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A REVIEW ON EVIDENCE OF VISUAL HALLUCINATION ON METOPROLOL USAGE

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ABSTRACT

Metoprolol, a widely used beta blocker, has been associated with visual hallucinations and CNS disorders. Multiple reasons can lead to under- recognition and under-reporting of this adverse drug effect by both patients and physicians. The true incidence of metoprolol-related visual hallucinations is unknown. Doctors are urged to maintain diligent vigilance when managing patients receiving this medicine. We suspect that metoprolol-induced visual hallucinations may be under- recognized and under-reported. Patients may often fail to recognize this adverse effect, believing they are just dreaming, or may be ashamed to report visions that they think will not be perceived by others as real. Similarly, healthcare professionals may also fail to recognize this visual toxicity or attribute visual hallucinations to concomitant illness or other medications. Physicians should maintain diligent vigilance when managing patients receiving this medicine.

KEYWORDS: Metoprolol, Visual Hallucination.

INTRODUCTION

Metoprolol is a widely used beta-adrenergic blocker, usually prescribed for a variety of cardiovascular syndromes and conditions. Although adverse effects of the central nervous system have been well described with most beta-blockers (especially lipophilic agents such as propranolol), visual hallucinations have rarely been described with metoprolol.

Here, we report the cases of three patients with metoprolol-induced visual hallucinations; We reviewed the literature on this topic and hypothesized why this neurological toxicity may be under-recognized and under-reported.[1]

Case Presentations

Case 1 was an 84-year-old Caucasian woman with a history of hypertension and osteoarthritis, suffering from visual hallucinations that she described as people in her bedroom at night. They would be standing in front of the bed or sitting in chairs watching her as she slept. Numerous medications were discontinued before the doctor realized that metoprolol was the causative agent. The hallucinations were resolved only after discontinuation of this medicine. Case 2 was a 62-year-old Caucasian male with cardiac arrest complicated lower- wall myocardial infarction who was successfully resuscitated and discharged from the hospital with metoprolol. About 18 months after discharge, he reported to the doctor that he was seeing dead people at night. He related his belief that since he had "died and been brought back to life," he was now seeing afterlife. Following discontinuation of metoprolol, visual disturbances resolved within a few days. Case 3 was a 68-year-old Caucasian woman with a history of severe hypertension and depression who reported visual hallucinations at night for years while taking metoprolol. This included waking up at night with people in her room and watching objects in her room turn into animals. After a new doctor switched her from metoprolol to atenolol, visual hallucinations ceased within four days. We suspect that metoprolol-induced visual hallucinations may be under- recognized and under-reported. Patients may often fail to recognize this adverse effect, believing they are just dreaming, or may be ashamed to report visions that they think will not be perceived by others as real. Similarly, healthcare professionals may also fail to recognize this visual toxicity or attribute visual hallucinations to concomitant illness or other medications. Physicians should maintain diligent vigilance when managing patients receiving this medicine.

We reviewed the literature on this topic and hypothesized why this neurological toxicity may be under-recognized and under-reported. Let's consider the above 3 cases discussed above more briefly. An 84-year-old Caucasian woman with a history of hypertension and osteoarthritis suffered visual hallucinations for several years. She would wake up at night to see people standing at the foot of the bed or sitting in a chair in the bedroom watching her sleep. These people didn't talk to her, but they were scary. She had no history of neurological or psychiatric illness, nor had significant neuropsychiatric findings on physical examination. His medications consisted of aspirin, a calcium channel blocker, an

angiotensin converting enzyme inhibitor, and metoprolol tartrate 50 mg orally twice a day to control blood pressure. She used acetaminophen to control her arthritis symptoms.

She had no hallucinations at any other time of day or night. A neurological examination included an MRI of the brain, an electroencephalography and neurocognitive tests, which revealed nothing. A complete set of laboratory tests showed normal thyroid functions, vitamin B12 and folate levels. She had no history of alcohol or drug use. She wasn't sure how long she took all the drugs, but she knew she had been taking metoprolol for at least two years. All of his antihypertensive medications were discontinued in addition to the beta- adrenergic blocker before his doctor realized that the causative agent was metoprolol. Her visual hallucination completely stopped within several days of stopping the medication.

A 62-year-old Caucasian man had a lower-wall myocardial infarction that was complicated by cardiac arrest shortly after arrival at the emergency department. He was successfully resuscitated after approximately one to two minutes of ventricular fibrillation with electrical defibrillation. Otherwise, he recovered uneventfully and was discharged on aspirin, isosorbide, lisinopril, and metoprolol tartrate 100 mg orally twice daily. He had no history of neurological or psychiatric abnormalities or significant findings on physical examination. He rarely used alcohol, but there was no illicit drug use.

About 18 months after discharge, our patient asked to speak to his doctor confidentially. He asked his wife not to be informed and later reported that he was seeing dead people at night. He would wake up and see faceless figures sitting by the bed; the figures would disappear when he was fully awake. He believed that because he "died and came back to life" during the acute phase of his myocardial infarction, he was now seeing people from the afterlife. He also saw animals sometimes. Visual hallucinations began immediately after he was discharged from the hospital, at which time he was placed on metoprolol. Following discontinuation of metoprolol, visual disturbances resolved within a few days. Our patient asked to restart metoprolol after considering the beneficial aspects of the drug in his heart disease. He now understood that visual hallucinations were drug-related and no longer frightening to him when they occurred later.

A 68-year-old Caucasian woman suffering from severe hypertension, hypothyroidism, and depression reported visual hallucinations at night for two years while taking metoprolol 100 mg oral orally once daily. This included waking up at night with people in your room and seeing objects in your room that turned into animals. Its other medications include amlodipine, enalapril, escitalopram, levothyroxine and aspirin. When questioned, she believed that hallucinations began around the same time she was put on metoprolol for hypertension. Physical examination and laboratory evaluation revealed nothing. She had no history of alcohol or illicit drug use. She described visual disturbances to her previous family doctor, who felt that it was probably related to her medical problems, including her depression. His neurological and psychiatric examinations were uncommon except for a direct effect. She later visited a new doctor who switched her from metoprolol to atenolol, resolving her nocturnal visual hallucinations in four days.[1]

Evidence of Visual Hallucination by Metoprolol

Beta-adrenergic blocking agents have been known to cause adverse CNS effects for decades, including psychiatric syndromes, bizarre and vivid dreams, sleep disorders, delirium, psychosis and visual hallucinations. The medical and pharmacological literature clearly describes highly lipophilic agents, such as propranolol, as those most frequently with neurological toxicities. In 1978, Fleminger reported a 14.3% to 17.5% incidence of visual hallucinations and propranolol illusions among patients seen at a hypertension clinic. Metoprolol is a popular cardiovascular drug, the widespread use of which can be attributed to its affordable, short- and long-term formulations of action, and its established safety and efficacy in treating a variety of cardiovascular disorders such as hypertension, arrhythmias, angina pectoris. chest, acute coronary syndromes. and congestive heart failure. There is a lack of data on the occurrence of CNS side effects with metoprolol administration. Metoprolol, which has an intermediate degree of lipophilicity (a property known to increase CNS drug penetration as opposed to hydrophilicity, which limits brain entry), has rarely been reported to cause visual hallucinations, despite its common use. In the light of our experience, we suspect that visual hallucinations with this medicine may occur more often than previously reported.

Underreporting and underreporting of hallucinations caused by metoprolol may be due to several factors. First, patients may not complain of visual disturbances because they cannot connect symptoms to the drug, as in our second case. Some patients may attribute hallucinations associated with beta blockers in dreams or nightmares. As Fleminger reported with propranolol, all three patients had their visual hallucinations while wakening from sleep in the hypnopompic state. In addition, patients may be ashamed to discuss delusions they fear may be confused by others as a result of mental illness or excessive use of drugs or alcohol. Finally, physicians may also fail to recognize this adverse effect of the drug and may consider that the visual disturbance is related to existing medical or psychiatric conditions, as in the first and third cases. It was reported that hallucinations associated with metoprolol may remain an isolated symptom, or may progress to delirium in older patients with cognitive deficits. For the two patients he described, visual hallucinations began within 24 hours of starting metoprolol and the side effect was discovered

soon after hospitalization. This is different from our patients, who did not recognize the adverse reaction or recognized it by their doctor for a long time. Delay in diagnosing the cause of hallucinations in our patients was related to the patient's reluctance to inform anyone about visual disturbances, the patient's family associating hallucinations with other medical or psychiatric disorders that they thought the patient had or the disability of the patient. physician to recognize the drug as the etiology of the disorder. Our patients had no visual disturbances at other times, nor a psychiatric or medical motive that would otherwise be responsible for hallucinations. The hallucinations in the cases described were realistic enough to cause considerable anxiety and fear for these patients. Most hallucinations caused by beta-adrenergic agents usually stop within days of drug discontinuation, as occurred in our patients. Depending on the diagnosis, patients with metoprolol-related hallucinations may tolerate switching to a more hydrophilic beta-blocker such as atenolol or bisoprolol.

Interestingly, the latest third generation of beta-blockers such as nebivolol and carvedilol, which are often used to treat patients with congestive heart failure and hypertension, have so far not been associated with visual hallucinations, despite their moderate to high lipophilic nature. Thus, it is assumed that there may be other factors that may influence the degree of CNS blocker side effects besides lipophilicity. Other parameters, such as specific structural details of beta-blocker molecules, drug-induced increases in plasma catecholamine levels and a decrease in melatonin levels have been proposed to affect the penetration of beta blockers into the blood brain barrier or the occurrence of CNS side effects. These third generation beta blockers may be a good alternative to metoprolol if visual hallucinations occur.[1]

Nightmares caused by Medication

Nightmares are common, beginning early in childhood and extending throughout their lifespan. The condition is strongly associated with stress, anxiety and trauma.

Although nightmares are by definition not pathological, those that are frequent or disabling and impair social, occupational, emotional and physical well-being are considered a disorder and are often a sign of underlying and treatable psychopathology. Common causes include stress, negative life events, experience of trauma such as posttraumatic stress disorder (PTSD), depression, other psychiatric disorders, and side effects of Metoprolol.

A systematic review of over 100 studies found that nightmares are more commonly reported by women than men during adolescence and young adulthood (approximately 1.5 to 1 ratio).[3] No gender differences were present in younger children or in adults 60 years of age and older. The content and frequency of nightmares, like dreams, can also vary across cultures.

Medications most commonly associated with nightmares include those that affect the signalling of norepinephrine, serotonin, metoprolol, dopamine, acetylcholine or gamma-aminobutyric acid (GABA).[2]

Visual Hallucination

Hallucinations, defined as the perception of an object or event (in any of the 5 senses) in the absence of an external stimulus, are experienced by patients with conditions that span multiple fields (eg, psychiatry, neurology, and ophthalmology). When observed by non-psychiatrists, visual hallucinations, a type of sensory misperception, often trigger requests for psychiatric consultation, although visual hallucinations are not pathognomonic of a primary psychiatric illness. Visual hallucinations have numerous etiologies. Here we discuss possible mechanisms and offer a differential diagnosis of visual hallucinations, with emphasis on conditions that arise in the context of medical and surgical diseases. Treatment is usually based on the underlying etiology; therefore, timely recognition and understanding of causal mechanisms are crucial.[4]

What Causes Visual Hallucination

Numerous hypotheses have been suggested to explain the genesis of visual hallucinations. These were summarized and categorized by Asaad and Shapiro: psychophysiological (that is, as a disorder of brain structure), psycho biochemistry (as a disorder of neurotransmitters) and psychodynamic (as an emergence of the unconscious in consciousness). Visual hallucinations can be the result of all three processes, given the interaction between disorders of brain anatomy, brain chemistry, previous experiences, and psychodynamic meaning.

Metoprolol, Beta-adrenergic blockers causes central nervous adverse effect in which visual hallucination is rarely seen. So far, only some neural mechanism has explained all kinds of visual hallucinations; however, the similarity of visual hallucinations associated with apparently diverse conditions suggests a final common path. Manford and Andermann summarized three pathophysiological mechanisms considered responsible for complex visual hallucinations.

The first mechanism involves irritation (eg, seizure activity) of the cortical centers responsible for visual processing. Irritation of primary visual cortex causes simple elementary visual hallucinations, while irritation of cortices of visual association causes more complex visual hallucinations. These data are supported by electroencephalographic recordings (EEGs) and direct stimulation experiments.

Injuries that cause deafferentation of the visual system can lead to the phenomenon of cortical release, including visual hallucinations. Normal entrances are thought to be under the control of inhibitory processes that are effectively removed by deaferencing. It has also been

suggested that deferenced neurons undergo specific biochemical and molecular changes that lead to a general increase in excitability (similar to denervation hypersensitivity observed in phantom limb syndrome experienced by amputees).

A multitude of injuries can cause this loss of input and inhibit other cognitive functions. It is important to note that visual hallucinations can be induced by prolonged visual deprivation. One study reported visual hallucinations in 10 out of 13 blindfolded healthy individuals for a period of 5 days; This finding strongly supports the idea that simply losing normal visual information is enough to cause visual hallucinations. Finally, due to its role in maintaining arousal, the reticular activation system has been implicated in the genesis of visual hallucinations. Brainstem lesions led to visual hallucinations (as in peduncular hallucinosis). In addition, visual hallucinations are common in those with certain sleep disorders and occur most often in those who are sleepy. The observation that visual hallucinations occur more often in those who are sleepy (even in the absence of open sleep pathology) suggests that the reticular activation system plays a role in visual hallucinations, although the precise mechanism has not yet been established.[4]

How can the etiology of visual hallucination be determined?

Given the wide variety of potential etiologies of visual hallucinations described earlier, it is clear that accurate diagnosis is required before effective treatment can be initiated. A thorough history and clinical examination are the most vital elements of an investigation for visual hallucination.

Symptoms and associated characteristics of visual hallucinations themselves may aid in direct diagnosis (Table 1). Obtaining signs or symptoms of psychosis, inattention, parkinsonism, impaired vision, or headache will narrow the diagnosis and lead to further diagnostic studies. An EEG is potentially the most revealing diagnostic study because it not only highlights seizure activity but also detects delirium (with decreased theta-delta), delirium tremens (with rapid beta activity) and CJD (with occipital periodic non-generalized complexes). 54,55 An MRI of the brain can uncover tumors or infarcts that may be responsible for Anton syndrome or peduncular hallucinosis, and may also show the characteristic “pulvinar signal” associated with CJD.[4]

Table 1: Features of Visual Hallucinations Indicative of Etiology.

Features of Visual Hallucination	**Most Likely Etiologies**
Simple patterns, spots, shapes, or lines; unilateral distribution; associated with headache	Migraine, seizure, tumor
Macropsia, micropsia, metamorphopsia	Seizure, Creutzfeldt-Jakob disease
Features of Visual Hallucination	**Most Likely Etiologies**
Confabulation of all vision	Anton's syndrome
Frightening content	Psychotic disorder, delirium, hallucinogenic drug
Good insight	Charles Bonnet syndrome, migraine, peduncular hallucinosis

Neuroleptic drugs (ie dopamine antagonists) are the basis of treatment for visual hallucinations due to primary psychotic disease. These drugs are also beneficial for the management of delirium (in which hallucinations are thought to be caused.

by the release of endogenous dopamine), with intravenous haloperidol providing more evidence for safety and efficacy.[5] Unfortunately, due to their dopamine blocking activity, most neuroleptics significantly exacerbate parkinsonian symptoms in patients with DLB or Parkinson's disease-associated dementia. Quetiapine and clozapine have a niche role in treating these patients, as their very low affinity for dopamine receptors makes them less likely to cause this serious adverse effect.55 Like other forms of Alzheimer's dementia, dopamine inhibitors cholinesterase may have some benefit in subsequent cortical atrophy.More focal causes of visual hallucinations may require more focal treatment. Seizures may be treated with anticonvulsants, tumors with surgery and radiation, and migraines with triptans or β-blockers. Unfortunately, some causes of visual hallucinations (eg, CJD) have no definitive treatment. For these patients, neuroleptics can minimize visual hallucinations and distress. Most patients with visual hallucinations, regardless of cause, will benefit from the safety of their caregivers. Some may also benefit from more formal psychotherapeutic interventions (eg, cognitive behavioral therapy) aimed at improving perception.[4]

Metoprolol

Metoprol Description

Metoprolol tartrate is a selective beta 1-adrenoreceptor blocking agent available in 25 mg, 37.5 mg, 50 mg, 75 mg and 100 mg tablets for oral administration. Metoprolol tartrate, USP, is a white crystalline powder with a molecular weight of 684.82. It is very soluble in

water; freely soluble in methylene chloride, chloroform and alcohol; slightly soluble in acetone; and insoluble in ether. Each tablet for oral administration contains 25 mg, 37.5 mg, 50 mg, 75 mg or 100 mg metoprolol tartrate and the following inactive ingredients: lactose monohydrate, colloidal silicon dioxide, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, titanium dioxide, sodium starch glycolate, talc and D&C Red # 30 Aluminum Lake.[5]

Metoprolol causing Visual Hallucination and other Side Effects

Beta1-adrenergic receptor blockers are known to cause central nervous system (CNS) effects including bizarre or vivid dreams, sleep disorders, delirium, psychosis and visual hallucinations. Psychosis and delirium have been reported for metoprolol and propranolol.4, These effects are not dose dependent and appear to be partly due to the lipophilic properties of the drugs: Hydrophilic agents such as atenolol are excreted unchanged by the kidneys, while lipophilic agents such as propranolol and metoprolol are metabolised by the liver and believed to cross. the blood-brain barrier. Other factors that affect beta-blocker penetration of the blood-brain barrier and its ability to cause CNS effects include molecule-specific structural details, drug- induced increases in plasma catecholamine levels, and decreased melatonin levels.

The neuropsychiatric effects of ACE inhibitors are limited; however, visual hallucinations associated with the use of these agents have been reported, especially in elderly patients. The implicated agents include quinapril, enalapril, captopril, lisinopril, rinopril, ramipril and perindopril. 2 hours to 6 years after initiation of an ACE inhibitor and resolved within 1 to 30 days after discontinuation. Age advancement and underlying CNS disorders may be risk factors for ACE inhibitor-induced psychosis.

Other cardiac agents that can induce psychosis include diuretics, calcium channel blockers, and various antiarrhythmic agents.

The medication most often associated with visual hallucination include those used to treat high blood pressure, erectile dysfunction, psychiatric and mood disorders, movement disorders like parkinsonism and some antibiotics.

Visual phenomena can result from constriction or dilation of the middle cerebral artery which supplies the occipital cortex, or other key blood vessels. Widely prescribed drugs of this type include blood pressure medications, especially beta-blockers and antianginal drugs like nitroglycerin.[6]

Other Medication causing Visual Hallucination

Hallucinations occur when you feel something that is not really present. Hallucination types include visual, auditory, olfactory, tactile, taste and somatic somatic.

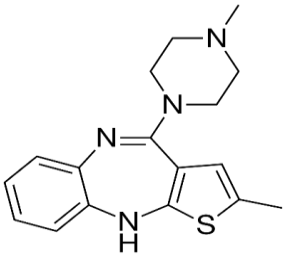
Hallucinations are a common symptom of schizophrenia, but they can also be caused by excessive alcohol consumption, drug abuse, depression, sleep deprivation, dementia or certain prescription drugs.

Several psychiatric drugs such as olanzapine (Zyprexa), quetiapine (Seroquel) and haloperidol (Haldol) have been associated with hallucinations, in addition to zolpidem (Ambien), eszopiclone (Lunesta), clonazepam (Klonopin), lorazepam (Ativan), ropinirol and some seizure medications.

Cephalosporins and sulfa drugs, which are two common classes of antibiotics, have been associated with causing hallucinations in rare cases. Amoxicillin is a broad spectrum penicillin-based antibiotic (Box). Its possible psychiatric side effects include encephalopathy, irritability, sedation, anxiety and hallucinations. These symptoms are usually managed by reducing the dose or stopping the medicine.

People who take Viagra or other erectile dysfunction drugs may notice a distinct bluish tint in their vision. These drugs have dose dependent effects for example only about 5% of patients taking 50mg a day haver symptoms but 100% taking 200mg a day will be effected.[6]

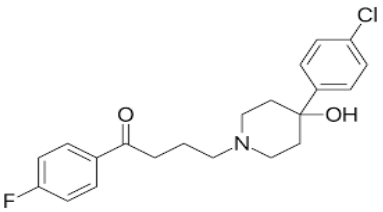
Olanzapine



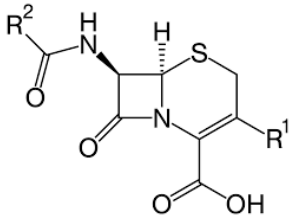
Molecular Weight: 312.4 g/mol pKa: 10.57

Boiling Point: 476 ºC Melting Point: 189-195 °C Solubility: Partly miscible.

Haloperidol



Cephalosporin



Molecular Weight: 387.4 g/mol
pKa: 1.83
Boiling Point: 814.7 ºC Mel melting oint: 189-195 °C
Solubility: Partly miscible.

CONCLUSION

Metoprolol, a widely used beta blocker, has been associated with visual hallucinations and CNS disorders. Multiple reasons can lead to under- recognition and under-reporting of this adverse drug effect by both patients and physicians. The true incidence of metoprolol-related visual hallucinations is unknown. Doctors are urged to maintain diligent vigilance when managing patients receiving this medicine.

We suspect that metoprolol-induced visual hallucinations may be under- recognized and under-reported. Patients may often fail to recognize this adverse effect, believing they are just dreaming, or may be ashamed to report visions that they think will not be perceived by others as real. Similarly, healthcare professionals may also fail to recognize this visual toxicity or attribute visual hallucinations to concomitant illness or other medications. Physicians should maintain diligent vigilance when managing patients receiving this medicine.

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