CASE REPORT

Successful treatment of intractable visual hallucinations with 5-HT$_{2A}$ antagonist ketanserin

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SUMMARY

Hallucinations, visual, auditory or in another sensory modality, often respond well to treatment in patients with schizophrenia. Some, however, do not and can be very chronic and debilitating. We present a patient with schizophrenia with intractable hallucinations despite state of the art care, including high-dose clozapine and transcranial magnetic stimulation. Based on the possible role of the 5-HT$_{2A}$ receptor in hallucinations, we treated her with the antihypertensive drug ketanserin, a 5-HT$_{2A}$ receptor antagonist.

This significantly reduced her visual but not her auditory hallucinations, suggesting a possible role of the 5HT$_{2A}$ receptor in the pathophysiology of specifically visual hallucinations. This is the first time ketanserin has been described to successfully reduce visual hallucinations in a patient with schizophrenia.

BACKGROUND

Hallucinations are a prevalent and distressing symptom of many neuropsychiatric disorders. In schizophrenia, auditory hallucinations are most prevalent, followed by visual hallucinations. Many patients experience perceptual deviations in multiple modalities.[1]

While most patients show clear improvement of hallucinations with antipsychotic medication,[2] a significant minority of about 30% is burdened with medication-resistant hallucinations. Focal stimulation techniques can modestly reduce medication-resistant auditory hallucinations.[3] Visual hallucinations, however, can become chronic and be particularly frightening and disabling.

Here, we describe the first successful treatment of a patient with schizophrenia with severe, persistent visual hallucinations with the 5-HT$_{2A}$ antagonist ketanserin. This is in line with the theory that the 5-HT$_{2A}$ receptor plays a role in the pathogenesis of hallucinations, possibly specifically in the visual modality.

CASE PRESENTATION

The 29-year-old woman suffered from severe, treatment-resistant, chronic psychosis since the age of 12 and was diagnosed with childhood-onset schizophrenia. For >10 years she was almost constantly suffering from multimodal hallucinations. She was hearing voices, both accusing her of misbehaviour and commanding her what to do, and was seeing strange objects, animals and frightening people. Additionally, cups or bottles often took the form of a pig or a dog's head while she was drinking from them (visual illusions). Several times a week, her environment changed completely (scenic hallucinations) and she perceived it as something else, that is, a swimming pool or an attraction park.

These hallucinations made it very hard for her to keep her attention on conversations, work and entertainment. Furthermore, their frightening nature made it almost impossible for her to sleep. Apart from these hallucinations, she held the delusional beliefs of being a bad person and guilt, such as being guilty of the death of beloved family members. Neuropsychological assessment revealed impaired cognition congruent with severe schizophrenia and a normal eye examination ruled out a possible Charles Bonnet syndrome.

She had tried several antipsychotic medications at adequate doses and duration, several courses of cognitive behavioural therapy and even focal stimulation (transcranial magnetic stimulation and transcranial direct current stimulation), all to no avail. She had used high doses of clozapine (600 mg/day) most of her psychotic years, achieving blood levels >500 ng/mL (therapeutic benchmark: 400 ng/mL) as this produced a welcome sedation.

TREATMENT

In an attempt to reduce her hallucinations, she was started on ketanserin 20 mg/day. This dose was gradually increased up to 80 mg/day while continuing her olanzapine depot injections at 300 mg per 2 weeks. She did not use any other antipsychotics during treatment with ketanserin.

OUTCOME AND FOLLOW-UP

At 80 mg/day, she noted a remarkable improvement of some of her most bothersome visual hallucinations, most notably her visual illusions and scenic hallucinations. Her cups did not look like pigs anymore and her scenic hallucinations of swimming pools and attraction parks disappeared. This effect remained up to the last follow-up at 6 months. Her auditory hallucinations did not improve, nor did her delusions.

After starting ketanserin, she initially experienced a headache and dizziness, both potential side-effects, spontaneously disappearing within weeks. Her blood pressure initially dropped from 120–140/80–90 mm Hg to 110/70 mm Hg, but stabilised around 120/80 mm Hg in a matter of weeks.

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DISCUSSION

The serotonergic receptor 5-HT_{2A} has been suggested to play a role in the pathogenesis of (mainly visual) hallucinations. This is based on the hallucinogenic potency of 5-HT_{2A} receptor agonists, such as psilocybin, mescaline and Lysergic acid diethylamide (LSD). Additionally, apomorphine has been suggested to treat visual hallucinations as a 5-HT_{2A} receptor antagonist in Parkinson's disease (PD).[4] The role of the 5-HT_{2A} receptor in visual hallucinations in PD is supported by positron emission tomography (PET) studies comparing patients with PD with and without visual hallucinations, demonstrating an increased 5-HT_{2A} binding in the prefrontal and visual processing areas of the hallucinating patients.[4 5]

Clozapine, the most effective antipsychotic drug, has high binding potential at the 5-HT_{2A} receptor,[6] and several inverse agonists of this receptor have shown marginal efficacy for psychosis in schizophrenia.[7] The ineffectiveness of clozapine versus ketanserin in our case might be due to ketanserin's relative selectiveness to the 5-HT_{2A} receptor.

In addition, the selective 5-HT_{2A} inverse agonist pimavanserin was recently introduced in some countries. It is beneficial in psychosis in PD patients with PD, however this effect was not significant for visual hallucinations.[8] A large augmentation study in patients with chronic schizophrenia showed improvement on total Positive and Negative Symptom Scale (PANSS) score for pimavanserin combined with risperidone, but not for pimavanserin added to haloperidol.[9]

Patient's perspective

The following was translated by the authors from the original Dutch written by the patient herself.

Before starting with ketanserin for my visual hallucinations, I did not expect much of it, because most medications never seem to work for me. However, I can't say that anymore. Since using 80 milligrams per day, I'm noticing a clear difference. Not all my symptoms have improved but nonetheless it helps me.

Visual distortions bother me a lot less now. For example, whereas I used to drink coffee out of a pig, an elephant, or some type of appliance, now I usually drink from an actual cup. Also, during a meeting for instance, I would often be at a cemetery or amusement park or whatever, which really bothered me. This happens a lot less now. I could name a million other instances in which it has helped. Another important one would be the absence of suddenly appearing and disappearing cars while I am driving.

Unfortunately, I still see worrying images like people with severed limbs, hanging in trees, following me, cameras and so on. I also experienced some side-effects, mainly headaches and dizziness, but these did not bother me a lot. They are well worth the improvement and I am very happy I started on ketanserin.

Learning points

- Visual hallucinations can be a medication-resistant and debilitating symptom across multiple diagnoses.
- The 5-HT_{2A} receptor has been implicated in the pathogenesis of (visual) hallucinations.
- The antihypertensive drug ketanserin is a selective 5-HT_{2A} receptor antagonist that might ameliorate visual hallucinations.

Ketanserin is a selective 5-HT_{2A} antagonist available in most countries, but primarily indicated for hypertensive crises. Efficacy of ketanserin on visual hallucinations has been described by Vollenweider *et al* and Kometer *et al* as this drug could effectively and rapidly block the hallucinogenic and corresponding neurophysiological effects of psilocybin in humans.[10 11] Additionally, ketanserin has been shown to block the perceptual effects of MDMA,[12] and dream-like effects of LSD,[13] both serotonergic hallucinogens similar to psilocybin.

Our patient suffered from a relatively rare type of schizophrenia, namely with childhood onset, raising the question whether the effect of ketanserin is generalisable to other patients. However, our goal was to treat bothersome medication-resistant hallucinations rather than the whole set of symptoms known as schizophrenia, moving towards a personalised treatment of hallucinations as we argue for elsewhere.[14] The effect of ketanserin on the described types of visual hallucinations may very well be generalisable, even across diagnoses, as the 5-HT_{2A} receptor is implicated in the pathogenesis of hallucinations in both schizophrenia and PD.

Still, the effect of ketanserin in our case could be a placebo effect. However, the facts that many other interventions including high-dose clozapine and transcranial stimulation had no such effect, that our patient expressed little confidence in the ketanserin treatment beforehand and that there appeared to be a dose-dependent effect, do suggest otherwise.

Ours is the first described case that suggests blocking the 5-HT_{2A} receptor with ketanserin can selectively improve visual hallucinations, but not auditory hallucinations in patients with visual hallucinations. Ketanserin might be an antihallucinogenic drug, potentially repurposing its original use as an antihypertensive drug.

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