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Pharmacists' Roles in the Management of Hyponatremia in Patients with Heart Failure

Saepudin[1,2*], Lexin Wang[2], Patrick A. Ball[3]

[1] Department of Pharmacy, Universitas Islam Indonesia, Jl. Kaliurang KM 14.5 Sleman 55000 Yogyakarta Indonesia
[2] School of Biomedical Sciences, Charles Sturt University, Wagga Wagga 2650 NSW Australia
[3]School of Psychological and Clinical Sciences Charles Darwin University, Ellengowan Dr. Casuarina 0810 NT Australia

Review Article

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Corresponding Author:

Saepudin
School of Biomedical Sciences, Charles Sturt University, Wagga Wagga 2650 NSW Australia
Email: *saepudin@uii.ac.id*

Abstract

Hyponatremia is one of the most important problems that potentially present in managing patients with heart failure (HF). It is well known significantly to contribute to morbidity, mortality, as well as to increase medical expenditure on HF patients. This problem is still rarely recognised and treated sufficiently due to lack of a diagnostic measurement and doubts about the efficacy of available treatment options. Some new drugs having ability to antagonize the vasopressin receptor, called the vaptans group, have been approved for treatment of hyponatremia including for HF patients. Nonetheless, these drugs may be cannot be used in some clinical settings. Some conventional treatment options exist and should be the treatment of choice in many situations. The main objective of this paper is to increase awareness of pharmacists toward hyponatremia, especially in HF patients, as awareness among health care professional toward this problem is still lacking. This paper will discuss some potential roles that can be played by pharmacists in managing hyponatremia through their pharmaceutical care practice. The roles include helping physicians in recognizing hyponatremia, managing medication-induced hyponatremia, optimizing medication regimen for treatment of hyponatremia and conducting further studies for better treatment of hyponatremia. Active contribution of pharmacists through these roles will be very helpful to achieve maximum therapeutic benefits and to minimize harmful adverse events in the management of hyponatremia in patients with heart failure.

Keywords: *Heart failure, hyponatremia, pharmacist*

Introduction

As an advanced stage of cardiovascular disorder, heart failure (HF) is still the most common cause of death from cardiovascular diseases around the world (1-4). Although the trend of HF morbidity and mortality varies among countries, epidemiological data shows that the mortality rates of HF globally is still higher than mortality rate from cancer and infectious diseases (5-7). In spite of variability in morbidity and mortality between countries, it is very clear that elderly people are the most vulnerable group suffering from HF complications (8-10).

One of the most important problems that potentially present in managing patients with HF, especially among elderly patients, is hyponatremia that shares many pathophysiologic and prognostic features with HF (11-14). Patients with HF have a high probability of suffering from hyponatremia, either as a result of disease progression or adverse effect of medications (13, 15). As well as being a common and important complication, hyponatremia is also a strong independent predictor of quality of life and mortality in patients with HF (16-18).

Among electrolyte abnormalities, hyponatremia is the most often observed particularly in hospital settings. It appears that it is rarely recognised and treated sufficiently (19, 20). This may be because the symptoms are very similar to dementia/delirium, or may be due to the low awareness of clinicians, lack of diagnostic measurements, and doubt about efficacy of available treatment options (19, 21). Although type and degree of hyponatremia varies among patients, it is clearly found that hyponatremia significantly contributes to patients' morbidity and mortality, as well as to increase medical expenditure (22-24).

HYPONATREMIA AMONG HEART FAILURE PATIENTS AND ITS SIGNIFICANCE

HF patients are one of the most vulnerable groups to experience hyponatremia (11-14). When hyponatremia is defined as serum sodium concentration < 135 mEq/L the incidence was between 15-30% among hospitalised heart failure patients (11, 12, 18, 25). Moreover, the incidence of hyponatremiain a general geriatric ward can be higher than in an intensive care unit (ICU) (11, 26).

Although the incidence of hyponatremia in ambulatory and community settings is lower, its negative impact on patients' morbidity has already been established (20, 27-29).

In HF patients, hyponatremia may occur with a complex process of pathophysiology related to some disturbances contributing to HF, including hormonal and neurologic disorders (25, 30). Chronic activation of rennin-angiotensin-aldosterone system (RAAS) concurrently with stimulation of sympathetic nervous systems as a response to inadequate tissue perfusion stimulate a counter-productive effect including cardiac remodelling and water- sodium retention (17, 30). Arginine-vasopressin (AVP) is also released as a response to low cardiac output, basically to increase intravascular volume. However, the effect is even further counter-productive for cardiac workload as the preload will increase (15, 31).

The risk of hyponatremia among patients with HF often has a high concordance with the severity of the HF itself (12). When the severity of ventricular dysfunction increased, the counter-productive regulation of neurohormonal response will also increase, leading to an excessive water re-absorption, after which hyponatremia will occur (30). The lower the cardiac output, the more AVP hormone will be released, and prolonged elevation of this hormone in systemic circulation will result in an increase of water retention leading to dilutional process which will result in hyponatremia(13, 17).

As an important complication potentially encountered by patients with HF, hyponatremia still requires more attention either in investigation and treatment. Studies demonstrate that hyponatremia significantly contributes to clinical outcomes in HF patients, but the awareness toward this problem is still lacking (12, 16, 18, 32, 33). Development of hyponatremia during hospitalisation is independently related to in-hospital mortality and long-term survival after hospital discharge (24, 32, 34, 35). Furthermore, hyponatremia either in chronic conditions and acute hospitalisation is also associated with higher expenditures (36-38).

CONTRIBUTING RISK FACTORS FOR DEVELOPING OF HYPONATREMIA

While several diseases have been definitely known as aetiologies of hyponatremia, contributing risk factors for development of hyponatremia in some particular conditions have been also identified. The syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been identified over five decades ago as the main cause of hyponatremia(19, 25). Patients with particular malignancies, pulmonary diseases and nervous system disorders will potentially develop SIADH. In addition to SIADH, hypothyroidism and glucocorticoid deficiency are also known as causes of hyponatremia(23, 25)

In some particular conditions, which hyponatremia may be only encountered by small portion of patients, older age is the strong independent risk factor for developing hyponatremia(39, 40). Tseng et al (2012) found anaemia, hypouricemia and placement of any tubes as contributing risk factors of hyponatremia among elderly people (41). Stelfox et al (2010) also reported that age, diabetes, APACHE II score, mechanical ventilation, length of stay in ICU, serum glucose level and serum potassium level are associated with ICU-acquired hyponatremia(40).

In cases of medication-induced hyponatremia, several classes of drugs those are in top of list including diuretics, selective serotonin receptor inhibitors (SSRIs) and antagonist of renin-angiotensin-aldosterone system (40, 42-44).Several studies also reported contributing risk factors for developing of hyponatremia among patients taking antidepressants and diuretics. Movig et al (2002) studied antidepressant-induced hyponatremia and found that older age and concomitant diuretics used increased risk of hyponatremia(45). Jacob and Spinler (2006) studied SSRIs-induced hyponatremia and found that older age, female gender, concomitant use of diuretics, lower body weight and lower baseline sodium level are risk factors for development of hyponatremia in patients taking SSRIs (46). For diuretic-induced hyponatremia, Chow et al (2003) reported that older ages, lower body weight and lower serum potassium level contribute for developing of hyponatremia among patients taking thiazides diuretics (47).

TREATMENT OPTIONS OF HYPONATREMIA

Conventionally, hyponatremia can be managed with several treatment options. One of the most used as a standard treatment of hyponatremia is limitation of fluid intake. This is best known as the safest option (48). However, this option is not efficacious for patients with acute and symptomatic hyponatremia, as the goal of serum sodium concentration cannot be rapidly achieved. In addition, thirst induced by the treatment will potentially lower patients' adherence (48, 49).

Another option for treating hyponatremia patients, especially in hospital setting, is administration of sodium chloride solution (25, 50). Isotonic solution of sodium chloride is very good for patients with hypovolemic hyponatremia, whereas the hypertonic one has an efficacious effect for hyponatremia patients in hypervolemic or euvolemic condition (48, 50, 51). The most important aspect in administering the solution is the rate of administration, particularly for patients with acute hyponatremia. Overly rapid administration of hypertonic solution of sodium chloride can induce neuron obstruction leading to severe neurologic disorder (48, 49).

Several drugs have also been known to have a useful effect in treatment of hyponatremia. Loop diuretics can be used as an option for treatment of hyponatremia in hypervolemic patients, either as a single or in combination with sodium chloride solution or tablet (25, 52). The dose of diuretic must be adjusted accordingly based on serum sodium concentration, so that the serum sodium concentration must be monitored adequately. Demeclocycline is another drug that has been used for treating hyponatremic patients, particularly for

patients with fluid restriction resistant, but the use of this drug is very limited as it can induce a severe renal dysfunction (25, 51). Urea has also been widely used in treatment of hyponatremia orally, as an alternative to sodium chloride tablets, and showing a good efficacy and safety profile (53, 54). The biggest disadvantage of urea is an uncomfortable taste leading the patients to reject the treatment (15, 25).

The newest drugs have been approved to be used in treatment of hyponatremia are derivates of arginine vasopressin receptor antagonist, more famous as the "vaptans" group (21, 48, 55). The drugs act by inhibiting the receptors of AVP so then causing an aquaresis effect, an increase in water excretion with an insignificant effect on solute excretion. The drugs had a good efficacy for treatment of hyponatremia patients either in hypervolemic or euvolemic status, and show a tolerable adverse effect in short-term use (12, 13). Fluid intake limitation is not needed in patients receiving vaptans therapy, making the patients more comfortable with the treatment (23, 55, 56).

Results from clinical trials show that the vaptans have a good efficacy and safety profile in treatment of hyponatremia patients (25, 57). However, there are several factors that must be considered in using the drugs in practice. One of the most important factors is the long-term safety profile if the drugs are to be used widely for treatment of chronic hyponatremia. One of the vaptans has been studied for its long-term safety profile, and showed an insignificant benefit compared with conventional treatment (58). In addition, the cost of the treatment is also must be considered as the drugs are highly expensive (21, 58).

While the studies of vaptans for treatment of hyponatremia are developing, several studies on the use of conventional treatment options for hyponatremia have also shown that the conventional treatment options are still feasible, and should be the treatment of choice in some situations (58). Administration of hypertonic solution of sodium chloride with an adequate volume and rate of administration has shown a good efficacy and safety (50, 58). The use of urea tablets also showed a good efficacy for treatment of chronic cases with an insignificant difference in efficacy and safety profile compared with vaptans (54).

PHARMACISTS' ROLE IN MANAGING HYPONATREMIA

To achieve maximum benefits and to minimize harmful events from medication use are the main goal of pharmaceutical care provision. It requires that pharmacists should contribute onto therapeutic management with main focus on drug related problems. Positive impact of pharmacist contribution toward patients' therapeutic outcome has been also proved by a lot of evidence (59). Nevertheless, there are still a lot of challenges need to be conquered in regard with new and complicated disorders/diseases.

As awareness toward hyponatremia among clinicians is still lacking, the problem seems similar to pharmacists. It means that to improve pharmacists' awareness onto hyponatremia in several patients' condition is urgently needed. Hyponatremia in HF patients is one of the challenging problems because the prevalence of HF tends to increase and HF patients are one of the most vulnerable groups to suffer from hyponatremia. While studies and attempts to establish evidence-based therapeutic management for hyponatremiain HF patients are still on its way, pharmacists have opportunities to play several important roles upon this problem. Below are some challenges that need to be taken into account by pharmacists either in hospitals or communities in regard with attempts to increase pharmacists' contribution onto the management of hyponatremia in HF patients.

To help clinicians in identifying and recognizing hyponatremia in HF patients

Identification of hyponatremia with its specific condition is so important that pharmacists need to know the signs and symptoms either of severe acute or chronic hyponatremia. Furthermore, understanding on the assessment of patients' volume status, both by clinical and laboratory assessment, is also needed.Based upon the apparent signs and symptoms conjoined with the volume status hyponatremic patients can be classified accurately as having chronic or acute hyponatremia with hypovolemic, euvolemic, or hypervolemic status(12, 18, 42). Timely and accurate diagnosis of hyponatremia will help to assist pharmacists in deciding the appropriate treatment recommendation and further will increase the chance to achieve targeted therapeutic goals.

While symptoms of severe acute hyponatremia could be recognized more easily through apparent severe neurologic symptoms, more attention should be paid deliberately to recognize symptom in patients with chronic hyponatremia as these patients mostly are asymptomatic. In addition to confusion and dizziness, patients with other persistent neuro-cognitive and motor deficit should be suspected as hyponatremic. Gait instability, falls and fracture have been found to be associated with chronic hyponatremia (60, 61) as well as osteoporosis (62). Therefore, serum sodium should be monitored more closely in such particular patients to identify wether hyponatremia is presence or not.

To identify medications which potentially or actually contribute to the development of hyponatremia.

If hyponatremia occurs as medication-induced disorder, discontinuation of suspected medication is the best approach in managing the problem. This approach will also help in reducing unnecessary treatment. Hence, as part of pharmaceutical care, identification of medication-induced hyponatremia is one of the main focuses of pharmacists' role.

Several medications have been known can contribute to the development of hyponatremia through several mechanisms. Interestingly, some main medications for treating HF can also contribute to the development of hyponatremia. Therefore, pharmacists should put serum sodium as one of

important parameter that needs to be monitored among HF patients as well as the clinical signs and symptoms. More attention should be paid onto the patients using more complex medications particularly medication which can increase the risk of developing hyponatremia. Table 1 shows some medications that potentially contribute to the development of hyponatremia.

Table 1 Medications potentially induce hyponatremia (25, 44)

Mechanisms of drug-induced hyponatremia	Examples of medication
To induce inappropriate release of antidiuretic hormone	Selective serotonin re-uptake inhibitors, tricyclic antidepressants, theophylline, amiodarone, carbamazepine, chlorpromazine
To impair water excretion	Nonsteroidal anti-inflammatory drugs, Thiazide diuretics
To increase extracellular volume	Hypotonic parenteral nutrition, dextrose 5%

To optimize medications regimen

Although the options for treatment of hyponatremia are very limited, pharmacists still need to pay careful attention before recommending the treatment of choice. It is very important for pharmacists to know the available treatment options for treating hyponatremia in their local practice as well as to know the appropriate dosage, administration and duration. Even if the option is fluid intake limitation, pharmacists should know the way to recommend fluid restriction rationally.

Until now, specific guideline on the therapeutic management of hyponatremia in HF patients is not available. Limited evidences is one of the most probably reasons behind this. Therefore, empirical treatment is the most common used for managing hyponatremia in HF patients. In the last published guideline on the management of HF, American College of Cardiology Foundation/American Heart Association (ACCF/AHA) has put recommendation on use of vasopressin receptor antagonists for treatment of hypervolemic hyponatremia in patients with active cognitive symptoms (63). Nonetheless, in addition to the price, the drugs have not been widely available yet. Therefore, saline solution and other conventional options are still need to be considered as treatment of choice as it is the most probably available option.

For acute severe hyponatremia, saline solution is the best option in case of vaptans unavailability. Accordingly, it can be prescribed as isotonic or hypertonic solutions. While choosing appropriate tonicity of saline solution based upon patients' condition, recommendation on appropriate rate of serum sodium correction is also very important. Some formulas can be used to estimate the rate of serum sodium correction so that pharmacists need to be familiar with these formulas. Table 2 shows the most common formulas for estimating the rate of serum sodium correction.

Table 2 Common formulas for estimating infusion rate of saline solution

Formula	Pros and Cons
Adrogue-Madias Formula(64)	Easy to calculate, underestimate the change in serum sodium
Barsoum-Levine Equation(65)	More precise in estimation, more complex formula which considering urinary losses

Infusion rate is one of the crucial factors in administering saline solution. Serious neurologic injury can be resulted from inappropriate infusion rate, either overly rapid infusion rate in patients with chronic hyponatremia or too slowly infusion rate in patients with severe acute hyponatremia. Furthermore, it is important to bear in mind that the formulas in Table II do not replace the need for adequate monitoring and clinical assessment. Instead of using these formulas alone, careful monitoring of electrolyte and assessment of clinical signs and symptoms are still needed to adjust the infusion rate and further to avoid harmful adverse effect.

If vaptans will be recommended as the treatment of choice, common related problems to new released drugs need to be kept in mind. General principles of pharmacovigilance should be applied into practice to ascertain that maximum benefit is achieved and adverse effects could be minimized. Pharmacists should know the pharmacologic properties of available vaptans so that it can be took into account in making recommendation. Table 3 shows some vaptans with their brief characteristics.

Table 3 Antagonists of vasopressin receptors for treatment of hyponatremia in HF patients (25, 48, 53, 55, 66)

Name	Characteristics			
	Route of administration	Dosage	Antagonism to VR	FDA approval
Lixivaptan	Oral	50-100 mg twice daily	VR2 selective	Not yet FDA approved
Tolvaptan	Oral	15-60 mg once daily	VR2 selective	FDA approved for treatment of hypervolemic and euvolemic hyponatremia (2008)
Conivaptan	Intravenous	20-40 mg/day as continuous infusion	VR1a and VR2 non-selective	FDA approved for euvolemic hyponatremia (2005) and hypervolemic hyponatremia (2007)

VR=vasopressin receptor

Despite the reports stating that adverse effects of vaptans are mostly mild and tolerable, including thirst, dry mouth, weakness and constipation, overcorrection can also be resulted that further can lead to serious problems. In addition, drug interaction is one of the most important problems related with vaptans use because all available vaptans are both substrates and inhibitors of cytochrome P450 3A4 (CYP3A4). Therefore, concomitant use of vaptans with strong inhibitors and moderate inhibitors of CYP3A4 is contraindicated and should be avoided, respectively. Vaptans has been also known as substrates and inhibitors of p-glycoprotein and it will be a problem for HF patients taking digoxin as part of their medication therapy (66). Potential drug interactions should be identified if patients are taking other drugs, especially for drugs as substrates and inhibitors of CYP3A4.

Other pharmacologic agents such as demeclocycline, lithium, urea, and salt tablet can be considered as alternatives (25). Safety issue is the main problem in the use of demeclocycline and lithium as the drugs have significant side effects and toxicities. For treatment of chronic hyponatremia, salt tablet or urea will be more reasonable and can be prescribed concomitantly with fluid restriction therapy, in which salt tablet and urea will help patients to get less strict regimen of fluid restriction. However, adherence needs to be considered, as patients will be likely uncomfortable with the taste.
Whatever medication regimen being prescribed, monitoring of patients' response should be a part of pharmacists' responsibility. Patients with acute severe condition receiving an aggressive treatment need to be monitored more closely either to avoid over- or under-correction of serum sodium level. Laboratory parameters should be monitored regularly as well as clinical signs and symptoms and accordingly medication regimens can be adjusted. Although patients with chronic hyponatremia will be more unlikely to have serious problems with their hyponatremia-medication therapy, monitoring is needed to ensure that serum sodium is already corrected and significant adverse effects are absence, particularly for patients taking long-term therapy for hyponatremia.

To conduct further studies on hyponatremia in HF patients

While the significance of hyponatremia in HF patients has been already known, many questions related to hyponatremia in HF patients still need the answers. To optimize prevention strategies research on contributing risk factors for developing hyponatremia in HF patients is still needed. Appropriate use and monitoring of saline solution, management of chronic hyponatremia, long-term use of vaptans, still need to be studied in order to improve patients' outcome.
According to health care settings, more research in community setting need to be considered. As the survival rate of HF patients has improved, there will be more HF patients in the community. Therefore, more studies on management of chronic hyponatremia for HF patients in community settings are important to be conducted in order to improve patients' quality of life. All those studies will be very helpful to establish guideline on management of hyponatremia in HF patients.

Conclusion

Along with pharmaceutical care implementation, pharmacists can make a contribution in the management of hyponatremia in patients with heart failure. Active collaboration with physicians is needed to promptly recognize hyponatremia among heart failure patients including medication-induced hyponatremia. While pharmacists still need to be more familiar with conventional treatment options of hyponatremia, the presence of vaptans as new agents for treatment of hyponatremia in HF patients provide a new strategy and some potential problems which need to be taken into consideration in pharmaceutical care of HF patients.

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Endocrinology Department, Kovai Medical Center and Hospital, Coimbatore, India.

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AUTHORS' CONTRIBUTIONS

Authors contributed equally to all aspects of the study.

PEER REVIEW

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CONFLICTS OF INTEREST

The authors declare that they have no competing interests.