AM-201 for Antipsychotic-Induced Weight Gain

Betahistine spray for intranasal use

Auris Medical
Cochlear therapies

About AM-201

AM-201 is a spray formulation of betahistine dihydrochloride. Betahistine is a small molecule drug that acts as a partial H_1 histamine receptor agonist and a H_3 receptor antagonist. The compound increases inner ear and cerebral blood flow, histamine turnover and histamine release in the brain, and also the release of acetylcholine, dopamine and norepinephrine. Further, it leads to general brain arousal.

AM-201 is being developed for the prevention of weight gain and drowsiness (somnolence), which are frequent major side effects of antipsychotic drugs used for treating schizophrenia or bipolar disorder. These side effects are related to the drugs' inhibition of the H_1 receptor which plays a key role in the brain's regulation of food intake and wakefulness. AM-201 relieves this inhibitory effect and increases histamine release.

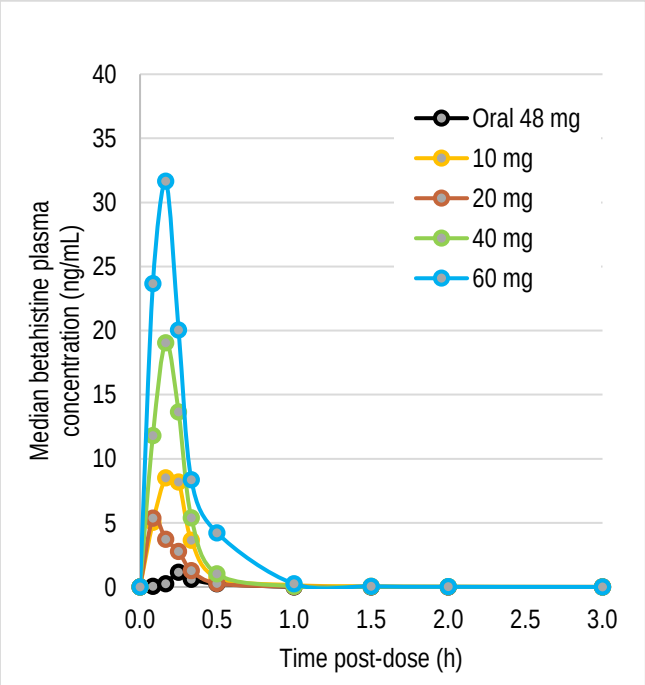
Treatment Effects of Betahistine

In a rat model, betahistine attenuated olanzapine induced weight gain by counteracting increased expression of the H_1 histamine receptor, pAMPK, orexigenic neuropeptide Y and decreased expression of the anorexigenic neuropeptide pro-opiomelanocortin.[1,2] In humans, a pilot study in 36 patients with a diagnosis of schizophrenia or schizoaffective disorder who were treated with olanzapine for 16 weeks evaluated the effects of concomitant administration of oral betahistine at the approved daily dose of 48 mg/day.[3] The study showed no interference of betahistine with the antipsychotic effect of olanzapine, and a trend for reduction in weight gain against placebo (+5.6 vs. +6.9 kg). In a subsequent study with a threefold higher betahistine dose (144 mg/day) administered concomitantly with olanzapine for three weeks to healthy volunteers (n=48), significant reductions in weight gain and somnolence were observed compared against placebo: +1.2 kg vs. +1.9 kg (p=.049) and +1.8 vs. +3.6 units in the daytime Epworth sleepiness score (p=.042).[4]

Improving Betahistine's Bioavailability

Pre-clinical and clinical studies have demonstrated or suggested that betahistine's efficacy is dose- and time-dependent. Therefore higher doses and longer treatment periods are expected to enhance betahistine's effects.

However, when administered orally, betahistine is rapidly and almost completely metabolized into 2-pyridylacetic acid, also known as 2-PAA, which lacks pharmacological activity. Due to rapid and extensive metabolism, bioavailability of oral betahistine is very low in humans. A phase 1 study demonstrated superior bioavailability over a range of four intranasal betahistine doses compared to the approved daily dose of oral betahistine, with plasma exposure being 6 to 29 times higher (p-value between 0.056 and p<0.0001).



AM-201 Development Program

Auris Medical plans to initiate a randomized double blind placebo controlled proof-of-concept study with AM-201 in healthy volunteers in the first quarter of 2019. This Phase 1 pharmacokinetic/pharmacodynamic study will evaluate AM-201's preventive effects on olanzapine-induced weight gain and somnolence and assess potential drug-drug interactions. In the next step, Auris Medical plans to assess AM-201 in a Phase 2 trial in patients with schizophrenia or bipolar 1 disorder.

[1] *Deng C et al. (2012). Reducing olanzapine-induced weight gain side effect by using betahistine: a study in the rat model. J Psychopharmacol. 26(9):1271-9.*
[2] *Lian J et al. (2014). Preventing olanzapine-induced weight gain using betahistine: a study in a rat model with chronic olanzapine treatment. PLoS One 9(8):e104160.*
[3] *Barak N et al. (2016). Betahistine decreases olanzapine-induced weight gain and somnolence in humans. J Clin Psychopharmacol 30(3): 237-41.*
[4] *Barak N et al. (2016). A randomized, double-blind, placebo-controlled pilot study of betahistine to counteract olanzapine-associated weight gain. J Clin Psychopharmacol. 36(3):253-6.*