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CCC: 0377-8282/2003

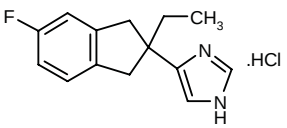
Fipamezole Hydrochloride

Prop INNM

Antiparkinsonian
α_2-Adrenoceptor Antagonist

JP-1730

4-(2-Ethyl-5-fluoroindan-2-yl)-1*H*-imidazole hydrochloride



C14 H15 F N2 . HCl
Mol wt: 266.7454
CAS: 150586-72-4
CAS: 150586-58-6 (as free base)
EN: 202370

Abstract

Dopaminergic agents, particularly levodopa and direct or indirect dopamine agonists, are the mainstay of treatment for Parkinson's disease. However, while treatment with these agents is effective in the early phases of the disease, the benefits decrease with disease progression and problems such as dyskinesia and on-off phenomenon begin to manifest. An interesting therapeutic strategy that has recently drawn attention is increasing (nor)adrenergic tone by blocking presynaptic α_2-adrenoceptors. This mechanism could be effective against dyskinesia, including levodopa-induced dyskinesia and related movement disorders. Fipamezole hydrochloride is one such novel α_2-adrenoceptor antagonist that exhibits potent antagonism against all human α_2-adrenoceptor subtypes. The agent has shown excellent preclinical activity and was chosen for further development as a treatment for Parkinson's disease with emphasis on dyskinesia and related movement disorders. The agent is currently undergoing phase II development for the treatment of Parkinson's disease.

Synthesis

The nitration of atipamezole, 4-(2-ethylindan-2-yl)-1*H*-imidazole (I) by means of urea nitrate and sulfuric acid gives 4-(2-ethyl-5-nitroindan-2-yl)-1*H*-imidazole (II), which is reduced with H_2 over PtO_2 in ethanol to provide 4-(5-amino-2-ethylindan-2-yl)-1*H*-imidazole (III). Finally, this compound is fluorinated by means of $NaNO_2$ and fluoroboric acid in water (1). Scheme 1.

Introduction

Parkinson's disease is a progressive neurodegenerative disease afflicting an estimated 5-24 per 10,000 population worldwide. Approximately 1.5 million Americans have been diagnosed with the disease with an estimated 35-42% of cases thought to be undiagnosed. The disease is characterized by bradykinesia, rigidity, tremor at rest, propensity to bend the trunk forward and instability. In a healthy individual, control of movement and muscle tone is achieved through the extrapyramidal system, with particular regulation by the striatum. Activity of the striatum is finely controlled via glutaminergic pathways in the cortex and dopaminergic pathways in the substantia nigra. Activity of the striatum includes inhibitory GABAergic, enkephalinergic and substance-P-mediated signals to the thalamus, subthalamic nuclei, substantia nigra and globus pallidus. Pathologically, the symptoms of Parkinson's disease are primarily due to the gradual loss of dopaminergic cells in the substantia nigra and degeneration of the nigrostriatal pathway. A pronounced inhibition of the thalamus by the substantia nigra is evident resulting in an inability to control muscle tone and movement (2).

To date no cure for Parkinson's disease has been discovered. However, agents are available that alleviate symptoms, reduce functional disability and slow or arrest progression of the disease resulting in a near normal life expectancy and satisfactory quality of life. Dopaminergic agents, particularly levodopa and direct or indirect dopamine agonists, are the mainstay of treatment for Parkinson's disease. However, although this form of treatment is effective in the early phases of the disease, its

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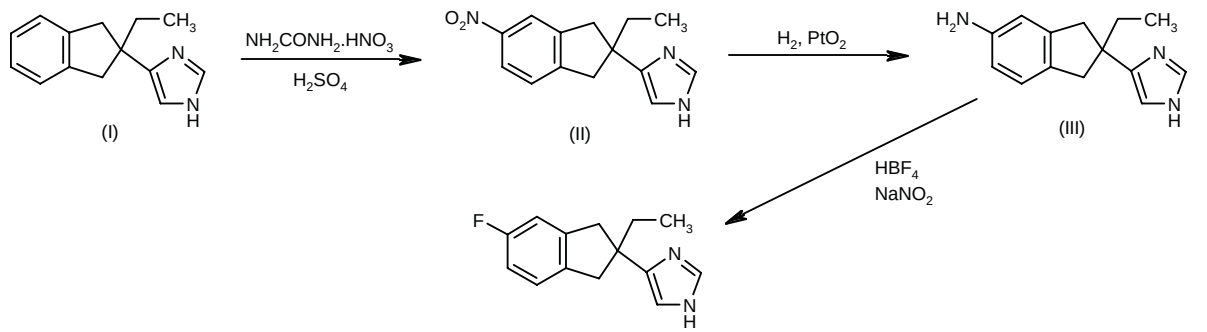
Scheme 1: Synthesis of Fipamezole Hydrochloride



benefit decreases with disease progression and problems such as dyskinesia and on-off phenomenon begin to manifest. An interesting therapeutic strategy that has recently drawn attention is increasing (nor)adrenergic tone by blocking presynaptic α_2-adrenoceptors. Presynaptic α_2-adrenoceptors mediate a negative feedback on noradrenergic neurons from the locus coeruleus that project to the brain cortex, thalamus and neostriatal nuclei. Thus, antagonism of α_2-adrenoceptors would result in an increase in noradrenergic tone. It has been hypothesized that this mechanism could be effective against dyskinesia, including levodopa-induced dyskinesia and related movement disorders. Fipamezole hydrochloride (JP-1730) is one such novel α_2-adrenoceptor antagonist that exhibits potent antagonism against all human α_2-adrenoceptor subtypes. The agent has shown excellent preclinical activity and was chosen for further development as a treatment for Parkinson's disease with emphasis on dyskinesia and related movement disorders.

Pharmacological Actions

The binding affinity of fipamezole for α_2-adrenoceptors was examined in [^{3}H]-rauwolscine binding assays using membranes from Shinogi S115 cells expressing stably transfected human α_2-adrenoceptor subtypes. The agent displayed high binding affinity for all subtypes tested, including the α_{2A} (9.2 nM), α_{2B} (17nM) and α_{2C} (55 nM) adrenoceptors. Fipamezole exhibited low binding affinity (> 3000 nM) for the rat brain α_1-adrenoceptor and nonadrenergic imidazoline I_2 binding sites in the rat liver. Further experiments involving [^{35}S]-GTPγS binding assays and using membranes of CHO cells expressing human α_2-adrenoceptors revealed that the agent was a competitive antagonist for the α_{2A}, α_{2B} and α_{2C} adrenoceptor subtypes (K_B = 8.4, 16 and 4.7 nM, respectively). The *in vitro* activity of the 2 enantiomers of fipamezole were similar to activity observed for the racemic compound (3).

Preclinical studies have demonstrated that fipamezole potently inhibits the α_2-adrenoceptor. Experiments using isolated rat vas deferens and examining electrical field stimulated contractions *in vitro* showed that fipamezole inhibited the activity of medetomidine, an α_2-adrenoceptor agonist, with a pA_2 value of 9.7. Medetomidine-induced sedation in mice was inhibited by treatment with the agent, indicating antagonism of central α_2-adrenoceptors. In addition, medetomidine-induced mydriasis in rats was blocked by s.c. fipamezole (0.3-3 mg/kg) with an increase in noradrenaline turnover observed in the brain 60 min postdosing; dopamine and serotonin turnover were unaffected by s.c. treatment. Experiments using rats with unilateral substantia nigra 6-OHDA lesions showed that fipamezole (0.3 mg/kg s.c.) enhanced apomorphine (0.5 mg/kg s.c.)-induced circling behavior. Fipamezole (administered 15 min before 10 mg/kg levodopa + 5 mg/kg benserazide p.o.) was also shown to have a biphasic effect on levodopa- and D-amphetamine-induced circling in rats with unilateral substantia nigra 6-OHDA lesions. Treatment with the agent first attenuated and then prolonged levodopa- or D-amphetamine-induced circling. These results suggest that increasing noradrenergic tone via α_{2A}-adrenoceptor antagonism improves dopaminergic signaling involved in movement control. Further characterization of the effects of fipamezole revealed that the agent may enhance the therapeutic effects of levodopa in the treatment of Parkinson's disease. In rats with unilateral substantia nigra 6-OHDA lesions also treated with levodopa (50 mg/kg i.p.) + benserazide (25 mg/kg i.p.) for 12 days to produce a sensitized circling response to acute levodopa, treatment with fipamezole (0.-1 mg/kg) slightly increased the acute levodopa effects; atipamezole (0.3-1 mg/kg s.c.) and yohimbine (1 mg/kg) had a similar enhancing effect on levodopa-induced circling (4-7).

Studies involving rats treated with reserpine to deplete monoamines and high dose levodopa (150 mg/kg) showed that administration of fipamezole dose-dependently reduced the incidence of levodopa-induced inappropriate hyperkinesia. Similar dose-dependent

Box 1: Safety and tolerability of fipamezole hydrochloride in healthy volunteers (11) [from Prous Science Integrity®).

Design	Dose-finding, placebo-controlled clinical estudy
Population	Healthy volunteers
Treatments	Fipamezole, 0.75 mg by buccal spray Fipamezole, 1.5 mg by buccal spray Fipamezole, 3 mg by buccal spray Fipamezole, 7.5 mg by buccal spray Fipamezole, 15 mg by buccal spray Fipamezole, 30 mg by buccal spray Fipamezole, 60 mg by buccal spray Fipamezole, 90 mg by buccal spray Placebo
Conclusions	There were no dose-dependent changes in plasma hormone levels, laboratory parameters or cardiovascular parameters, including QTc duration. Buccal erythema and whitening was observed frequently but resolved spontaneously

antidyskinesia effects of fipamezole (1-10 mg/kg p.o.) were observed in MPTP (2 mg/kg s.c. for 5 days)-lesioned marmosets (a model of Parkinson's disease) (7).

The efficacy of fipamezole was further demonstrated in parkinsonian marmosets, with results suggesting that the agent may be useful as an adjunct to levodopa to improve dyskinetic adverse effects without affecting the antiparkinsonian action of levodopa. Studies using previously primed MPTP-lesioned marmosets reported that treatment with a combination of fipamezole (1-10 mg/kg p.o.) and levodopa (8 and 12 mg/kg p.o.) resulted in antiparkinsonian activity comparable to that obtained with levodopa (15 mg/kg) monotherapy but with less dyskinesia (40% with 10 mg/kg fipamezole) and no extension of on-time. Naive parkinsonian marmosets treated b.i.d. with a combinaation of fipamezole + levodopa also displayed similar antiparkinsonian effects as those observed with levodopa monotherapy. However, in contrast to combination treatment including fipamezole, severe dyskinesia (characterized by a mixture of chorea and dystonia) occurred by day 8 in animals treated with levodopa alone which worsened with continued treatment. Combination treatment was associated with a slower onset of dyskinesia (not until day 19). A wearing-off effect or reduction in the duration of actions was observed with repeated levodopa monotherapy but not with the fipamezole + levodopa combination (8-10).

Clinical Studies

Because results from the first phase I pharmacokinetics study involving healthy male volunteers administered single-dose fipamezole (0.5-60 mg) in an oral solution concluded that absorption from the gastrointestinal tract was limited due to significant first-pass metabolism, another phase I trial was initiated in which fipamezole was administered to healthy male volunteers in a buccal spray. This phase I, ascending single-dose, placebo-controlled study examined the safety and tolerability of buccal fipamezole (0.75, 1.5, 3, 7.5, 15, 30, 60 and 90 mg buccal spray). Absorption of the agent from the buccal mucosa was rapid and dose-dependent. The apparent elimination half-life ranged from 1.2-3.5 h. C_{max} and AUC_{∞} values were found to correlate linearly with dose. All doses were well tolerated, with no significant dose-related changes in plasma hormone levels (*e.g.*, adrenaline, noradrenaline, human growth hormone, cortisol, aldosterone, antidiuretic hormone), cardiovascular parameters or laboratory parameters noted. Administration of the agent was frequently associated with transient buccal erythema and whitening (11) (Box 1).

Fipamezole is currently undergoing phase II development as a treatment for dyskinesias associated with late stage Parkinson's disease and received fast track designation from the FDA for this indication (12).

Sources

Discovered at Orion Corporation (FI) and licensed to Juvantia Pharma Ltd. (FI).

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