SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

DDAVP® Injection

COMPOSITION

Each ml contains 4 μg desmopressin acetate in an isotonic solution, adjusted to pH 4.

Excipients: sodium chloride and water for injection.

PHARMACOLOGICAL CLASSIFICATION

A 18.1 Coagulants, haemostatics

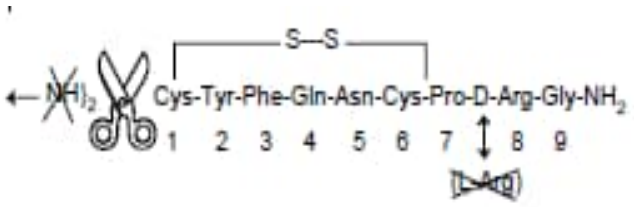
PHARMACOLOGICAL ACTION

Pharmacodynamic properties

DDAVP® (desmopressin) is a synthetic structural analogue of the natural human hormone, arginine vasopressin (AVP). The molecule has undergone two changes:

1. At the N-terminal position 1 the amino group has been removed

2. L-Arginine in position 8 has been replaced by D-arginine.



The clinical significance of this changed ratio of antidiuretic to vasopressor effect is that clinically active antidiuretic doses are far below the threshold level for a vasopressor effect, with a consequent reduction in unwanted pressor side effects. Moreover, the change in the molecule has also resulted in a considerable increase in the otherwise very short half-life for vasopressin.

Effect on Factor-VIII:

High doses of DDAVP® may produce increases of Factor-VIII clotting activity (VIII:C) as well as Factor-VIII related antigen (VIII R:Ag).

At the same time plasminogen activator is released.

INDICATIONS

***Selected cases of mild Haemophilia A and Von Willlebrand`s Disease*:**

(TYPE 1) – where an increase of Factor –VIII levels and/or a decrease in bleeding time have been demonstrated after administration of an initial dose.

Diabetes Inspidus:

Central diabetes insipidus. Diagnosis of central diabetes insipidus. The use of DDAVP® in patients with an established diagnosis will result in a reduction in urinary output with increase in urine osmolality and a decrease in plasma osmolality. This will allow the resumption of a more normal life style with a decrease in urinary frequency and nocturia.

Urinary Concentration Capacity Test:

DDAVP® can be used to test the capacity of the kidneys to concentrate urine. This serves as a diagnostic aid in adults and children in the examination of the kidney function. This is especially useful in the differential diagnosis of urinary tract infections such as cystitis and pyelonephritis which may cause a subnormal ability to concentrate urine.

CONTRAINDICATIONS

Hypersensitivity to any of the ingredients, including excipients.

WARNINGS and SPECIAL PRECAUTIONS

Overhydration:

The risk of overhydration including cardiac failure should be borne in mind, especially in children or the elderly or the patient who is on fluid supplements either orally or parenterally.

Children should be closely observed to avoid over-ingestion of fluid. Excessive water intake can produce hyponatraemia with associated effects.

In haemophilia: Precautions must be taken to prevent fluid overload, since DDAVP® will suppress urine

formation and so lead to retention of water given in excess of the patient's requirements. Fluid should therefore not be forced, orally or parenterally, and patients should only take as much fluid as they require to satisfy thirst. Intravenous infusions should not be left up as a routine after surgery. Fluid accumulation can be readily monitored by weighing the patient or by estimating plasma sodium or osmolality.

DDAVP® should not be used to treat patients with Type II B. Von Willebrand`s Disease since platelet aggregation may be induced. Injections should not be used in infants younger than 3 months in the treatment of Haemophilia A or Von Wilebrand`s Disease.

For Surgical Procedures:

Blood samples should be taken before and 20 minutes after the DDAVP® infusion for Factor-VIII assay which should be carried out promptly so that the patient's response is known before surgery. If Factor-VIII coagulant activity is present at less than 5 % of normal, DDAVP® should not be relied upon.

Pressor effects: Large doses may produce pressor effects in patients and especially in those who are anaesthetised, or who are taking ganglion or adrenergic neurone blockers, or who have defects in sympathetic outflow. Patients with a history of heart disease or hypertension should be treated with caution, and their blood pressure should be monitored.

Myocardial ischaemia: Myocardial ischaemia could be induced or exacerbated.

Sensitivity: Patients with known sensitivity to ADH, should be tested for sensitivity to DDAVP® before the full dose is given. DDAVP® should be used with caution in patients with cystic fibrosis.

INTERACTIONS

Indomethacin in combination with DDAVP® increases the magnitude, but not the duration, of the response to DDAVP®.

Glibenclamide: A few cases, where the antidiuretic response induced by DDAVP® was reduced, were reported.

Carbamazepine may also prolong the action of DDAVP®.

PREGNANCY AND LACTATION

Safety during pregnancy and lactation has not been established.

DOSAGE AND DIRECTIONS FOR USE

Mild Haemophilia A and Von Willlebrand`s Disease:

DDAVP® Injection is administered by intravenous route.

When using doses of less than 4 μg, the dose should be drawn up from the ampoule as a fraction of a millilitre using a 1 ml syringe and not prepared by dilution or given by infusion. This is necessary because of the tendency of peptides to adhere to the glass surfaces when in very dilute solutions.

It has been demonstrated that intravenous infusions of DDAVP® can produce an increase of Factor-VIII levels in patients with mild Haemophilia A and mild Von Willebrand`s Disease. Increases of 2-3 times the pre-treatment level may be attained. In appropriate cases, therefore, cover may be provided for dental extractions or minor surgery without the use of blood products or with only supplementary doses, depending on the pre-treatment level. The response to DDAVP® should be ascertained prior to its prophylactic or therapeutic use.

The treatment schedule below has been prepared from clinical experience obtained so far.
An anti-fibrinolytic agent should be given concurrently.

DDAVP® Injection is administered as an intravenous infusion at a dose of 0,3 μg DDAVP®/kg body mass diluted in sterile physiological saline and infused slowly over 15 – 30 minutes.

In adults and children weighing 10 kg or more, 50 ml diluent is used.
In children weighing 10 kg or less, 10 ml of diluent is used.

Blood pressure and pulse should be monitored during infusion. If DDAVP® Injection is used pre-operatively, it should be administered 30 minutes prior to the scheduled procedure.

The critical haemostatic level for dentistry or surgery should be judged by the same criteria as if the patient were being managed with blood products, except that the level may be expected to continue to rise for an hour or two after the assay rather than beginning to fall immediately.

However if a sufficient level has not been reached to cover the intended surgical procedure, Factor-VIII concentrate should be given to make up the deficit. If expertise in the management of bleeding disorders is not locally available, advice may be obtained from the nearest Haemophilia Centre.

A further Factor-VIII assay should be undertaken approximately 6 hours after the infusion if the initial response was not adequate, so that a further supplementary dose of Factor-VIII may be given if necessary. If a sufficient response was obtained to the initial dose of DDAVP®, further doses may be given at 12-hourly intervals so long as cover is required: the Factor-VIII levels must be monitored since patients have shown a diminishing response to successive infusion.

With prolonged treatment, particular attention must be paid to the fluid balance. The patient should be weighed twice daily; if this is impractical, the plasma sodium and/or osmolality should be measured instead. A progressive increase in mass should not occur, the plasma sodium should remain above 130 mmol/l and the osmolality above 270 mOsm/kg. If the body mass of an adult increases by more than 3 kg or if the plasma sodium falls below 130 mmol/l or the plasma osmolality below 270 mOsm/kg the control of fluid intake has clearly been insufficient and fluids must be drastically restricted.

Central Diabetes Insipidus:

This formulation is administered by direct intravenous injection.

DDAVP® Injection (desmopressin) dosage must be determined for each patient and adjusted according to the pattern of response. Response should be estimated by two parameters: adequate duration of sleep and adequate water turnover.

The injection may be used when the intranasal administration is considered unsuitable. Individually adjusted doses, after testing the effect on urine osmolality and diuresis at direct dose levels, is recommended.

Normal dosage, intravenous injection:

Adults 1 – 4 μg (0, 25 – 1ml) 1 – 2 times daily.

Children above the age of 1 year 0, 4 – 1 μg (0,1 – 0,25 ml) 1 – 2 times daily.

Children below the age of one year 0,2 – 0,4 μg (0,05 – 0,1 ml) 1 – 2 times daily.

For patients who have been controlled on intranasal DDAVP® and who must be switched to the injection form, either because of poor intranasal absorption, or because of the need for surgery, the comparable antidiuretic dose of the injection is about 10 % of the intranasal dose.

Urinary Concentration Capacity Test:

Normal adult dose by intramuscular or subcutaneous injection is 4 μg (1 ml).

For children over 12 months of age the dose is 1 – 2 μg (0, 25 – 0, 5 ml).

For children under 12 months of age the dose is 0,4 μg (0,1 ml).

For children it is recommend to use primarily the intranasal presentation. After administration of DDAVP® the first portion of urine is discarded. Urine from the next 6 hours is collected for measurement of osmolality. A restricted water intake is recommended for the first 12 hours after administration. The reference level for normal urine osmolality after DDAVP® is 800 mOsm/kg for most patients. With values under this level, the test should be repeated. A repeated low result indicates an impaired ability to concentrate urine and the patient should be referred for further examination into the underlying cause of the malfunction.

SIDE EFFECTS

Excessive doses may cause tachycardia, headaches, mild abdominal cramps, nausea, vomiting, facial flushing, vulva pain or water intoxication from overhydration. In such cases the dosage should be reduced, frequency of administration decreased, or the medicine withdrawn according to severity of the condition.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

At high doses, a transient fall in blood pressure with a reflex tachycardia and facial flushing may occur at the time of administration. There is no known specific antidote for DDAVP®. Toxic effects are unlikely to occur even at very high doses.

IDENTIFICATION

DDAVP® is identified as a clear, colourless solution.

PRESENTATION

A box of ten colourless, glass ampoules of 1 ml containing 4 μg/ml of desmopressin acetate.

STORAGE INSTRUCTIONS

Store at 2 °C – 8 °C. Protect from light. Use before expiry date shown. Do not freeze.

KEEP OUT OF REACH OF CHILDREN.

REGISTRATION NUMBER

S/8.1/360

NAME AND BUSINESS ADDRESS OF THE HOLDER OF CERTIFICATE OF REGISTRATION

Packed by:



St. Prex, Switzerland for:

Ferring (Pty) Ltd.

Route 21 Corporate Park

6 Regency Drive

Irene Ext 30, South Africa

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