

## Hyponatremia as drug-induced or secondary to endocrine disorder electrolyte abnormality

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### ABSTRACT:

**Introduction:** Hyponatremia is one of the most commonly occurring electrolyte disorder. The main clinical symptoms of sodium imbalance are weakness, loss of appetite, headache, nausea with or without vomiting or altered mental status with somnolence or even seizures and death.

**Purpose:** To present a list of drugs pretending to occurrence or sodium serum level reduction and known endocrine disorder causing hyponatremia.

**Summary:** Hyponatremia is very common electrolyte disorder. Changes that may develop in human organism in the presence of this type of dyselectrolytemia, may be extremely dangerous for proper functioning and life of the entity. It's well known, that hyponatremia may be caused by multiple factors, such as hormonal disturbances, taking special medicines or even excessive physical activity. It may also develop due to popular health conditions, for example congestive heart failure, liver cirrhosis, malignancies, neurological disorders or human-immunodeficiency virus infection<sup>1</sup>.

The huge amount of patients that are hospitalized in Chair and Department of Endocrinology in Lublin has prompted us to right analysis, due to available medical literature - the endocrine causes of hyponatremia. In second part of this review paper we aimed to enumerate drugs, that are able to result in developing hyponatremia.

**Keywords:** hyponatremia; drug-induced hyponatremia; adrenal insufficiency; hypothyroidism; SIADH

### **Introduction**

Hyponatremia is very common, but also dangerous electrolyte disorder that may occur in progress of multiple diseases or due to used chemicals. Usually it develops in case of presence excess of water compared to ions of natrium. The most popular cause of this phenomenon is handicap excretion of excess water – due to elevated serum level of antidiuretic hormone (ADH). Primary causes of hiponatremia were presented in Table. 1. Due to the serum concentration of sodium, we can enumerate mild, moderate and heavy character of discussed issue, otherwise it may be recognized by acute or chronic abnormality.

The main symptoms suggesting the presence of hyponatremia are weakness, loss of appetite, headache, nausea with or without vomiting or altered mental status, somnolence extremely with seizures and death.

Table. 1 Main causes of hiponatremia

CAUSES OF HYPONATREMIA	
endocrinological	adrenal insufficiency
	hypothyroidism
drug-induced hyponatremia	Thiazide and thiazide-like diuretics (TIH)
	Drug-induced SIADH
lifestyle factors	excessive physical activity
	low-sodium diet
	excessive water intake
cardiac insufficiency	
liver cirrhosis with ascites	
hyperglycemia	
syndrome of inappropriate antidiuretic hormone secretion (SIADH)	Due to: - neoplasms - lung and central nervous system disorders - drugs

### State of knowledge

#### HYPONATREMIA SECONDARY TO ENDOCRINOPATHIES

As it was mentioned above, hyponatremia is dangerous and quite often occurring disturbance of water and electrolyte economy of the organism. During the diagnostic process of hyponatremia, some particular endocrinological causes should be definitely excluded. Well known are two hormonal diseases that may effect in decreased serum sodium level, e.g. adrenal insufficiency and hypothyroidism. Glicocorticosteroids and mineralocorticosteroids deficiency usually results in hyponatremia, because of abolishment their tonic influence on vasopressin release<sup>2</sup>. According to the literature, hyponatremia may develop due to primary or secondary adrenal insufficiency. Primary dysfunction of adrenal glands may occur because of autoimmune process, or less commonly in progress of adrenal tuberculosis or bleeding, whereas secondary disorder develop due to pituitary gland or hypothalamus disability. Supplementation of adrenal hormones usually results in normalization of serum sodium level, then.

Hypothyroidism may be a rare cause of hyponatremia. Following Liamis and others, we want to notice, that decrease of serum sodium level observed in this state develops due to reduced capacity

of water excretion secondary to elevated antidiuretic hormone levels. Not without significance seems to be the fact, that cardiac output is also decreased<sup>3</sup>. Also in this case implementation of causal treatment, i.e. levothyroxine-replacement therapy, is remedy for electrolyte disregulation – as primary, as secondary pathology of the thyroid.

## **DRUG-INDUCED HYPONATREMIA**

Nowadays a lot of people need to be treated because of hypertension. Besides such groups of drugs as angiotensin-converting enzyme inhibitors (ACE-I) or calcium channel antagonists, also diuretics are used in the hypotensive therapy, often thiazides (bendroflumethiazide and hydrochlorothiazide) and thiazide-like (indapamide and chlortalidone) diuretics. Due to Nadal and others, thiazide-induced hyponatremia (TIH) is the most common cause of drug-induced hyponatremia that require hospitalization in United Kingdom<sup>4</sup>, mainly because of popular usage of mentioned drugs. Some insight into the pathogenesis of TIH is possible due to observation of action of thiazides in Gordon's Syndrome, known also as pseudohypoaldosteronism type II (PHA2). It's autosomal dominant disease characterized by salt-dependent hypertension, metabolic acidosis and hyperkalemia. Chloride-dependence present in this disorder, subordinate to function of thiazide-sensitive sodium chloride co-transporter (NCC), can be corrected by usage of thiazide diuretics. Concluding, thiazides act in the distal convoluted tubule of the nephron by binding to the luminal side of NCC, that is responsible for around 5–7% of renal sodium reabsorption<sup>4</sup>. Probable is, that hyponatremia secondary to usage of thiazide diuretics may have some genetic predisposition.

## **Medication-induced SIADH**

In publication presented by Fenoglio and others in 2011, analyzing series of 54 Cases Notified to The Regional Center of Pharmacovigilance of Saint-Etienne, majority of patients with diagnosed drug-induced hyponatremia, developed this state in progress of syndrome of inappropriate antidiuretic hormone secretion (SIADH)<sup>5</sup>. Typical for this disorder are clinical euvolemic hyponatremia, normal kidney function and elevated urinary sodium excretion with inadequate urinary concentration of natrium. What's significant, other potential causes of hyponatremia have to be primarily excluded.

Most commonly SIADH is secondary to neoplasms, lung and central nervous syndrome disorders or drugs. Shepshelovich and others in 2017 have presented interesting report, summarying the presence of hyponatremia secondary to drug-induced SIADH<sup>2</sup>. They have listed five main groups of drugs that may result in hyponatremia, e.g.: antidepressants, anticonvulsants, antipsychotic agents, cytotoxic agents and pain medications. Due to their review, 82.3% of drug-induced SIADH was caused by drugs belonging to one of above groups. Demir and other has published a case report of

patient with hyponatremia in progress of SIADH due to NSAID's treatment (in this particular research meloxicam)<sup>6</sup>. It's not excluded, that hyponatremia develops due to impaired prostaglandin production. Browsing the available literature, reader may encounter reports about developing SIADH secondary to treatment with usage of another drugs, for example amiodarone<sup>7,8</sup>, tacrolimus,<sup>8</sup> moxifloxacin<sup>9</sup> or boceprevir<sup>10</sup>.

Besides all of mentioned above reviews and publication, great summary was made by Liamis and others<sup>11</sup>. They presented in very clear way possible pathomechanisms of developing hyponatremia per se and specifying drug-induced hyponatremia as consistent with extra-cellular volume depletion and the second one when secretion of antidiuretic hormone is increased (Syndrome of inappropriate antidiuretic hormone secretion [SIADH]). Medicines may interfere water homeostasis in three possible ways: increasing ADH secretion centrally, escalating its effect in renal medulla or resetting the osmostat. Due to cited partition, we can assign drugs, that are able to cause hyponatremia into three responsible groups. Psychotropic agents, such as antidepressants (predominantly selective serotonin reuptake inhibitors – SSRIs) or antipsychotic medicines antiepileptics, antineoplastic and analgesics act by increasing vasopressin secretion. Going forward, antiepileptics, hypoglycemic and anticancer drugs, as well as nonsteroidal anti-inflammatory drugs (NSAIDs) have an ability to strengthen the action of ADH in kidneys, whereas drugs inducing labor have an ability to influence function of osmostat (see Table 2). Despite substances, that may result in translocational hyponatremia (e.g. mannitol), authors enumerate another groups of chemicals, that may result in sodium serum reduction, for example: angiotensin-converting enzyme inhibitors (ACE-I) used with or without loop diuretic, trimethoprim-sulfamethoxazole, antiarrhythmic drugs (for example amiodarone), calcium channels blockers, theophylline and proton pump inhibitors (PPIs).

Great supplement of the above review constitutes publication prepared by Salem and others, where the authors extend the list of drugs resulting in hyponatremia mainly by colchicine, dopaminergic agents, methyl dopa, hydroxyurea, azithromycin, clonidine, glipizide, unfractionated heparins or even nikotine patch therapy<sup>12</sup>.

Quite astonishing case was presented by Hamasaki, who described the presence of SIADH secondary to consumption of Manda Koso (MK), some special fermented food, that is prepared from several dozen of plants, vegetables and fruits with the addition of ginger<sup>13</sup>. This case should mobilize clinicians to search any connection of even uncommon drugs or supplements with the presence of unknown- origin SIADH.

Table 2. Drugs inducing hyponatremia due to development of SIADH.

WAY OF ACTION	GROUPS OF DRUGS	DRUGS	
Increase ADH secretion	Psychotropic agents:		
	antidepressants	-selective serotonin reuptake inhibitors – SSRIs -tricyclics -monoamine oxidase inhibitors (MAO-I)	
	antipsychotics	- phenothiazines - butyrophenones	
	antiepileptics	- carbamazepine - oxcarbamazepine	
	antineoplastic	- vincristine, vinblastine - cisplatin, carboplatin -cyclophosphamide -methotrexate	
	immunomodulators	-interferon -interleukin 2 -levamisole -monoclonal antibodies	
	analgesics	- morphine and other opiats	
	strengthening the action of ADH in kidneys	antiepileptics	- carbamazepine -lamotrigine
		hypoglycemic	- chlorpropamide -tolbutamide -metformin
		antineoplastic	-cyclophosphamide
nonsteroidal anti-inflammatory drugs (NSAIDs)			
dysregulation of osmostat	drugs inducing labor	-oxytocin -ADH, ADH-analogue	

Summarizing, hyponatremia is a frequent and dangerous dyselectrolytemia. Proper diagnosis and adequate treatment is essential for patient prognosis.

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