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Mini-Narrative Review

Standardized Oral Urea for the Treatment of Hyponatraemic Conditions: Pharmacological and Pharmacoeconomic Consideration

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A Narrative Mini Review

Hyponatremia (HN) is the most common disorder of electrolytes encountered in clinical setting [1]. HN is a frequent finding in hospitalized subjects with a reported frequency of 10-30% of the cases with 2% of these with plasma levels lower than 125 mEq/L [2]. In acute and severe ill subjects (i.e., neurosurgical units, subjects with subarachnoid haemorrhage ect.) the prevalence of hyponatraemia could be observed in up to 50% of patients [3]. HN is associated with high morbidity and mortality [4]. HN is defined as a plasma concentration less than 135 mEq/L [5]. Plasma sodium levels of 130-135 characterize mild form of hyponatraemia where sodium concentration lower that 120-125 mEq/L are characteristic of severe HN states. There are two main mechanisms responsible of reduced sodium plasma concentration: a marked increase in water intake (polydipsia) or an impaired water excretion [6]. For the latter condition, the most common mechanism is related to a persistent and inappropriate release of Antidiuretic Hormone (ADH) [7]. Severe and acute HN is a medical emergency with a high mortality rate requiring prompt and effective treatment strategies [8]. In acute HN the most common symptoms are headache, nausea vomiting and muscle cramps, but also, lethargy, disorientation and reduced reflexes. Rapidly evolving HN can be associated with seizures, coma and permanent brain damage. Mild "chronic" asymptomatic HN is associated with impaired cognition, and increased risk of falls and fractures [9]. The duration, the severity of the hyponatraemia and the presence and severity of symptoms are aspects influencing the type of treatment strategies [10]. These considerations underline the need of effective diagnostic procedures to choose the correct treatment approach. In addition, an effective therapeutic intervention is important also in subjects with mild HN. As stated before, the main pathogenetic mechanisms of HN are an increase water intake or, more commonly, an impaired real water excretion caused by advanced kidney failure or persistent and inappropriate release of Antidiuretic Hormone (ADH) [11]. Arginine vasopressin, also known as antidiuretic hormone, is a hormone responsible for promoting water absorption in the collecting duct of the nephron [12]. The Syndrome of ADH Inappropriate Secretion (SIADH) is one of the most common causes of HN [13]. An excess of ADH secretion induces an excess of total body water content as a consequence of a decrease in electrolytes free water excretion. When evaluating a subject with HN, for an appropriate diagnostic approach is to consider the plasma osmolarity and the circulating volume [14]. Therefore, hyponatraemic states could be classified in hypo-, normo- and hypertonic and hypo-, eu- or hyper-volemic [15]. Therefore, the calculation of plasma osmolarity and the evaluation of plasma volume are relevant in the diagnostic algorithm of HN conditions [16]. Another important clinical aspect of HN evaluation is the speed of the alteration in the plasma sodium levels [17]. The therapeutic approaches of HN depend on the severity and on the character of HN (acute vs. chronic) [18]. In fact, the determination of HN and the determination of the severity of HN are crucial for the choice of the therapeutic strategy to adopt. In acute conditions, consensus guidelines recommend an initial rise in serum sodium of 4–6 mmol/L over 4 hours, using intravenous boluses of hypertonic (3%) sodium chloride [19]. In chronic HN conditions the goal of initial therapy is to raise the serum sodium concentration by 4-6 mEq/L in 24 hours [20]. This increase appears to be sufficient to correct the most severe manifestation of HN. The usual thera-

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peutic options in chronic HN conditions are fluid restriction (i.e 800-1200 mL/d), use of furosemide, oral salt supplementation and demeclocycline [21]. More recently, a drug treatment approach of HN is the use oral non-peptide vasopressin V2-receptors antagonists (Vaptans). Four vaptans (satavaptan, tolvaptan, conivaptan and lixivaptan) have been evaluated and available [22]. Some limitations should be taken in consideration regarding the role of the drug class [23]. First, the clinical efficacy is maintained as long as the product is taken [24]. When vaptans treatment is stopped hyponatraemia recurred in most subjects. The second limitation is the cost of therapy [25]. The public price for a daily treatment with a vaptan is around 40€. Oral urea is an interesting alternative to vaptans treatment [26,27]. Urea is an osmotically active molecule with a MW of 60.Also known as carbamide, urea is an organic compound with chemical formula CO (NH2)2 (Figure 1) [28]. Urea acts as an active osmotic and diuretic molecule [29]. The intake of urea (30-60 g/daily) can increase the renal excretion of water and at the same time to reduce the renal excretion of sodium [30]. After 12 hours from the initiation of the urea supplementation a gradual increase of plasma sodium levels is observed with in general an increase of 5 mEq/L, never reaching however increments higher that 12 mEq/L [31]. In fact, one of the most important therapeutic goals of HN treatment is to avoid overcorrection [32]. Rapid correction of severe chronic HN can lead to severe and irreversible neurological diseases such as osmotic demyelination syndrome [33]. Data suggest that an increase in sodium plasma levels of no more than 10 mEq/L/24 hours could be considered safe. This gradual increase underlines the very good safety profile of oral urea supplementation. The use of oral urea has been demonstrated to be an efficacious strategy in the treatment of HN associated to SIADH, in critically ill subjects, non-traumatic subarachnoid haemorrhage and psychogenic polydipsia [34]. Some authors consider oral urea as the gold standard treatment of chronic HN [35]. Urea is rapidly absorbed after oral ingestion in the gastrointestinal tract. The osmotic diuresis effect is gradual and not too rapid, therefore allowing the physician to control and modulate the plasma sodium concentration increasing effect [36]. Urea can penetrate the capillary membrane in the central nervous system in a slow manner. This is helpful in treating the cerebral oedema which is commonly associated with several HN conditions. The use of urea as a therapeutic strategy for HN condition is associated with a very low or nil risk of osmotic demyelination syndrome [37]. We performed a PubMed search (from database inception to November 2022) using the terms “hyponatriemia” and “oral urea”. There are at least seven trials [38,-44] (Table 1) evaluating the efficacy of oral urea supplementation in HN patients; of these three were prospective trials and four retrospectives. In total 167 subjects were evaluated. Oral urea daily supplementation ranged between 7 g to 90 g (average 15-30 g daily).All these trials reported a clinically significant increase in serum sodium levels: baseline plasma sodium concentrations were on average 123-127 mEq/L and increased to 133-136 mEq/L after treatment. These data support the concept that oral urea supplementation is associated with increases in sodium plasma levels among hospitalized subjects. A direct comparison trial evaluating efficacy and tolerability of oral urea (30-60 g/day) in subjects with chronic SIADH has shown that this treatment has a similar efficacy (increase of sodium levels of 10 mEq/L with urea and 10 mEq/L with vaptans) with a good tolerance profile [41]. One limitation of the use of urea with the oral use is the bitter taste of this molecule. However standardized new formulations of urea for oral administration (as food for special medical purposes) are now available (sachet of 15 g) overcoming this limitation. From a pharmaco economic point of view the use of oral-urea supplementation as chronic treatment of HN, could be considered very convenient with a daily cost of 3-6 € representing a 90% lower cost of treatment in comparison with vaptans (public price). In consideration of its efficacy, safety profile and direct treatment cost oral urea could be considered as a potential standard treatment of hyponatraemia especially for the chronic forms.

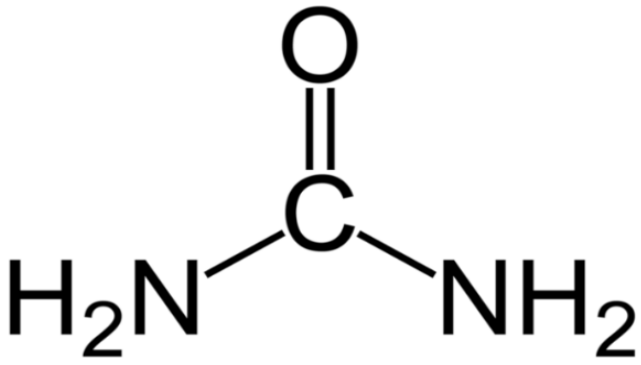

Figure 1: Urea Molecule.

Table 1: Human *in vivo* studies on the oral use of urea as treatment of hyponatriemia. PubMed was searched (from database inception to November 2022) using the terms “hyponatriemia” and “oral urea”. Case reports were excluded from the collection.

Study type	Patients	Clinical comparison	Experimental design	Outcomes	Conclusion	Reference
1)Intervention study	Patients (n=7) with polydipsiahyponatremia syndrome (PHS)	NA	Patients were treated during 4 to 18 months with urea (0.3-0.9 g/kg/day)	Natremia Urea therapy increased morning SNa: - SNa baseline: 127.5±3.4 mmol/L - SNa urea second month of treatment: 136.5±2.4 mmol/L (p <0.01)	Urea appears to be an effective therapeutic approach for the PHS	[38]
2)Retrospective study	Children (n=4) with SIADH	NA	Children were started on a 30% to 50% oral urea solution; the dose was titrated until normal SNa was achieved	All patients normalized their SNa	No side or toxic effects were observed	[39]

3)Intervention study	Schizophrenic patients (n=7)	NA	Patients were treated with 30 g/d of urea for 2 months. After, the dosage was increase to 45 g/d for additional 3 months. Finally, the dose was increase to 67.5 g/d, for additional 2 months	Natriemia SNa baseline: 127.6±3.0 SNa 30 g/die: 128.9±3.5 SNa 45 g/die: 131.7±3.9*† SNa 67.5 g/d: 133.5±3.0‡§ *p<0.01 vs baseline; †p<0.05 vs 30g; ‡p<0.001 vs baseline; §p<0.001 vs 30 g	The oral urea treatment reduces the risk of severe hyponatremia	[40]
4)Prospective, long-term study	Patients (n=13) with the SIADH	Vaptans (satavaptan, 5–50 mg/d, or tolvaptan, 30–60 mg/day)	Patients were treated with vaptans for 1 year. After an 8-day holiday period, they received oral urea (15–30 g/d) for an additional 1-year follow-up	Natremia SNa baseline: 125±63 mEq/L SNa vaptans: 135±63 mEq/L SNa urea: 135±62 mEq/L	Urea and vaptans have similar tolerability and efficacy	[41]
5)Retrospective study	Patients (n=42) with subarachnoid haemorrhage that developed acute SIADH	NA	Patients received orally doses of 15-30 g three or four times a day for a median of 5 (IQR, 3-7) days	The median plasma sodium increase, over the first day of treatment, was 3 (IQR, 1-6) mEq/L. Hyponatremia was corrected in all patients, with median times to Na+ >130 and >135 mEq/L of 1 (IQR, 1-2) and 3 (IQR, 2-4) days, respectively	Urea was well tolerated, and no adverse effects were reported	[42]
6)Retrospective study	Patients (n=58) with hyponatremia who received urea, including a subgroup of patients who received urea as the sole drug therapy (n=12)	NA	Patients received urea (7.5–90 g/d) over a median of 4.5 (interquartile range, 3–8) days	Patients showed an increase in SNa from 124 mEq/L (interquartile range, 122–126) to 131 mEq/L (interquartile range, 127–134; P<0.001). Among 12 urea only–treated patients, plasma sodium increased from 125 mEq/L (interquartile range, 122–127) to 131 mEq/L (interquartile range, 129–136; P=0.001) by the end of urea therapy. A larger increase in SNa at 24 hours in urea only–treated patients compared with urea-untreated patients was observed (2.5 mEq/L; interquartile range, 0–4.5 versus 20.5 mEq/L; interquartile range, 22.5 to 1.5; P=0.04).	Urea seems to be effective, safe and well tolerated, for the treatment of hyponatremia	[43]
7)Retrospective study	Cancer patients (n=36) affected by SIADH-induced chronic hyponatremia	NA	Oral urea treatment (initial daily dose 15 g or 30 g)	SNa baselina: 123± 4 mmol/L SNa 24 hours: mean increase of 5±3 mmol/L Eunatremia was reached by 55.6%, 86.1% and 91.7% patients within 14, 30 and 60 days of treatment, respectively	Urea was useful in correcting chronic hyponatremia among cancer patients affected by SIADH	[44]

SIADH: syndrome of Inappropriate Antidiuretic Hormone Secretion; NA: Not Available; SNa: Serum Sodium Concentration; PHS: Polydipsiahyponatremia Syndrome; SIADH: Syndrome of Inappropriate Antidiuretic Hormone Secretion; NA: Not Available; SNa: Serum Sodium Concentration

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