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Review Article

A REVIEW OF PHARMACOLOGICAL AND PHARMACEUTICAL PROFILE OF IRBESARTAN

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ABSTRACT

Irbesartan is classified as an angiotensin II receptor type 1 antagonist. Angiotensin II receptor type 1 antagonists are widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Irbesartan is an orally active lipophilic drug and possesses rapid oral absorption. It causes reduction in blood pressure and is used in treatment of hypertension. Irbesartan delays progression of diabetic nephropathy and is indicated for the reduction of renal disease progression in patients with type 2 diabetes. It is jointly marketed by Sanofi-Aventis and Bristol-Myers Squibb under the trade name Aptovel®, Karvea® and Avapro®. Irbesartan is also available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive effect. This paper reviews the pharmacological and pharmaceutical properties of Irbesartan. Irbesartan could be an attractive target for the generic industries.

Keywords: Irbesartan, Hypertension, ACE inhibitors, Diabetes, Diuretic.

INTRODUCTION

Irbesartan, an angiotensin II receptor antagonist, is used mainly for the treatment of hypertension. It is an orally active nonpeptide tetrazole derivative and selectively inhibits angiotensin II receptor type1[1,2]. Angiotensin II receptor type1 antagonists have been widely used in treatment of diseases like hypertension, heart failure, myocardial infarction and diabetic nephropathy. Irbesartan, classified as high permeability and low solubility drug, is slightly soluble in alcohol and methylene chloride, and practically insoluble in water. It is a lipophilic drug and possesses rapid oral absorption[2].

Hypertension is one of the most prevalent cardiovascular diseases in the world, affecting a big proportion of the adult population. Furthermore, hypertension is an independent risk factor for cardiovascular disease and is associated with an increased incidence of stroke and coronary heart disease. Although there have been many advances in the treatment over the past several decades, less than 25% of all hypertensive patients have their blood pressure adequately controlled with available therapies. The angiotensin II angiotensin blockers (ARBs)

represent a newer class of antihypertensive agents[3]. Their mechanism of action differs from that of the angiotensin-converting enzyme (ACE) inhibitors, which also affect the rennin angiotensin system. The ARBs were developed to overcome several of the deficiencies of ACE inhibitors: competitive inhibition of ACE results in a reactive increase in renin and angiotensin I levels, which may overcome the blockade effect; ACE is a relatively nonspecific enzyme that has substrates in addition to angiotensin I, including bradykinin and other tachykinins, and thus, inhibition of ACE may result in accumulation of these substrates; production of angiotensin II can occur through non-ACE pathways as well as through the primary ACE pathway, and these alternative pathways are unaffected by ACE inhibition; specific adverse effects are associated with ACE inhibitor effects on the enzyme; and ARBs may offer more complete angiotensin II inhibition by interacting selectively with the receptor site[4]. All 7 drugs (sartans) in this class are approved by the Food and Drug Administration for the treatment of hypertension, either alone or in combination with other drugs. Unlabeled uses include the treatment of congestive heart failure and, for losartan and irbesartan, diabetic nephropathy[5]. Irbesartan is indicated for the treatment of hypertension. Irbesartan also delays progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria or proteinuria[6-8].

History & Development[3-5, 9, 10]

Irbesartan was first developed by Sanofi Research (now part of Sanofi-Aventis) and jointly marketed by Sanofi-Aventis and Bristol-Myers Squibb under the trade name Aptovel®, Karvea®, and Avapro®. It may be used alone or in combination with other antihypertensive medications. Thus, Irbesartan is available in a combination formulation with a low dose thiazide diuretic, invariably hydrochlorothiazide, to achieve an additive antihypertensive effect. Irbesartan/hydrochlorothiazide combination preparations are marketed under similar trade names to irbesartan preparations, including Irda®, Colda®, CoAProvel®, Karvezide®, Avalide® and Avapro HCT®.

The renin-angiotensin aldosterone system (RAAS) plays an essential role in the regulation of blood pressure. Renin, a proteinase enzyme, is secreted by the kidney in response to a reduction in renal blood flow, blood pressure or sodium concentration. Renin then converts angiotensinogen, which is secreted by the liver, to the decapeptide angiotensin I (AI). AI is cleaved by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II (AII). AII produces potent vasoconstriction via interaction with vascular angiotensin receptors (AT receptors). AII also promotes aldosterone secretion and therefore sodium retention by stimulation of angiotensin receptors present on the adrenal cortex. These actions result in elevated blood pressure secondary to the vasoconstriction and enhanced cardiac output secondary to sodium retention. In addition to its normal regulatory role, the RAAS also contributes to pathological conditions such as renovascular hypertension, essential hypertension and congestive heart failure. Thus over the past several decades research efforts have been directed toward developing drugs capable of suppressing of RAAS by inhibiting renin release, by blocking the formation of AII via inhibition of ACE, or Antagonism of AII at its physiologic receptors. In the past most clinically relevant success involved the development of ACE inhibitors (ACEIs), beginning with the introduction of captopril in 1981, followed by enalapril (Vasotec®), lisinopril (Prinivil®, Zestril®), benazepril (Lotensin®), fosinopril (Monopril®), quinapril (Accupril®), ramipril (Altace®), moexipril (Univasc®) and trandolapril (Mavik®). ACEIs have been successfully employed in the management of various forms of hypertension as well as congestive heart failure. However, ACE has other physiologic actions not related to the regulation of RAAS, including the degradation

of bradykinin and other peptides including substance P. These additional actions are also inhibited by ACEIs, and this may account for some of the adverse reactions of these drugs including dry cough. Thus in recent years renin inhibitors and AII receptor antagonists were targeted for development as more specific inhibitors of the RAAS and as a direct approach to block the system independent of AII production. These efforts led to the introduction in recent years of several non-peptide heterocyclic AII antagonists including losartan (Cozaar®), followed by valsartan (Diovan®) and now irbesartan. Irbesartan is well-absorbed orally, long-acting allowing for once-daily administration, and unlike losartan, does not exert a uricosuric effect. Irbesartan also is reported to demonstrate dose-response efficacy while maintaining placebo-level side effects at doses.

Physicochemical Properties[11]

Irbesartan is 2-butyl-3-({4-[2-(2*H*-1,2,3,4-tetrazol-5-yl)phenyl]phenyl}methyl)-1,3-diazaspiro [4.4]non-1-en-4-one (Figure1), with chemical formula $C_{25}H_{28}N_6O$ & molecular weight of 428.53 g/mol. Irbesartan is white crystalline powder with melting point 180-182 °C. It is soluble in alcohol and methylene chloride, and practically insoluble in water. Irbesartan is a tetrazole derivative (five-membered heterocyclic ring with 4 nitrogen atoms) that contains acid (pKa = 4.24) groups making the compound soluble in the neutral pH range. It is a nonpolar compound with a partition coefficient (octanol/water) of 10.1 at pH of 7.4. In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism. There was no induction or inhibition of 3A4. Irbesartan have different type of impurities such as 1-pentanoylamino-cyclopentanecarboxylic acid [2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-amide,2-Butyl-3-[[4-[2-(2-trityl-tetrazol-5-yl) phenyl] phenyl]methyl]-1,3-iazaspiro[4.4] non-1-en-4- one, 2-Butyl-4-spirocyclopentane-2-imidazolin-5-onehydrochloride,5-(4'-(Bromomethyl) (1,1'-biphenyl)-2-yl)-1-trityl-1H-tetrazole(Irbesartan Bromo Impurity), 4'-[(2-Butyl-4-oxo-1,3-diazaspiro[4.4]non-1-en-3-yl) methyl] biphenyl-2-carbonitrile. It is also called as Irbesartan USP Related Compound A, Irbesartan N1-trityl impurity, Irbesartan lactam impurity, Irbesartan bromo impurity, and Irbesartan cyano impurity, respectively.

PHARMACOLOGY

Mechanism of Action[5, 12-14]

Angiotensin II is a potent vasoconstrictor formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kinase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system (RAS) and also stimulates aldosterone synthesis and secretion by adrenal cortex, cardiac contraction, renal reabsorption of sodium, activity of the sympathetic nervous system, and smooth muscle cell growth. Irbesartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively binding to the AT1 angiotensin II receptor. There is also an AT2 receptor in many tissues, but it is not involved in cardiovascular homeostasis.

Irbesartan is a specific competitive antagonist of AT_1 receptors with a much greater affinity (more than 8500-fold) for the AT1 receptor than for the AT_2 receptor and no agonist activity.

Blockade of the AT1 receptor removes the negative feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and circulating angiotensin II do not overcome the effects of irbesartan on blood pressure.

Irbesartan does not inhibit ACE or renin or affect other hormone receptors or ion channels known to be involved in the cardiovascular regulation of blood pressure and sodium homeostasis. Because irbesartan does not inhibit ACE, it does not

affect the response to bradykinin; whether this has any clinical relevance is not known. In healthy subjects irbesartan (150 or 300 mg), like other angiotensin antagonists, inhibits the pressor effects of infused AII producing peak inhibition of both systolic and diastolic blood pressure rise within 2-4 h with residual effects persisting for 24 h. Irbesartan has been found safe in subjects with pregnancy.

Pharmacokinetic & Pharmcodynamic Profile

Irbesartan is an orally active agent that does not require biotransformation into an active form. The oral absorption of irbesartan is rapid and complete with an average absolute bioavailability of 60-80%. Following oral administration of irbesartan, peak plasma concentrations of irbesartan are attained at 1.5-2 h after dosing. Food does not affect the bioavailability of irbesartan. The pharmacokinetics of irbesartan has been compared to the other available angiotensin receptor antagonists (Table1). The oral bioavailability of this AT_1 antagonist is relatively high.

Irbesartan is more completely absorbed from GI tract than other AT antagonists and reaches peak plasma concentrations within 2 h. Irbesartan is not as extensively bound to plasma proteins and does not require metabolism to the active form. It is metabolized hepatically to inactive metabolites via cytochrome P450 2C9 (CYP29). It is excreted by both biliary and renal routes and has a longer elimination half-life (11-15 h) than other angiotensin antagonists. The pharmacokinetics of irbesartan are not significantly altered by renal or mild-to-moderate hepatic impairment, age or by co-administration of hydrochlorothiazide[5, 15-17].

Distribution

Irbesartan is 90% bound to serum proteins (primarily albumin and α1-acid glycoprotein) with negligible binding to cellular components of blood. The average volume of distribution is 53-93 liters. Total plasma and renal clearances are in the range of 157-176 ml/min and 3.0-3.5 ml/min, respectively. With repetitive dosing, irbesartan accumulates to no clinically relevant extent[18.]

Metabolism and Elimination[19, 20]

Irbesartan is partly metabolized and excreted mainly in bile. It is metabolized via glucuronide conjugation and oxidation. Following oral or intravenous administration of 14C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary circulating metabolite is the inactive irbesartan glucuronide conjugate (approximately 6%). The remaining oxidative metabolites do not add appreciably to pharmacologic activity irbesartan. Irbesartan and its metabolites are excreted by both biliary and renal routes. There is either oral or intravenous administration of 14C-labeled irbesartan; about 20% of radioactivity is recovered in the urine and the remainder in the feces, as irbesartan or irbesartan glucuronide.

In vitro studies of irbesartan oxidation by cytochrome P450 isoenzymes indicated irbesartan was oxidized primarily by 2C9; metabolism by 3A4 was negligible. Irbesartan was neither metabolized by, nor did it substantially induce or inhibit, isoenzymes commonly associated with drug metabolism (1A1, 1A2, 2A6, 2B6, 2D6, 2E1). There was no induction or inhibition of 3A4.

THERAPEUTIC EFFICACY[5, 15, 21-25]

In a number of multicenter, randomized, placebo-controlled, double-blind studies in patients with mild to moderate hypertension, statistically significant reductions in trough systolic and diastolic blood pressures were observed in patients receiving irbesartan in doses of 75 mg daily or greater. Greater reductions in blood pressure occurred when the dose was increased, but this effect leveled off at about 300 mg. The blood pressure lowering effects of irbesartan were apparent after the first dose, and reached maximal effect within 4-6 weeks. Irbesartan was found to be effective in reducing

blood pressure regardless of patient age, gender or race. However, the effect in black patients, typically a low renin population, is somewhat lower. In comparative trials irbesartan was shown to be at least as effective as hydrochlorothiazide, atenolol and the full dosage of enalapril. And in combination trials, greater reductions in blood pressure were observed when irbesartan was combined with the diuretic hydrochlorothiazide. As a result of these findings, irbesartan is indicated for the once daily treatment of hypertension and may be used alone or in combination with other antihypertensive agents.

The antihypertensive effects of irbesartan were examined in 7 major placebo-controlled 8-12 week trials in patients with baseline diastolic blood pressures of 95-110 mm Hg. Doses of 1-900 mg were included in these trials in order to fully explore the dose-range of irbesartan. These studies allowed comparison of once- or twice-daily regimens at 150 mg/day, comparisons of peak and trough effects, and comparisons of response by gender, age, and race. Two (2) of the 7 placebo-controlled trials identified above examined the antihypertensive effects of irbesartan and hydrochlorothiazide in combination. The 7 studies of irbesartan monotherapy included a total of 1915 patients randomized to irbesartan (1-900 mg) and 611 patients randomized to placebo. Once-daily doses of 150 and 300 mg provided statistically and clinically significant decreases in systolic and diastolic blood pressure with trough (24 h post-dose) effects after 6-12 weeks of treatment compared to placebo, of about 8-10/5-6 and 8-12/5-8 mm Hg, respectively. No further increase in effect was seen at dosages greater than 300 mg.

Once-daily administration of therapeutic doses of irbesartan gave peak effects at around 3-6 h and, in one ambulatory blood pressure monitoring study, again around 14 hours. This was seen with both once- and twice-daily dosing. Trough-to-peak ratios for systolic and diastolic response were generally between 60-70%. In a continuous ambulatory blood pressure monitoring study, once-daily dosing with 150 mg gave trough and mean 24 h responses similar to those observed in patients receiving twice-daily dosing at the same total daily dose. In controlled trials, the addition of irbesartan to hydrochlorothiazide doses of 6.25, 12.5, or 25 mg produced further dose-related reductions in blood pressure similar to those achieved with the same monotherapy dose of irbesartan. HCTZ also had an approximately additive effect.

Analysis of age, gender, and race subgroups of patients showed that men and women, and patients over and under 65 years of age, had generally similar responses. Irbesartan was effective in reducing blood pressure regardless of race, although the effect was somewhat less in blacks (usually a low-renin population). The effect of irbesartan is apparent after the first dose and it is close to its full observed effect at 2 weeks. At the end of an 8 week exposure, about 2/3 of the antihypertensive effect was still present 1 week after the last dose. Rebound hypertension was not observed. There was essentially no change in average heart rate in irbesartan-treated patients in controlled trials.

Renal Insufficiency

The pharmacokinetics of irbesartan was not altered in patients with renal impairment or in patients on hemodialysis. Irbesartan is not removed by hemodialysis. No dosage adjustment is necessary in patients with mild to severe renal impairment unless a patient with renal impairment is also volume depleted.

Hepatic Insufficiency

The pharmacokinetics of irbesartan following repeated oral administration were not significantly affected in patients with mild to moderate cirrhosis of the liver. No dosage adjustment is necessary in patients with hepatic insufficiency.

Impaired Renal Function

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal

function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system (e.g., patients with severe congestive heart failure), treatment with angiotensin-converting-enzyme inhibitors has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Irbesartan would be expected to behave similarly. In studies of ACE inhibitors in patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or BUN have been reported. There has been no known use of irbesartan in patients with unilateral or bilateral renal artery stenosis, but a similar effect should be anticipated.

Pregnancy

Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to drugs that act on the renin-angiotensin system, and they should also be told that these consequences do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. These patients should be asked to report pregnancies to their physicians as soon as possible.

Carcinogenesis, Mutagenesis, and Impairment of Fertility

No evidence of carcinogenicity was observed when irbesartan was administered at doses of up to 500/1000 mg/kg/day (males/females, respectively) in rats and 1000 mg/kg/day in mice for up to 2 years. For male and female rats, 500 mg/kg/day provided an average systemic exposure to irbesartan [AUC (0-24h) bound plus unbound] about 3 and 11 times, respectively, the average systemic exposure in humans receiving the maximum recommended dose (MRD) or 300 mg irbesartan/day, whereas 1000 mg/kg/day (administered to females only) provided an average systemic exposure about 21 times that reported for humans at the MRD. For male and female mice, 1000 mg/kg/day provided an exposure to irbesartan about 3 and 5 times, respectively, the human exposure at 300 mg/day.

Irbesartan was not mutagenic in a battery of in vitro tests (Ames microbial test, rat hepatocyte DNA repair test, V79 mammalian-cell forward gene-mutation assay). Irbesartan was negative in several tests for induction of chromosomal aberrations (in vitro -human lymphocyte assay; in vivo -mouse micronucleus study).

Irbesartan also delays progression of diabetic nephropathy and is also indicated for the reduction of renal disease progression in patients with type 2 diabetes, hypertension and microalbuminuria or proteinuria.

SAFETY AND TOLERABILITY[5, 11,12,16,17]

The safety of antihypertensive deserves a special importance because they are likely to be used long term in general practice in a number of patients. Irbesartan has a good tolerability profile consistent over the wide dose range. Irbesartan had no adverse effects on fertility or mating of male or female rats at oral doses ≤650 mg/kg/day, the highest dose providing a systemic exposure to irbesartan (AUC0-24h bound plus unbound) about 5 times that found in humans receiving the maximum recommended dose of 300 mg/day.

Adverse Reactions[5, 15, 26, 27]

Irbesartan has been evaluated for safety in more than 4300 patients with hypertension and about 5000 subjects overall. This experience includes 1303 patients treated for over 6 months and 407 patients for 1 year or more. Treatment with irbesartan was well-tolerated, with an incidence of adverse events similar to placebo. These events generally were mild and transient with no relationship to the dose of irbesartan. In placebo-controlled clinical trials, discontinuation of therapy due to a clinical adverse event was required in 3.3% of patients treated with irbesartan, versus 4.5% of patients given placebo. In placebo-controlled clinical trials, the adverse event experiences that occurred in at least 1% of patients treated with irbesartan (n=1965) and at a higher incidence versus placebo (n=641) included diarrhea (3% Vs 2%), dyspepsia/heartburn (2% Vs 1%),

musculoskeletal trauma (2% Vs 1%), fatigue (4% Vs 3%), and upper respiratory infection (9% Vs 6%).

The following adverse events occurred at an incidence of 1% or greater in patients treated with irbesartan, but were at least as frequent or more frequent in patients receiving placebo: abdominal pain, anxiety/nervousness, chest pain, dizziness, edema, headache, influenza, musculoskeletal pain, pharyngitis, nausea/vomiting, rash, rhinitis, sinus abnormality, tachycardia, and urinary tract infection. Irbesartan use was not associated with an increased incidence of dry cough, as is typically associated with ACE inhibitor use. In placebo controlled studies, the incidence of cough in irbesartan treated patients was 2.8% Vs 2.7% in patients receiving placebo. The incidence of hypotension or orthostatic hypotension was low in irbesartan treated patients (0.4%), unrelated to dosage, and similar to the incidence among placebo treated patients (0.2%). Dizziness, syncope, and vertigo were reported with equal or less frequency in patients receiving irbesartan compared with placebo.

Fetal/Neonatal Morbidity and Mortality

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature in patients who were taking angiotensin-converting-enzyme inhibitors. When pregnancy is detected, irbesartan should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester.

Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of irbesartan as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to a drug acting on the renin-angiotensin system will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, irbesartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Gender differences

No gender related differences in pharmacokinetics were observed in healthy elderly (age 65-80 years) or in healthy young (age 18-40 years) subjects. In studies of hypertensive patients, there was no gender difference in half-life or accumulation, but

somewhat higher plasma concentrations of irbesartan were observed in females (11-44%). No gender-related dosage adjustment is necessary.

Geriatric

In elderly subjects (age 65-80 years), irbesartan elimination half-life was not significantly altered, but AUC and Cmax values were about 20-50% greater than those of young subjects (age 18-40 years). No dosage adjustment is necessary in the elderly.

DRUGS INTERACTIONS[15, 26-30]

No significant drug-drug pharmacokinetic (or pharmacodynamic) interactions have been found in interaction studies with hydrochlorothiazide, digoxin, warfarin and nifedipine.

In vitro studies show significant inhibition of the formation of oxidized irbesartan metabolites with the known cytochrome CYP 2C9 substrates/inhibitors sulphenazole, tolbutamide, and nifedipine. However, in clinical studies the consequences of concomitant irbesartan on the pharmacodynamics of warfarin were negligible. Based on in vitro data, no interaction would be expected with drugs whose metabolism is dependent upon cytochrome P450 isozymes.

In separate studies of patients receiving maintenance doses of warfarin, hydrochlorothiazide, or digoxin, irbesartan administration for 7 days had no effect on the pharmacodynamics of warfarin (prothrombin time) or pharmacokinetics of digoxin. The pharmacokinetics of irbesartan was not affected by co- administration of nifedipine or hydrochlorothiazide.

DOSAGE[5, 22-29]

Irbesartan is available as white and off-white biconvex oval tablets in 75, 150 and 300 mg strengths. The drug may be administered with or without food and the recommended initial dose of irbesartan is 150 mg once daily. Patients treated vigorously with diuretics or on hemodialysis (volume-depleted patients), however, should receive an initial dose of 75 mg. Those patients requiring further blood pressure reduction may be titrated to 300 mg once daily. It is unlikely that higher doses or twice daily dosing will produce additional antihypertensive effects. No dosage adjustment is necessary in elderly patients or those with hepatic impairment or mild to severe renal impairment. If blood pressure is not controlled by irbesartan alone, another antihypertensive may be added. Also, low doses of a diuretic such as hydrochlorothiazide may be added to improve therapeutic effect. The recommended initial dose of irbesartan is 150 mg once daily. Patients requiring further reduction in blood pressure should be titrated to 300 mg once daily.

A low dose of a diuretic may be added, if blood pressure is not controlled by irbesartan alone. Hydrochlorothiazide has been shown to have an additive effect. Patients not adequately treated by the maximum dose of 300 mg once daily are unlikely to derive additional benefit from a higher dose or twice-daily dosing. No dosage adjustment is necessary in elderly patients or in patients with hepatic impairment or mild to severe renal impairment. Irbesartan may be administered with other antihypertensive agents. Irbesartan may be administered with or without food. A lower initial dose of irbesartan (75 mg) is recommended in patients with depletion of intravascular volume or salt (e.g., patients treated vigorously with diuretics or on hemodialysis).

Irbesartan Dosing for High Blood Pressure

The recommended starting dosage of irbesartan for most people with high blood pressure (hypertension) is 150 mg once a day. Based on the blood pressure response and/or irbesartan side effects, the dosage may be increased or decreased. With each change in dosage, it may take several weeks to see the full effects on blood pressure.

Irbesartan Dosing for Diabetic Nephropathy

The recommended starting dosage of irbesartan for people with diabetic nephropathy is 300 mg once a day.

Overdosage[26, 30]

No data are available in regard to overdosage in humans. However, daily doses of 900 mg for 8 weeks were well-tolerated. The most likely manifestations of overdosage are expected to be hypotension and tachycardia; bradycardia might also occur from overdose. Irbesartan is not removed by hemodialysis. To obtain up-to-date information about the treatment of overdosage, a good resource is a certified Regional Poison Control Center. In managing overdose, consider the possibilities of multiple-drug interactions, drug-drug interactions, and unusual drug kinetics in the patient. Laboratory determinations of serum levels of irbesartan are not widely available, and such determinations have, in any event, no known established role in the management of irbesartan overdose. Acute oral toxicity studies with irbesartan in mice and rats indicated acute lethal doses were in excess of 2000 mg/kg, about 25- and 50-fold the maximum recommended human dose (300 mg).

In healthy subjects, single oral irbesartan doses of up to 300 mg produced dose-dependent inhibition of the press or effect of angiotensin II infusions. Inhibition was complete (100%) 4 h following oral doses of 150 or 300 mg and partial inhibition was sustained for 24 h (60% and 40% at 300 mg and 150 mg, respectively). In hypertensive patients, angiotensin II receptor inhibition following chronic administration of irbesartan causes a 1.5- to 2-fold rise in angiotensin II plasma concentration and a 2- to 3-fold increase in plasma renin levels. Aldosterone plasma concentrations generally decline following irbesartan administration, but serum potassium levels are not significantly affected at recommended doses. In hypertensive patients, chronic oral doses of irbesartan (up to 300 mg) had no effect on glomerular filtration rate, renal plasma flow or filtration fraction. In multiple dose studies in hypertensive patients, there were no clinically important effects on fasting triglycerides, total cholesterol, HDL-cholesterol, or fasting glucose concentrations. There was no effect on serum uric acid during chronic oral administration, and no uricosuric effect.

CONCLUSION

Irbesartan is a potent, long-acting, nonpeptide angiotensin II receptor antagonist having high selectivity for the AT1 subtype (angiotensin I). It is potentially safe and more tolerable than other classes of antihypertensive drugs. Irbesartan reduces the chances of cardiac failure, myocardial infarction, sudden death, and death from progressive systolic failure. Irbesartan is an effective antihypertensive agent in patients with mild to moderate hypertension. The drug also reduces blood pressure when used as monotherapy in patients with severe hypertension or when used adjunctively in patients with resistant hypertension. Importantly, Irbesartan appears to be as effective and well tolerated as other commonly used antihypertensive agents. The drug therefore represents a useful therapeutic option in the management of patients with hypertension and diabetic nephropathy will be particularly useful in patients not responding to, or intolerant of, anti-hypertensive agents from other drug classes. Irbesartan may be an appropriate choice for first-line treatment of patients with mild-to-moderate hypertension, heart failure, myocardial infarction and diabetic nephropathy.

Table 1: Pharmacokinetic profile of Irbesartan with other sartans

Parameter	Losartan	Valsartan	Irbesartan
Oral bioavailability, %	33	25	60-80
Food effect, (AUC/Cmax)	10% redn.	40% redn.	None
Protein binding, %	99	95	90
Distribution, L	34	17	50-90
Elimination half-life, hrs)	2	6	11-15
Metabolism, %	14	20	<20
Metabolic enzymes	CYP2C9	CYP2C9	CYP2C9
Urinary recovery, %	35	13	20
Fecal recovery, %	60	80	80

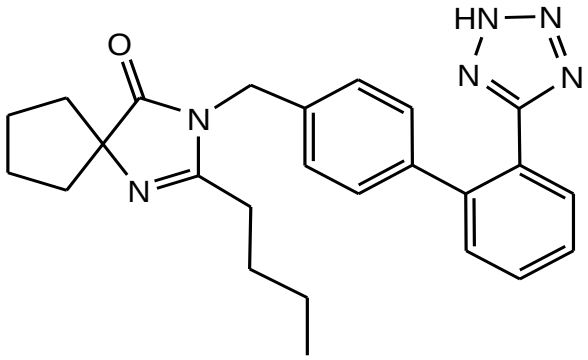

Figure 1: Chemical structure of Irbesartan

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