Kidney Medicine

Use of Desmopressin in Hyponatremia: Foe and Friend

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Use of desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP), a synthetic vasopressin receptor agonist, has expanded in recent years. Desmopressin leads to renal water retention, and iatrogenic hyponatremia may result if fluid intake is not appropriately restricted. It is common practice to stop a medication that is causing toxicity, and this advice is promulgated in Micromedex, which suggests withholding desmopressin if hyponatremia occurs. If intravenous saline solution is administered and desmopressin is withheld at the same time, rapid changes in serum sodium levels may result, which puts the patient at risk for demyelinating lesions. In the management of desmopressin-associated hyponatremia with neurologic symptoms, the drug should not be withheld despite the presence of hyponatremia. The medication should be continued while administering intravenous hypertonic saline solution. Desmopressin is also used to minimize water excretion during the correction of hyponatremia during water diuresis. When treating hyponatremia, clinicians should monitor closely to avoid free-water diuresis. To prevent ongoing water losses in urine and overly rapid "autocorrection" of serum sodium level, desmopressin can be given to reduce free-water losses. These treatment recommendations are the authors' perspective from previously published work and personal clinical experience.

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INTRODUCTION

Use of desmopressin (1-deamino-8-D-arginine vasopressin; DDAVP, Ferring Pharmaceuticals), a synthetic vasopressin receptor agonist, has expanded beyond the treatment of diabetes insipidus in recent years. Desmopressin leads to renal water retention, and iatrogenic hyponatremia may result, which is not an infrequent clinical occurrence.[1-3] The increase in desmopressin use for causes unrelated to central diabetes insipidus, ease of administration of intranasal preparations, and recent approval (March 2007)[4] of desmopressin for the treatment of enuresis in the elderly have all been factors favoring the increasing use of this medication in the outpatient setting.[5]

Desmopressin use in nursing home settings for enuresis can be particularly problematic because many patients are actively encouraged to drink liquids to avoid dehydration. Additionally, desmopressin is increasingly being used in the hospital setting specifically for limiting free-water excretion when managing complex hyponatremia cases in which overcorrection of serum sodium level is a concern. Therefore, desmopressin can either be a foe or a friend in the management of hyponatremia, on one hand leading to iatrogenic hyponatremia while on the other hand being used to limit free-water excretion and potential overcorrection of serum sodium level.

DESMOPRESSIN-ASSOCIATED HYPONATREMIA: DESMOPRESSIN AS A FOE

An illustrative case involves a 77-year-old woman who is a nursing home resident. She has severe cognitive impairment and has been taking desmopressin for the treatment of enuresis. She is receiving oral desmopressin each night before sleep. The nursing staff at this center encourages all patients to drink plenty of fluids, especially during the warmer summer months. She presents to the emergency department at 10:00 AM with increased confusion and having had a tonic-clonic seizure. Urine osmolality is 550 mOsm/kg and urine sodium excretion is 85 mmol/L. Serum sodium level is 109 mmol/L.

Desmopressin therapy is discontinued and the patient is treated with 3% saline solution in the emergency department at a rate of 15 mL/h. Six hours after admission to the intensive care unit, serum sodium level is 122 mmol/L and urine output has increased substantially. Urine osmolality is now 80 mOsm/kg; 3% saline solution treatment is discontinued and the patient is placed on 125 mL/h of 5% dextrose and water intravenously. Six hours later, the patient's serum sodium level is 133 mmol/L and her high urine output continues. Although the infusion rate of dextrose and water is increased to 200 mL/h, serum sodium level stabilizes at 141 mmol/L. Three to 4 days later, the patient starts to develop spasticity and becomes poorly responsive; brain magnetic resonance imaging findings are consistent with cerebral demyelination.

Desmopressin-associated hyponatremia occurs when failure to appropriately restrict water intake while taking desmopressin leads to hyponatremia.[1] Because desmopressin will cause the kidneys to concentrate urine, fluid intake must be carefully monitored. Urine osmolality during therapy with desmopressin has been shown to increase to the 600-mOsm/kg range in the critically ill[1] and up to 879 mOsm/kg in healthy volunteers,[6] leading to abrupt decreases in urine output that are sustained for up to 8 to 12 hours.[7] For this reason, improper fluid restriction during desmopressin administration can lead to hyponatremia. It is important that patients taking desmopressin be counseled about the proper degree of fluid intake and that hospitalized patients do not receive

hypotonic intravenous fluids, unless during the correction of hypernatremia. Women are more sensitive to the effects of desmopressin and experience worse outcomes from hyponatremia. Therefore, doses may need moderation in this group.[8-10]

Hyponatremic encephalopathy, symptomatic cerebral edema secondary to hyponatremia, can have a fulminant presentation, but early signs are nonspecific, such as nausea, vomiting, and headaches, and can go unrecognized.[8,9,11] Early manifestations are signs of cerebral edema; as the edema worsens, seizures may occur.[7] If uncorrected, the ultimate manifestations (respiratory failure and death) are due to brainstem herniation.[8]

It is common practice to stop treatment with a medication that is causing toxicity, and this advice is promulgated in Micromedex (Thomson Reuters [Healthcare] Inc), which suggests withholding desmopressin if hyponatremia occurs; however, no suggestions regarding fluid therapy are offered.[12] In the case of desmopressin-associated hyponatremia, withholding the drug may have untoward consequences. Therefore, treatment of symptomatic desmopressin-associated hyponatremia with neurologic symptoms can be a clinical challenge. Increasing serum sodium level with hypertonic saline solution acutely is indicated; however, if use of the medication is simply discontinued, a spontaneous free-water diuresis will occur due to the decrease in urine osmolality, and rapid autocorrection of serum sodium level is possible. If desmopressin is withheld while administering intravenous saline solution, there also is potential for rapid changes in serum sodium level.[1,2] These factors combined can contribute to overly rapid correction of serum sodium level, putting the patient at risk for neurologic injury due to osmotic demyelination syndrome. A patient with desmopressin-associated hyponatremia will initially be in an antidiuretic state and, if acutely symptomatic, will need early intervention with hypertonic saline solution to increase serum sodium concentration and avoid cerebral edema.

Our group recently reported 13 cases of neurologic injury and/or death due to inappropriate correction of serum sodium level when stopping desmopressin treatment during the management of symptomatic desmopressin-associated hyponatremia.[1] This report highlights the potential dangers of desmopressin-induced hyponatremia and severe neurologic outcomes that can ensue.[2] Discontinuing desmopressin treatment in the management of desmopressin-associated hyponatremia can lead to autocorrection of serum sodium level and significant overcorrection can occur, especially if intravenous saline solution (especially a hypertonic solution) is given at the same time (as was seen in our case series in which serum sodium level corrected on average by 37 mEq/L over 48 hours).[1] If desmopressin treatment is stopped, free-water excretion can then occur unabated. Of additional concern, if desmopressin is withheld in patients with central diabetes insipidus, overcorrection past normonatremia is possible and is an additional risk factor for cerebral demyelination.[13]

In managing desmopressin-associated hyponatremia with neurologic symptoms, despite the presence of hyponatremia, use of the medication should be continued.[1,2,7] Symptomatic patients should be given hypertonic saline solution while continuing to receive desmopressin. The approach to treatment of desmopressin-associated hyponatremia with hypertonic saline solution is summarized in Figure 1. The most critical point to emphasize is that in cases of desmopressin-associated hyponatremia, the medication should be continued despite symptomatic hyponatremia, and hypertonic saline solution should be given to treat the hyponatremia.

DESMOPRESSIN AS A THERAPEUTIC TOOL IN MANAGING SEVERE HYPONATREMIA: DESMOPRESSIN AS A FRIEND

This next case demonstrates severe symptomatic hyponatremia due to thiazide use[7] in which 3% saline solution was used initially and desmopressin was added to treat a water diuresis and prevent overcorrection (Fig 2).

A 63-year-old woman with a history of alcohol abuse presents to the emergency department with 4 days of confusion followed by a tonic-clonic seizure, after which she is transported to the hospital by ambulance. She is found to be obtunded and her initial serum sodium level is 102 mEq/L. Following the initial correction of serum sodium level, the patient starts to undergo a water diuresis. Her sodium level initially corrects 13 mEq in the first 12 hours and she has no further seizures. With ongoing water losses, she would quickly exceed the safe limit of sodium level correction for the first 48 hours. Because the long-term consumption of alcohol raises the risk for cirrhosis, it is important that serum sodium level correction not be excessive in such cases. The decision is made to therapeutically slow the correction of serum sodium level with desmopressin. She is kept strictly without enteral fluid intake and is treated with a combination of subcutaneously administered desmopressin and intravenous 0.9% saline

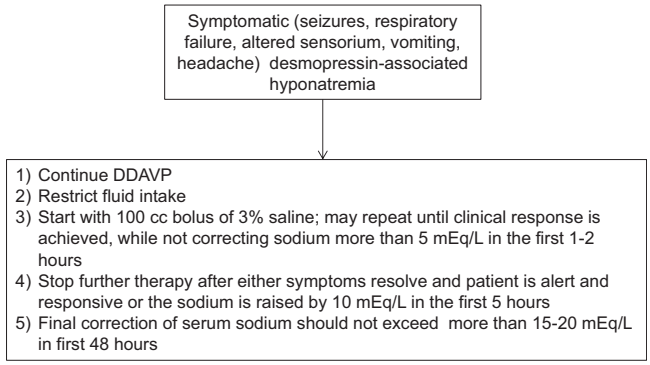

Figure 1. Treatment of desmopressin (DDAVP)-associated hyponatremic encephalopathy.

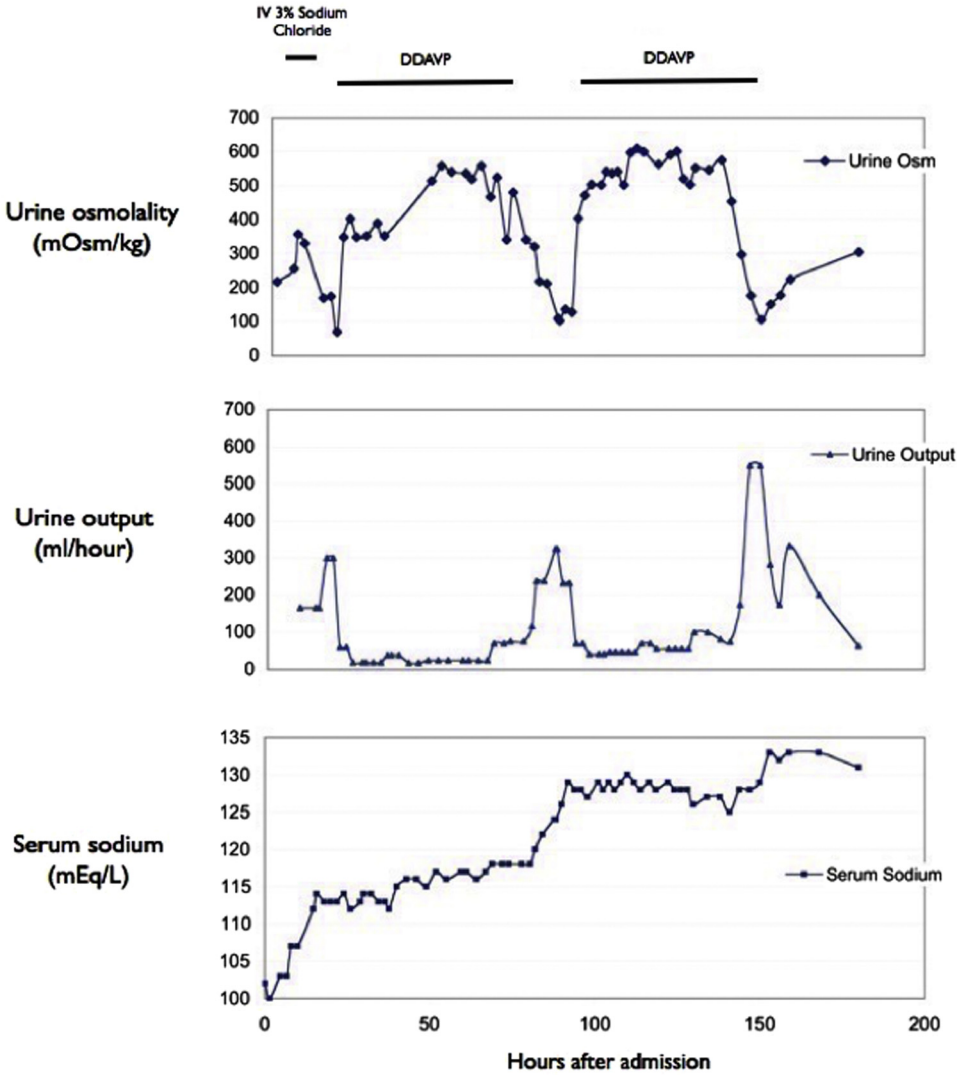

Figure 2. Treatment of severe symptomatic hyponatremia with intravenous (IV) 3% saline solution and subcutaneous desmopressin (DDAVP). Abbreviation: Osm, osmolality. Achinger and Ayus[7]; reproduced with permission from Wolters Kluwer Health, Inc.

solution. When a patient is treated with hypertonic saline solution, ongoing water losses need to be continually assessed to be vigilant for water diuresis, as occurred in the case presented.

We have previously introduced the concept that desmopressin could be used to minimize water excretion during correction of hyponatremia in cases that involve the risk for large-volume water diuresis; for example, compulsive water drinking, cortisol deficiency, thyroid deficiency, and medication-induced hyponatremia (eg, thiazide diuretics).[14] This concept has been validated in several subsequent articles and case reports, showing the clinical utility of this therapeutic maneuver.[1,15-27] This situation is termed a reversed urine osmolality.

Conceptually, reversed urine osmolality is a convenient nomenclature for categorizing conditions in which urine osmolality changes from high to low in the course of treatment of hyponatremia. Reversed urine osmolality is defined in contrast to fixed urine osmolality, which does not decrease significantly during the treatment of hyponatremia (Fig 3). Examples of hyponatremia causes for which reversed osmolality tend to be problematic are volume depletion, adrenal insufficiency, medication associated (especially desmopressin), and hypothyroidism.

When treating hyponatremia, clinicians need to monitor closely to avoid free-water diuresis. Desmopressin can be given to increase the urine concentration and reduce free-water loss, thereby limiting autocorrection of serum sodium level. It is vital that this be done carefully, and the patient must have strict fluid restrictions or have no enteral intake. Severe hyponatremia can develop if there is unrestricted fluid intake while desmopressin is being administered. The first sign that water diuresis is occurring is increased urine output; thus, hourly urine output should be monitored in all patients with hyponatremic encephalopathy, especially those with drug-induced hyponatremia.

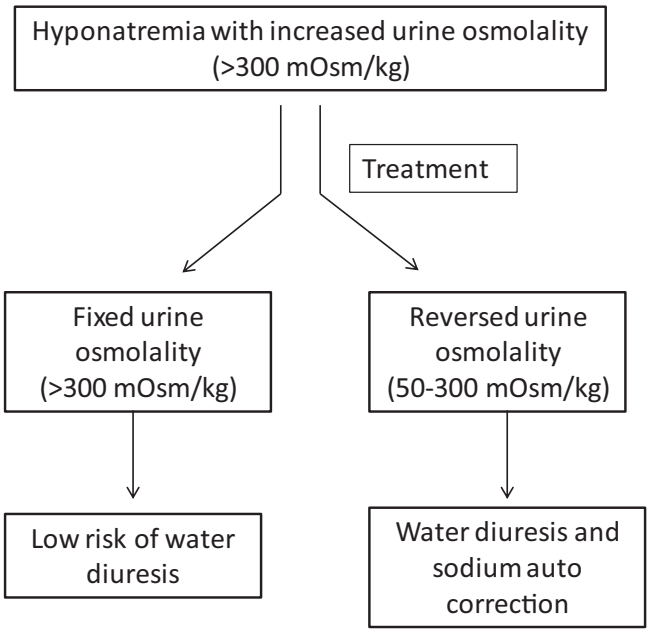

Figure 3. Changes in urine osmolality during hyponatremia treatment.

Desmopressin should only be used in situations in which free-water diuresis is either occurring or is imminent. Indiscriminate use of desmopressin in the treatment of hyponatremia can lead to iatrogenic hyponatremia and unnecessarily long durations of fluid restrictions.

Medication-induced hyponatremia is a common clinical syndrome.[5] Thiazide diuretics, select antidepressants, and anticonvulsants are frequently associated with hyponatremia. In all cases of drug-induced hyponatremia, the potential exists for rapid correction of hyponatremia, especially when the offending agent is withdrawn because there is a risk for water diuresis when urinary concentration decreases and free-water excretion increases. We refer to this situation as reversed urine osmolality, in which initially there is antidiuretic hormone release and high urine osmolality due to a reversible condition, which reverses when this condition resolves and urine osmolality decreases. This situation can lead to unanticipated free-water losses. This can occur in several commonly seen clinical scenarios (Fig 4). In this regard, desmopressin-associated hyponatremia shares this basic similarity with all cases of drug-induced hyponatremia.

Because desmopressin reduces free-water excretion, it is very important that exogenous fluid intake (both enteral and parenteral) be restricted to prevent iatrogenic hyponatremia and possible treatment-related injury. Hospitalized patients often have conditions that can lead to increased thirst or increased fluid intake (such as dry mouth, delirium, or psychiatric illness) and iatrogenic hyponatremia can develop. We do not advocate the routine use of desmopressin in treating hyponatremia; rather, desmopressin use is advisable in patients with either: (1) desmopressin-associated hyponatremia accompanied by symptoms of encephalopathy in whom prompt correction of hyponatremia is warranted with hypertonic saline solution or (2) high risk for overcorrection of hyponatremia due to free-water diuresis.

We recommend using subcutaneous desmopressin at 2 μg every 12 hours or intranasal desmopressin, 20 μg, every 12 hours; however, other routes of administration also may be appropriate. The hourly urine output should decrease substantially in the first 1 to 2 hours after administration. To further verify therapeutic efficacy, urine osmolality should be checked to ensure that urine osmolality has increased; typically, in the 500- to 600-mOsm/kg range should ensure a significant antiaquaretic effect.

The majority of cases in the literature reported to date describe the use of desmopressin to prevent overcorrection when water diuresis has occurred or to use as an adjunct with hypotonic fluids to re-lower sodium level when

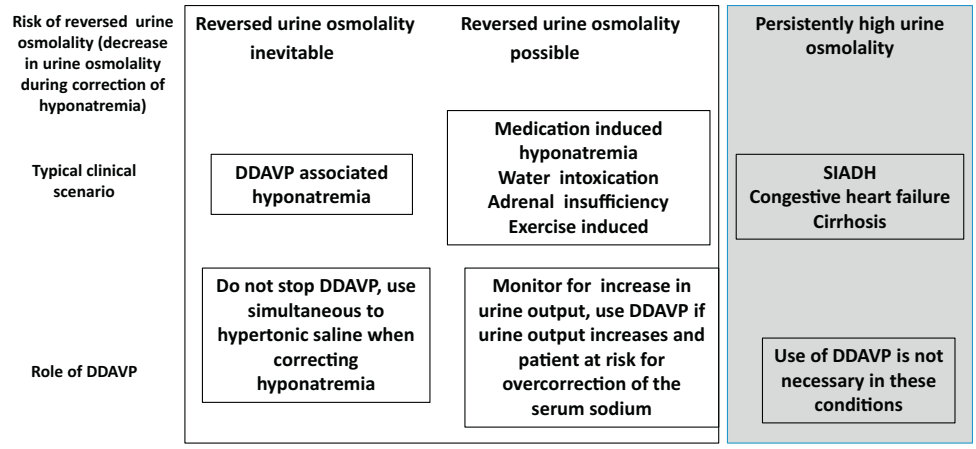

Figure 4. Recognizing clinical scenarios in which desmopressin (DDAVP) may be needed to correct hyponatremia safely. Abbreviation: SIADH, syndrome of inappropriate antidiuretic hormone. Achinger and Ayus[7]; reproduced with permission from Wolters Kluwer Health, Inc.

overcorrection has taken place (Table 1). However, the use of desmopressin in cases of syndrome of inappropriate antidiuretic hormone (SIADH) or other states associated with an elevated vasopressin level has also been advocated in the literature.[17] In states of elevated circulating vasopressin such as SIADH, we believe that it is of no benefit to administer desmopressin. This treatment is potentially deleterious if patients are not adequately fluid restricted and may lead to prolonged recovery times.[26,27] We advocate that patients treated for hyponatremic encephalopathy be monitored for the development of water diuresis with accurate and timely measurements of urine output and desmopressin should be administered only in cases in which free-water diuresis is occurring.

SUMMARY

Desmopressin use has been associated with iatrogenic hyponatremia, and treatment of this condition has potential pitfalls if the medication is withheld during therapy. Continuing desmopressin use during treatment of severe symptomatic desmopressin-associated hyponatremia

Table 1. Studies Evaluating the Use of Desmopressin in Prevention of Overcorrection of Hyponatremia

Study	Study Type	Timing of Desmopressin Administration	Outcome
Goldszmidt & Iliescu[15] (2000)	Single case report	Desmopressin administered after sodium increased 19 mmol/L in first 19 h of therapy, in patient with polydipsia	No neurologic injury noted
Perianayagam et al[16] (2008)	Retrospective review of 20 cases	Retrospective chart review of 6 patients with hyponatremia administered desmopressin after sodium corrected by >12 mEq/L in 24 h and 14 patients with hyponatremia given desmopressin concurrently with 3% sodium chloride solution	No neurologic injury noted in either group
Sterns et al[17] (2010)	Single case report	Desmopressin administered concurrently with 3% sodium chloride solution in patient with alcoholism, using a thiazide diuretic and serum sodium of 96 mEq/L	No neurologic injury noted
Tomlin et al[18] (2011)	Single case report	Desmopressin administered after sodium increased 12 mmol/L in first 18 h of therapy in patient with volume depletion and sodium of 109 mmol/L	No neurologic injury noted
Quinn et al[19] (2012)	Single case report	Use of desmopressin and fluid restriction to treat patient with psychogenic polydipsia and seizures	No long-term sequelae
Sood et al[20] (2013)	Retrospective chart review of 25 cases	Use of desmopressin and hypertonic saline solution at outset of therapy	No neurologic injury noted
Lum[21] (2013)	Single case report	Desmopressin administrated to patient with schizophrenia and alcohol abuse; serum sodium increased from 106 to 126 mmol/L in first 2 hospital d, then stabilized	No neurologic injury noted
Gharaibeh et al[22] (2013)	Single case report	Desmopressin administered with hypotonic fluids after serum sodium increased rapidly (19 mEq/L) in first 12 h of therapy	No neurologic injury noted
Rafat et al[23] (2014)	Retrospective review of 20 cases	Desmopressin administered with hypotonic fluids after serum sodium increased rapidly (19 mEq/L) in first 12 h of therapy	1 case of mild osmotic demyelination in patient with comorbid alcohol abuse
Changal et al[24] (2014)	Single case report	Desmopressin administered with hypotonic fluids after development of central pontine myelinolysis	Survival with residual neurologic deficit
Achinger et al[1] (2014)	Case series	2 patients with hyponatremia and neurologic symptoms treated with desmopressin at onset of free-water diuresis; serum sodium had not yet increased beyond acceptable limits; overall correction 11 mEq/L over 48 h	No neurologic symptoms or injury
De Vecchis et al[25] (2017)	Single case report	Desmopressin administered after rapid correction of sodium in patient with congestive heart failure	No neurologic injury noted
MacMillan & Cavalcanti[26] (2017)	Retrospective observational study of 1,450 hospital admissions	Desmopressin administered in 254 patients as either a reactive or proactive strategy	4/1,450 patients had suspected demyelination syndrome; hospital length of stay was longer in proactive strategy group
Ward et al[27] (2018)	Retrospective observational comparison study	16 patients received desmopressin, 5 patients received proactive strategy, 9 patients received reactive strategy, 2 received "reserve" therapy to reverse an overcorrection	No episodes of overcorrection or neurologic injury occurred; no difference in change in serum sodium, but desmopressin treatment group had longer length of hospital stay

appears to be a better strategy for managing this condition. This is because continuing the medication prevents free-water diuresis from occurring. Furthermore, in other causes of hyponatremia associated with reversed urine osmolality (such as drug induced or polydipsia), desmopressin can be used to slow the autocorrection of serum sodium level if free-water diuresis complicates therapy. The use of desmopressin in cases of SIADH or other states associated with an elevated vasopressin level, as has been advocated in the literature, is unnecessary in our view and subjects patients to unneeded therapy and may lead to prolonged recovery times.

ARTICLE INFORMATION

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