

Aripiprazole-Induced Hyperhidrosis: Two Case Reports



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SUMMARY

Many drugs including anti-depressants and anti-psychotics are known to cause excessive sweating (hyperhidrosis). Hyperhidrosis may be caused by drugs acting at the hypothalamus, spinal thermoregulatory centres, and sympathetic ganglia or at the eccrine-neuroeffector junction. Hyperhidrosis can be distressing and embarrassing symptom, which if not addressed properly, may lead to non-concordance to medication. Two female patients are reported here who developed hyperhidrosis with aripiprazole. Both the patients stopped experiencing hyperhidrosis after their aripiprazole was discontinued. To the best of the knowledge of the author, no case of aripiprazole induced hyperhidrosis has been published in the literature.

Keywords: aripiprazole, hyperhidrosis, case reports

INTRODUCTION

Sweat glands are present all over the body with highest density in the region of axilla, palms and sole of the feet and perform an important physiological function of thermoregulation by producing a thin secretion which is hypotonic to plasma (Sato et al. 1989). The heat and cold receptors are situated in the skin and viscera and are responsible for passing impulses to the brain (Ogawa and Low 1997).

The thermoregulatory pathways begin in the hypothalamus and descend to the intermediolateral column of spinal cord from where preganglionic sympathetic nerve fibres arise to synapse within the ganglia of sympathetic chain. The post-ganglionic sympathetic nerve fibres then emerge to innervate 2-5 million eccrine sweat glands (Cheshire and Fealey 2008, Cheshire and Freeman 2003, Craig 1970). Well-coordinated reflexes are initiated from sympathetic nervous system in response to raised body temperature due to either

increased metabolic activity or exposure to heat. These reflexes lead to vasodilatation, generalised sweating and hyperpnoea which help the body to restore the normal body temperature (Marcy and Britton 2005, Edwards and Anderson 1999). Acetylcholine, released in response to sympathetic nerve impulses, plays a key role in the whole thermoregulatory pathway. It binds to cholinergic muscarinic (M3) receptors and results in myoepithelial cell contraction to produce sweat. Any drug that augments cholinergic transmission may increase sweating (Kennedy et al. 1994).

Hyperhidrosis is excessive production of sweat than needed to maintain normal body temperature and homeostasis. According to a US study, the prevalence of hyperhidrosis is around 2.5 % in general population. However, this study did not assess to what degree the drugs are responsible for hyperhidrosis (Strutton 2004).

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Different drugs can influence the pharmacologically complex system of thermoregulatory system by acting at different level and triggering the production of sweating resulting in hyper or hypohidrosis. These drugs can influence medial preoptic area of the hypothalamus and junction between eccrine sweat gland and sympathetic nerve endings (Cheshire and Freeman 2003, Craig 1970). Anti-depressants like selective serotonin reuptake inhibitors (SSRIs) with minimal effects on norepinephrine may cause hyperhidrosis by their serotogenic effect on hypothalamus or spinal cord (Cheshire and Fealey 2008). The tricyclic anti-depressants, with well recognised anti-cholinergic effects, occasionally cause hyperhidrosis by norepinephrine reuptake inhibition with stimulation of peripheral adrenergic receptors (Marcy and Britton 2005, Beasley et al. 2000).

Many drugs, including antipsychotics, may cause hyperhidrosis by influencing different pathways of thermoregulatory system and should be considered as one of the potential causes of hyperhidrosis (Cheshire and Fealey 2008). Recently, a case of Zolopine-Haloperidol combination inducing hyperhidrosis has been published by Huang and Chang (2012). On the contrary two cases of anti-depressant-induced sweating alleviated by aripiprazole have been reported (Lu et al. 2008).

Case reports

Case 1

SM is a 36- years- old white woman who has a long standing diagnosis of emotionally unstable personality disorder (EUPD) and depressive disorder. She also suffers from clinically controlled hypothyroidism. During her adolescence, SM started exhibiting various symptoms of EUPD mainly in the form of impulsivity, outburst of intense anger, aggression, short lived mood swings, hypersensitivity, feeling of emptiness, unclear sexual preferences, and various difficulties in relationships. She also experienced depressive symptoms, anxiety features and occasionally heard a single voice inside her head. She indulged in self- harm behaviour mainly in the form of taking overdoses, punching doors or walls and self-mutilating.

A few years back, she was diagnosed with a moderate to severe depressive episode without psychotic symptoms as she reported anhedonia, low energy levels, poor appetite, early morning awakening, and low self-esteem poor concentration, feelings of hopelessness, worthlessness and suicidal ideation. She was treated with Sertraline 200 mg a day and quetiapine 150mg/day, to which she responded well but discontinued taking quetiapine due to weight gain. Although she recovered from depression, she continued to struggle with symptoms of EUPD. A few months back, aripiprazole was added to her sertraline which was later increased to 15 mg a day, following which she started experiencing generalised excessive

sweating which was quite distressing and embarrassing to her. The generalised excessive sweating was not accompanied by restlessness, tremors, shivering, myoclonus, confusion or convulsions. Her vital signs and neurological examination were unremarkable. She continued to experience hyperhidrosis for couple of months before she presented herself for clinical review in the clinic and her aripiprazole was stopped while she continued with sertraline 200mg a day. Her problem of excessive sweating disappeared in about a week time.

Case 2

AM is a 40 years old white woman who has a diagnosis of schizo-affective disorder and emotionally unstable personality disorder and is known to psychiatric services for many years. As a teenager she experienced difficulties related to impulsivity, outburst of anger, regulating her emotions, keeping herself out of trouble and maintaining relationships. She also exhibited self-harm behaviour, marked sensitivity to any criticism and mood swings.

She needed 3 admissions into hospital for alcohol detoxification. Since her last detoxification in 2006, she has been drinking alcohol in moderation.

In 2004, she was diagnosed with post-natal depression which was later changed to bipolar affective disorder (mixed type) as she presented with elation of mood, increased psychomotor activity, anxiety and depressive symptoms. Subsequently, as she showed symptoms of elevation of mood, irritability, psychotic features, thought broadcasting, paranoid delusions and auditory hallucinations, her diagnosis was changed to Schizo-affective disorder.

Few months ago she was on mirtazapine 30mg a day and Aripiprazole 20 mg a day when she started sweating excessively which was quite distressing to her and lowered her self-esteem. The sweating was generalised with nocturnal exacerbations. It was not associated with Serotonin syndrome symptoms such as restlessness, tremors, shivering, myoclonus, confusion or convulsions. Her vital signs and neurological assessment were of no concern. Her mirtazapine was discontinued but she did not notice any change in her excessive sweating. Later, the dose of aripiprazole was reduced to 10mg/day but her excessive sweating continued and hence her aripiprazole was discontinued after she continued to experience hyperhidrosis for more than three months. She stopped experiencing hyperhidrosis about ten days after the discontinuation of aripiprazole.

DISCUSSION

The routine haematological and biochemical investigations including blood glucose level and thyroid functions were unremarkable in both the cases. There was no history of

hyperhidrosis in the families of these two patients. Apart from hypothyroidism in case 1 and hypertension in case 2, there was no other associated physical health problem.

Acetylcholine is the main neurotransmitter that acts on the cholinergic muscarinic (M3) receptors of the thermoregulatory system between spinal cord and the sweat gland in producing the sweat. Dopaminergic activity is important for hypothalamic thermoregulation and is evident from increased sweating in Parkinson disease which is associated with reduced dopaminergic activity (Gurrera 1999, Lee et al. 1985).

Many drugs are known to cause hyperhidrosis by acting at different sites ranging from hypothalamus to eccrine sweat glands. Various drugs that may influence serotonin, norepinephrine or opioid receptors can also influence sweat production. Serotonin reuptake inhibitors may cause episodic or nocturnal hyperhidrosis in some patients but other antidepressants with SSRIs properties such as venlafaxine, trazadone or duloxetine may induce hypohidrosis (Cheshire and Fealey 2008, Cheshire and Freeman 2003). It is yet not clear whether anti-depressant induced sweating is due to altered serotonergic or dopaminergic in the hypothalamus or is as a result of direct adrenergic stimulation of the sympathetic system (Marcy and Briton 2005)

According to prescribing information of aripiprazole (Abilify PI sheet), aripiprazole shows high affinity for dopamine at D2 and D3, serotonin 5-HT1A and 5-HT2A receptors (Ki values of 0.34 nM, 0.8 nM, 1.7 nM, and 3.4 nM, respectively). It is a partial agonist at the D2 and 5-HT1A receptors while it is an antagonist at serotonin 5-HT2A receptors. Aripiprazole has a moderate affinity for D4, 5-HT2C and 5-HT7, α 1-adrenergic and H1 receptors (Ki values of 44 nM, 15 nM, 39 nM, 57 nM, and 61 nM, respectively). It also has a moderate affinity for the serotonin reuptake site (Ki=98 nM). However, aripiprazole exhibits no appreciable affinity for cholinergic muscarinic receptors (IC50>1000 nM) (PI Abilify).

It is hard to explain the underlying mechanism of aripiprazole-induced hyperhidrosis in these two patients. The possible mechanism of aripiprazole induced hyperhidrosis could be the depletion of dopamine in hypothalamus due to partial agonist influence of aripiprazole on dopamine receptors in mesolimbic system and or increase in the level of serotonin due to its affinity on serotonin receptors (Cheshire and Fealey 2008). On the other hand two cases of anti-depressant-induced sweating alleviated by aripiprazole have been reported

(Lu et al. 2008). As stated above, aripiprazole has affinity for a range of receptors and it is difficult to determine which of these got affected and resulted in hyperhidrosis.

To conclude, in both the patients, hyperhidrosis was induced by aripiprazole which could possibly be due to depletion of dopamine and increase in serotonin. Besides the rare potential risks of hypothermia, dehydration and electrolytes depletion, hyperhidrosis can be a source of unpleasantness and embarrassment to the patients. It is, therefore, imperative to raise the awareness of this uncommon potential side effect of aripiprazole which may otherwise promote non concordance with medication, if not addressed adequately.

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