LITERATURE REVIEW

Physicochemical properties

Atenolol, a synthetic, β_1-selective (cardioselective) adrenoceptor blocking agent, may be chemically described as benzeneacetamide, 2-[4-(2-hydroxy-3-isopropylaminopropoxy) phenyl]acetamide [4]. The chemical structure is shown in Figure 1.

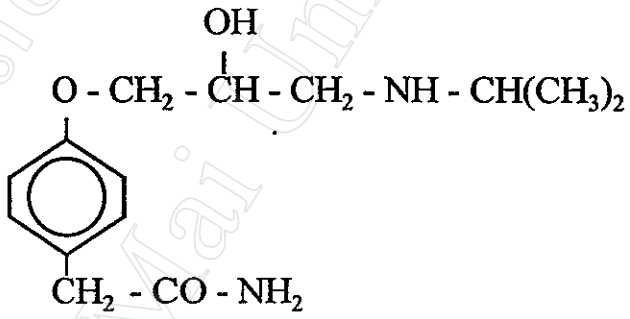

Figure 1. Chemical structure of atenolol ($C_{14}H_{22}N_2O_3$).

Atenolol (free base) has a molecular weight of 266. It is a relatively polar hydrophillic compound with a water solubility of 26.5 mg/ml at 37 °C and a log partition coefficient (octanol/water) of 0.23. It is freely soluble in 1 N HCl (300 mg/ml at 25 °C) and less soluble in chloroform (3 mg/ml at 25 °C). Atenolol marketed in Thailand is available as 50 and 100 mg tablets for oral administration. Atenolol for parenteral administration is available as atenolol injection (i.v.)

containing 5 mg atenolol in 10 ml sterile, isotonic, citrate-buffered aqueous solution. The pH of the solution is 5.5-6.5 [4].

Inactive ingredients contained in oral atenolol preparation are magnesium stearate, microcrystalline cellulose, povidone, sodium starch glycolate [4]. Atenolol as powder and in tablets remains stable and unchanged in appearance after storage at 50% to 60% relatively humidity and 45 °C to 50 °C for 7 days [8].

Atenolol composes of the two racemic mixtures; S (-) and R (+) enantiomers. The two enantiomers have different pharmacodynamic and pharmacokinetic properties [9]. Only the S (-) enantiomer exerts β-blockade or therapeutic activity [10]. After oral administration of atenolol, the peak concentrations, the area under the plasma concentration-time curve, and the amount excreted in the 24 hour urine are significantly greater for R (+) enantiomer than for S (-) enantiomer, although their renal clearances and half-lives are not different [9, 10]. The ratio of enantiomer concentrations is affected by several factors such as routes of administration, disease states, drug interactions and physical activities. During exercise, the levels of active S (-) enantiomer will increase because it is taken up into and released from adrenergic cells [11, 12]. When either one of the pure enantiomer is administered, exercise results in elevation only of the S (-) but not the R (+) racemic form. However, when the drug is administered in the mixed racemic form, exercise results in elevation of both enantiomers' levels [10, 12]. The reason why the R (+) enantiomer increased only in the presence of the elevated S (-) enantiomer is unclear [11,.12].

Pharmacodynamic Properties

Atenolol is a selective and long acting β-adrenergic antagonist [3, 4]. In patients with hypertension, oral administration of atenolol significantly reduces resting systolic [13] and diastolic blood pressures and attenuates the blood pressure increase induced by exercise [11, 12]. Atenolol improves indices of oxygen consumption in patients with acute myocardial infarction [14]. Short or long term administration of atenolol 50 to 100 mg daily reduces blood pressure in pregnant women [15].

Although impaired glucose tolerance and increased insulin resistance have been reported in some patients treated with atenolol, improved glucose tolerance has been reported in others [8]. Increase in plasma total triglycerides and very low density lipoprotein triglycerides, and decrease in high density lipoprotein cholesterol generally occur after several months of treatment with atenolol, but these changes are less pronounced than those associated with propranolol [5].

Single or multiple 50 to 125 mg doses of atenolol impairs respiratory function in asthmatic patients to a lesser extent than propranolol, and does not significantly decrease the bronchodilatation effect of inhaled salbutamol during short or long term treatment [16, 17].

Pharmacokinetic Properties

Following oral administration, about 50 to 60% of an atenolol dose is absorbed with maximal plasma concentrations within 2 to 4 hours. Atenolol is widely distributed in the body (although only a small proportion of an administered dose reaches the brain), and readily crosses the placenta. In adult patients with normal renal function the elimination half-life is about 5 to 7 hours and total clearance is about 6 L/h (100 ml/min) per 1.73 m^2. A shorter elimination half-life (4.5 hours) has been observed in children. However, there is wide intra- and inter-individual differences in the pharmacokinetic properties of atenolol. Most absorbed atenolol is excreted unchanged in the urine. Accumulation into breast milk has been reported but plasma concentrations are negligible in infants. In patients with renal dysfunction the elimination rate is decreased and is related to glomerular filtration rate [5, 18].

Therapeutic Efficacy

During long term follow-up trials with atenolol, generally 50 to 100 mg once daily alone or combination with a diuretic, goal blood pressures are achieved in about two-thirds of all patients with mild to moderate hypertension [5]. The greatest reductions in blood pressure occur in the first 2 weeks of treatment, and blood pressure remains within normal limits during extended therapy without major adjustment of dosage [19].

Atenolol 50 to 100 mg daily is clearly more effective than placebo in reducing blood pressure and in comparative trials it reduces blood pressure in a similar proportion of patients, and to similar extent, as usual therapeutic doses of other β-adrenoceptor antagonists (acebutol, nadolol, metoprolol SR, pindolol SR, propranolol SR), ACE inhibitors (captopril 100 mg, enalapril 20 to 40 mg and lisinopril 20 to 80 mg, calcium antagonists (amlodipine 2.5 to 10 mg, diltiazem 240 to 360 mg, felodipine 10 to 20 mg, nifedipine SR 20 to 40 mg and verapamil SR 240 mg), doxazosin 1 to 16 mg, ketanserin 40 to 80 mg and α-methydopa 1500 mg daily [5]. Elderly patients and women with hypertension associated with pregnancy respond well to treatment with 50 mg and 50 to 200 mg atenolol daily, respectively [15, 20, 21].

Tolerability

The most frequently reported adverse effects experienced during oral atenolol therapy for hypertension, angina pectoris and arrhythmias are bradycardia (0.6 to 10%), cold extremities/Raynaud's phenomenon (2 to 35 %), gastrointestinal symptoms (0.5 to 32%), fatigue/weakness (1 to 51%), nightmares/sleep disturbances (6 to 26%), headache (1 to 18%), and sexual disturbances (1 to 14%) [5]. In general these effects are mild, occurred more frequently during baseline phases, usually become less frequent with continued therapy and in most studies, necessitated withdrawal of treatment from only 3 to 6% of patients. Data from comparative studies suggest that the tolerability profile of atenolol is similar to that of other antihypertensive agents although the pattern of

effects differs between drug classes. Both hypertension and bradycardia have been observed after intravenous administration of atenolol in patients with myocardial infarction. Atenolol therapy has not been associated with ophthalmological changes or clinically significant changes in hematological or biochemical indices [19].

Dosage and Administration

The initial antihypertensive dose is usually 50 mg, given once a day. The dose may be increased up to 100 mg but the dose beyond 100 mg/day is not recommended since it is not associated with increasing antihypertensive effect. Following oral doses, a reduction of exercise tachycardia is maximal at about 2-4 hours and persist for 24 hours. This effect is dose related and also bears a linear relationship to the logarithm of its plasma concentration. On the other hand, a reduction of blood pressure will be established after 1-2 weeks of treatment. The antihypertensive effect does not appear to be related to plasma level. Patients being treated with atenolol should be advised against abrupt discontinuation of therapy [3, 4, 5].

Drug interactions

Atenolol decreases the clearance rate of antipyrine, suggesting that it may inhibit microsomal oxidative enzymatic activity, but did not influence prothrombin time or plasma clotting factor VII activity in volunteers [22], or the pharmacokinetic properties of lignocaine [23].

Concomitant administration of atenolol and hydrochlorothiazide in healthy volunteers results in impaired absorption and elimination of hydrochlorothiazide, although the diuretic effect the latter drug is unaltered [24]. Decreased oral absorption of atenolol has been reported in healthy volunteers during combined oral administration (for 1 day) of ampicillin 1 gm as a single dose (-51% in AUC) or in 4 divided doses (-18%) or after 6 days of combined administration (24% decrease in bioavailability) [5].

A decrease in the antihypertensive efficacy of atenolol 100 mg occurs during concomitant administration of indomethacin 50 mg daily to 9 patients [25]. Cessation of smoking significantly increases the effects of atenolol on exercise heart rate and workload before ST-segment depression in patients with angina pectoris [26].