Assessment and validation of a defined fluid restriction in the use of subcutaneous desmopressin (DDAVP) for children with inherited bleeding disorders

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INTRODUCTION

- Desmopressin (DDAVP) has been used in children with von Willebrand Disease (VWD) and mild haemophilia A (HA) for over 35 years
- DDAVP has lowered the number of children exposed to human plasma derived products with a good safety profile and low cost
- Hyponatremia is a rare but potentially dangerous side effect of DDAVP that is thought to be more frequent in young children
- Fluid restriction around DDAVP use is known to reduce the risk of hyponatremia but no specific paediatric guideline exists

STUDY AIMS

- Primary aim: assess whether a '2/3 maintenance' fluid restriction was effective in preventing hyponatremia in children receiving subcutaneous (SC) DDAVP in the course of both formal DDAVP trials and therapeutically in the perioperative period
- Secondary aims: demonstrate adequate biological and clinical responses to SC DDAVP

PATIENTS AND METHODS

- A retrospective chart analysis was undertaken of all children who were prescribed DDAVP in our institution between 2008 and 2013
- The subgroup of children who underwent a formal SC DDAVP trial as per our institutional protocol were identified and biological response as well as side effects documented
  - Biological response in haemophilia A was defined as follows: complete (FVIII: C >0.50 IU/ml), partial (FVIII: C 0.30-0.50 IU/ml) or no response (FVIII:C < 0.30 IU/ml) 90 minutes after DDAVP administration
  - Biological response in VWD was defined as at least a 3-fold increase of baseline levels of FVIII:C and VWF:Rco with post levels of at least 0.50 IU/ml 90 minutes after DDAVP administration
- Children who used DDAVP for perioperative bleeding prophylaxis were identified and haemostasis outcomes and side effects assessed. In these children daily weights, adherence to the prescribed fluid restriction and formal electrolytes (where measured) were documented

RCH DDAVP PROTOCOL

Morning of Procedure

- Apply LMX-4™ 30 min prior to injection.
- DDAVP comes in 2 strengths, the correct strength for subcutaneous administration is:
  - **Octostim® 15µg/ml in 1 ml ampoules for subcutaneous administration. Peak levels 90mins post administration.**
- Hyponatremia can be a dangerous side effect of DDAVP when repeated doses are required. To ensure that this does not occur from excess fluid retention the patient must have:
  - daily weight
  - **Serum sodium (U&E's) taken and reviewed by medical staff before all DDAVP injections (this will be a minimum of daily)**
  - Strict fluid balance chart
  - Fluid restriction to 2/3 maintenance _____**ml. per 24hrs post each DDAVP dose**
- **90mins pre-operatively the patient should receive a 0.3 microgram/kg dose of DDAVP subcutaneously.**

DDAVP administration

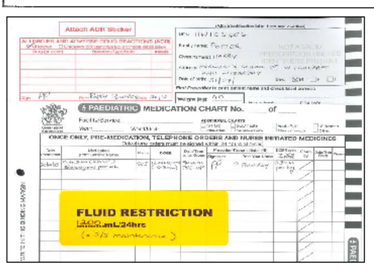
- DDAVP is obtained from pharmacy and should be stored in the fridge.
- Administration should be 90 minutes prior to the scheduled procedure. Peak levels of Factor VIII and von Willebrand factor occur about 90 minutes after subcutaneous injection.
- The dose is 0.3µg/kg and this is administered as a subcutaneous injection.
- ***Patients should have baseline observations done, (T.P.R. & B.P.), and then every 10 minutes during the infusion or for 30 minutes post subcutaneous injection (T.P.R. & B.P.).***
- The most common side-effect is peripheral vasodilatation resulting in facial flushing. This is harmless and is not an allergic reaction.
- There may be mild tachycardia and some patients experience a mild headache. Slowing the rate of administration reduces such effects.
- Other potential side effects include; hypertension, hypotension, water retention, mild stomach cramps, nausea, vomiting, and dizziness.

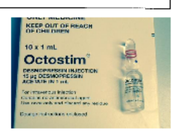
Post – Op

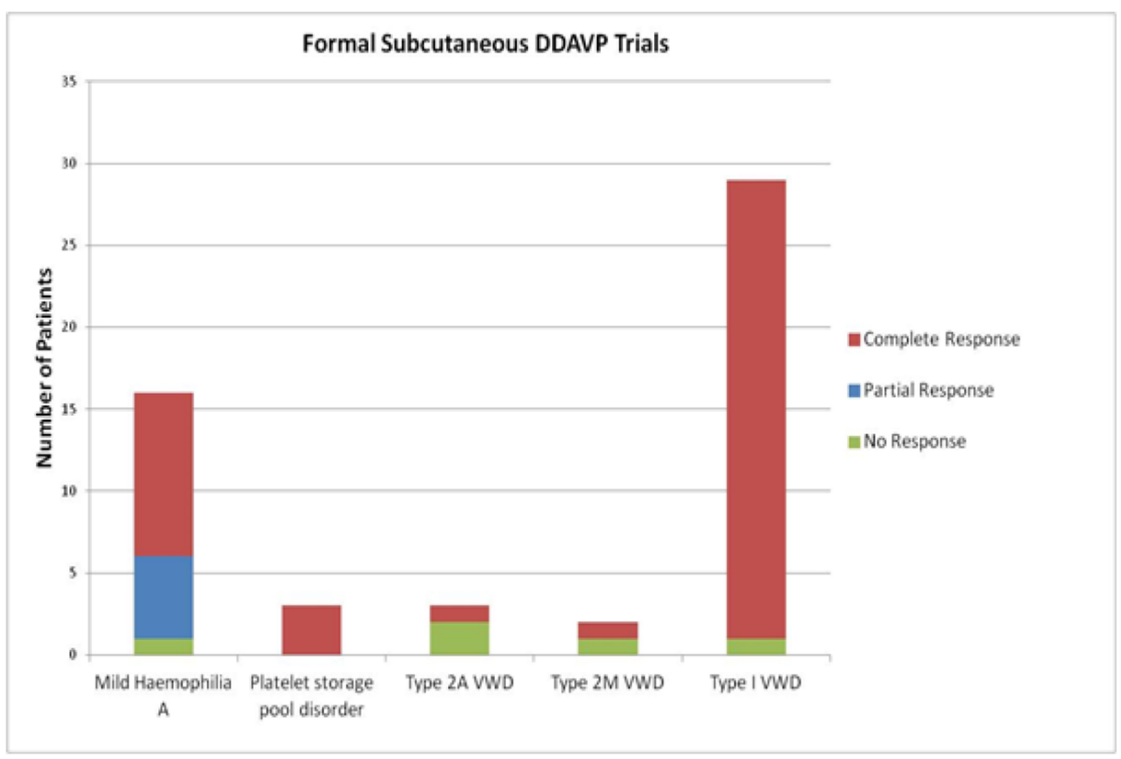
When the patient returns to the ward and as soon as they are able they should be commenced on Tranexamic Acid (15-25mg/kg) 8 hourly. This is to be administered orally tds for a total of 14 days.

Repeat Doses

- **Each morning:** Bloods for U & E's, vwFAc are taken for urgent processing. (URGENT – notify coag lab on Ext 68071)
- DDAVP DOSES – ONLY TO BE ADMINISTERED AFTER THE SODIUM (Na) RESULT HAS BEEN REVIEWED BY A DOCTOR and is within normal ranges.
- **Subsequent doses of DDAVP will be either given 12 hourly or daily depending on results of serum sodium concentrations and VWF levels. The Haemophilia team will document this plan in chart**
- **If there is any bleeding intra-operatively or post-operatively please contact Haematology Registrar or Dr Simon Brown (via RCH switchboard), or Joanna McCosker, Haemophilia CNC.**



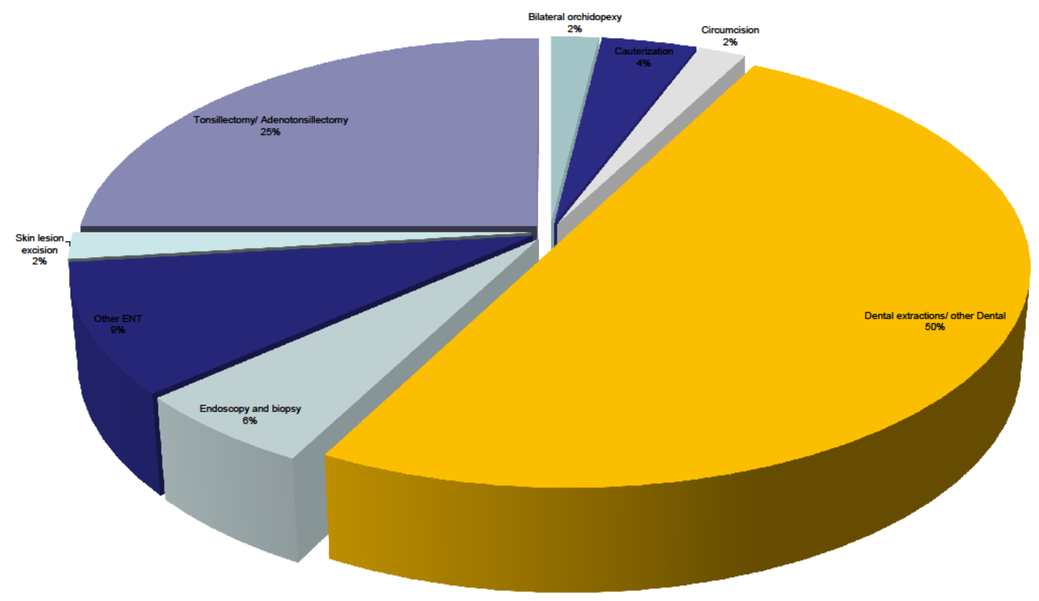




RESULTS

- 69 total children received SC DDAVP with 2/3 maintenance fluid restriction post dose
- Children diagnosed with mild HA (16), VWD (48) or platelet storage pool disorder (5)
- DDAVP was used in 52 procedures including dental work (26 cases), adenotonsillectomy (13 cases), endoscopy (3 cases), nasal cauterization (2 cases), orchidopexy (1 case), circumcision (1 case), skin excision (1 case), rectal biopsy (1 case) other ENT procedures (5 cases)
- 46/52 were shown to respond to DDAVP prior to receiving DDAVP for surgery
- Of the 6 children who did not have a DDAVP test dose prior to surgery
  - 3 were possible VWD with immediate family members who had a documented response to DDAVP
  - 2 were older children with possible VWD undergoing minor procedures
  - 1 child had a mild platelet storage pool disorder (dense body deficiency) with minimal clinical bleeding symptoms
- The administration of subcutaneous DDAVP in the perioperative setting was associated with an adequate haemostatic response in all patients. No child required plasma derived products unexpectedly
- Repeat dosing as part of a perioperative haemostasis plan was undertaken in 19 children
- There were no cases of symptomatic hyponatremia
- There were 7 cases of asymptomatic hyponatremia ($Na^+ \leq 133$ mmol/L, range 129-133)
  - 3 of these patients had an incomplete fluid balance
  - 2 patients clearly exceeded the recommended fluid restriction by >500mls
  - 1 patient inadvertently received a 2nd dose of DDAVP before the sodium was checked
  - 1 patient with a Na of 133 who received an appropriate dose and adhered to the restriction
- Transient facial flushing was noted in 28% of children post DDAVP; Other side effects were mild, and included headache (2 children) and transient asymptomatic hypotension (1 child)

52 Surgical Procedures Covered with DDAVP



SUMMARY

- A two thirds maintenance regimen prevented significant hyponatremia in our cohort, and is now the standard protocol for fluid restriction post DDAVP administration in our centre
- A trial dose of SC DDAVP produced a complete response in all but one patient with definite or possible type 1 VWD (97% of patients tested)
- A complete or partial response was achieved in 94% of patients with mild HA
- Planned perioperative use of SC DDAVP provided adequate haemostasis in all patients (no requirement for vWF or FVIII concentrate)
- SC DDAVP was well tolerated – no serious side effects were observed
- Although not formally assessed, our institutional experience suggests that use of SC DDAVP is generally more acceptable to the child and family (compared to our previous standard intravenous protocol)

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