

# Zolpidem Induced Hyponatremia: A Case Report

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## ABSTRACT

Zolpidem is a non-benzodiazepine hypnotic that acts by binding to (GABAA) receptor. This is a case report of a patient with chronic insomnia for which he had initially been receiving benzodiazepine hypnotic alprazolam and for the past three years, he had switched himself to non-benzodiazepine hypnotic, zolpidem and had progressively increased the dose to 20 mg. The patient presented with history of drowsiness, nausea and vomiting of short duration. Investigations revealed that the patient had hyponatremia. Decreased serum sodium, elevated urine sodium with normal urine osmolarity was detected. Therefore, we report this as a case of drug induced syndrome of inappropriate antidiuretic hormone (SIADH) as other likely causes were ruled out by appropriate investigations. The causality assessment was done according to the WHO scale and found to be "Probable".

**Keywords:** GABA<sub>A</sub> receptor, Hyponatremia, Insomnia, SIADH, Zolpidem

## CASE REPORT

A 62-year-old male patient, doctor by profession, was admitted with gradual onset of drowsiness, nausea and vomiting of short duration. He was a known case of hypertension, diabetes mellitus and intervertebral disc prolapse of L3 -L4, L4- L5 joints for which midline decompression and laminectomy was done three years back. Despite the surgery, he continued to have low back ache and was later diagnosed with failed back syndrome for which he is on regular orthopaedic follow up.

The patient also had a long history of insomnia for which he was receiving benzodiazepine alprazolam at bedtime for more than 10 y. He was initially taking nightly dose of 0.25 mg which he had gradually increased to 0.5 mg and then to 1 mg. He claims to have started taking the drug for sleeping difficulty but later continued it mainly due to pain related insomnia. About three years back, the patient had changed his medication to non-benzodiazepine hypnotic, zolpidem. He had started off with a dose of 5 mg, after which, he had progressively increased the dose to 10 mg and continued it for a period of upto four months before the date of admission for his present complaints. In the last 4 months, he had taken a high dose of 20 mg bed time daily. He was also receiving the combination of gliclazide 40 mg with metformin 250 mg twice daily, metoprolol 25 mg and the fixed drug combination of aspirin 75 mg and atorvastatin 10 mg once daily for the past five years.

At admission, clinically the patient was found to be drowsy, arousable and moving all four limbs. He was euvolemic. His blood pressure was 120/80 mmHg. Complete blood counts showed leucocytosis, with a normal urine routine on investigation. Biochemically, he had severe hyponatremia, low serum osmolarity, elevated urine spot sodium with normal urine osmolarity [Table/Fig-1]. Renal, liver and thyroid function tests were normal. Serum cortisol was elevated [Table/Fig-1] and lipid profile was within normal limits. Random and fasting blood glucose levels were normal. Serum calcium and lactate levels were also normal. Blood and urine culture were sterile and ultrasound of the abdomen done showed fatty liver with cholelithiasis and grade I prostatomegaly.

He was treated with fluid restriction, 3% saline infusion and vasopressin receptor antagonist, tolvaptan 15 mg once daily for a period of about 10 d for adequate correction of serum sodium in addition to withdrawal of the offending drug. Serial investigations done on the ensuing days showed normalization of sodium levels [Table/Fig-2]. His general condition progressively improved. During subsequent follow up, his sodium level was within normal limits

(137meq/L). His insomnia improved with cognitive behavioural therapy and adequate pain management and thus he was successfully weaned off the hypnotic medication.

## DISCUSSION

Zolpidem is an imidazopyridine, a chemically novel non-benzodiazepine hypnotic agent which acts as an agonist at the GABAA receptor. Due to its selective binding to the receptor isoforms with  $\alpha 1$  subunit of GABAA receptor, it lacks anxiolytic, myorelaxant and anticonvulsant properties but is a potent hypnotic [1]. It binds with high affinity and acts as a full agonist at the  $\alpha 1$ -containing GABAA receptors, whereas it exhibits about 10-fold lower affinity for those containing the  $\alpha 2$ - and  $\alpha 3$ - GABAA receptor subunits and has no appreciable affinity for  $\alpha 5$  subunit-containing receptors [2,3].  $\omega 1$  type GABAA receptors are the  $\alpha 1$ -containing GABAA receptors and  $\omega 2$  type receptors are the  $\alpha 2$ -,  $\alpha 3$ -,  $\alpha 4$ -,  $\alpha 5$ -, and  $\alpha 6$ -containing GABAA receptors.  $\omega 1$  GABAA receptors are found predominantly in the brain, whereas  $\omega 2$  receptors are found primarily in the spine and zolpidem preferentially binds to the GABAA-benzodiazepine receptor complex in the brain [4].

The efficacy of zolpidem as hypnotic is similar to that of benzodiazepines. But zolpidem differs from benzodiazepines in terms of sleep onset latency, total sleep duration, number of nocturnal awakenings, adverse events, tolerance and rebound insomnia [5]. Zolpidem is shown to increase the slow wave sleep but has no effect on stage 2 sleep [6].

This is a case of high dose zolpidem induced syndrome of inappropriate anti-diuretic hormone manifesting with hyponatremia. SIADH is a well-recognized complication of many psychotropic drugs [7]. Also, there are a few reports of benzodiazepine like lorazepam induced hyponatremia in literature [8]. But till date, there are no reports of zolpidem induced SIADH.

Though zolpidem, a non-benzodiazepine hypnotic, acts selectively via the  $\alpha 1$ -subunit of GABAA receptors at therapeutic doses, it is possible that the reaction could have resulted from loss of receptor selectivity at high doses, leading to an adverse effect similar to that of benzodiazepines. The hypothesis is further emphasized by previous studies that have proved the muscle relaxant action of zolpidem at high doses. It is well-recognized that zolpidem does not have any muscle relaxant activity at therapeutic dose, but high dose zolpidem has been shown to improve the symptoms of spasticity and this effect is attributed to its action on GABAA receptor with  $\alpha 2$ -receptor and  $\alpha 3$ -receptor subunits [9].

Laboratory investigation	Values at the time of admission	Normal reference values
Serum osmolarity (mOsm/kg)	219.04	280-301
Urine osmolarity (mOsm/kg)	371.27	50-1400
Serum sodium (mEq/L)	106	135-145
Urine spot sodium (mEq/L)	110	~20
Serum cortisol (micro.g/dl)	33.85	6.2-19.4

[Table/Fig-1]: Biochemical laboratory investigations at the time of admission

Serum electrolytes	On Admission	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9
Sodium (mEq/L)	106	116	120	124	128	129	131	129	129	136
Potassium (mEq/L)	4.21	2.98	3.29	3.20	3.18	3.48	4.02	*	*	4.57

[Table/Fig-2]: Serial estimation of serum electrolytes

Causality assessment of the adverse drug reaction was done to assess the causal relationship of zolpidem with the hyponatremia event using the structured "Probability scale" system proposed by World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO-UMC) [10]. The causality assessment done according to the WHO-UMC scale revealed that there was reasonable temporal relationship of the event with the drug intake and also the reaction could not be explained by his co-morbid diseases or concurrent drugs administered. Moreover, the patient also exhibited a positive dechallenge test since the patient's sodium levels improved with withdrawal of zolpidem. Therefore, even though rechallenge was not done for ethical reasons, the causality assessment category in this case is considered to be "Probable".

## CONCLUSION

Thus, the case study of this patient has revealed that zolpidem could be causally related to the hyponatremia event. Although, the precise

mechanism is unclear, hyponatremia in the face of euolemia, low serum osmolarity, elevated urine sodium and normal urine osmolarity favors the diagnosis of zolpidem induced SIADH since other causes of hyponatremia were ruled out by suitable investigations. Thus the case study high lightens the importance of monitoring serum sodium for all patients on chronic zolpidem therapy for insomnia especially at high doses.

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