Supplementary appendix

Use of desmopressin acetate in the setting of severe hyponatremia in the ICU

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Neurological variables of interest

The lowest level of consciousness of the patient, as assessed by the Glasgow coma scale (GCS) was noted, unless generalized seizures occurred in which case patients were attributed the lowest possible GCS mark (GCS=3). The patient neurological condition was evaluated either upon hospital discharge or at 3 weeks following admission in those patients discharged before that time interval.

Organ failure definitions

Acute kidney injury was defined as meeting at least the "Risk" category according to the modified "Risk, Injury, Failure, Loss, End-stage criteria" (RIFLE), at any time during the first 48 hours of medical management [16]. We recorded the number of patients who required mechanical ventilation, whether non-invasive or invasive, for at least 12 hours or more, and patients who required a vasopressor support.

Calculated urine osmolarity

Urine osmolarity was calculated according to the following formula: $U_{osm}= 2 \times (U_{Na}+U_{K}) +U_{urea}$ where U_{Na}, U_{K} and U_{urea} represent urinary sodium level, urinary potassium levels and urinary urea nitrogen determined on urine samples collected at the predefined time points.

Method used for PNa kinetics calculations

a) The PNa correction rate was established before and after the first DDAVP administration through the following calculation (Figure E1):

- Before DDAVP: PNa correction rate= $(PNa_{bef}-PNa_{i})/T_{bef}$

- After DDAVP: PNa correction rate= $(PNa_{aft24}-PNa_{aft})/T_{aft,}$

where $PNa_{i,}$ stands for the first recorded PNa at hospital admission (Ti), PNa_{bef} for the last PNa assessment before the first DDAVP administration and PNa_{aft} the first PNa obtained 2 to 6 hours after the first DDAVP administration. PNa_{aft24} stands for the PNa assessment obtained 24 hours after the first DDAVP administration, or prior a subsequent DDAVP administration when it occurred less than 24 hours after the first DDAVP injection. T_{bef} represents the time elapsed between Ti and PNa_{bef} . T_{aft} represents the time elapsed between the PNa_{aft24} and PNa_{aft} assessments.

b) The maximal magnitude of PNa variation before and after DDAVP (Figure E1) were determined as:

- Delta PNa pre-DDAVP=PNa_{maxbef}-PNa_{minbef}

- Delta PNa post-DDAVP=PNa_{maxaft}-$PNa_{minaft,}$

where PNa_{maxbef} and PNa_{minbef} represent the highest and the lowest PNa noted prior to the first DDAVP administration, respectively and PNa_{maxaft} and PNa_{minaft} represent the highest and the lowest PNa recorded within 24 hours after the first administration of DDAVP.

c) The 24-hour and 48-hour increases in PNa after initial assessment (Ti) defined by:

- Delta PNa_{24}= PNa_{24}-PNai

- Delta PNa_{48}= PNa_{48} − PNai

where PNa_{24} represents the PNa level obtaiend 24 hours after initial assessment (Ti) and PNa_{48} the PNa level obtained 48h after initial assessment (Ti). For all patients the lowest PNa recorded was recorded at initial assessment and is therefore equal to PNai. It follows that PNa_{minbef} is also equal to PNai.

d) The PNa correction rate over time before and after DDAVP administration, estimated with a linear mixed-effects model to take into account for the existence of a correlation between repeated measurements. We used a piecewise linear model of the form: E(PNa) = α_0 + α_1*I(t > T0) + β_0*t + β_1*I(t > T0)*(t-T0), where T0 stands for the time of the first injection of DDAVP,

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and t the time of follow-up. In this model, α_0 represents the initial sodium plasma level, α_1 the change of sodium plasma level at the time of the first injection of DDAVP, β_0 the slope of the variation before DDAVP, and $\beta_0 + \beta_1$ the slope of the variation after DDAVP. Quadratic terms were tested, as for random intercepts and random slopes terms. Specifically this model provides for an estimate of: 1) the slope of the course of PNa before DDAVP, 2) the slope of the course of PNa after DDAVP, and 3) the change of PNa at the "breakpoint", that is the time point whereby the course of PNa was altered following the first DDAVP injection. A Student t test was used to compare the slope of the course of PNa prior and following DDAVP injection.

Re-lowering of PNa after DDAVP administration

Patients were classified in the re-lowering group when a negative PNa correction rate within 24 h after DDAVP was observed and/or when a Delta PNa at H48 was lower than a Delta PNa at H24. An episode of re-lowering was defined by consecutive decreases in two or more PNa levels. In patients undergoing re-lowering the following parameters were evaluated (Figure E3)

The magnitude of re-lowering (Delta re-lowering) determined as:

- Delta re-lowering= PNa_{bef}- $PNa_{relowering}$

Where PNa_{bef} stands for the last PNa recorded prior to DDAVP injection and the $PNa_{relowering}$ the minimum PNa level recorded during at the end of the first episode of PNa re-lowering. The results are expressed as absolute value.

The time to re-lowering was defined as the time elapsed between the first DDAVP injection and the first PNa evidencing a decrease in PNa.

The duration (T1) of the first episode of PNa re-lowering (PNa re-lowering rate 1) was defined by the time elapsed between consecutive decreases in PNa levels.

The PNa re-lowering rate 1 was determined as:

- PNa re-lowering rate 1 = $(PNa_{bef} - PNa_{relowering})$/T1.

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In patients with subsequent episode(s) of re-lowering we recorded the nadir of PNa (PNa_{nadir}), the delay in which it was reached (T2) and we calculated its corresponding correction rate (PNa re-lowering rate 2) as follows:

- PNa re-lowering rate 2= (PNa_{bef} −PNa_{nadir})/T2

In 6 instances $PNa_{relowering}$ was equal to PNa_{nadir} either because there was only one episode of re-lowering (n=3) or because the nadir of PNa was reached during the first episode of re-lowering (n=3).
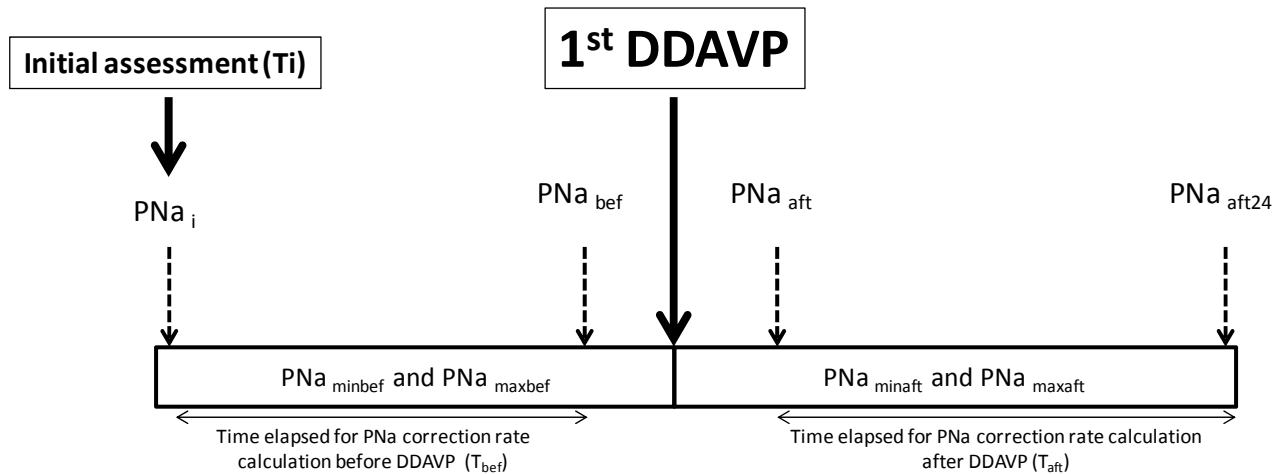
Figure E1: Time points and variables recorded for sodium level assessment before and after DDAVP administration

- PNa_i=PNa at initial assessment (Ti), for all patients the lowest PNa recorded before DDAVP administration was recorded at initial assessment and is therefore equal to PNai
- PNa_{maxbef} =Maximum PNa recorded from initial assessment (Ti) to 1st DDAVP administration
- PNa_{minbef} = Minimum PNa recorded from initial assessment (Ti) to 1st DDAVP administration. For all patients the lowest PNa recorded before DDAVP administration was recorded at initial assessment and is therefore equal to PNai
- PNa_{maxaft} = Maximum PNa recorded within 24 hours after 1st DDAVP administration
- PNa_{minaft} =Minimum PNa recorded within 24 hours after 1st DDAVP administration
- PNa_{bef} = Last recorded PNa before the 1st DDAPV administration
- PNa_{aft} = First recorded PNa after the 1st DDAPV administration (i.e 2-6h after administration for all patients)
- PNa_{aft24} = PNa 24 hours after the 1st DDAVP administration or less in case of a 2^{sd} DDAVP administration prior to 24h
- T_{bef} = Time elapsed betweeen initial assessment (Ti) and the last recorded PNa before the 1st DDAVP administration (PNa_{bef})
- T_{aft} = Time elapsed between PNa_{aft} assessment and PNa_{aft24} or less in case of a 2^{sd} DDAVP administration prior to 24h
- PNa correction rate before DDAVP administration = $(PNa_{bef}-PNa_{ai})/T_{bef}$
- PNa correction rate after DDAVP administration = $(PNa_{aft24}-PNa_{aft})/T_{aft}$
- Delta PNa pre-DDAVP = $PNa_{maxbef}- PNa_{minbef}$
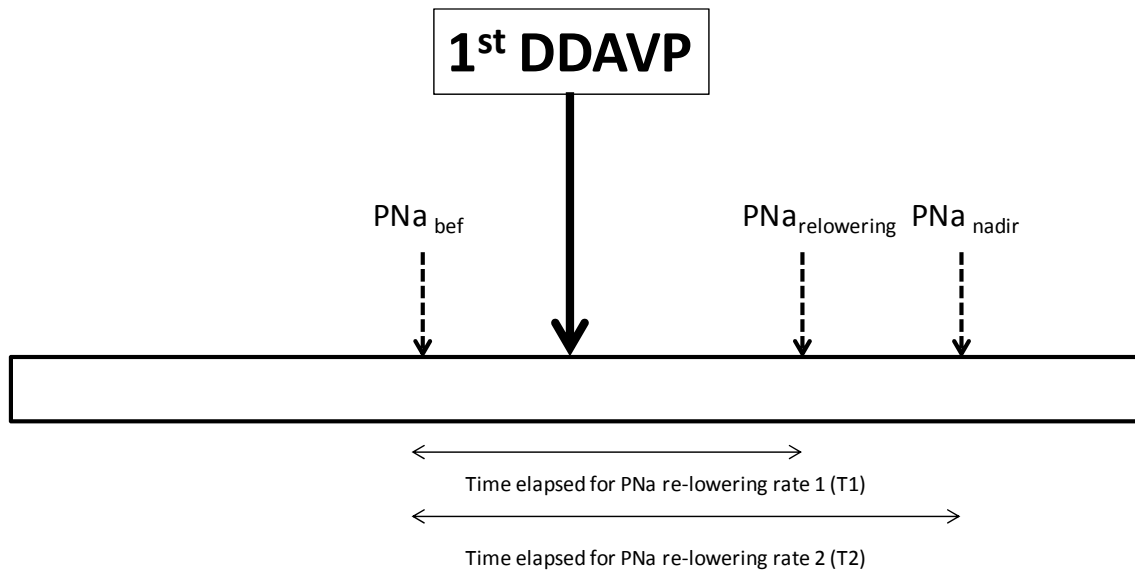- Delta PNa post-DDAVP = $PNa_{maxaft} - PNa_{minaft}$

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Figure E2: Time points and variables recorded related to PNa re-lowering after DDAVP administration

- PNa_{bef} = Last recorded PNa before the 1st DDAPV administration
- $PNa_{re-lowering}$=Minimum PNa recorded during the first episode of re-lowering
- PNa_{nadir}=Lowest PNa recorded after the 1st DDAPV administration
- PNa re-lowering rate related to the first episode of re-lowering: $PNa_{relowering\ 1}$= (PNa_{bef} - $PNa_{relowering}$)/T1
- PNa re-lowering rate related to the minimum PNa: $PNa_{relowering\ 2}$= (PNa_{nadir} –PNa_{bef})/T2
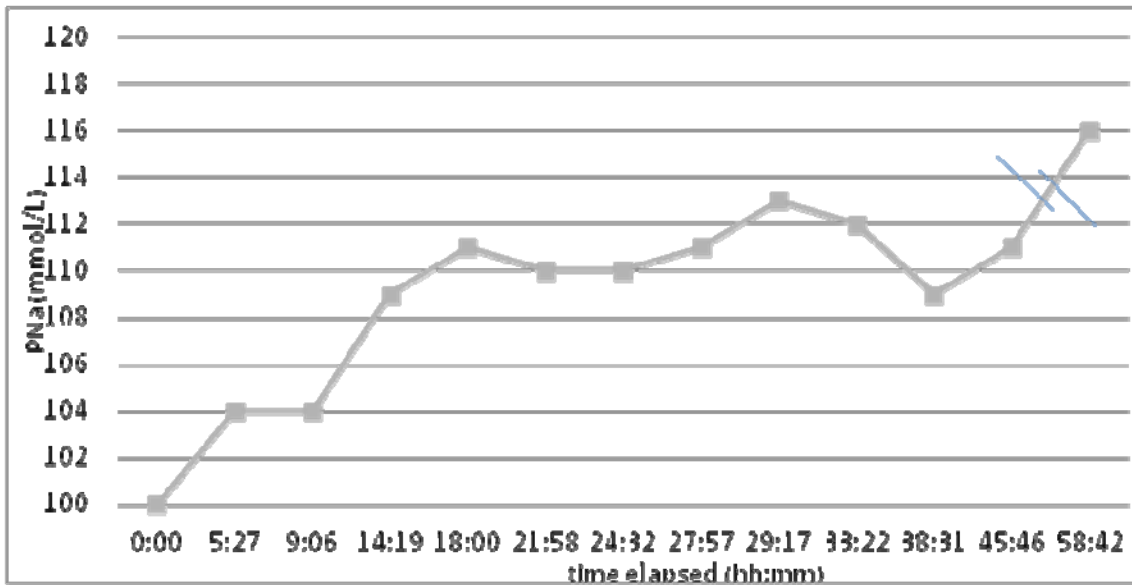
Figure E3: Time course of PNa in patient#8 in whom central pontine myelinolysis occurred