

**CONTINUING PHARMACY EDUCATION SERIES:
NOBIVOLOL AND VALSARTAN – OVERVIEW**

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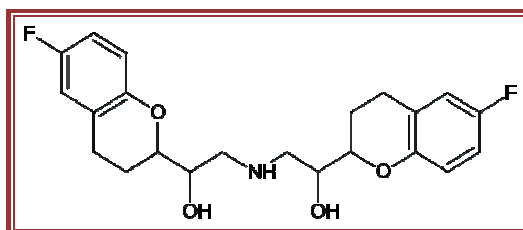
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NOBIVOLOL

DESCRIPTION

Nebivolol is a β_1 receptor blocker with nitric oxide-potentiating vasodilatory effect used in treatment of hypertension and, in Europe, also for left ventricular failure. It is highly cardioselective under certain circumstances (1). Nebivolol is unique as a beta-blocker and 5-(4-[2-(5-ethylpyridin-2-yl) ethoxy] benzyl) thiazolidine-2, 4-dione, which has the following structural formula:



PHARMACOLOGY ACTION

Nebivolol is the racemate (dl-nebivolol) of the enantiomers l-nebivolol and d-nebivolol. It is a competitive and highly selective beta-1 receptor antagonist with mild vasodilating properties, possibly due to an interaction with the L-arginine/nitric oxide pathway. In animal models nebivolol has been shown to induce endothelium-dependent arterial relaxation in a dose dependent manner, by stimulation of the release of endothelial nitric oxide. Nitric oxide is produced in artery walls and acts to relax vascular smooth muscle cells. It also inhibits platelet aggregation and adhesion and may protect against vascular damage as it inhibits leukocyte activation and vascular smooth muscle cell proliferation.

B1 SELECTIVITY

It is thought that beta blockers help patients with cardiovascular disease by blocking β_1 receptors, while many of the side-effects of these medications are caused by their blockade of β_2 receptors (2). For this reason, beta blockers that selectively block β_1 receptors (termed cardioselective or β_1 -selective beta blockers) are thought to produce fewer adverse effects than those drugs that non-selectively block both β_1 and β_2 receptors.

VASODILATOR ACTION

Nebivolol is unique as a beta-blocker (3). Like carvedilol, it has a nitric oxide (NO)-potentiating, vasodilatory effect (4, 5) Along with labetalol and carvedilol, it is one of three beta blockers to cause dilation of blood vessels in addition to effects on the heart (5).

ANTIHYPERTENSIVE EFFECT

Nebivolol lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output (6) The net hemodynamic effect of nebivolol is the result of a balance between the depressant effects of beta-blockade and an action that maintains cardiac output (7) Antihypertensive responses were significantly higher with nebivolol than with placebo in trials enrolling patient groups considered representative of the US hypertensive population, in Black patients, and in those receiving concurrent treatment with other antihypertensive drugs (8).

PHARMACOKINETIC

The absorption of nebivolol is rapid and not affected by food. It is extensively metabolised, partly to active hydroxy-metabolites. The metabolism by aromatic hydroxylation is subject to the CYP2D6 dependent genetic oxidative polymorphism. Phenotypically extensive metabolisers of nebivolol predominate over poor metabolisers by approximately 10 to 1. Although no difference in haemodynamic effect has been shown between poor and extensive metabolisers, the dose of nebivolol may need to be adjusted in poor metabolisers (9, 10). Urinary excretion of unchanged nebivolol is less than 0.5% of the dose (9, 10) but increased plasma concentrations of the drug and the hydroxyl metabolites have been found in hypertensive patients with moderate to severe renal disease [8]. In renal insufficiency therefore, the recommended starting dose is 2.5mg daily which may be increased to 5mg, if necessary. Nebivolol is contraindicated in hepatic insufficiency or impaired liver function, due to lack of data (9).

SIDE EFFECTS

Like all medicines, Nebivolol can cause some side-effects. Some common side effects reported with this medicine include the following. Call your doctor right away if you notice any of these side effects:

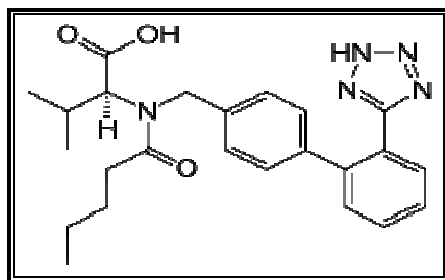
- ✚ Headache
- ✚ Fatigue
- ✚ dizziness
- ✚ Paraesthesias
- ✚ Tiredness,
- ✚ coldness of the extremities (fingers, toes and nose),

- ✚ disturbed sleep,
- ✚ nightmares,
- ✚ shortness of breath,
- ✚ upset tummy,
- ✚ skin rashes,
- ✚ dry eyes,
- ✚ fluid retention (swelling of the feet and ankles),
- ✚ depression,
- ✚ Problems with eye sight, pins and needles or sexual problems.

VALSARTAN

DESCRIPTION

Valsartan is an angiotensin II receptor antagonist (more commonly called an "ARB", which stands for angiotensin receptor blocker), with particularly high affinity for the type I (AT₁) angiotensin receptor. In the U.S., Valsartan is indicated for treatment of high blood pressure, congestive heart failure (CHF), or post-myocardial infarction (MI). Nebivolol is AT receptor blocker and (S)-3-methyl-2-[N-(4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl] phenyl) methyl) pentanamido] butanoic acid which has the following structural formula:



MECHANISM OF ACTION

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin converting enzyme. Angiotensin II is the principal pressor agent of the renin angiotensin system, with effect that includes vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and reabsorption of sodium. Valsartan blocks the vasoconstrictors and aldosterone secreting effect of angiotensin II by selectively blocking the binding of angiotensin II to the AT₁

receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT₂ receptor found in many tissues, but AT₂ is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000 fold) for the AT₁ receptor than for the AT₂ receptor. The increased plasma levels of angiotensin II following AT₁ receptor blockade with Valsartan may stimulate the unblocked AT₂ receptor. The primary metabolite of Valsartan is essentially inactive with an affinity for the AT₁ receptor about one-200th that of Valsartan itself. Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because Valsartan does not inhibit ACE, it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in the cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of Valsartan on blood pressure.

SIDE EFFECTS

Valsartan is generally well-tolerated and side effects are rare. The most common side effects include headache, dizziness, fatigue, abdominal pain, cough, diarrhea and nausea. Patients may also experience hyperkalemia, impotence, reduced renal function, and allergic reactions. Rhabdomyolysis (inflammation and destruction of muscles) and angioedema (swelling of soft tissues including those of the throat and larynx) are rare but serious side effects of Valsartan.

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