Nebivolol

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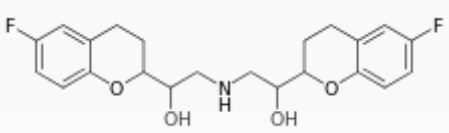

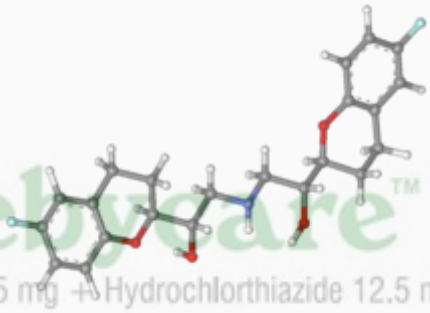

Systematic (IUPAC) name	
1-(6-Fluorochroman-2-yl)-{[2-(6-fluorochroman-2-yl)-2-hydroxy-ethyl]amino}ethanol OR 2,2'-Azanediylbis(1-(6-fluorochroman-2-yl)ethanol) OR 1-(6-Fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-{[2-(6-fluoro-3,4-dihydro-2*H*-1-benzopyran-2-yl)-2-hydroxyethyl]amino}ethan-1-ol	
Clinical data	
Trade names	Nebilet, Bystolic
AHFS/Drugs.com	monograph
MedlinePlus	a608029
Licence data	US FDA:link
Pregnancy cat.	C (US)
Legal status	POM (UK) ℞-only (US)

Routes	Oral
Pharmacokinetic data	
Protein binding	98%
Metabolism	Hepatic (CYP2D6-mediated)
Half-life	10 hours
Excretion	Renal and fecal
Identifiers	
CAS number	99200-09-6
ATC code	C07AB12
PubChem	CID 71301
DrugBank	DB04861
ChemSpider	64421
UNII	030Y90569U
KEGG	D05127
ChEMBL	CHEMBL434394
Chemical data	
Formula	$C_{22}H_{25}F_2NO_4$
Mol. mass	405.435 g/mol
SMILES	

- Fc4cc1c(OC(CC1)C(O)CNCC(O)C3Oc2ccc(F)cc2CC3)cc4

InChI

InChI=1S/C22H25F2NO4/c23-15-3-7-19-13(9-15)1-5-21(28-19)17(26)11-25-12-18(27)22-6-2-14-10-16(24)4-8-20(14)29-22/h3-4,7-10,17-18,21-22,25-27H,1-2,5-6,11-12H2

Key:KOHIRBRYDXPAMZ-UHFFFAOYSA-N

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.[1] It is highly cardioselective under certain circumstances.[1]

Pharmacology and biochemistry

β1 Selectivity

Beta blockers help patients with cardiovascular disease by blocking β receptors, while many of the side-effects of these medications are caused by their blockade of β2 receptors.[2] For this reason, beta blockers that selectively block β1 receptors (termed cardioselective or β1-selective beta blockers) produce fewer adverse effects (for instance, bronchoconstriction) than those drugs that non-selectively block both β1 and β2 receptors. Nebivolol has been marketed by Cipla Ltd under brand name Nebicip; by Forest Laboratories under the name Bystolic; by Micro Labs under the brand name Nebilong; ; and by Menarini under the names Hypoloc, Lobivon, Nebilet, Nebilox, Nobiten, and Temerit. In a laboratory experiment conducted on biopsied heart tissue, nebivolol proved to be the most β1-selective of the β-blockers tested, being approximately 3.5 times more β1-selective than bisoprolol.[3] However, the drug's receptor selectivity in humans is more complex and depends on the drug dose and the genetic profile of the patient taking the medication.[4] The drug is highly cardioselective at 5 mg.[5] However, at doses above 10 mg, nebivolol loses its cardioselectivity and blocks both β1 and β2 receptors.[4] (While the recommended starting dose of nebivolol is 5 mg, sufficient control of blood pressure may require doses up to 40 mg).[4] Furthermore, nebivolol is also not cardioselective when taken by patients with a genetic makeup that makes them “poor metabolizers” of nebivolol (and other drugs) or with CYP2D6 inhibitors.[4] As many as 1 in 10 whites and even more blacks are poor CYP2D6 metabolizers and therefore might benefit less from nebivolol's cardioselectivity although currently there are no directly comparable studies.

Vasodilator action

Nebivolol is unique as a beta-blocker.[6] Unlike carvedilol, it has a nitric oxide (NO)-potentiating, vasodilatory effect.[7][8] Along with labetalol, celiprolol and carvedilol, it is one of four beta blockers to cause dilation of blood vessels in addition to effects on the heart.[8] However, recent studies question the clinical relevance of this property to Nebivolol's efficacy.[9]

Antihypertensive effect

Nebivolol lowers blood pressure (BP) by reducing peripheral vascular resistance, and significantly increases stroke volume with preservation of cardiac output.[10] 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.[11] Antihypertensive responses were significantly higher with nebivolol than with placebo in trials enrolling patient groups considered representative of the U.S. hypertensive population, in Black patients, and in those receiving concurrent treatment with other antihypertensive drugs.[12]

Pharmacology of side-effect

Several studies have suggested that nebivolol has reduced typical beta-blocker-related side effects, such as fatigue, clinical depression, bradycardia, or impotence.[13][14][15] However, according to the FDA[16]

> “ Bystolic is associated with a number of serious risks. Bystolic is contraindicated in patients with severe bradycardia, heart block greater than first degree, cardiogenic shock, decompensated cardiac failure, sick sinus syndrome (unless a permanent pacemaker is in place), severe hepatic impairment (Child-Pugh > B) and in patients who are hypersensitive to any component of the product. Bystolic therapy is also associated with warnings regarding abrupt cessation of therapy, cardiac failure, angina and acute myocardial infarction, bronchospastic diseases, anesthesia and major surgery, diabetes and hypoglycemia, thyrotoxicosis, peripheral vascular disease, non-dihydropyridine calcium channel blockers use, as well as precautions regarding use with CYP2D6 inhibitors, impaired renal and hepatic function, and anaphylactic reactions. Finally, Bystolic is associated with other risks as described in the Adverse Reactions section of its PI. For example, a number of treatment-emergent adverse events with an incidence greater than or equal to 1 percent in Bystolic-treated patients and at a higher frequency than placebo-treated patients were identified in clinical studies, including headache, fatigue, and dizziness. ”

FDA warning letter about advertising claims

In late August 2008, the FDA issued a Warning Letter to Forest Laboratories citing exaggerated and misleading claims in their launch journal ad, in particular over claims of superiority and novelty of action.[16]

Contraindications

- Hepatic insufficiency
- Children
- Pregnancy
- Lactation

Adverse drug reactions

- Headache
- Parasthesia
- Dizziness

History

Mylan Laboratories licensed the U.S. and Canadian rights to nebivolol from Janssen Pharmaceutica N.V. in 2001. Nebivolol is already registered and successfully marketed in more than 50 countries, including the United States where it is marketed under the brand name Bystolic from Mylan Laboratories and Forest Laboratories. Nebivolol is manufactured by Forest Laboratories.

References

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Hydrochlorothiazide

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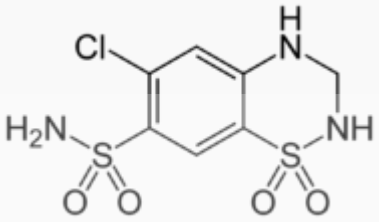

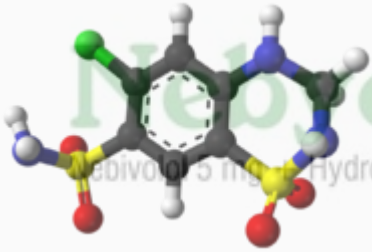

Systematic (IUPAC) name	
›-1,1-dioxo-3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide	
Clinical data	
Trade names	Apo-hydro, Aquazide h, Dichlotride among others, Oretic
AHFS/Drugs.com	monograph
MedlinePlus	a682571
Pregnancy category	B (D if used to treat pregnancy-induced hypertension)
Legal status	℞ (Prescription only)
Routes of administration	Oral (capsules, tablets, oral solution)
Pharmacokinetic data	
Bioavailability	Variably absorbed from GI tract. Bioavailability ~ 70%

Metabolism	does not undergo significant metabolism (>95% excreted unchanged in urine)[1]
Biological half-life	5.6–14.8 h
Excretion	Primarily excreted unchanged in urine
Identifiers	
CAS Registry Number	58-93-5 ✓
ATC code	C03AA03
PubChem	CID: 3639
IUPHAR/BPS	4836
DrugBank	DB00999 ✓
UNII	0J48LPH2TH ✓
KEGG	D00340 ✓
ChEBI	CHEBI:5778 ✗
ChEMBL	CHEMBL435 ✓
Chemical data	
Formula	$C_7H_8ClN_3O_4S_2$
Molecular mass	297.74 g/mol
SMILES[show]	
InChI[show]	
✗ (what is this?) (verify)	

Hydrochlorothiazide (abbreviated **HCTZ**, **HCT**, or **HZT**), is a diuretic medication often used to treat high blood pressure andswelling due to fluid build up.[2] Other uses include diabetes insipidus, renal tubular acidosis, and to decrease the risk of kidney stones in those with high calcium level in the urine.[2] For high blood pressure it is often recommended as a first line

treatment.[2][3]HCTZ is taken by mouth and may be combined with other blood pressure medications as a single pill to increase the effectiveness.[2]

Potential side effects include poor kidney function, electrolyte imbalances especially low blood potassium and less commonly low blood sodium, gout, high blood sugar, and feeling faint initially upon standing up.[2] While allergies to HCTZ are reported to occur more often in those with allergies to sulfa drugs this association is not well supported.[2] It may be used during pregnancy but is not a first line medication in this group.[2]

It is in the thiazide medication class and acts by decreasing the kidneys' ability to retain water.[2] This initially reduces blood volume, decreasing blood return to the heart and thus cardiac output.[4] Long term, however, it is believed to lower peripheral vascular resistance.[4]

Two companies, Merck and Ciba, state they discovered the medication which became commercially available in 1959.[5] It is on theWorld Health Organization's List of Essential Medicines, the most important medications needed in a basic health system.[6] In 2008 it was the second most commonly used blood pressure medication in the United States.[4] It is available as a generic drug[7] and is relatively affordable.[7]

Contents [hide]

Medical uses[edit]

Hydrochlorothiazide is frequently used for the treatment of hypertension, congestive heart failure, symptomatic edema, diabetes insipidus, renal tubular acidosis.[2] It is also used for the prevention of kidney stones in those who have high levels of calcium in their urine.[2]

Most of the research supporting the use of thiazide diuretics in hypertension was done using chlorthalidone, a different medication in the same class. Some more recent studies have suggested that chlorthalidone might be the more effective thiazide diuretic.[8]

It is also sometimes used for treatment of hypoparathyroidism,[9] hypercalciuria, Dent's disease, and Ménière's disease. For diabetes insipidus, the effect of thiazide diuretics is presumably mediated by a hypovolemia-induced increase in proximal sodium and water reabsorption, thereby diminishing water delivery to the ADH-sensitive sites in the collecting tubules and increasing the urine osmolality.

Thiazides are also used in the treatment of osteoporosis. Thiazides decrease mineral bone loss by promoting calcium retention in the kidney, and by directly stimulating osteoblast differentiation and bone mineral formation.[10]

It may be given together with other antihypertensive agents in fixed combination preparations, such as inhydrochlorothiazide/losartan.

Adverse effects[edit]

- Hypokalemia, or low blood levels of potassium are an occasional side effect. It can be usually prevented by potassiumsupplements or by combining hydrochlorothiazide with a potassium-sparing diuretic.

- Other disturbances in the levels of serum electrolytes including hypomagnesemia (low magnesium), hyponatremia (low sodium), and hypercalcemia (high calcium).
- Hyperuricemia, high levels of uric acid in the blood.
- Hyperglycemia, high blood sugar.
- Hyperlipidemia, high cholesterol and triglycerides.
- Headache
- Nausea/vomiting
- Photosensitivity
- Weight gain
- Gout
- Pancreatitis

These side effects increase with the dose of the medication and are most common at doses of greater than 25 mg per day.

Package inserts, based on case reports and observational studies, have reported that an allergy to a sulfa drug predisposes the patient to cross sensitivity to a thiazide diuretic. A 2005 review of the literature did not find support for this cross-sensitivity.[11]

Mechanism of action[edit]

Hydrochlorothiazide belongs to thiazide class of diuretics. It reduces blood volume by acting on the kidneys to reduce sodium (Na^+) reabsorption in the distal convoluted tubule. The major site of action in the nephron appears on an electroneutral NaCl co-transporter by competing for the chloride site on the transporter. By impairing Na transport in the distal convoluted tubule, hydrochlorothiazide induces a natriuresis and concomitant water loss. Thiazides increase the reabsorption of calcium in this segment in a manner unrelated to sodium transport.[12] Additionally, by other mechanisms, HCTZ is believed to lower peripheral vascular resistance.[13]

Society and culture[edit]

Co-Diovan (valsartan and hydrochlorothiazide)

Benazepril hydrochloride 20 mg / hydrochlorothiazide 25 mg oral tablet

Brand names[edit]

Hydrochlorothiazide is sold both as a generic drug and under a large number of brand names, including BP Zide 12.5 & 25 (Stadmed), Apo-Hydro, Aquazide H, Dichlotride, Hydrodiuril, HydroSaluric, Hydrochlorot, Microzide, Esidrex, and Oretic.

Hydrochlorothiazide is also used in combination with many other classes of hypertensive drugs such as ACE inhibitors, angiotensin receptor blockers, and beta blockers. These are sold under brand names including Diovan HCT, Zestoretic, Ziac, Benicar HCT, Olmy-H, Atacand HCT, and Lotensin HCT, Temax-H and others.

Sport[edit]

Hydrochlorothiazide was detected in the urine of the Russian cyclist Alexandr Kolobnev during the 2011 Tour de France.[14] Kolobnev was the only cyclist to leave the 2011 race in connection with adverse findings at a doping control.[15] While hydrochlorothiazide is not itself a performance-enhancing drug, it may be used to mask the use of performance-enhancing drugs, and is classed by the World Anti-Doping Agency as a "specified substance". Kolobnev was subsequently cleared of all charges of intentional doping.[16][17]

See also[edit]

- Benicar HCT
- Diovan HCT

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