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A CASE REPORT ON THE 'SILENT EPIDEMIC' OF CHLORTHALIDONE INDUCED HYONATREMIA; ROLE OF CLINICAL PHARMACIST

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ABSTRACT

Thiazide diuretics are of proven efficacy and substantial benefits for the treatment of uncomplicated hypertension. But the hyponatremia caused by thiazides are often overlooked. This is a case report of 70 year old female patient who was taking chlorthalidone since two months and developed acute sodium deficiency. Factors that influence risk of hyponatremia include advanced age, body weight, renal function, dietary intake and drug interactions. Therefore patients who are at increased likelihood should be identified earlier. Timely intervention by a clinical pharmacist to an extent, can deter these adverse drug events and utilise the health care facility in a cost effective manner.

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INTRODUCTION

Most crucial treatment decision for hypertension is choosing a drug class for the initial therapy. The globally advocated first line agents for systemic hypertension are thiazide and thiazide like diuretics^[1]. Chlorthiazide was the first isolated thiazide in late 1950's and even past half-century, they remain as the predominant antihypertensive drug^[2]. About 4 mm Hg to 6 mm Hg pulse pressure reduction can be achieved by thiazides which transcends the mean 3 mm Hg reduction by ACE inhibitors, ARBs and renin inhibitors^[3]. Several important side-effects of thiazides such as hypokalaemia, hyperglycaemia and hyperuricaemia are well addressed. However thiazide induced hyponatremia (TIH) often goes unnoticed despite being the most common electrolyte imbalance in the clinical practice^[4].

Hyponatremia is defined as a serum sodium concentration below 136 meq/L characterized by disorientation, lethargy, vomiting and depressed reflexes. The most common manifestations of acute hyponatremia (developed in less than 48 h) as well as conditions associated with chronic hyponatremia due to any cause are more pronounced and severe in geriatric patients probably because of the interaction of diseases and drugs with the aging associated physiological and psychological changes. Delayed recognition can culminate in severe consequences including cerebral edema and possibly irreversible neurological damage^[5,6].

THIAZIDE INDUCED HYPONATREMIA (TIH)

The Systolic Hypertension in the Elderly Program (SHEP) study reported hyponatremia (serum sodium concentration < 130 mmol/L) in 4.1% of patients taking chlorthalidone compared with 1.3% in the control group^[5]. Usually sodium deficit occurs within 2 weeks of initiating diuretics however it can happen at any time depending on risk factors such as worsening renal function, concomitant drug usage and excessive intake of sodium or water^[7].

Thiazides usually do not alter the urine concentrating capacity of kidneys but by mechanisms such as cortical sodium and chloride transport inhibition; vasopressin release; reduction of glomerular filtration and enhanced water reabsorption, they impede dilution at distal convoluted tubule and affects the water flow at collecting duct. It leads to water retention and resultant hyponatremia^[8].

The best mode of treatment is discontinuation of thiazides, fluid restriction to <1 L/day and administration of isotonic or hypertonic saline infusions to increase the serum sodium concentration at a rate of <0.5 mmol/l/h^[4]. Euvolemic and hypervolemic hyponatremia can be managed with tolvaptan, a selective vasopressin V₂-receptor antagonist and it is also useful for the management in outpatient settings.^[9].

ROLE OF CLINICAL PHARMACIST

Clinical pharmacists have the proficiency to address therapy induced illness during and after hospitalization^[10]. Pharmacist interventions focus on clarifying medication regimens; reviewing indications, directions, and potential side effects of medications; screening for barriers to adherence and early side effects; and providing patient counseling and/or physician feedback when appropriate and discuss significant findings with the medical team. The primary outcome is the reduction of preventable ADEs.

CASE REPORT

A 70 year old female patient came to emergency department with complaints of generalized weakness, reduced responsiveness and multiple episodes of vomiting. The patient was a known case of coronary artery disease (CAD) and hypertension. Vital signs were checked and BP was 180/100 mm Hg. She was administered with Injection labetalol 10mg and blood pressure was reduced to 130/70 mmHg. Laboratory investigations were carried out revealing a serum sodium value of 110 mmol/L. Remaining test reports including the blood sugar levels and hemogram were within the normal range and the patient was found to have acute episode of hyponatremia. Evaluation was done to identify the aetiology of the electrolyte imbalance. Patient medication history was taken by the clinical pharmacist and found out that she had been taking telmisartan+ Chlorthalidone since two months. Other significant causes of sodium loss including congestive cardiac failure, cirrhosis, hypothyroidism, uncontrolled diabetes and nephrotic syndrome were ruled out. Hence a final diagnosis of Chlorthalidone induced hyponatremia was made. The drug was immediately discontinued and started infusion of 200 ml, 3% sodium chloride at the rate of 30ml/hour. Repeat sodium analysis showed a value of 112mmol/L and hypertonic saline infusion was continued. Patient health status improved and she was switched to tolvaptan 15mg once daily.

Patient continued hospitalisation for three more days and she was discharged in a hemodynamically stable condition. Patient education was done by the clinical pharmacist which focused to avoid unnecessary fear on further therapy, life style modifications to be followed and the need for regular follow up.

DISCUSSION

Hospitalization and subsequent discharge home usually causes interruption in patient care and follow up resulting in multiple changes in medication regimens and leads to adverse drug events (ADEs) and avoidable health care utilisation. However it could be hampered by a clinical pharmacist in action, who can provide discharge medication counseling and screen for non-compliance even after discharge^[11]. A study reveals that approximately 12-17% of discharge patients suffer from drug side effects at home, of which more than half were ameliorable^[12].

Diuretics are currently recommended by the Seventh Report of the Joint National Commission on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure as first-line therapy for the treatment of hypertension and congestive heart failure^[13]. Hyponatremia is a significant metabolic side effect of thiazides. Some reports suggest that the best present explanation of chlorthalidone-hyponatremia is thiazide-induced over expression of aquaporin-2 in the collecting duct in susceptible individuals^[4].

A drug sub-class comparison between loop diuretic and thiazide by Moshe sonneblik et al found out that none of the patients in the former group developed sodium deficiency^[14]. A population-based cohort study by Eline.m. Rodenburg et al revealed that thiazide use is accompanied by a substantially increased risk of sodium depletion^[15]. An article discussing the common side effects of diuretics by Dominic a sica et al highlights hyponatremia as the most ignored drug reaction of thiazides^[13]. Approximately 3 in 10 patients exposed to thiazides who continue to take them develop hyponatremia^[16]. Chlorthalidone is considered as one of the most potent thiazide with apparent pleiotropic effects, however it poses a higher risk for side effects as substantiated in a case control study by van.c.et al. It compared the drug to hydrochlorothiazide and found sodium deficit was more common with chlorthalidone than with latter at equal dose per day^[17].

Clinical pharmacist has defining roles for themselves in hospital environment. The patient's medication history assessment revealed a previous episode of sodium imbalance wherein an article by Eitan friedman et al in hyponatremic patients pointed out the body changes secondary to polydypsia as the key pathogenic phenomenon in recurrence^[18].

A case series by osama.s.ashouri states that the occurrence of hyponatremic adverse effects of diuretics are predisposed by age, sex and body weight where as the subject of this report is an 70 year old underweighted female^[19]. The preponderance of TIH in geriatrics warns to choose a safer and wiser antihypertensive in this age group^[20]. Therefore, only minimal doses of diuretics should be used in elderly hypertensive women, with regular monitoring of serum sodium and potassium levels^[21].

On the contrary, Moshe sonneblik et al oppose with the age- hyponatremia relationship and focuses on other risk factors such as hypokalemia and excessive water intake^[14]. The subject has a serum potassium value of 3.1 mmol/L. A case control study by Ivaker rastogi accounted that patients with hypokalemia has 40% increased probability for hyponatremia^[22]. Sodium loss apparently results from potassium depletion, which exaggerates the volume receptor release of vasopressin that is the response to minimal diuretic-induced sodium deficit^[23]. Since the subject was a CAD patient, she was on aspirin and clopidogrel for months. Concomitant NSAIDS use is a risk factor for TIH. A most plausible justification could be the diminished prostaglandin synthesis, which arises from concurrent diseases or the inclination of the elderly for polypharmacy^[20].

A clinical pharmacist can make remarkable contribution to all aspects of healthcare by abating drug induced illness and resultant cost implications. His educational endeavors can focus on (1) increased awareness on commonly encountered side effects (2) identification of drug-drug interactions, (3) the importance of drug withdrawal, and (4) the various approaches to treatment^[24].

CONCLUSION

Even though hyponatremia is a well recognized consequence of thiazide therapy, it often goes unnoticed or neglected resulting in mortality and prolonged hospitalization particularly among the elderly. However it is absolutely avertable when proper discharge counseling is given about monitoring of serum sodium concentration and avoiding excessive fluid intake, thereby avoiding unnecessary financial burden. This is an excellent scenario to portray how a timely intervention and patient education by a clinical pharmacist can yield a better health outcome and economic benefits.

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