reported between 2 days and 2 months after the start of therapy [Searle/ Pfizer, 2005]**.**

Cardiovascular effects: Fluid retention and peripheral oedema were observed in some patients. An increased risk of heart attack and stroke was found in a National Cancer Institute study involving the use of 400-800 mg celecoxib daily for the prevention of colorectal adenoma. The relative risk ratio was obtained as 2.3 to 3.4 in comparison to placebo treatment [Solomon et al., 2005].

Central nervous system effects: Headache, dizziness and delirium (confusion, disorientation, and auditory and visual hallucination) have been reported in rare cases.

Gastrointestinal effects: A preliminary 6-month study demonstrated a significant reduction in the incidence of GI ulceration in those taking celecoxib versus ibuprofen or diclofenac [Silverstein et al., 2000]. Reported GI effects of the drug were dyspepsia, diarrhoea,

exacerbation of inflammatory bowel disease, abdominal pain and flatulence [Malhotra et al., 2004].

Nephrotoxicity: NSAIDs, in general, have been associated with papillary necrosis and other renal injury and may precipitate acute renal failure in patients who are dependent on renal prostaglandins for maintenance of renal blood flow. Celecoxib causes sodium and potassium retention and lowers the glomerular filtration rate and effective renal plasma flow.

Hepatotoxicity: Borderline elevations in one or more liver function tests and serious hepatic reactions (jaundice, hepatitis, liver failure) have been reported.

Ocular effects: Orange-tint chromatopsia described as orange-coloured spots within both visual fields, which resolves within 3 days of discontinuing celecoxib, has been reported.

Respiratory effects: Upper respiratory tract infection, sinusitis, pharyngitis and rhinitis have been reported.

Dermatologic effects: Celecoxib was associated with an increased incidence of cutaneous reactions (rash, pruritis, urticaria) when compared to patients receiving other NSAIDs (diclofenac and ibuprofen). Patients may develop acute neutrophilic dermatosis (Sweet's Syndrome) and initially develop multiple, painful erosions of the nasal mucosa, accompanied by wrist and knee arthralgias, and painful erythematous plaques on hands, neck, legs and perianal area. Delayed cutaneous hypersensitivity reaction may occur after treatment. Patient may develop erythematous, maculopapular rashes without mucous membrane involvement. Pseudoporphyria presented with blisters and crusted erosions of face and dorsum of hand also occurred in patients taking celecoxib.

Anaphylaxis: Celecoxib may produce hypersensitivity reactions in the form of severe bronchospasm, which can be often fatal, in patients with aspirin sensitive asthma.

2.1.9. Overdosage

There is no reported clinical experience of overdose. Single doses up to 1200 mg and multiple doses up to 600 mg twice daily have been administered to healthy subjects without clinically significant adverse effects.

2.1.10. Marketed dosage forms and storage

Celecoxib is marketed as capsules and tablets. Celecoxib in capsule or tablet formulations is reported to be stable at 15-30 ^{o}C.

2.2 Acyclovir

Acyclovir is a synthetic acyclic purine nucleoside analogue of the natural nuleoside 2'-deoxyguanine (purynic nucleoside) with potent antiviral activity [Wagstaff et al., 1994; Rossel et al., 2000; Jarvis et. al., 2003].

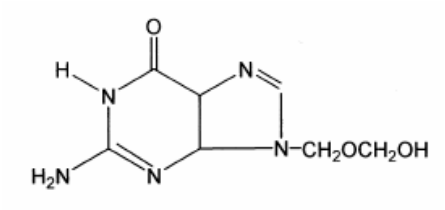
2.2.1. Chemistry

Name : Acyclovir

Chemical name : 2-amino-1, 9-dihydro-9-[(2-hydroxyethoxy)methyl]6-H-purin-6-one

Molecular formula : $C_8H_{11}N_5O_3$

Chemical structure :



Molecular weight : 225.21

Chemical Class : Nucleoside analogue

Therapeutic Class : Antiviral

Description : White to off-white crystalline powder

Melting point : 256 ºC

Solubility : Maximum solubility in water at 37 °C is 2.5 mg/ml

pK_a's : 2.27 and 9.25

log P : - 1.740

2.2.2. Official methods of analysis

Acyclovir is official only in United States Pharmacopoeia, in which UV spectrophotometeric and liquid chromatographic methods for the analysis of acyclovir in pure form and in pharmaceutical formulations and UV spectroscopic method for dissolution studies of tablets/ capsules containing acyclovir have been reported [USP, 2006]. The details of the two methods are presented below.

Liquid chromatographic method: USP-2006 recommends liquid chromatographic (LC) methods for analysis of related substances in acyclovir and assay of acyclovir in pharmaceutical dosage forms (capsules, injection, ointment, oral suspension and tablets). The method involves the use of mobile phases of glacial acetic acid in water (1 in 1000

parts), 0.02 M acetic acid and variable mixtures of solution A (acetic acid: methanol at 125:8) & solution B (methanol) respectively at flow rates of 3, 1.5 and 1 ml/min respectively, using guanine as the internal standard, on a 4.2/ 4.6 mm × 25 cm column that contains L1 packing with UV detection at 254 nm [USP, 2006].

UV spectrophotometric method: USP-2006 recommends UV spectrophotometric method for assay of acyclovir in dissolution samples of acyclovir capsules and tablets. In this method, 0.1 N hydrochloric acid (HCl) is used as the solvent system with a wavelength of detection ($?_{det}$) of 254 nm [USP, 2006].

Three chromatographic techniques for the analysis of acyclovir in pure form and in pharmaceutical formulations reported in peer-reviewed journals have been discussed in Chapter 3 of this thesis. In the present thesis, in-house developed and validated UV-visible spectrophotometric method was used for the analysis of acyclovir in pure form, in designed formulations and in various in vitro studies. The developed method has been described in detail in Chapter 3.

2.2.3. Therapeutic indications and dose

Following dosage regimen has been reported in literature for various infections.

Herpes zoster infection: 800 mg of acyclovir every 4 hours orally, five times daily for 7 to 10 days is indicated for the acute treatment of herpes zoster infection (shingles) [Medline Plus, 2006].

Genital herpes infection: Acyclovir is indicated for the treatment of initial episodes and the management of recurrent episodes of genital herpes [Lietman, 1982; Fletcher and Chinnock, 1985; Medline Plus, 2006].

- **Initial genital herpes/ herpes simplex infection:** 200 mg of acyclovir administered 5 times daily at 4 hourly intervals for 5-10 days.
- **Chronic suppressive therapy for recurrent disease:** 200 mg of acyclovir administered 4 times daily at 6 hourly intervals or 400 mg every 12 hourly for 6 to 12 months, followed by re-evaluation to assess the need for continuation of therapy.
- **Intermittent therapy:** 200 mg every 4 hours, five times daily for 5 days initiated at the earliest sign or symptom of recurrence.
- **Immuno-compromised patients:** 200 mg of acyclovir is given 4 times daily at 6 hourly intervals. In severely immuno-compromised patients, or impaired absorption from the gut, dosage is doubled to 400 mg.

- **Topical therapy:** Topical acyclovir does not cure herpes simplex, but helps to relieve the pain and discomfort and aids the sores to heal faster. Adults- cream/ ointment should be applied to the affected area(s) i.e., skin, mucous membranes, and genitals, 4 to 6 times a day, for up to 10 days, or every 3 hours, for a total of 6 times a day, for 7 days.

Varicella zoster infection: Acyclovir is indicated for the treatment of chickenpox [Medline Plus, 2006].

- **Children:** To children, 2 years of age and older, 20 mg/kg per dose is given orally 4 times daily (80 mg/kg/day) for 5 days.
- **Adults and children over 40 kg:** 800 mg 4 times daily for 5-7 days is prescribed at the earliest sign or symptom of chickenpox. Intravenous acyclovir is indicated for the treatment of varicella zoster infections in immunocompromised patients.

Patients with Acute or Chronic Renal Impairment: In patients with renal impairment, the dose of acyclovir capsules/ tablets is modified according to the level of impairment [Medline Plus, 2006].

- **During hemodialysis:** The mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60 % decrease in plasma concentrations following a 6-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.
- **During peritoneal dialysis:** No supplemental dose appears to be necessary after adjustment of the dosing interval.

2.2.4. Mechanism of action

Acyclovir has in vitro and in vivo inhibitory activity against herpes simplex virus types 1 and 2 (HSV-1 & 2), and varicella-zoster virus (VZV). In cell culture, acyclovir's highest antiviral activity is in the order HSV-1 > HSV-2 > VZV [Fletcher and Chinnock, 1985; Miwa et al., 2005].

The inhibitory activity of acyclovir is highly selective due to its affinity for the enzyme thymidine kinase (tk) encoded by HSV and VZV. Acyclovir has poor affinity for host cell thymidine kinase [Miwa et al., 2005]. This viral tk enzyme converts acyclovir into acyclovir monophosphate, a nucleotide analogue. The monophosphate is further converted into diphosphate by cellular guanylate kinase and into triphosphate by a number of cellular enzymes. In vitro, acyclovir triphosphate stops replication of herpes viral DNA (deoxyribonuleic acid) by a two-pronged mechanism of action: (i) it competes with 2-deoxyguanosine triphosphate as a substrate for viral DNA polymerase and (ii) once it

becomes incorporated into the replicating viral DNA, it acts as a chain terminator because it does not have a terminal 3´ hydroxyl group [Laskin et al., 1982; Zacchigna et al., 2002]. The greater antiviral activity of acyclovir against HSV compared to VZV is due to its more efficient phosphorylation by the viral tk in HSV than in VZV [Elion, 1982; Wagstaff et al., 1994].

2.2.5. Clinical pharmacology

2.2.5.1. Pharmacokinetics

Absorption of orally administered acyclovir is slow, variable and incomplete with an oral bioavailability of 15-30 % [Hamada et al., 1975; Corrigan and Stanly, 1982]. The effects of dosage size on the extent of oral absorption are not well understood. Some reports suggest that absorption from the GIT may be a saturable, non-dose-dependent process through active transport in the narrow absorption window as less than proportional increase in plasma acyclovir concentrations were observed on increasing the dose [Bridgen et al., 1980; Fletcher and Chinnock, 1985; Vergin et al., 1995]. In contrast, another study reported no change in the urinary recovery of unchanged drug and in the bioavailability calculated from urinary excretion data, concluding that the net absorption of acyclovir is nearly proportional to the dose [de Miranda et al., 1982; Rossel et al., 2000].

Acyclovir pharmacokinetic parameters after oral administration in healthy human subjects are summarized in Table 2.2 [Lietman, 1982; Fletcher and Bean, 1985; Fletcher and Chinnock, 1985].

Table 2.2: Pharmacokinetic characteristics of acyclovir

Plasma protein binding (%)	Time to attain peak plasma level (h)	Plasma elimination half-life (h)	Average oral bioavailability (%)
9-33	2.0	2.5 to 4.0	13-30

In cross-over design study, after i.v. injection to male beagle dogs, the acyclovir plasma concentration-time profile, determined by radioimmunoassay, exhibited a biexponential decay with a terminal $t_{1/2}$ of 2.2 to 3.6 h. Plasma clearance of 3.48-5.83 ml/min/kg approximated the normal glomerular filtration rate in dogs and the V_d (apparent volume of distribution) beta (0.97-1.17 L/kg) indicated distribution of the drug into tissues. Similar kinetic findings were obtained after i.v. administration of ^{14}C-labelled acyclovir to dogs. The radioactivity recovered in the urine was 95 % of the dose and 92 % of the urinary ^{14}C

was identified as acyclovir. The remainder of ^{14}C corresponded to minor urinary metabolites.

The plasma acyclovir concentration-time curves generated from oral (capsule and gavage) data were fit to a one-compartment open pharmacokinetic model. The elimination half-life and V_d parameters were similar to those calculated for the i.v. route. Peak plasma drug concentrations were reached within 2 h of dosing. Good oral bioavailability of 91 and 80 % was observed after the administration of a capsule at the lower doses of 5 and 20 mg/kg respectively, but bioavailability declined to 52 % at the 50 mg/kg dose indicating the possibility that the gastrointestinal absorption of acyclovir is a saturable process [Krasny et al., 1981]. The pharmacokinetic profiles of BioVir™ CR (gastroretentive bioadhesive trilayered tablets) and Zovirax® (IR formulation) were assessed in fed beagle dogs. There was a 72 % increase in absolute bioavailability of acyclovir from gastroretentive bioadhesive formulations [Jacob et al., 2006].

There was no effect of food on the absorption of acyclovir (n=6). There is no active metabolite of acyclovir. Renal elimination is seen in case of acyclovir. The only known urinary metabolite is 9-[(carboxymethoxy) methyl] guanine. No pre-systemic metabolism has been observed for the drug.

2.2.5.2. Special populations

Elderly and pediatric population: Reported clinical experience with acyclovir has not identified differences in responses between elderly and younger patients. Safety and effectiveness in children less than 2 years of age have not been adequately studied. In general, the pharmacokinetics of acyclovir in pediatric patients is similar to that of adults. Mean half-life after oral doses of 300 mg/m^2 and 600 mg/m^2 in pediatric patients in the age group 7 months to 7 years was 2.6 h (range 1.59 to 3.74 h) [Rossel et al., 2000].

Adults with Impaired Renal Function: The half-life and total body clearance of acyclovir are dependent on renal function. A dosage adjustment is recommended for patients with reduced renal function.

2.2.5.3. Drug interactions

Acyclovir interacts with other nephrotoxic agents. Drugs that may interact with acyclovir include atovaquone, fosphenytoin, phenytoin, probenecid, valproic acid, and zidovudine [Stein et al., 1994; Parmeggiani, 1995 Medline Plus, 2006].

2.2.6. Contraindications

Acyclovir is contraindicated only for patients who develop hypersensitivity or intolerance to the components of the formulations [Fletcher and Chinnock, 1985; Medline Plus, 2006].

2.2.7. Precautions

Acyclovir should be administered to pregnant woman or nursing mother with caution and only when indicated. There are no adequate and well-controlled studies in pregnant women. Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times the corresponding plasma levels. These concentrations would potentially expose the nursing infant to a dose of acyclovir as high as 0.3 mg/kg/day. Acyclovir was not reported to be teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.), or rat (50 mg/kg/day, s.c.) studies. It did not impair fertility or reproduction in mice (450 mg/kg/day, p.o.) or in rats (25 mg/kg/day, s.c.). At higher doses (50 mg/kg/day, s.c.) of 11 to 22 and 16 to 31 times human levels, respectively in rats and rabbits, implantation efficacy was decreased but no effect was seen on litter size.

Topical acyclovir has not been shown to cause birth defects or other problems in animal as indicated by studies using mice, rats, or rabbits, except when given in very high doses. It has not been reported to cause problems in nursing babies, even though small amounts of topical acyclovir are absorbed through the mother's skin and mucous membranes.

Peroral administration of acyclovir has no statistically significant difference in the incidence and latency period of tumors between treated and control animals (rats and mice). In vitro assay showed evidence of mutagenicity in 3 samples out of 16 genetic toxicity assays, [Fletcher and Chinnock, 1985].

2.2.8. Adverse reactions

Acyclovir is shown to have different type and extent of adverse reaction in case of infections.

Herpes simplex infection: In case of short-term administration for 10 days, nausea and/ or vomiting were reported in 2.7 % patients out of 298 patients. In case of long-term administration for 1 year in 586 patients, nausea and diarrhoea were reported in 4.8 % and 2.4 % patients respectively. Out of 589 patients receiving intermittent treatment of recurrences for a period of 1 year, diarrhoea, nausea and headache were reported in 2.7 %, 2.4 % and 2.2 % patients respectively [Lietman, 1982; Fletcher and Chinnock, 1985].

Herpes zoster infection: Malaise at 11.5 % and 11.1 % level was reported during three clinical trials in 323 patients and 323 placebo recipients respectively [Lietman, 1982].

Chickenpox: During three clinical trials, 3.2 % patients reported diarrhoea out of 495 patients in drug group as compared to 2.2 % in case of 498 patients receiving placebo [Lietman, 1982; Fletcher and Chinnock, 1985].

Voluntary reports of adverse events in the US, which have been received since market introduction, include: fever, headache, pain, peripheral oedema, anaphylaxis (rare), confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (in older adults), diarrhoea, elevated liver function, GI distress, nausea, leukopenia, lymphadenopathy, myalgia, alopecia, pruritus, rash, urticaria, visual abnormalities and elevated creatinine [Medline Plus, 2006].

2.2.9. Overdosage

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects [Medline Plus, 2006]. Precipitation of acyclovir in renal tubules may occur when the solubility of 2.5 mg/ml is exceeded in the intra-tubular fluid [Lietman, 1982; Fletcher and Chinnock, 1985].

2.2.10. Marketed dosage forms and storage

Injections, tablets, dispersible tablets, capsules, suspensions, ointments, creams and gels are available in the market for acyclovir. The drug is stable, but is incompatible with strong oxidizing agents. It should be stored at 15 to 25 °C and protected from moisture.

2.3. References

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