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RISK-BENEFIT ANALYSIS AND RISK MINIMIZATION OF QUINAPRIL: A REVIEW

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ABSTRACT

The purpose of this review is to give the readers an insight about the risks and benefits of 'quinapril', a potent Angiotensin Converting Enzyme Inhibitor (ACEI). Quinapril is a highly effective novel drug indicated for treatment of congestive heart failure and hypertension. Despite of the fact that safety profile is quite well with low incidence of adverse effects, an attempt has been made to minimize the risks and subsequently minimizing the adverse consequences of this competitive inhibitor, thereby increasing the benefits of this enzyme inhibitor in day to day clinical practice.

Keywords: Quinapril, Benefit, Risk, Hypertension

1. INTRODUCTION

Sylvester Klutchkow a chemist at Parke-Davis invented Quinapril in 1982. In 1991 November, FDA approved Quinapril along with other 3 ACE inhibitors (Ramipril, Benazepril and Fosinopril) (Jie, 2009). Quinapril is a prodrug that belongs to the Angiotensin Converting Enzyme (ACE) inhibitor class of medications. It is metabolized to Quinaprilat (Quinapril diacid) in liver following oral administration. Quinaprilat is a competitive inhibitor of ACE, the enzyme responsible for the conversion of Angiotensin I (ATI) to Angiotensin II (ATII). ATII regulates blood pressure and is a key component of the Renin-Angiotensin-Aldosterone System (RAAS) (Khalil *et al*., 2001; Barry, 1992). Quinapril has a rapid onset of action and inhibits local tissue converting enzyme systems in kidney, heart and brain, as well as in the circulating renin-angiotensin system (Barry, 1992; Kieback *et al*., 2009; Egido and Ruiz-Ortega, 2007). Quinapril has a rapid onset of action and inhibits local tissue converting enzyme systems in kidney, heart and brain, as well as in the circulating renin-angiotensin system (Kieback *et al*., 2009). Therapeutic indication of Quinapril is for the management of hypertension and heart Failure (Khalil *et al*., 2001; Kieback *et al*., 2009).

2. GLOBAL BURDEN OF CARDIOVASCU-LAR DISORDERS

CVDs are the number one cause of death globally. An estimated 17.3 million people died from CVDs in 2008, representing 30% of all global deaths (WHO, 2011a). Of these deaths, an estimated 7.3 million were due to coronary heart disease and 6.2 million were due to stroke (WHO, 2011b). The number of people, who die from CVDs, mainly from heart disease and stroke, will increase to reach 23.3million by 2030. CVDs are projected to remain the single leading cause of death (Mathers and Loncar, 2006).

Worldwide, raised blood pressure is estimated to cause 7.5 million deaths, about 12.8% of the total of all deaths (WHO, 2013a). High blood pressure is one of the most important causes of premature death worldwide killing nearly 9.4 million people every year globally and the problem is growing. Over 1 billion people are living with high blood pressure. In 2008, globally, the overall prevalence of high blood pressure (including those on

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medication for high blood pressure) in adults aged 25 and above was around 40%. Among all WHO regions, the prevalence of raised blood pressure was highest in the African Region (46%) and lowest in the Region of the Americas (35%). In the South-East Asia Region, 36% of adults have hypertension. The prevalence of raised blood pressure in low, lower-middle and upper-middle income countries is higher (40%) than in high-income countries (35%) (WHO, 2013b). The prevalence of hypertension in the last six decades has increased from 2 to 25% among urban residents and from 2 to 15% among the rural residents in India. According to Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, the overall prevalence of hypertension in India by 2020 will be 159.46/1000 population (Whelton, 1994).

3. BENEFITS OF QUINAPRIL THERAPY

The Pharmacological and clinical effect of Quinapril have been described in many well controlled investigative trials. Whilst primarily used for the treatment of all grades of essential hypertension. Quinapril is effective as mono-therapy or concomitantly with diuretics in patients with hypertension (Hermida *et al*., 2013; Kanorskii *et al*., 2012; Sari *et al*., 2011; Perez-Castrillon *et al*., 2003; Laragh, 1990). Treatment of congestive heart failure with Quinapril should always be initiated under close medical supervision (Guillaume *et al*., 1997; Pflugfelder *et al*., 1993).

The mechanism of action of Quinapril is likely to be multifactorial, reflecting the drugs average molecular weight, high solubility and other parameters mentioned in **Table 1** (http://www.drugbank.ca/drugs/DB00881).

3.1. Hypertension

Administration of Quinapril to patients with essential hypertension results in a reduction of both sitting and standing blood pressure with minimal effect on heart rate. Antihypertensive activity commences within 1 h with peak effects usually achieved by 2 to 4 h after dosing. Achievement of maximum blood pressure lowering effects may require 2 weeks of therapy in some patients. Hemodynamic assessments in patients with hypertension indicate that blood pressure reduction produced by Quinapril is accompanied by a reduction in total peripheral resistance and renal vascular resistance with little or no change in heart rate, cardiac index, renal blood flow, glomerular filtration rate, or filtration fraction (Hathaway *et al*., 1999; Townend *et al*., 1992).

The effect of Quinapril on Blood Pressure (BP), Heart Rate (HR) and their variability's in 12 patients with severe congestive heart failure (New York Heart Association class III and IV) was assessed using ambulatory electro cardio-graphic and intra-arterial monitoring (**Table 2**). Long term Quinapril caused clinically unimpor-tant decreases in BP in patients with severe congestive heart failure. An increase in vagal activity caused by the reduction in circulating angiotensin II may account for the effect of converting enzyme inhibition on HR and its variability (Townend *et al*., 1992; Banas, 1989).

3.2. Heart Failure

The active metabolite of Quinapril reduced pulmonary capillary wedge pressure and systemic vascular resistance and increased cardiac output/index. Quinapril reduced renal hepatic vascular resistance and increased renal and hepatic blood flow with glomerular filtration rate remaining unchanged. Beneficial effects on the severity of heart failure as measured by New York Heart Association (NYHA) classification and Quality of Life and on symptoms of dyspnea, fatigue and edema were evident after 6 months in a double-blind, placebo-controlled study.

Quinapril Ischemic Event Trial (QUIET) is the first study to address the long term effect of ACE inhibitor on the natural history of coronary artery disease in a normolipidemic population without left ventricular dysfunction, both in terms of clinical end point and angiographically. It stipulate that Quinapril reduces ischemic events (the occurrence of cardiac death, resuscitated cardiac arrest, nonfatal myocardial infarction, coronary artery bypass grafting, coro-nary angioplasty, or hospitalization for angina pectoris) and the angiographic progression of coronary artery disease in patients without systolic left ventricular dysfunction (Pitt *et al*., 2001).

Quinapril effectively changed LV structural geometric parameters and systolic function and also associated with improvement of Renin Angiotensin System (RAS), elevation of tolerance to physical effort and increased VO2max (maximal oxygen consumption). Quinapril more substantially lowered NT-proBNP (N-terminal precursor of brain natriuretic peptide) level (Kanorskii *et al*., 2012; Guillaume *et al*., 1997; Seino *et al*., 2004).

Table 1. Characteristics of Quinapril (http://www.drugbank.ca/drugs/DB00881)

Mol. weight	438.516
Solubility	Freely soluble in aqueous solvents
Absorption	Peak plasma concentration occur within 1 h Extend of absorption is at least 60%
Metabolism	Hepatic
Elimination	Primarily by renal excretion

3.3. Other Beneficial Effects of Quinapril

Many alterations in extracellular metabolism of calcium have been associated to hypertension, but the number of studies relating this disease with osteoporosis is extremely low. One study shows that the effect of Quinapril on calcium, 25-Hydroxy Vit D, 1,25- Dihydroxy Vit D, calciurea and calcium/creatinine ratio. This result (**Table 3**) reveals that Quinapril have a beneficial effect on BMD and calcium metabolism alterations in hypertensive subjects (Perez-Castrillon *et al*., 2003).

One study shows that Quinapril increased flow-mediated dilation with significant improvement persisting 1 week after discontinuation of therapy (6.7±2.5%, $p<0.01$). However, quina-pril decreased serum nitrogen oxide levels by 19±17% compared with pretreatment values (**Table 4**). Thus, ACE inhibitor therapy with Quinapril selectively improves endothelium-dependent vasodilator responsiveness by increased NO bioactivity in relation to vascular smooth muscle in patients with coronary artery disease, an effect achieved at a lower rate of NO release from the endothelium. These findings suggest that ACE inhibitors may reduce angiotensin II-induced oxidant stress within the vessel wall and protect NO from oxidative inactivation. This effect may reduce endothelial NO synthesis required for vasomotor regulation (Hathaway *et al*., 1999).

One study shows that Quinapril improve the anti-inflammatory response of Atorvastatin and Aspirin in patients with coronary heart disease (Wright *et al*., 2003) and also reduces microalbuminuria in essential hypertensive and in diabetic hypertensive subjects (Dominguez *et al*., 1996; Bus *et al*., 1996). Quinapril is a potent and selective inhibitor of both plasma and tissue ACE, has demonstrated anti-inflammatory properties in many disease states such as atherosclerosis, nephritis, scleroderma, diabetes and arthritis and, thus, offers new therapeutic possibilities for disease treatment (Egido and Ruiz-Ortega, 2007).

Angiotensin-converting enzyme inhibitors including Quinapril have been shown experimentally to prevent restenosis after balloon injury. Clinical outcomes show that the benefit of Quinapril in patients following Percutaneous Coronary Intervention (PCI) is maintained for 4 years (Otsuka *et al*., 2004).

Table 2. Effect of Quinapril BP, HR and their variabilities (Townend *et al*., 1992)

	Baseline	After 16 weaks of therapy with quinapril	P-Value
Mean day time BP (mmHg)	122/75±20/15	113/70±13/16	>0.05 for systolic and diastolic BP
Mean night time BP (mmHg)	114/69±19/14	107/69±15/14	>0.05 for systolic and diastolic BP
Mean day time HR (beats/min)	Mean daytime HR was unchanged		
Mean night time HR (beats/min)	77±11	71±10	0.020
HR Variability (ms)	91±34	134±47	0.008
RR Variability (ms)	17±4	31±6	0.020

BP-Blood Pressure, HR-Heart Rate, RR-Respiration Rate

Table 3. Effect of quinapril on metabolism of Ca (Perez-Castrillon *et al*., 2003)

	Quinapril treatment		
	Before	After	P-Value
Vit D (mg/dL)	9.5±0.6	9.6±0.3	0.0100
25-Hydroxy Vit D (nmol/L)	46±22	58±22	0.0260
1, 25-Dihydroxy Vit D (nmol/L)	64±23	43±16	0.0001
Calciurea mg/24hr	209±93	161±93	0.0022
Ca/Creatinine ratio	0.21±0.09	0.17±0.11	0.0400

Table 4. Effect of Quinapril on flow mediated dilation

	Pretreatment	After treatment	P-Value
Flow mediated dilation	2.4±0.4	10.8±2.2	<0.001
Serum nitrogen oxide µmol/L	58.2±19.0	46.0±13.3	<0.01

Quinapril was associated with a significant reduction in total cholesterol, Low-Density Lipoprotein (LDL)-cholesterol and triglycerides, along with an increase in High-Density Lipoprotein (HDL)-cholesterol over 3 to 6 months treatment in 6000 hypertensive patients which included 154 patients with baseline hyperlipidemia (Koskinen *et al*., 1988).

4. RISK OF QUINAPRIL THERAPY

Clinically significant adverse effects of Quinapril occur at low rates (Materson, 1992; Knapp *et al*., 1990; Canter *et al*., 1990).

4.1. Cardiovascular Events

Most commonly observed cardiovascular events are hypotension (2.9%) (Canter *et al*., 1990; Frank, 1989; Sedman and Posvar, 1989; PI, 2009; Mets *et al*., 1992), chest pain (2.4%) palpitation, vasodilation and tachycardia. First-dose hypotension has been reported with patients with Quinapril therapy (Frank, 1989). Hypotension occurring with the first dose of quinapril is more likely to occur in volume-depleted patients (Sedman and Posvar, 1989). Incidence of occurrence of Tachycardia was found to be 0.5-1% (PI, 2009). Overdose of Quinapril can lead to prolonged hypotension and less frequently, transient renal impairment (Van Reet and Dens, 2006). Other rare events include heart failure, hyperkalemia, myocardial infarction, cerebrovascular accident, hypertensive crisis, angina pectoris, orthostatic hypotension, cardiac rhythm disturbances and cardiogenic shock (PI, 2009; Thomas, 1996; Materson, 1992; Zannad, 1999; 2001).

4.2. Gastrointestinal Events

Nausea and vomiting (1.4-2.4%), abdominal pain (1.7%), Diarrhoea (1%), Flatulence, dry mouth or throat and constipation are the most frequently occurring adverse event and rarely gastrointestinal hemorrhage, Pancreatitis, abnormal liver function tests and dyspepsia were reported (PI, 2009; Materson, 1992; Zannad, 1999; 2001).

4.3. Nervous/Psychiatric Events

Dizziness (3.9 to 7.7%), Headache (1.7 to 6.9%), syncope esomnolence, vertigo nervous-ness, depression, insomnia and paresthesia are the various nervous/psychiatric adverse events. Syncope occurred in 0.5% to 1% of hypertensive or congestive heart failure patients receiving Quinapril in controlled or uncontrolled trials (PI, 2009; Materson, 1992).

4.4. Other Adverse Events

Cough (2 to 4.3%) (Materson, 1992), Fatigue (2.6%), Serum blood urea nitrogen raised (2 to 8%), Serum creatinine raised (2 to 11%), Angioedema (0.1%) Agranulocytosis, hemolytic anemia, alopecia, increased sweating, pemphigus, pruritus, exfoliative dermatitis, rashes, photosensitivity reaction, dermatopolymyo-sitis (PI, 2009; Zannad, 1999; 2001; Kaufman, 2013), Gynecom-astia (Hurley, 1995; Llop *et al*., 1994), hyperglycemia (Ostman *et al*., 1998; PI, 1999) and hyperkalemia (Reardon and Macpherson, 1998) are the rare adverse effect with only a few reported cases.

5. RISK MINIMIZATION OF QUINAPRIL

Quinapril was found to be teratogenic in second and third trimesters of pregnancy. It may cause fetal and neonatal morbidity and death. Therefore discontinue therapy when pregnancy is detected (PI, 2012; 2013).

Agranulocytosis has been reported with Quin-april, especially in patients with renal impair-ment and in the presence of collagen vascular disease. Monitoring is recommended for such kind of patients (PI, 2012; 2013).

Angioedema has been reported in patients receiving Quinapril (0.1%). Black patients are at higher risk of angioedema than nonblack patients. Angioedema associated with laryngeal edema may be fatal. If angioedema of the face, extremities, lips, tongue, glottis and/or larynx occurs, treatment with Quinapril should be discontinued and appropriate therapy institute immediately (PI, 2012; 2013).

Concomitant hemodialysis and Quinapril therapy should be avoided, because anaphylactoid reactions have been reported, concomitant hymenoptera venom desensitization treatment with Quinapril shows life-threatening anaphylactoid reactions, in order to minimize such events, Quinapril should not give to patients with such kind of treatment (PI, 2012; 2013).

Concomitant use with other agents that affect the renin-angiotensin system increased the risk of hypotension, hyperkalemia and changes in renal function. Diuretic therapy, high-dose, or increase in diuretic dose, hyponatremia, volume-and/or salt-depleted patients increases the risk of excessive hypotension sometimes associated with oliguria, progressive azotemia and/or acute renal failure or death. Monitoring

recommended in patients who are receiving concomitant therapy (PI, 2012; 2013).

Hepatic syndrome starting with cholestatic jaundice and progressing to fulminant hepatic necrosis and death has been reported with ACE inhibitors; discontinue therapy if there is jaundice or marked elevations of hepatic enzymes (PI, 2012; 2013).

There is a risk of increased serum creatinine or BUN in patients with renal impairement or renal artery stenosis. Monitoring should be recomm-ended for such patients (PI, 2012; 2013). Dosing of Quinapril in patients with CHF should be based on their renal function (Begg *et al*., 1994).

6. CONCLUSION

The Pharmacological and clinical effect of Quinapril have been described in many well controlled investigative trials. Quinapril is well effective for the management of hypertension and congestive heart failure. Clinically significant adverse effects of Quinapril occur at low rates. Quinapril is effective and safe for maintaining clinical stability in patients with moderate congestive heart failure. Withdrawal of Quinapril from patients with heart failure results in a slow progressive decline in clinical status. Extensive clinical experience with Quinapril is considered to have demonstrated the therapeutic value of the compound. The benefit/risk is therefore considered to be positive.

7. LIMITATIONS

Although quinapril therapy is quite effective in the management of hypertension and congestive heart failure with a beneficial effect on calcium metabolism, the limitations of quinapril therapy lies in the adverse effects associated with it which may involve the cardiovascular, neuropsychiatric, gastrointestinal and teratogenic events, therefore the risk minimization with the quinapril therapy utilizes close monitoring and dose adjustment as well as institution with safer alternative especially when the high incidence of serious events is anticipated.

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