Desmopressin acetate is a synthetic analogue of arginine vasopressin, an endogenous hormone synthesized by the hypothalamus and released from the posterior pituitary gland.\(^1\)\(^-\)\(^3\) Endogenous arginine vasopressin release occurs as a physiologic response to increased serum osmolality, decreased blood volume, or decreased mean arterial pressure.\(^1\) Arginine vasopressin exerts its effects through several vasopressin receptors located in various tissues in the body. Activation of the vasopressin receptor 1 in the vasculature results in vasoconstriction.\(^2\) Vasopressin works at this receptor and is commonly given in the intensive care unit (ICU) to increase mean arterial pressure.\(^4\) In contrast, activation of vasopressin receptor 2 in the kidneys leads to water reabsorption from urine.\(^5\) For this reason, arginine vasopressin is sometimes referred to as antidiuretic hormone. Desmopressin mimics the actions of antidiuretic hormone at this receptor subtype in the kidney, with 10 times greater antidiuretic activity and 1500 times less vasoconstrictor activity compared with vasopressin.\(^4,\)\(^6\) Vasopressin receptor 2 is also present on endothelial cells and platelets and plays a role in hemostasis.\(^6\) Therefore, desmopressin, as a specific vasopressin receptor 2 agonist, is useful for 2 primary purposes in critically ill patients: treatment of sodium and water disorders and maintenance of hemostasis.

### Maintenance of Sodium and Water Balance

Desmopressin has been introduced into clinical practice for a variety of functions, including treatment of central diabetes insipidus (CDI) in 1972, bleeding disorders in 1977, and nocturnal enuresis in 1980 (Table 1).\(^2,\)\(^6\) However, in the ICU, this agent is primarily used in patients with specific sodium and water abnormalities amenable to desmopressin therapy.\(^2\) Of these sodium and water abnormalities, diabetes insipidus (DI) has become a well-established indication for desmopressin.\(^5\)

Diabetes insipidus occurs due to decreased antidiuretic hormone secretion from the posterior pituitary gland (central DI) or decreased antidiuretic hormone activity at the level of the kidney (nephrogenic DI).\(^1,\)\(^5\) Causes of CDI include traumatic brain injury, tumors, or neurosurgical procedures (eg, transsphenoidal tumor resection). However, CDI may also be idiopathic.\(^21\) Patients with CDI generally produce large volumes (3-20 L/d) of dilute urine, and hypernatremia

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may develop in the absence of a normal thirst response. Urine osmolality is normalized in CDI once the low or absent serum antidiuretic hormone is supplemented with desmopressin. Nephrogenic DI, however, does not typically respond to desmopressin therapy and often requires alternative treatments.

The lack of pituitary-hypothalamic axis activity in patients with brain death may lead to CDI. Patients in whom brain death develops require pharmacotherapy to optimize organ recovery and donation. Arginine vasopressin analogues, such as vasopressin or desmopressin, serve as one of the four classes of hormones needed for this purpose and increase the quantity and quality of organs procured. Because up to 70% to 80% of patients with brain death have a loss of the pituitary-hypothalamic axis due to pituitary compression from brain herniation, therapy to replace hormones normally regulated by this axis is essential. Although vasopressin helps restore vascular tone in these patients, desmopressin may also be used to treat hyponatremia and restore normal urine osmolality.

Last, in patients receiving treatment for hyponatremia, desmopressin may be used to avoid or treat overcorrection of serum sodium concentrations. In patients with hyponatremia, rapid sodium correction, resulting in fluid shifts from the brain to the plasma, may lead to devastating and permanent brain damage through osmotic demyelination syndrome. Because of the risks associated with rapid or excessive sodium correction in patients with hyponatremia, experts recommend an increase in serum sodium of no greater than 8 mEq/L per day in patients at high risk for osmotic demyelination syndrome. Desmopressin may be administered proactively to blunt increases in serum sodium when correcting hyponatremia with hypertonic saline in the context of an initial serum sodium level less than 120 mEq/L. In addition, desmopressin may be given reactively when the serum sodium level trends rapidly upward during hyponatremia treatment and as a rescue agent if serum sodium has overcorrected.

### Maintenance of Hemostasis

<table>
<thead>
<tr>
<th>Indication</th>
<th>Role</th>
<th>Mechanism</th>
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<tbody>
<tr>
<td>Intracranial hemorrhage with antiplatelet therapy</td>
<td>Treatment of bleeding</td>
<td>Promote platelet adhesion and activation</td>
</tr>
<tr>
<td>von Willebrand disease (types 1, 2A, 2M, and 2N)</td>
<td>Prevention and treatment of bleeding</td>
<td>Increase the release of von Willebrand factor</td>
</tr>
<tr>
<td>Mild hemophilia A</td>
<td>Prevention and treatment of bleeding</td>
<td>Increase plasma concentrations of factor VIII</td>
</tr>
<tr>
<td>Platelet dysfunction</td>
<td>Prevention and treatment of bleeding in patients with uremia</td>
<td>Promote platelet adhesion and activation</td>
</tr>
</tbody>
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antiplatelet therapy. Other uses of desmopressin for the maintenance of hemostasis are not endorsed by specific clinical guidelines. However, Ozgönenel et al reported use of desmopressin in von Willebrand disease, hemophilia A, and platelet dysfunction. Some authors also suggest, controversially, a role for desmopressin in reducing postoperative blood loss and transfusions.

Mechanistically, desmopressin establishes hemostasis primarily through activation of endothelial vasopressin receptor 2. This receptor activation results in the release of von Willebrand factor, which promotes platelet adhesion and activation. Desmopressin administration also results in increased glycoprotein expression on the surface of platelets, which enhances platelet and endothelial binding. A few of the common etiologies of platelet dysfunction amenable to desmopressin therapy include uremia, exposure to antiplatelet agents (eg, aspirin, clopidogrel), and congenital defects in platelet function.

Chronic kidney disease commonly results in the accumulation of uremic toxins such as urea or creatinine within the blood plasma. These various uremic toxins may lead to platelet dysfunction through multiple pathways. However, increases in plasma von Willebrand factor levels due to desmopressin administration may overcome the impaired adhesion of platelets in the context of uremia. In fact, desmopressin significantly reduces the duration of bleeding in this population. Evidence supports the use of desmopressin for the treatment of uremic bleeding in patients with chronic kidney disease and for surgical bleeding prophylaxis in patients with uremia.

Bleeding in the setting of platelet dysfunction due to antiplatelet therapy may also be effectively treated with desmopressin. In a recent meta-analysis of 10 trials involving patients who underwent cardiac surgery with cardiopulmonary bypass or who had antiplatelet therapy–induced platelet dysfunction, researchers found a significant reduction in transfusion requirements, blood loss, and bleeding resulting in reoperation in patients who received desmopressin, as compared with those receiving standard of care. However, this study was limited by inclusion of investigations conducted in the early 1990s, underrepresentation of nonaspirin antiplatelet agents, differences in desmopressin dosing, and use of concomitant hemostatic agents (eg, tranexamic acid) among the included trials. These authors found no increased risks for death or thrombotic events but did find an increased risk for clinically significant hypotension with desmopressin administration compared with placebo. Nonetheless, the potential benefits of desmopressin outweigh the risks in the setting of bleeding due to platelet dysfunction. Therefore, clinical guidelines support desmopressin administration in patients with intracranial hemorrhage due to antiplatelet therapy.

Last, desmopressin may be useful as a hemostatic agent in congenital bleeding disorders such as von Willebrand disease and hemophilia A. A full review of the classification of von Willebrand disease is beyond the scope of this discussion, but it is worth noting that differences among von Willebrand disease subtypes result in variable effectiveness of desmopressin therapy. Patients with mild hemophilia A (factor VIII deficiency) may benefit from desmopressin therapy because of its ability to increase factor VIII levels by 2- to 6-fold, with subsequent hastening of factor X activation and coagulation.

**Pharmacokinetic Considerations**

The antidiuretic effect of intranasal desmopressin begins at 15 to 30 minutes, peaks at approximately 1 hour, and lasts approximately 6 to 14 hours after administration. The oral formulation has a similar pharmacokinetic profile except for decreased absorption (bioavailability) and a longer time to onset (1.0-1.5 hours) and peak (4-7 hours) antidiuretic effects. After intravenous administration of desmopressin, the hemostatic effect begins at approximately 30 minutes and peaks at 90 to 120 minutes on the basis of its effects on coagulation factor levels (ie, factor VIII). Typically, tachyphylaxis develops with repeated desmopressin administration, and a lapse of 48 hours may be required between doses to obtain the full hemostatic effect. The half-life of desmopressin is 3 hours in patients with normal renal function; however, because desmopressin is a renally excreted medication, the half-life in severe renal impairment is extended to 9 hours. Desmopressin is thus contraindicated in patients with a creatinine clearance of less than 50 mL/min. Patients with renal disease may have a higher risk of water and sodium imbalances after desmopressin administration. Of note, desmopressin has
been used to treat uremic bleeding in patients with end-stage renal disease, and this contraindication may be less of a concern after a single dose for this particular indication.17

Last, several drug-drug interactions may alter the efficacy and safety of desmopressin. Medications that affect sodium and water homeostasis (eg, nonsteroidal anti-inflammatory drugs, diuretics, glucocorticoids) and those directly associated with altered antidiuretic hormone activity (eg, antipsychotics, antidepressants, anticonvulsants associated with syndrome of inappropriate antidiuretic hormone) may lead to profound hyponatremia when given concomitantly with desmopressin.25 Although not necessarily contraindicated for indications in the ICU, the combination of desmopressin with these interacting medications warrants close electrolyte and fluid-balance monitoring.

### Dosing and Administration

Desmopressin may be given via intravenous, intramuscular, subcutaneous, intranasal, oral, or sublingual routes (Table 2).5 Desmopressin injection is available as a 1-mL, single-use ampule and a 10-mL, multidose vial in a concentration of 4 μg/mL.25 The Neurocritical Care Society guidelines for reversal of antithrombotic agents in patients with intracranial bleeding suggest using desmopressin as a single, intravenous 0.4-μg/kg dose in patients with intracranial hemorrhage in the context of antiplatelet use.14 Specific administration instructions are not provided for this indication; however, larger doses of intravenous desmopressin are typically given over 10 to 30 minutes for other indications.23 In general, the dose of desmopressin is 0.3 to 0.4 μg/kg per dose in hemophilia A, mild/moderate type 1 von Willebrand disease, and uremic
bleeding. For these hemostatic indications, desmopressin is given 30 minutes prior to a scheduled procedure, or urgently in scenarios of spontaneous or traumatic bleeding. Much smaller doses of 2 to 4 μg (0.5-1.0 mL) are administered via the intravenous or subcutaneous routes in 2 divided daily doses for patients with CDI. Intravenous desmopressin at these small doses does not require further dilution and may be given as an intravenous push. Of note, doses of 4 μg or less may require the use of small syringes (eg, a 1-mL tuberculin syringe) to avoid dosing errors.

Other dosing options for patients with CDI include the intranasal and oral routes. Outside of the ICU, where intravenous use predominates, the intranasal formulation is preferred to the oral formulation because of increased potency and bioavailability. Intranasal desmopressin is generally initiated at 10 μg daily or a single insufflation (ie, 10 μg per insufflation). A rhinal tube may be used to deliver the medication in patients who require dosing outside of multiples of 10 μg per dose. The conversion from intranasal to intravenous routes is approximately one-tenth of the maintenance intranasal desmopressin dose. Oral desmopressin may be given for CDI at a starting dose of 0.05 mg (50 μg) every 12 hours. Of note, the oral formulation is 10 to 40 times less potent than intranasally administered desmopressin and may not produce an adequate response in some patients. Desmopressin is generally titrated to maintain a daily urine output of 1.5 to 2 L while maintaining normonatremia in adult patients with CDI.

For patients with brain death, urine output determines the dose of desmopressin; the desired target is 1 to 3 mL/kg per hour. One suggested dosing regimen includes administering desmopressin 0.5 to 2 μg intravenously every 2 to 3 hours. However, treatment guidelines suggest an initial intravenous dose of 1 to 4 μg followed by 1 to 2 μg every 6 hours to maintain urine output of less than 4 mL/kg per hour with maintenance of appropriate serum sodium and urine osmolality. Similarly, when correcting hyponatremia with hypertonic saline, desmopressin may be given to prevent overcorrecting the serum sodium at 1 to 2 μg intravenously or subcutaneously every 6 to 8 hours for 24 to 48 hours until the serum sodium level is greater than 125 to 128 mEq/L.

Adverse Effects and Monitoring

Desmopressin administration is associated with a low rate of adverse effects (<5%) but may result in headache, nausea, tachycardia, abdominal pain, vulvar pain, facial flushing, dizziness, diarrhea, mild/severe hyponatremia, and consequences of hyponatremia (eg, seizure). Rhinitis or epistaxis also may be associated with intranasal administration. Hyponatremia occurs in approximately 1% of patients with long-term desmopressin use but is most common early in therapy when dose titrations are undertaken. Increases in blood pressure or hypotension with reflex tachycardia have been observed infrequently after intravenous desmopressin administration. These changes in vital signs are more likely to occur during rapid intravenous administration of high-dose desmopressin. Last, cutaneous and vascular changes such as erythema, burning, or swelling may occur at the injection site.

During intravenous desmopressin infusions, vital signs should be monitored to detect changes in blood pressure and heart rate. Because desmopressin directly affects salt and water homeostasis, fluid intake and urine output should be carefully monitored after multiple desmopressin doses. Hyponatremia may develop during desmopressin therapy and generally results in vague signs and symptoms such as nausea, vomiting, headache, confusion, and fatigue. Once severe (eg, serum sodium level < 120 mEq/L), hyponatremia may cause seizures or coma. Therefore, serum sodium level should be monitored at least daily in patients receiving desmopressin therapy for CDI. In addition, patients’ urine specific gravity and osmolality should be monitored regularly. Specific bleeding times or coagulant factor levels (eg, factor VIII) may be used to measure the effects of desmopressin when given for hemostasis.

Warnings, Contraindications, and Special Populations

Several warnings and precautions for desmopressin exist. Thrombotic events (eg, stroke, acute myocardial infarction) have been reported rarely with desmopressin use. Large intravenous doses, such as those used for hemostasis, should be administered over 10 to 30 minutes to avoid hypotension. Last, fluid restriction is recommended to avoid severe
hyponatremia in patients receiving chronic desmopressin therapy for the treatment of CDI.25

Desmopressin is contraindicated in severe renal impairment (ie, creatinine clearance < 50 mL/min), in patients with hyponatremia or a history of hyponatremia and in patients with a hypersensitivity to desmopressin.25

However, as mentioned, desmopressin has been used in studies of patients with end-stage renal disease for the treatment of uremic bleeding and as an adjunctive agent in patients with hyponatremia when correcting the low serum sodium level with hypertonic saline.10-12,17,18 In these settings, the indication should be clarified prior to administering desmopressin to optimize outcomes.

Conclusion

Desmopressin has a role in select critically ill patients because of its many unique pharmacologic effects, its demonstrated efficacy for the treatment of multiple disease states, and its relatively favorable safety profile. Through its selectivity for the vasopressin receptor 2, desmopressin may be used to correct sodium and water imbalances in scenarios such as CDI and brain death and to maintain hemostasis in the context of platelet dysfunction or congenital bleeding disorders. Patients who receive desmopressin may experience mild adverse effects such as headache, nausea, and flushing. Serious adverse effects may rarely occur after desmopressin administration (eg, seizure, hypotension). Severe adverse effects are rare; nevertheless, patients should receive close monitoring of vital signs, serum sodium concentrations, and volume status during treatment with desmopressin to optimize outcomes.

REFERENCES


CE Evaluation Instructions

This article has been designated for CE contact hour(s). The evaluation tests your knowledge of the following objectives:

1. Describe the therapeutic roles of desmopressin in the intensive care unit.
2. Correlate the pharmacologic actions of desmopressin to its therapeutic and adverse effects.
3. Assess the appropriate use of desmopressin as it relates to dosing, administration, patient monitoring, and contraindications.

Contact hour: **1.0**
Pharmacology contact hour: **1.0**
Synergy CERP Category: **A**

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