

The New Angiotensin II Receptor Antagonist, Irbesartan

Pharmacokinetic and Pharmacodynamic Considerations

Hans R. Brunner

This article reviews the pharmacokinetics and pharmacodynamics of angiotensin II (AII) receptor antagonists (AIIRA), with particular focus on the novel compound irbesartan. Irbesartan has the highest oral bioavailability in its class (60% to 80%) and, unlike valsartan, its absorption is not affected by food. Irbesartan displays linear, dose related pharmacokinetics and, with the exception of tasosartan's active metabolite, has the longest elimination half-life of the AIIRA (11 to 15 h). Irbesartan exhibits the lowest amount of protein binding, limiting its potential for drug interactions. No drug interactions with irbesartan have been identified. Unlike losartan, candesartan, and tasosartan, irbesartan does not require biotransformation for AII blockade. The pharmacokinetics of irbesartan are not altered in

renally or hepatically impaired patients, probably owing to excretion characteristic by both biliary and renal routes, or by differences in gender or age. Within its therapeutic dose range (150 to 300 mg), irbesartan shows sustained, dose related blockade 24 h after dosing. Irbesartan lowers blood pressure in a dose related manner up to 300 mg daily. Some clear differences in pharmacokinetics and pharmacodynamics exist among the AIIRA, which may have clinical implications. Am J Hypertens 1997;10:311S-317S © 1997 American Journal of Hypertension, Ltd.

KEY WORDS: Angiotensin II receptor antagonist, irbesartan, losartan, pharmacokinetics, pharmacodynamics.

Angiotensin II (AII) receptor antagonists (AIIRA) are a new class of antihypertensive agents that inhibit the renin-angiotensin system by selectively blocking the AT₁ subtype of AII receptors.¹ These compounds were developed based on the assumption that AII plays a role in the development of hypertension and cardiovascular disease. If this assumption is correct, it should be possible to show some direct relationship between these compounds and the doses administered, plasma

drug concentrations, and their effect on the AT₁ receptor. The pharmacokinetics and pharmacodynamics of AIIRA are reviewed in this article, with particular focus on the novel compound irbesartan (Figure 1). As will be shown, despite sharing a common mechanism of action, differences do exist among the AIIRA that may result in different efficacy or tolerability profiles.

PHARMACOKINETIC PROFILE OF IRBESARTAN

Irbesartan has an excellent pharmacokinetic profile that is unique among AIIRA (Table 1). It has the highest oral bioavailability in its class, is well absorbed in the presence or absence of food, has a prolonged elimination half-life ($T_{1/2}$), has the highest plasma free

From the Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

Address correspondence and reprint requests to Hans R. Brunner, MD, Professor of Medicine, Centre Hospitalier Universitaire Vaudois, Lausanne, Switzerland.

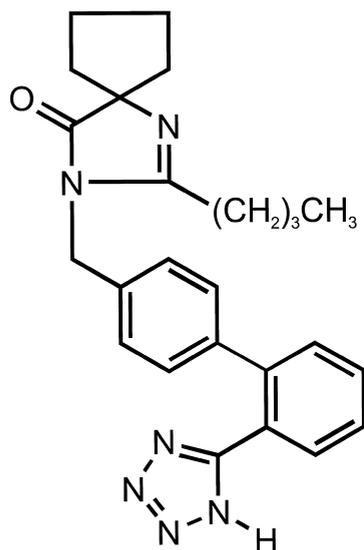


FIGURE 1. Chemical structure of irbesartan.

fraction of the AIIRA, and does not rely on biotransformation for its pharmacologic effect. In addition, the pharmacokinetics of irbesartan are not altered in patients with renal or hepatic impairment or based on differences in gender or age.

Absorption The oral absorption of irbesartan is rapid and complete, with an average absolute bioavailability of 60% to 80%.² Its oral bioavailability is higher than that of other AIIRA, including losartan (33%)³ and valsartan (10% to 35%) (Table 1).⁴ Peak plasma concentrations of irbesartan are attained within 1.5 to 2 h after oral administration (Figure 2).⁵ Food does not affect the bioavailability of irbesartan,^{6,7} whereas food decreases the area under the concentration-time curve (AUC) of valsartan by 40% and re-

duces the maximum concentration (C_{max}) by 50%.⁴ The absorption of losartan is slightly delayed by food.³

The results of two double-blind, placebo controlled studies involving 88 healthy subjects demonstrate that irbesartan displays linear, dose-related pharmacokinetics (Figure 3) and, with the exception of tasosartan's active metabolite, has the longest $T_{1/2}$ (11 to 15 h) of the AIIRA (Table 1)⁵ (data on file, Bristol-Myers Squibb/Sanofi). Steady state concentrations of irbesartan are achieved within 3 days of once daily oral dosing, and limited accumulation of irbesartan is observed in plasma with repeated administration.⁵

Protein Binding Another distinguishing feature of irbesartan is that it has the highest plasma free fraction (10%) in its class (data on file, Bristol-Myers Squibb/Sanofi), limiting the potential for interaction with drugs highly bound to proteins. Losartan,³ EXP 3174,³ valsartan,⁴ and candesartan⁸ are more highly bound to plasma proteins (Table 1).

Metabolism and Excretion Irbesartan does not require biotransformation for its pharmacologic activity.⁹ In contrast, much of the AII inhibiting effect of losartan, candesartan, and tasosartan can be attributed to their active metabolites—EXP 3174,¹⁰ CV-11974,⁸ and enoltasartan,¹¹ respectively. The results of in vitro studies indicate that glucuronidation and oxidation are the major routes of metabolism of irbesartan and that the cytochrome P450 isoform 2C9 is the primary pathway for oxidation¹² (data on file, Bristol-Myers Squibb/Sanofi). Metabolism by the cytochrome P450 isoform 3A4 is negligible.

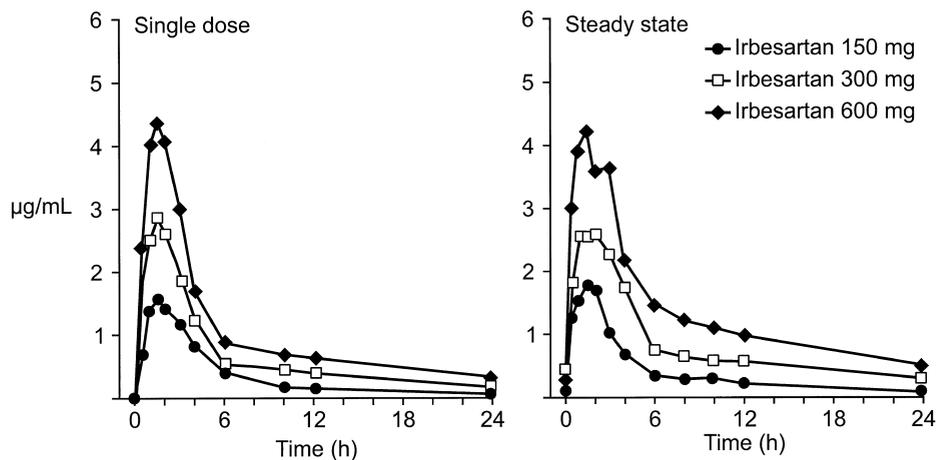
Irbesartan metabolites have been identified in human plasma, urine, and feces. Following oral or intravenous administration of ¹⁴C-labeled irbesartan, more than 80% of the circulating plasma radioactivity is attributable to unchanged irbesartan. The primary cir-

TABLE 1. OVERVIEW OF THE PHARMACOKINETICS OF ANGIOTENSIN II BLOCKERS

Drug [Active Metabolite]	Bioavailability	Food Effect	Active Metabolite	Half-life (h)	% Protein Binding	Dosage (mg)
Losartan ³ [EXP 3174]	33%	Minimal	Yes	2 [6–9]	98.7 [99.8]	50–100 daily or 50 twice daily
Valsartan ^{4,28}	25% range: 10%–35%	↓ 40%–50%	No	6	95.0	80–320 daily
Candesartan ^{8,29,30} [CV-11974]	N/A	No	Yes	3.5–4 [3–11]	99.5	N/A
Tasosartan ^{11,31} [Enoltasartan]	N/A	No	Yes	3–7 [34–43]	N/A	N/A
Irbesartan ^{2,5–7} (data on file, Bristol-Myers Squibb/Sanofi)	range: 60%–80%	No	No	11–15	90.0	150–300 daily

N/A, not available; ↓, decrease by.

FIGURE 2. Mean plasma concentrations of irbesartan after a single oral dose and at steady state after once daily oral dosing for 7 days in healthy subjects ($n = 8$ or 9/group).



culating metabolite is the irbesartan glucuronide (~6%). Irbesartan and its metabolites are excreted by both biliary and renal routes. About 20% of radioactivity is recovered in the urine and the remainder in the feces (data on file, Bristol-Myers Squibb/Sanofi).

Patients With Renal or Hepatic Impairment An open label, parallel study compared the single dose and steady state pharmacokinetics of irbesartan in 39 patients with varying degrees of renal function, as assessed by 24 h creatinine clearance (CrCl).¹³ Patients had either normal (24-h CrCl > 74 mL/min/1.73 m²), mild-to-moderate (24 h CrCl 30 to 74 mL/min/1.73 m²), or severe (24 h CrCl < 30 mL/min/1.73 m²) renal impairment, or required hemodialysis. Irbesartan was administered at a once daily dosage of 100 mg for 8 days. Patients on hemodialysis received a higher dose of irbesartan (300 mg) for 9 days to provide better blood pressure control. There were no statistically significant differences among the four groups in the dose normalized AUC for irbesartan (Figure 4) and no indication of drug accumulation. Irbesartan was not

cleared by hemodialysis, as the concentrations of irbesartan in the venous and arterial blood of patients during hemodialysis were similar.

Another open label, parallel study compared the single dose and steady state pharmacokinetics of irbesartan in 10 patients with hepatic cirrhosis and a matched group of 10 subjects with normal hepatic function.¹⁴ Irbesartan was administered at a once daily dosage of 300 mg for 7 days. There were no statistically significant differences between the two groups in AUC or C_{max} of irbesartan (Figure 5) and no indication of drug accumulation. The time of maximum concentration (T_{max}) and $T_{1/2}$ of irbesartan also remained constant.

Thus, the pharmacokinetics of irbesartan are not altered in patients with renal or hepatic impairment and, therefore, no adjustment of irbesartan dosage is necessary in these patient populations. These findings are likely due to irbesartan's dual excretion character-

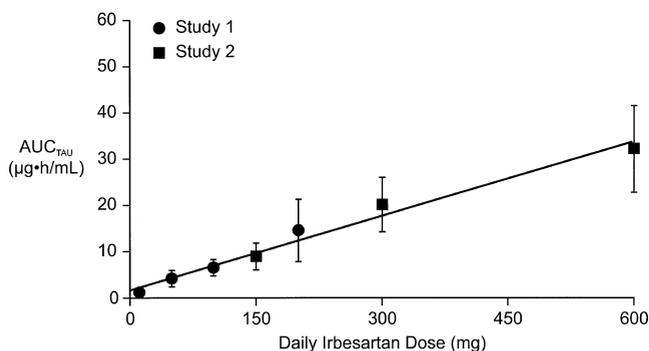


FIGURE 3. Mean area under the concentration–time curve during a dosing interval (AUC_{TAU}) at steady state after once daily oral dosing with irbesartan for 7 days in healthy subjects ($n = 8$ to 9/group); bars represent standard deviation.

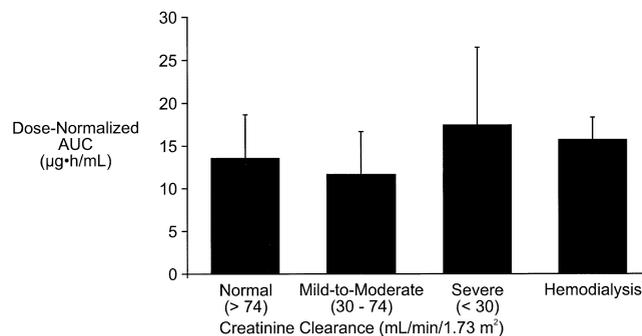


FIGURE 4. Dose normalized mean area under the concentration–time curve (AUC) at steady state after once daily oral dosing with irbesartan 100 mg for 8 days (or 300 mg for 9 days for the hemodialysis group) in patients with varying degrees of renal impairment ($n = 9$ to 10/group); bars represent standard deviation.

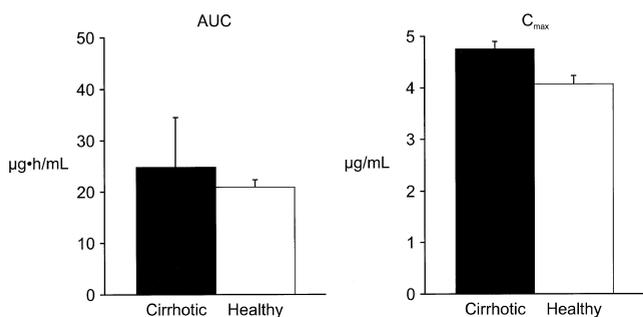


FIGURE 5. Mean area under the concentration–time curve (AUC) and maximum concentration (C_{max}) at steady state after once daily oral dosing with irbesartan 300 mg for 7 days in subjects with and without hepatic impairment ($n = 10/\text{group}$); bars represent standard deviation.

istic. In contrast, plasma concentrations of losartan and its active metabolite are reported to be 5 times and 1.7 times higher, respectively, in patients with mild-to-moderate hepatic cirrhosis compared with normal subjects.³ A lower starting dosage of losartan may therefore be required in patients with a history of hepatic impairment.³

Age or Gender Differences The single dose pharmacokinetics of irbesartan were assessed in an open label, parallel study involving 48 healthy subjects.¹⁵ Subjects were classified as young men (mean age, 30 years), young women (mean age, 31 years), elderly men (mean age, 72 years), and elderly women (mean age, 69 years). Irbesartan was administered as a 50 mg dose after an overnight fast. No statistically significant gender related effects were observed in AUC to infinity ($AUC_{0-\infty}$), C_{max} , T_{max} , or $T_{1/2}$. The geometric mean $AUC_{0-\infty}$ and C_{max} of irbesartan were statistically significantly increased in elderly subjects compared with those of young subjects; however, the $T_{1/2}$ of irbesartan and the total cumulative amount of irbesartan excreted unchanged in the urine were comparable in these patient subgroups.

Because the previous study was conducted with a 50 mg oral dose, which is not within the therapeutically effective dose range of irbesartan (150 to 300 mg), another open label, parallel study was performed to assess the effect of age on the pharmacokinetics of a higher dose of irbesartan.¹⁶ In this study, 12 healthy young subjects (mean age, 29 years) and 12 healthy elderly subjects (mean age, 69 years) received a single, oral dose of irbesartan 150 mg after an overnight fast. No statistically significant differences were observed between the two groups in $AUC_{0-\infty}$, C_{max} , T_{max} , or $T_{1/2}$; mean $AUC_{0-\infty}$ and C_{max} were about 20% higher in elderly subjects.

Based on the comparable efficacy and safety profile of irbesartan in young and elderly patients with hypertension (data on file, Bristol-Myers Squibb/Sanofi), the magnitude of the observed pharmacokinetic differences by age do not appear to be clinically significant. Thus, no adjustment of irbesartan dosage is necessary based on gender or age.

DRUG INTERACTIONS WITH IRBESARTAN

The pharmacokinetics of irbesartan are not affected by coadministration of nifedipine or hydrochlorothiazide. In addition, irbesartan has no effect on the pharmacodynamics of warfarin (prothrombin time) or the pharmacokinetics of digoxin.

Nifedipine In an open label, crossover study,¹⁷ 12 healthy subjects received irbesartan 300 mg once daily for 4 days in one period and irbesartan 300 mg once daily plus long acting nifedipine 30 mg once daily for 4 days in the other period. The order of treatment periods was randomized and a minimum 7 day wash-out phase separated the two periods. The pharmacokinetics of irbesartan were not altered by concomitant nifedipine administration. Furthermore, steady state AUC during a dosing interval (AUC_{TAU}) and C_{max} met the criteria for bioequivalence when irbesartan was administered alone or with nifedipine.

Hydrochlorothiazide A randomized, double blind, placebo controlled study in 36 patients with mild-to-moderate hypertension (seated diastolic blood pressure 95 to 110 mm Hg) compared the pharmacokinetics of irbesartan when administered alone and in combination with hydrochlorothiazide.¹⁸ The study consisted of a placebo lead in period to establish the stability of blood pressure, a 7 day, single blind treatment period (irbesartan 150 mg once daily), and a 7 day, double blind treatment period (irbesartan 150 mg once daily plus either placebo or hydrochlorothiazide 25 mg once daily). The pharmacokinetic profile of irbesartan was not affected by the addition of hydrochlorothiazide.

Warfarin A double blind, placebo controlled study in 16 healthy subjects assessed the effect of single and multiple doses of irbesartan on the pharmacodynamics of warfarin (data on file, Bristol-Myers Squibb/Sanofi). On day 1, all subjects received warfarin 10 mg. On days 2 to 14, subjects received individualized doses of warfarin (2.5 to 10 mg once daily) sufficient to achieve a prothrombin time ratio of 1.3 to 1.6. On days 15 to 22, irbesartan 300 mg once daily or placebo was added to the subject's individualized maintenance dosage of warfarin. No differences were observed between the two groups in mean changes from baseline in prothrombin time ratio. Thus, no adjustment of

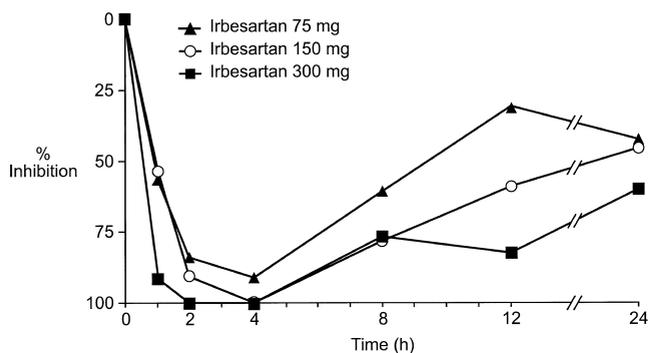


FIGURE 6. Time profile of the mean response to exogenous angiotensin II challenge after single oral doses of irbesartan in healthy subjects ($n = 6/\text{group}$).

warfarin dosage is necessary when administered with irbesartan.

Digoxin An open label study assessed the effect of concomitant administration of irbesartan on the steady state pharmacokinetics of digoxin (data on file, Bristol-Myers Squibb/Sanofi). Ten healthy subjects received digoxin 0.25 mg every 6 h on day 1, digoxin 0.25 mg once daily on days 2 to 7, and then digoxin 0.25 mg once daily plus irbesartan 150 mg once daily on days 8 to 14. Irbesartan did not affect the pharmacokinetics of digoxin.

DOSE RELATED PHARMACODYNAMIC EFFECTS OF IRBESARTAN

The effectiveness and persistence of AIIIRA at inhibiting the blood pressure response to AII in healthy subjects is a good predictor of their efficacy in hypertensive patients. Irbesartan has a dose related antihypertensive effect up to the highest clinical dose of 300 mg daily. With losartan such a clear dose-response relationship has not been demonstrated.

Preclinical Studies Irbesartan displays dose related and insurmountable antagonism *in vitro* in rabbit aorta⁹ and *in vivo* in pithed rats.¹⁹ Irbesartan blunts the maximal contractile response of rabbit aorta to high levels of AII. With increasing concentrations of irbesartan, the contractile response curve is shifted down and to the right, without total recovery of the maximal response (~60% of the maximal response to AII is achieved). This insurmountable activity of irbesartan is evident independent of AII concentrations and does not require conversion to an active metabolite.

Studies in Healthy Subjects Two randomized, double blind, placebo controlled, parallel studies involving a total of 42 healthy subjects assessed the ability of

irbesartan to inhibit the pressor response to exogenous AII.^{20,21} Irbesartan was administered at single, oral doses ranging from 25 to 300 mg. Irbesartan 150 and 300 mg inhibited the pressor response elicited by AII up to 100% at peak (2 to 4 h postdose), with 45% to 60% inhibition still present 24 h after dosing, respectively (Figure 6). Plasma concentrations of irbesartan were proportional to dose and paralleled the inhibition of the AII-induced pressor response. As presented in Figure 7, losartan 40 mg inhibited the same response by a maximum of 70%,^{22,23} whereas higher doses (80 and 120 mg)²⁴ caused near maximal inhibition (94%). The extent of inhibition with losartan was the same at 24 h (~45%), regardless of dose.²²⁻²⁴

Studies in Hypertensive Patients The interesting question is whether this model of exogenous AII challenge in healthy subjects reflects the efficacy observed in hypertensive patients. The results of seven randomized, placebo controlled studies demonstrate clinically significant reductions in blood pressure with irbesartan and a clear relationship between dose (up to 300 mg) and antihypertensive response (see Dr. Hubert Pouleur's "Clinical Overview of Irbesartan: A New Angiotensin II Receptor Antagonist"²⁵ in this supplement). Thus, a 300 mg dose of irbesartan provides maximal blockade of the AII pressor response in healthy subjects and appears to represent the upper end of the clinical dose range.

The first large scale, multicenter study with losartan included patients with an average baseline blood pressure of 157/104 mm Hg.^{26,27} Patients were randomly allocated to either double-blind losartan (10, 25, 50, 100, or 150 mg), 20 mg enalapril, or placebo once daily for 8 weeks. At week 8, neither the 10 mg nor the 25 mg doses of losartan caused statistically significant decreases in diastolic blood pressure at trough, whereas higher doses all statistically significantly reduced trough diastolic blood pressure compared with

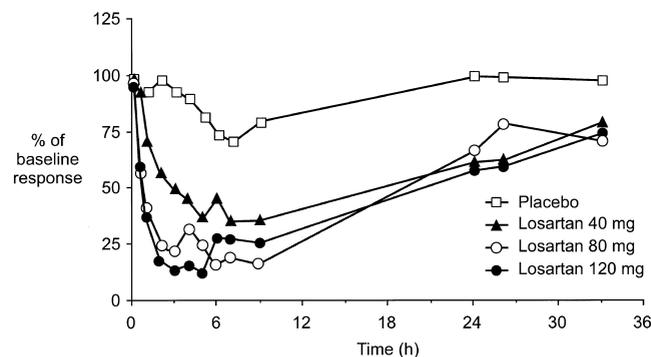


FIGURE 7. Time profile of the mean response to exogenous angiotensin II challenge after single oral doses of losartan in healthy subjects ($n = 6/\text{group}$); adapted from Munafò et al.²⁴

placebo. However, reductions in trough diastolic blood pressure associated with losartan 50 mg were at least equal to those produced with higher losartan doses, suggesting that a 50 mg dose may represent the upper end of the dose-response curve for losartan. The 50 mg dose of losartan is situated between the 40 and 80 mg doses that were predicted as the range for maximum AII blockade. The competition at the receptor site between losartan, a competitive antagonist, and its metabolite, a noncompetitive antagonist (both with different kinetics and affinity), might explain the lack of apparent dose related efficacy for this drug.

CONCLUSIONS

Angiotensin II blockers are an important addition to the treatment options for hypertension. Within this drug class, there exist some clear differences in pharmacokinetics (eg, oral bioavailability, food interaction, duration of effect, protein binding, and active metabolites). Irbesartan, a novel AIIIRA, has an excellent pharmacokinetic profile that seems to provide some advantages to those of other agents in its class. The pharmacokinetic and pharmacodynamic differences highlighted in this article may have clinical relevance. Potential differences in clinical effectiveness are currently being studied in blinded, randomized clinical trials.

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