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Desmopressin

Safety Considerations in Patients with Chronic Renal Disease

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Desmopressin is a synthetic analogue of mammalian 8-arginine vasopressin (antidiuretic hormone), which is a hormone crucial to renal water conservation. Desmopressin was first developed as antidiuretic-replacement therapy in the management of central diabetes insipidus and it thereafter came into use for the management of the transitory polyuria and polydipsia following head trauma and/or surgery in the pituitary region.[1] Desmopressin has since gained an indication for use in primary nocturnal enuresis and has been applied to the management of night-time urinary incontinence.[2,3] Desmopressin is also a well tolerated and conveniently administered haemostatic agent that can be used in a number of clinical conditions marked by a bleeding diathesis.[4,5] It causes the release of coagulation factor VIII, von Willebrand factor and tissue-type plasminogen activator, among other haemostatic properties.[6,7]

1. Desmopressin and Renal Disease

There are no specific haemostatic indications for desmopressin, yet this has become one of the more frequent and important off-label uses of this compound.[4,5,7] Desmopressin is widely used for the treatment of patients with von Willebrand disease, haemophilia A, a range of platelet disorders and chronic kidney disease-related bleeding.[5,8-10] The pathogenesis of this haemostatic abnormality observed in chronic kidney disease is multifactorial and includes effects of circulating toxins, platelet dysfunction, alterations of the vessel wall, anaemia, and other factors.[6,8-10] Desmopressin is effective in patients with chronic kidney disease, acting promptly in <1 hour, with the bleeding time shortening for at least 4 hours after infusion.[5,11,12] The reason why desmopressin works in chronic kidney disease is unknown. Because levels of factor VIII and von Willebrand protein are already increased in the condition, desmopressin-related elevation of these proteins appears not to be a specific mechanism. Patients can develop tachyphylaxis to desmopressin, rendering this agent of limited utility with repeated use.[11,12]

2. Administration and Pharmacokinetics

Desmopressin can be given intranasally, intravenously, subcutaneously or orally. The usual antidiuretic dose is 10–20μg intranasally (with a bioavailability of 10–20% from this location), 1–4μg subcutaneously or intravenously, and 100–800μg orally (after oral administration, desmopressin is largely destroyed in the gastrointestinal tract).

The recommended dose of desmopressin for patients with chronic kidney disease and active bleeding (or a bleeding tendency) is 0.3 μg/kg

bodyweight, which is one order of magnitude higher than the dose used for antidiuresis.[4,6,7] Tachyphylaxis to the antidiuretic effect of desmopressin does not occur. The antidiuretic effect of desmopressin is maintained for 12–24 hours following a dose, while the haemostatic effect of desmopressin quickly fades with repeat administration.[11,12]

The concentration-time curve for intraveneously administered desmopressin is best described by a biexponential term with a terminal half-life of approximately 3 hours.[13,14] Desmopressin is primarily eliminated by renal excretion, with its renal clearance being independent of the rate of diuresis.

The clearance of desmopressin is decreased by an average of 75% in patients with advanced chronic kidney disease and the terminal half-life of 10 hours is 2–3 times greater than that seen in healthy adults.[15,16] This renal failure-related fall in the systemic clearance of desmopressin relates to a decrease in both the renal and non-renal clearance of this compound.[16]

3. Adverse Effects

Common adverse effects with desmopressin include mild facial flushing and headache.[16] Desmopressin use can also be associated with a decrease in mean arterial pressure (10–15%) and an increase in pulse rate (20–30%).[17] Because of its potent antidiuretic effect, desmopressin can also cause sufficient water retention to bring about significant dilutional hyponatraemia.[17-20] The dilutional hyponatraemia observed with desmopressin is both dose- and fluid-intake dependent.

4. Perspective

Desmopressin use is presumably associated with a greater risk of hyponatraemia in elderly patients,[20] particularly in those elderly individuals with chronic mild-to-moderate kidney disease, wherein its half-life would be expected to be prolonged. This set of circumstances prompted a recent label change and desmopressin is now contraindicated in patients with moderate-to-severe renal impairment, defined as a creatinine clearance <50 mL/min.[21] Is such a label change truly needed in patients with renal failure?

It is accepted practice to adjust the dose of renally cleared drugs in the setting of chronic kidney disease and it is unclear as to why the same guiding principle was not applied for desmopressin, a renally cleared compound. When regulatory bodies have contraindicated use of a renally cleared drug in patients with chronic kidney disease, rather than suggesting that it be dose adjusted, it has been because the compound is felt to have such a narrow therapeutic/adverse-effect window that one could not safely administer it, even with dose adjustment. The application of this approach has been erratic for renally cleared compounds; for example, despite the relatively low risk of lactic acidosis with the renally cleared compound metformin, [22] it is contraindicated in even early-stage chronic kidney disease while proarrhythmic renally cleared antiarrhythmic compounds can be given (per label) to patients with chronic kidney disease but with dose adjustment.[23,24]

What is the state of affairs with desmopressin? If the major risk with desmopressin is that of hyponatraemia, then two circumstances arise in chronic kidney disease that lessen the risk of this electrolyte abnormality compared with individuals with healthy renal function. First, because there is a loss of urinary-concentrating ability with advancing renal failure, the antidiuretic effect of desmopressin is minimised. Secondly, the reduced glomerular filtration rate that defines chronic kidney disease in and of itself limits the filtered volume of water and thereby the amount that can be acted on by desmopressin. Together, these two disease-related changes lessen the pharmacodynamic antidiuretic effect (and thereby the likelihood of hyponatraemia) with desmopressin, irrespective of the drug having a

longer half-life in patients with chronic kidney disease.

How might the use of desmopressin play out in chronic kidney disease despite it being contraindicated? First, if a patient with chronic kidney disease also has diabetes insipidus, desmopressin remains the treatment of choice. Rather than it being contraindicated, it should be dose adjusted to the desired effect as would typically be the case for diabetes insipidus patients without renal disease. The longer half-life of desmopressin in such a patient should be no more than an administration consideration in its treatment use. Secondly, if desmopressin is being used in chronic kidney disease for haemostatic purposes, it is generally given only as one or two doses with precautions typically being taken to limit water intake. The confusing nature of such a recommendation becomes obvious in haemodialysis patients receiving desmopressin in whom hyponatraemia cannot occur.[12,25] Desmopressin is an important therapeutic option for patients with chronic kidney disease in need of short-term improvement in haemostatic parameters and cannot be withheld simply on the basis of half-life considerations increasing the risk of developing hyponatraemia.

5. Conclusion

Desmopressin is but one of several compounds whose label contains confusing statements that may not be directly applicable to how it is being used. As always, the benefit-risk ratio of a compound should be assessed prior to its use and the label for a compound (including statements of contraindication) should offer guidance and not a rigid and immutable treatment approach. Desmopressin is not technically indicated for haemostatic considerations and, as such, changes in the label considerations may not strictly apply to the off-label use of this compound.

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