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# Cerebral edema secondary to psychogenic polydipsia induced by tandospirone as add-on to olanzapine therapy

Takahiko Nagamine, M.D., Ph.D.

*Division of Psychiatric Internal Medicine, Ishii Memorial Hospital, 3-102-1Tada, Iwakuni city, Yamaguchi, 741-8585, Japan*

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Psychogenic polydipsia is not a rare complication in patients with schizophrenia, and has been recognized as a dangerous and potentially life-threatening disorder. Although multiple factors have been implicated, possibly including hypothalamic dysfunction, syndrome of inappropriate secretion of ADH (SIADH), and adverse medication effects, the underlying pathophysiology of psychogenic polydipsia is still unclear [1]. The author encountered a case of cerebral edema secondary to psychogenic polydipsia possibly related to the coadministration of tandospirone with olanzapine, which seems to reduce serotonergic activity, probably via its agonistic activity toward serotonin autoreceptors.

A 69-year-old female inpatient with schizophrenia was found with unconsciousness and generalized tonic clonic seizures 3 days after the initiation of tandospirone as add-on to olanzapine therapy. She had been diagnosed as schizophrenic since she was in her twenties, after her first psychotic break, and had been treated with several medications with varying degrees of success. Recently, her delusions had been well controlled by olanzapine 20 mg/day. Although she had been mildly but chronically polydipsic for many years, severe hyponatremia and convulsions had not been observed. Tandospirone 20 mg/day was added to olanzapine for the treatment of psychotic depression. However, she experienced convulsions 3 days after the initiation of tandospirone. A nasogastric tube was inserted, and a large amount of clear liquid was removed from her stomach. The patient's initial serum sodium level was 112 mmol/L, representing a marked decrease from the level of 142 mmol/L 20 days earlier (Fig.1) A non-contrast computed tomographic scan of the patient's brain revealed a loss of gray-white differentiation and sulcal effacement, consistent with cerebral edema. She was diagnosed as having acute hyponatremia, presumably secondary to psychogenic polydipsia. Based on the clinical severity of the cerebral edema, she was treated with the rapid infusion of normal saline and a loop diuretic at the rate required for sodium correction of 1.0 mmol/L/hr while her serum sodium level was closely monitored. The patient's serum sodium level rapidly increased from 112 mmol/L to 131 mmol/L in 24 hours, and she excreted 7.2 liters of urine in 24 hours. On day 3, the patient was awake and alert, and recovered her orientation to person, place and time, as her sodium level recovered to 137 mmol/L. However, after the patient's hyponatremia was corrected, she developed a substantial elevation in her creatine kinase (CK) level, indicating rhabdomyolysis, possibly due to the calcium-sodium exchange mechanism across the skeletal myocyte or the failure of cell volume regulation secondary to extracellular hypo-osmolality. Fortunately, the asymptomatic rhabdomyolysis resolved without treatment on day 9, and the patient's overall condition was good, and she did not experience any additional seizures (Fig. 1).

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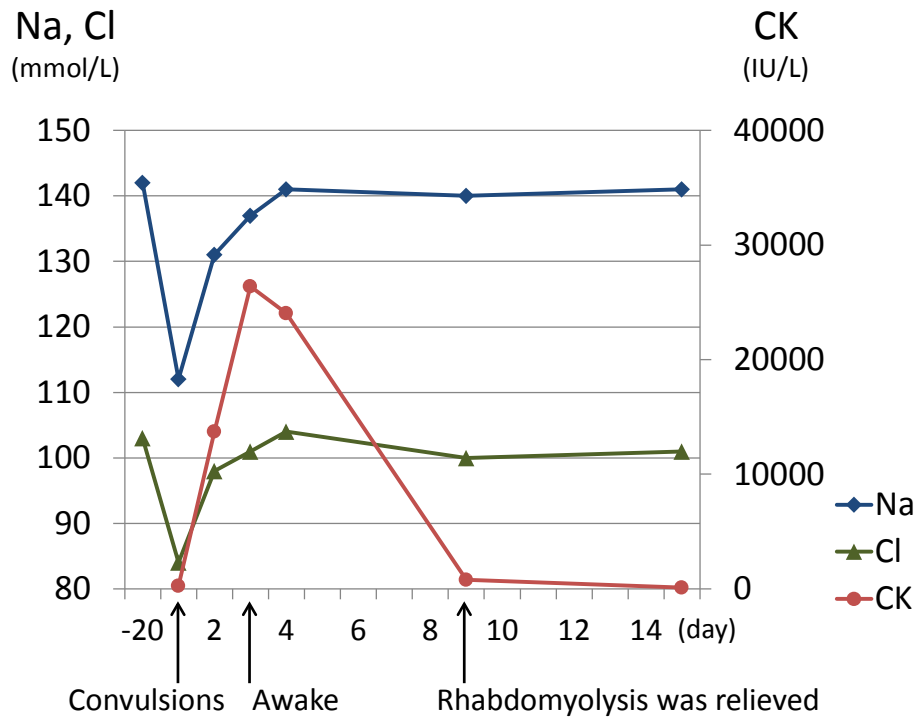
Corresponding Author: Takahiko Nagamine, M.D., Ph.D., Division of Psychiatric Internal Medicine, Ishii Memorial Hospital, 3-102-1Tada, Iwakuni city, Yamaguchi, 741-8585, Japan
e-mail: anagamine@yahoo.co.jp

Figure1. Clinical course of the levels of serum sodium, chloride, and creatinine kinase




In this case, a modest dose (20 mg/day) of tandospirone as add-on seemed to induce marked polydipsia. Can we conclude that the pharmacological action of tandospirone induces abrupt polydipsia? One possibility is that tandospirone may have altered serotonin (5-hydroxytryptamine: 5-HT) transmission in the brain, which may be linked to compulsive behavior. A more likely possibility is that 5-HT stimulants effectively reduce compulsive drinking in schedule-induced polydipsia, which is an established model for studies on compulsive behavior in rats [2]. Tandospirone acts as a potent and selective 5-$HT_{1A}$ receptor partial agonist with approximately 55-85% intrinsic activity [3]. In an animal study, treatment with tandospirone for 2 days resulted in markedly reduced firing activity of 5-HT neurones of the dorsal raphe, followed by a partial recovery after 7 days and by complete recovery after 14 days of administration of tandospirone [4]. These findings suggest that tandospirone reduces 5-HT neurotransmissions within the first week, probably via its agonistic activity toward serotonin autoreceptors, which may exacerbate compulsive drinking behavior in potentially or mildly polydipsic patients.

Moreover, the reduction in water intake produced by 5-HT agonists was blocked by 5-$HT_{2A}$ receptor antagonists, but not by 5-$HT_{2C}$ receptor antagonists, in rats with highly compulsive drinking behavior [2]. Olanzapine is a potent 5-$HT_{2A}$ antagonist and has a higher affinity for 5-$HT_{2A}$ receptors than dopamine $D_2$ receptors. In a clinical report, excessive drinking behavior started after the dose of olanzapine was increased, and ultimately resulted in fatal water intoxication [5]. It should be noted that 5-HT neurotransmission temporarily decreases after tandospirone and olanzapine combination therapy, possibly putting patients at greater risk of developing polydipsia or experiencing an exacerbation of their existing polydipsia until the 5-HT autoreceptors are desensitized by tandospirone. When tandospirone is coadministered with 5-$HT_{2A}$ antagonists, clinicians should monitor mildly but chronically polydipsic patients closely for an abrupt deterioration in compulsive drinking behavior, especially during the first week.

There may be a link between psychotropic medications and the development of water intoxication, with 5-HT antagonists being the primary offenders. It has also been pointed out that 5-$HT_{1A}$ partial agonists may further increase the risk of polydipsic behavior in the initial stages of tandospirone coadministration. Although 5-HT neurons might be at least partly involved in the mechanisms of compulsive water drinking, the neural circuits associated with polydipsia should be more comprehensively studied in the future.

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