

Non-Cardiac Effects of Atenolol



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Abstract

The advent of β -blockers especially atenolol, which is a selective β_1 blocker, is of paramount clinical importance in treating the cardiovascular disorders like hypertension, angina pectoris, and cardiac arrhythmias. In addition to its cardioprotective benefits, it also has some non-cardiac effects like antimigraine effect, antiglaucoma effect, antianxiety effect, reduces portal pressure, reduces vascularity of thyroid gland, inhibits platelet aggregation, aggravates peripheral vascular disease, decreases insulin sensitivity, alters lipid metabolism, causes sexual dysfunction, induces bronchospasm, etc. This article highlights the potentials and pitfalls of non-cardiac effects of atenolol.

Atenolol have been in use for nearly 25-30 years. It is a β_1 receptor selective antagonist, a drug belonging to the group of β -blockers. It was approved by the FDA in August 1981. In addition to its traditional role in treating hypertension and other cardiovascular disorders, atenolol, due to its extra-cardiac effects, are also used for additional purposes such as migraine headaches, hyperthyroidism, glaucoma, anxiety and various other disorders.

Atenolol is a hydrophilic drug. Atenolol does not have intrinsic sympathomimetic properties. Atenolol also does not possess membrane-stabilizing activity. After oral administration of atenolol, about 50- 60% of the dose is rapidly absorbed. t_{cmax} (time elapsed before maximal concentration in the blood plasma is reached) is 2 to 4 hours after oral dosing. However, the action of the usual oral dose lasts over a period of 24 hours. After parenteral administration, the peak effect is seen in 5 minutes and lasts less than 12 hours. Atenolol is minimally bound to plasma proteins, averaging only 10%, which, along with its low lipophilicity, may explain some of its distribution characteristics. Atenolol distribution into the central nervous system (CNS) by crossing the blood-brain barrier is minimal. The concentration found in brain tissue is approximately 15% of the plasma concentration only. The drug crosses the placenta barrier freely. In the milk of breastfeeding mothers, approximately 3 times the plasma concentrations are measured. Atenolol is almost exclusively eliminated renally and is well removable by dialysis. 40-50% of an oral dose is excreted renally as unchanged drug and the rest of the dose is excreted via the fecal route as unchanged drug.

Atenolol selectively blocks sympathetic stimulation mediated by β_1 adrenergic receptors in the heart and vascular smooth muscle. The pharmacodynamic consequences of this activity include: a negative chronotropic effect that decreases heart rate at rest and after exercise; a negative inotropic effect that decreases cardiac output; reduction of sympathetic outflow from the CNS; and suppression of renin release from the kidneys.

Noncardiac Effects of Atenolol

1. Reduces vascularity of thyroid gland
2. Antimigraine effect
3. Antiglaucoma effect
4. Reduces portal pressure
5. Reduces peripheral manifestations of tremors
6. Inhibits platelet aggregation

7. Impairs insulin sensitivity
8. Alters lipid metabolism
9. Enhances weight gain
10. Reduces exercise tolerance and causes fatigue, muscle weakness
11. Worsens sexual activity (erectile dysfunction, impotence and decreases libido)
12. Induces bronchospasm
13. Induces severe depression, nightmares, insomnia, hallucinations
14. Activates peripheral vascular disease (PVD) and exacerbates Raynaud's syndrome
15. Causes growth retardation in the fetus

Reduces vascularity of thyroid gland: Atenolol reduces vascularity of thyroid gland and controls palpitations, nervousness and tremors, therefore is commonly used as a sole agent or together with antithyroid drugs or radioiodine in perioperative management of thyroid surgery, until euthyroid state is achieved¹.

Antimigraine effect: Bengt Forssman et al.² showed the preventive effect of atenolol on migraine attacks by comparing to placebo in a double-blind cross-over study. The effect of atenolol was significantly better than that of placebo in reduction of the number of headache attacks. Atenolol possesses numerous mechanisms that may contribute to its efficacy in preventing migraine headaches. Possible mechanisms of action are beneficial vasoconstriction, peripheral vascular effects, a central action, 5-HT antagonism, an anxiolytic effect and a multifactorial action. The antimigraine effect is only prophylactic and not for attacks once they have occurred.

Antiglaucoma effect: Atenolol has been shown to have an action both orally and topically on the eye, causing a large and rapid fall of intraocular pressure. In contrast to miotics, it does not affect pupil size or tone of ciliary muscle and does not cause any diminution of vision. No definite hypothesis has been arrived at the mechanism of action of this drug in lowering the intraocular pressure. More extensive experimental and clinical work is necessary to postulate a definite hypothesis regarding the mechanism of action of this drug. Whether it is through adrenergic receptor which equalizes the blood flow in the ciliary process and intra-secleral venous plexus thereby changing the flow rate of aqueous humour or by an unknown mechanism that decreases the rate of aqueous humour formation, is still inconclusive.³ A clinical study by Chauhan JK et al.⁴ showed that atenolol produces significant and sustained fall in IOP in both normal and raised IOP patients besides lowering of systematic

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B.P. and pulse rate. Dhir S.P et al.⁵ showed that atenolol was found to control intraocular pressure in patients with chronic simple glaucoma and juvenile glaucoma but was found to be ineffective in angle closure glaucoma.

Reduces portal pressure: Atenolol was demonstrated to decrease portal venous pressure primarily by lowering heart rate and producing splanchnic vasoconstriction, which reduces portal blood flow.⁶ Nevertheless, it does not prevent the development of varices. As compared to non-selective β blockers, atenolol is less effective in reducing portal hypertension. However, no benefit was found in a randomized study.⁷ There is one head-to-head trial⁸ of β blockers for the treatment of bleeding esophageal varices. This trial compared the efficacy of atenolol and placebo in cirrhotic patients. No significant differences were found between atenolol at one year for percentage of patients with fatal/nonfatal rebleeding episodes or total deaths or deaths due to rebleeding liver failure or other unrelated causes.

Inhibits tremors: Atenolol inhibits adrenergic-provoked tremor, which is a peripheral action exerted directly on the muscle fibres, hence used in essential tremors.⁹

Inhibits platelet aggregation: Atenolol inhibits Thromboxane A2 formation in platelets from exogenous as well as endogenous arachidonic acid at rather high concentrations.¹⁰ However, the clinical impact of this positive effect in terms of prevention of cardiovascular complications remains to be clarified.

Reduces insulin sensitivity: Long term use of atenolol causes metabolic abnormalities that may be related to the increased incidence of diabetes in patients with hypertension. Studies have demonstrated that sensitivity to insulin decreases significantly during treatment with atenolol. Decreased sensitivity to the peripheral action of insulin may impair glucose tolerance and cause diabetes. There are several possible explanations for the diminished glucose disposal mediated by insulin during β -1 selective adrenergic blockade. The decrease in cardiac output during β -1 blockade may lead to reduced blood flow in muscles, thereby reducing the availability of glucose to the prime target tissue for glucose disposal.^{11,12} Two other studies have shown that clearance of insulin is reduced after blockade selective for the type of β adrenergic receptor.^{13,14}

The density of capillaries in skeletal muscle correlates with plasma insulin concentration." Lillioia et al¹⁵ showed that insulin action is determined by the density of the capillary supply to skeletal muscle, particularly around the type 1, oxidative, slow twitch fibres. Type 1 fibres are more sensitive to insulin and are equipped with more β - adrenergic receptors than type 2, glycolytic, fast twitch fibres. Thus, β blockade by atenolol may interfere with the capacity for glucose oxidation in insulin sensitive type 1 fibres. β -blockade may also influence glucose metabolism by its effect on the release of growth hormone.¹⁶

Moreover, in patients with insulin requiring diabetes, the risk of β blockade with atenolol is that it might mask the symptoms of hypoglycemia as it suppresses premonitory signs and symptoms of acute hypoglycemia (pulse rate, tachycardia, blood pressure changes). Unlike nonselective β -blockers, atenolol does not delay recovery of blood glucose to normal levels.

Alters lipid profile: Although many study results conflict, that β blockers may alter serum lipids concentrations, however, Thomas Pollare et al.¹⁷ study showed that β selective blockade like atenolol has little influence on serum cholesterol and low density lipoprotein cholesterol (LDL) concentrations but decreases high density lipoprotein cholesterol (HDL) concentration by about 7%¹⁸ and increases triglycerides levels; however, this

finding is not significant clinically. The atherogenic index (very low density lipoprotein plus low density lipoprotein/high density lipoprotein cholesterol) increases significantly during the treatment with atenolol. Increased serum triglyceride and decreased high density lipoprotein cholesterol concentrations are directly and inversely related to plasma insulin concentrations. The changes in basal glucose and plasma insulin concentrations during β selective blockade has a link between insulin resistance and abnormal lipid metabolism. There may, therefore, be a series of events, inducing a decrease in glucose disposal mediated by insulin and eventually ends with an increased burden of risk factors for ischaemic heart disease. During this course of events an increased serum triglyceride concentration, decreased serum high density lipoprotein cholesterol concentration and impaired glucose tolerance or diabetes are direct consequences of insulin resistance and hyperinsulinaemia.

Enhances weight gain: An increase in body weight has been noted in many studies during β -blockade by atenolol.¹⁹ The reason for this is not fully understood, although a lower metabolic rate may be contributory.^{20,21}

Reduces exercise tolerance: Atenolol by impairing biochemical-metabolic response at several levels (which may include hypoglycemia, impaired mobilization of free fatty acids and decreased breakdown of glycogen in skeletal muscle) limits the capacity for maximal exercise.²² So it tends to reduce exercise capacity by attenuating increase in blood flow to the exercising muscles^{22,23} as well as limiting glycogenolysis and lipolysis which provide fuel to the muscles, therefore causing fatigue²⁴ muscle weakness and reduction in exercise tolerance.

Sexual dysfunction: In clinical studies conducted before atenolol was approved, sexual dysfunction was not a documented side effect. In the time since atenolol was approved, however, sexual dysfunction like impotence has been reported occasionally in patients taking atenolol. But given how infrequently impotence is reported with atenolol and how common it is within the general population, it is difficult to state whether the impotence is actually caused by the medication, other factors, or a combination of both.

Roberto Fogari et al.²⁵ results showed atenolol induces a chronic worsening of sexual activity and number of sexual intercourse episodes per month, significantly declined with atenolol. Another study²⁶ results showed atenolol treatment in postmenopausal, sexually active hypertensive women, sexual function was worsened with atenolol treatment.

An interesting study²⁷ was conducted on whether being aware that impotence was a possible side effect would actually cause the sexual problem. The researchers found that people who knew that impotence was a side effect of atenolol were more likely to develop the problem. Their conclusion was that "the knowledge and prejudice about side effects of β blockers can produce anxiety that may cause erectile dysfunction." Interestingly, this study also found that a placebo (a "sugar pill" with no active ingredients) was just as effective as sildenafil (Viagra) for reversing impotence in these men taking atenolol.

Induces bronchospasm: Because of its relative β -1 selectivity, atenolol does cause bronchospasm, but as compared to nonselective agents it is less prone. However, at higher doses, cardioselective β blockers like atenolol react like nonselective β blockers with full potential for bronchospasm.

Exacerbates peripheral vascular disease: Atenolol can cause peripheral arterial vasoconstriction (due to unopposed arteriolar alpha-sympathetic activity) leading to exacerbation of peripheral

vascular disease, the development of Raynaud's phenomenon. Severe peripheral vascular disease and even peripheral gangrene may be precipitated.

Antianxiety effect: It also suppresses anxiety in short term stressful conditions, hence used in anxiety states. No overt central effects are produced by atenolol, however subtle behavioural changes, forgetfulness, increased dreaming and nightmares have been reported with long term use of relatively high doses.

Fetal injury: Atenolol crosses the placental barrier, so in pregnancy-induced hypertension, atenolol produces foetal bradycardia²⁸ and lower birth weights or placental weights are slightly common especially when administered in the second trimester.²⁹ No studies have been performed on the use of atenolol in the first trimester and the possibility of fetal injury cannot be excluded. Cases of neonatal hypoglycemia have been also reported following maternal use of atenolol at parturition or during breast-feeding as atenolol is excreted into breast milk.

Summary

Use of atenolol began in the 1980s and has risen dramatically since then. Due to its β -1 selectivity it offers more actions with fewer side effects. Uses for this drug continue to increase as their safety and efficacy become increasingly apparent. Today atenolol has widespread application in cardiovascular disease but in addition, due to its extracardiac effects, it is also being used in the management of endocrine disorders, neurologic situations, psychiatric disorders, gastrointestinal problems and sensory disorders. Many new noncardiac effects are still investigational and some effects show even greater promise for therapeutic applications in the future.

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