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Classification and some properties of triptans

Triptans are a group of tryptamine-based drugs used in the acute treatment of migraine headaches. Structurally related to the neurotransmitter serotonin, triptans acts by selectively binding to serotonin type-1D receptors. The present paper submitted the classification and some properties of triptans (almotriptan, eletriptan, frovatriptan, naratriptan, sumatriptan, rizatriptan, zolmitriptan).

Key words: Triptans, Classification, Properties.

Migraine is a common, chronic, multifactorial neurovascular disorder, typically characterised by recurrent disabling attacks of severe headache, autonomic nervous system dysfunction and, in up to a third of patients, neurological aura symptoms. The triptans, selective serotonin 5-$HT_{1B/1D}$ agonists, are very effective acute migraine drugs with a well developed scientific rationale [9]. Structurally related to the neurotransmitter serotonin, triptans acts by selectively binding to serotonin type-1D receptors. The mechanism of action of triptans drugs is not exactly known. However, it is thought to involve: the cranial blood vessels, the trigeminal innervation of these vessels, the reflex connection of the trigeminovascular system in the cranial parasympathetic outflow.

Sumatriptan was the first of these compounds to be developed. Later, second-generation triptans were developed, namely, almotriptan, eletriptan, frovatriptan, naratriptan, rizatriptan, and zolmitriptan. Triptans have selective pharmacology, simple and consistent pharmacokinetics, evidence-based prescribing instructions, well established efficacy, modest side-effects, and a well established safety record.

The most serious side effects of triptans are heart attacks and strokes. Triptans can interact with other drugs which cause a serotonin syndrome when given together with a selective serotonin reuptake inhibitor [17]. The chemical structure of triptans follows.

Almotriptan, a selective 5-hydroxytryptamine 1B/1D (5-$HT_{1B/1D}$) receptor agonist. Almotriptan binds with high affinity to 5-HT_{1D}, 5-HT_{1B} and 5-HT_{1F} receptors. Almotriptan malate is chemically designated as 1-[[[3-[2-(dimethylamino)ethyl]-1*H*-indol-5-l]methyl]sulfonyl]pyrrolidine (±)-hydroxy butanedioate (1:1), having a molecular weight of 469,56. Almotriptan malate is a white to slightly yellow crystalline powder which is soluble in water and sparingly soluble in methanol. It is chemically related to sumatriptan, selective for cranial, as opposed to peripheral vasculature and shown potent affinity for 5-$HT_{1B/1D}$ receptors in the central nervous system. The pharmacodynamic profiles of almotriptan were extensively investigated using in vitro and in vivo animal models. The drug is absorbed well orally, with an absolute bioavailability of around 70 % [1; 14; 16].

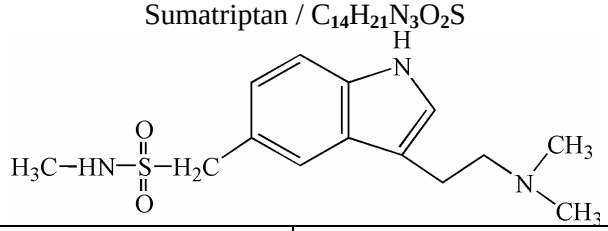
Eletriptan is a novel, orally active, selective serotonin 5-$HT_{1B/1D}$ receptor agonist. Eletriptan hydrobromide is chemically designated as (R)-3-[(1-methyl-2-pyrrolidinyl) methyl]-5-[2-(phenylsulfonyl) ethyl]-1H-indole monohydrobromide. Eletriptan hydrobromide used for the treatment of acute migraine headaches. Its pharmacological effects include the constriction of cerebral blood vessels and neuropeptides secretion blockade which eventually relieves the pain. The pharmacokinetics and metabolism of eletriptan hydrobromide have been investigated in the rat, dog and human. In all three species, eletriptan hydrobromide was rapidly absor-

bed and extensively cleared by metabolism. The pathways of eletriptan metabolism are similar in the rat, dog and human and principal routes include pyrrolidine N-desmethyl eletriptan, together with N-oxidation, oxidation of the pyrrolidine ring and formation of tetra cyclic quaternary ammonium metabolites [4].

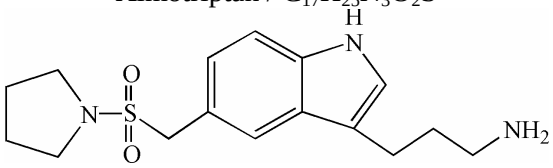
Sheme 1

Brutto and structural formulas of triptans

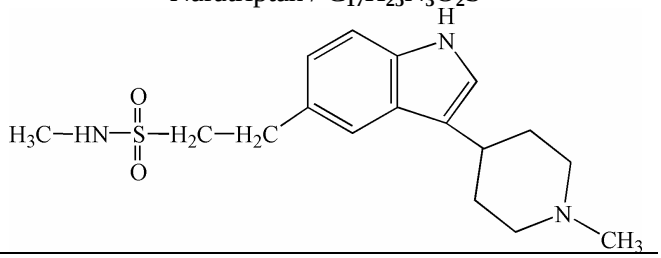
Sumatriptan / $C_{14}H_{21}N_3O_2S$



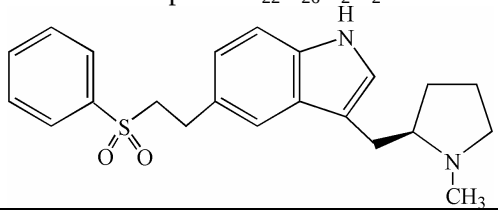
Almotriptan / $C_{17}H_{25}N_3O_2S$



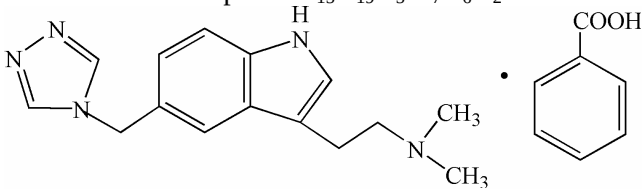
Naratriptan / $C_{17}H_{25}N_3O_2S$



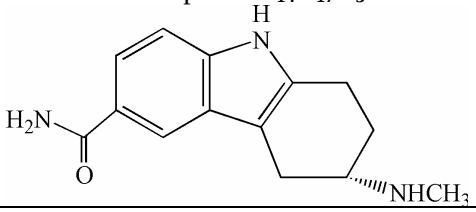
Eletriptan / $C_{22}H_{26}N_2O_2S$



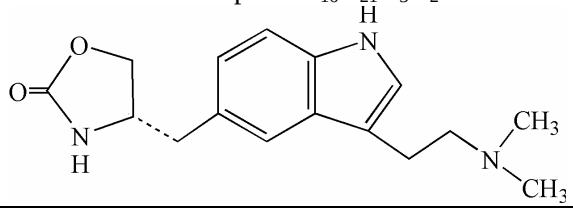
Rizatriptan / $C_{15}H_{19}N_5 \cdot C_7H_6O_2$



Frovatriptan / $C_{14}H_{17}N_3O$



Zolmitriptan /$C_{16}H_{21}N_3O_2$



Frovatriptan, administered as a single enantiomer (*R*)-(+)-3-(methylamino)-1,2,3,4-tetrahydro-9H-carbazole-6-carboxamide is a potent 5-$HT_{1B/1D}$ receptor agonist, one with a long duration of action and good tolerability. Frovatriptan reverses cerebral vasodilation by activating 5-HT_{1B}, and it prevents neurogenic inflammation by activating 5-HT_{1D}. Frovatriptan is not only more potent but also unlike sumatriptan, zolmitriptan and naratriptan which fall into the category of triptamine derivatives, does not appear to constrict human coronary and peripheral arteries. Molecular weight is 243,304 g/mol [6].

Naratriptan is chemically known as N-methyl-2-[3-(1-methylpiperidin-4-yl)-1*H*-indol-5-yl] ethane sulfonamide, which corresponds to a molecular weight of 335,47 g/mol. It is a triptan drug used for the treatment of migraine headaches, and is a selective 5-$HT_{1B/1D}$ receptor subtype agonist. The probable sites of therapeutic action of naratriptan include cranial vasculature; the peripheral terminations of trigeminovascular sensory nerves; the first order synapses of the trigeminovascular sensory system; the descending pain control system; and the nuclei of the thalamus. It is well absorbed (74 % oral bioavailability with peak plasma concentrations after 2−5 hours) having 28−31 % protein binding, and is metabolized by a wide range of cytochrome P450 isoenzymes into a number of inactive metabolites, and has a 5−8 hour half life [10; 15].

Sumatriptan (3-[2-(dimethylamino)ethyl]-*n*-methyl-1H-indole-5-methane-sulphonamide succinate) is a highly selective 5-$HT_{1B/1D}$ receptor agonist. It is a triptan drug which is effectively used in the treatment of migraine and cluster headache attacks. Sumatriptan is the first and most widely prescribed triptan. It is

administered in several dosage forms including products for nasal, oral and rectal delivery [10]. The drug is official in European, British and USP and suggests chromatographic methods for determination of sumatriptan in bulk and tablet formulations [5; 8; 18].

Rizatriptan (N,N-dimethyl-2-[5-(1,2,4-triazole-1-ylmethyl)-1H-indol-3-yl] ethanamine monobenzoate). Rizatriptan is also a triptan drug and it is a selective 5-$HT_{1B/1D}$ receptor agonist. Rizatriptan binds with high affinity to human cloned 5-HT_{1B} and 5-HT_{1D} κeceptors. Rizatriptan has weak affinity for other 5-HT_1 receptor subtypes (5-HT_{1A}, 5-HT_{1E}, and 5-HT_{1F}) and the 5-HT_7 receptor, but has no significant activity at 5-HT_2, 5-HT_3, α- and -adrenergic, dopaminergic, histaminergic, muscarinic or benzodiazepine receptors. After oral doses, peak plasma rizatriptan concentrations are obtained in about 1 to 1,5 hours depending on the formulation. Bioavailability is about 40 % to 45 %. Food may daily to the peak plasma concentrations of the tablet formulation by about 1 hr, plasma protein binding is low (14 %). Rizatriptan metabolized primarily by MOA type A to the inactive indole acetic acid derivative. The active metabolite N-monodesmethyl rizatriptan is formed to a minor degree, other mono metabolites are also produced. About 14 % of the indole acetic acid metabolite and 1% as N-monodesmethyl rizatriptan. The plasma half life is about 2−3 hours [3].

Zolmitriptan (4(S)-4-[3-(2-dimethylaminoethyl)-1H-5-indolylmethyl]-1,3-oxazolan-2-one) is a second-generation triptan prescribed for patients with migraine attacks, with and without an aura, and cluster headaches. It has a selective action on serotonin receptors and is very effective in reducing migraine symptoms, including pain, nausea and photo- or phonophobia. In liver, zolmitriptan is well absorbed and undergoes extensive metabolism. Its major metabolites are 4(S)-4-[3-(2-methylaminoethyl)-1H-5-indolyl-methyl]-1,3-oxazolan-2-one and (4S)-4-[3-[2-(dimethyloxidoamino)ethyl]-1H-indol-5-yl]methyl-2-oxazolidinon. It is currently available as a conventional tablet, an oral disintegrating tablet and a nasal spray. The absolute bioavailability of zolmitriptan is up to 40% for both oral and nasal dosage forms [2; 12; 13].

The triptans, selective serotonin 5-$HT_{1B/1D}$ agonists, are very effective acute migraine drugs with a well developed scientific rationale. Seven different triptans will soon be clinically available, making evidence-based selection guidelines necessary. Triptan trials have similar designs, facilitating meta-analysis; this will provide a foundation for using triptans in clinical practice [7].

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Антал Ірина. Класифікація та деякі властивості триптанів. Триптани – нова група ефективних протимігренних препаратів. Вони є специфічними селективними агоністами $5HT_{1D}$-серотонінових рецепторів. У статті наведено класифікацію та деякі властивості триптанів (алмотриптану, золмітриптану, наратриптану, суматриптану, ризатриптану, фроватриптану й елетриптану).

Ключові слова: триптани, класифікація, властивості.

Антал Ирина. Классификация и некоторые свойства триптанов. Триптаны – новая группа эффективных противомигренозных препаратов. Они являются специфическими селективными агонистами $5HT_{1D}$-серотониновых рецепторов. Статья содержит сведенья о классификации и некоторых свойствах триптанов (алмотриптана, золмитриптана, наратриптана, суматриптана, ризатриптана, фроватриптана и элетриптана).

Ключевые слова: триптаны, классификация, свойства.

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