Candesartan cilexetil – *Atacand*®, Astra Merck

Development and Pharmacology:[1-3]

The renin-angiotensin-aldosterone system (RAAS) plays a critical role in cardiovascular and renal function and therefore 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 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_1 receptors). AII also promotes aldosterone secretion and therefore sodium retention by stimulation of AT_1 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.

Over the past several decades research efforts have been directed toward developing drugs capable of suppressing of RAAS by inhibiting renin release, blocking the formation of AII via inhibition of ACE, or antagonism of AII at its physiologic receptors. These efforts led first to the introduction of clinically effective ACE inhibitors (ACEIs), beginning with captopril in 1981 and 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, angioedema, edema, and reflex tachycardia.

More recently AII receptor antagonists or blockers (ARBs) 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 of several non-peptide, heterocyclic ARBs including beginning with losartan (*Cozaar*) and followed by valsartan (*Diovan*), irbesartan (*Avapro*) and now candesartan cilexetil. All of the ARBs are selective in action, having much greater affinity for AT_1 than for AT_2 receptors (AT_2 receptors are found in many tissues but apparently not associated with cardiovascular homeostasis). Candesartan, the active form of candesartan cilexetil, displays higher receptor affinity and selectivity (relative AT_1/AT_2 affinity of 10,000) than other members of the ARB class. In vitro studies show that candesartan binds to AT_1 receptors with an affinity that is 80 times greater than that of losartan, 10 times greater than that of the active metabolite of losartan, and 7 times greater than angiotensin II. Candesartan also differs from other ARBs in that it is designed to bind tightly to, and dissociate slowly from, the AT_1 receptor. Thus it produces long-lasting AII receptor blockade characterized by a depression of the maximal response to angiotensin II. Like other ARBs, candesartan does not inhibit ACE (kininase II), the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin, nor does it bind to or block other hormone receptors or ion channels known to be important in

cardiovascular regulation. Furthermore, as observed to varying degrees with other ARBs, candesartan does not have a significant effect on glomerular filtration rate, renal plasma flow, filtration fraction, creatinine clearance, renal prostaglandin concentrations, fasting triglycerides, total cholesterol or HDL-cholesterol or fasting glucose concentrations.

Therapeutics:[3-5]

Candesartan is approved for the treatment of hypertension alone or in combination with other antihypertensive agents. The efficacy of this drug was demonstrated in a variety of placebo-controlled trials of 4 to 12 weeks in duration involving more than 2300 patients with baseline diastolic blood pressures of 95-114 mmHg. Most of these trials used candesartan cilexetil as a single agent in daily doses of 2 to 32 mg. Most studies showed significant, dose-related effects on trough (24 hour) systolic and diastolic pressures compared to placebo with doses of 8 to 32 mg producing reductions of 8-12 / 4-8 mmHg. Furthermore, most of the antihypertensive effect occurred within 2 weeks of initial dose and full effect was seen in 4 weeks. Also once-daily dosing provided a sustained antihypertensive effect over 24 hours, with trough to peak ratios of blood pressure effect generally greater than 80%. Longer term studies (1 year) demonstrate that the efficacy of candesartan is maintained, and there is no apparent rebound effect after abrupt withdrawal. In all trials candesartan displayed similar efficacy in men and women and in older and younger patients. Candesartan also significantly reduced blood pressure in all races, although it's efficacy generally was lower in blacks, a low renin population. In trials to date there were no significant changes in heart rate of patients treated with candesartan.

Adverse reactions:[2-5]

In clinical trials to date candesartan was well tolerated with an overall incidence of adverse reactions similar to placebo. The rate of drug withdrawal in all trials was 3.3% of patients treated with candesartan versus 3.5% of patients treated with placebo. The most frequent causes for withdrawal of candesartan were headache (0.6%) and dizziness (0.3%). The adverse reactions observed in at least 1% of patients treated with candesartan and occurring at a higher incidence than placebo included back pain (3%), dizziness (4%), upper respiratory tract infection (6%), pharyngitis (2%) and rhinitis (2%). A variety of other adverse events effecting mainly the GI and respiratory systems were also observed in more than 1% of the candesartan population, but these occurred at the same or greater incidence in patients receiving placebo. Cough, an adverse reaction frequently associated with ACEIs was reported in only 1.6% of the patients receiving candesartan. Overall, there was no significant difference in the rates of adverse reactions in men and women, older and younger patients and black and non-black patients. Candesartan has no clinically significant effects on laboratory, biochemical or ECG parameters. However, minor and transient increases in liver enzymes has been reported in several candesartan patients.

Drug Interactions:[2-5]

To date relatively few, controlled drug interaction studies have been reported with candesartan. No significant drug interactions have been reported in studies where candesartan was used concurrently with glyburide, nifedipine, digoxin, warfarin, HCTZ, and oral

contraceptives. This was anticipated since candesartan, unlike losartan, is not significantly metabolized by cytochrome P450 isozymes and does not induce or inhibit these enzymes.

Pharmacokinetics:[2-5]

The pharmacokinetics of candesartan and other available ARBs are summarized in the **Table**. Candesartan cilexetil is a true prodrug that is rapidly and completely bioactivated by ester hydrolysis during absorption from the GI tract to the therapeutically active form candesartan. The active metabolite candesartan is found in the plasma not the prodrug, and peak levels are attained within 3-4 hours. A fraction of candesartan undergoes hepatic metabolism via O-deethylation to form a minor inactive metabolite, but there is no accumulation of either metabolite in the serum when given in repeated daily doses. Candesartan is eliminated unchanged primarily in the feces; only a third of the oral dose is recovered in the urine. In comparison to other ARBs, candesartan has lower oral bioavailability, but food does not reduce AUC or C_{max} as observed with losartan and valsartan. Also candesartan cilexetil is rapidly and completely converted to an active metabolite while losartan requires hepatic cytochrome P450 metabolism to yield its primary active metabolite. Thus differences in individual metabolism can lead to variance in the antihypertensive activity of losartan. Overall, candesartan displays a terminal half-life and elimination profile similar to the other ARBs.

Dosage and Administration:[2]

Candesartan is supplied as 4, 8, 16 and 32 mg circular/biconvex tablets. While the dose should be individualized, the usual recommended initial dose is 16 mg once daily when used as monotherapy in patients who are not volume-depleted. Candesartan can be administered once or twice daily, with or without food, with total daily doses ranging from 8 to 32 mg. No adjustment in the initial dose is required in elderly patients or for patients with mildly impaired renal or hepatic function. However, with patients with possible intravascular volume depletion (e.g., patients treated with diuretics, particularly those with impaired renal function), candesartan therapy should be initiated under close medical supervision and possibly using a lower dose. Generally blood pressure response is dose-related over the range of 2 to 32 mg with larger not appearing to produce a greater effect. Most of the antihypertensive effect is seen within two weeks, but it may require four to six weeks of treatment to see maximum blood pressure reduction. If blood pressure is not controlled by candesartan alone, a diuretic (hydrochlorothiazide) or other antihypertensive may be added. Candesartan is contraindicated in pregnant women and patients allergic to the drug or other components of the product. Female patients that are of child bearing age should be warned of the effects the drug has during the second and third trimesters. These effects are not a problem during the first trimester; however, patients should report pregnancy as soon as possible.

Table. Pharmacokinetics of the Angiotensin II blockers[2]				
Parameter	**Losartan (Metabolite)**	**Valsartan**	**Irbesartan**	**Candesartan**
Bioavailability, %	≈33	≈ 25	60-80	≈15
Food Effect (AUC/C_{max}), %	Reduced 10 (reduced)	Reduced 40	No Effect	No Effect
Protein binding, %	98.7 (99.8)	95	90	>99
C_{max}, hr	1 (3-4)	2-4	1.5-2	3-4
Vol distr, L/kg	≈34 (≈12)	17	53-93	0.13
% Metabolized	(≈14)	≈ 20	< 20	Minor
Primary metabolic	CYP2C9 (CYP3A4)	Unknown	CYP2C9	No Data
Elimination t½, hr	» 2 (6-9)	≈ 6	11-15	≈ 9
Total plasma clearance	≈ 600 mL/min (≈50 mL/min)	≈ 2 L/hr	157-176 mL/min	0.37 mL/min/kg
Renal clearance	≈ 75 (≈ 25)	≈ 0.62 L/hr	3-3.5 mL/min	0.19 mL/min/Kg
Recovered in Urine, %	≈ 35	13	≈ 20	≈ 33
Recovered in feces**, %**	≈ 60	83	≈ 80	≈ 67

References:

1. Gums, JG and Nguyen BN. *Therapeutic Advances in Hypertension*. New York: A Jobson Publishing L.L.C., 1998.
2. Anon. Angiotensin II receptor antagonists. *Facts and Comparisons*. 165r-165x, 1998.
3. Harper, SQ. Astra Merck Information.1-6, 1998.
4. Nishikawa, Naka, et al. "Candesartan Cilexetil: a review of its preclinical pharmacy". *Journal of Human Hypertension.* 11:S9, 1997.
5. McClellan KJ and Goa KL. Candesartan Cilexetil: A review of its use in essential hypertension. *Drugs*. 56: 847-869, 1998.

Questions:

Candesartan cilexetil (*Atacand*®) produces its antihypertensive effects via:

A. Inhibition of angiotensin-converting enzyme
B. Inhibiting renin release
C. Blockade of angiotensin AT_1 receptors
D. None of the above

The recommended initial dose candesartan cilexetil (*Atacand*®) is:

A. 4 mg twice daily
B. 8 mg once daily
C. 16 mg once daily
D. 32 mg once daily

Candesartan cilexetil (*Atacand*®) is converted to its pharmacologically active form via:

A. Ester hydrolysis
B. Cytochrome-mediated deethylation
C. Reduction
D. Glucuronide conjugation

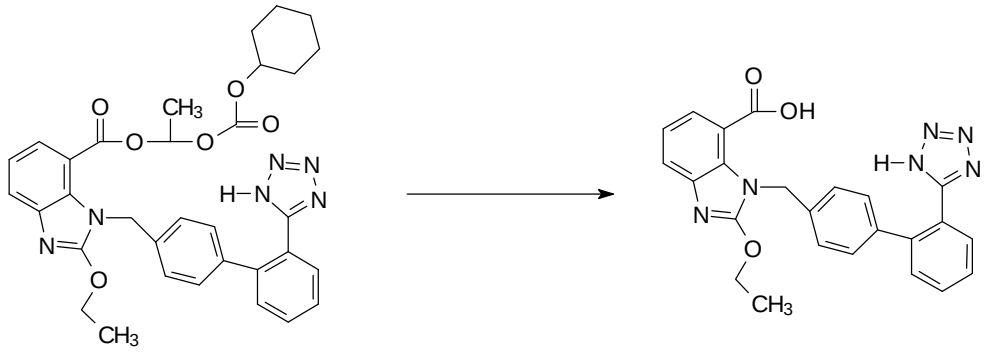

Figure. Bioactivation of Candesartan Cilexetil