Journal of Pediatric Urology (2015) 11, 200.e1–200.e8

Predictive parameters of response to desmopressin in primary nocturnal enuresis

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Keywords
Desmopressin; Oral; Tablet; Enuresis; Child; Screening

Received 11 December 2014
Accepted 13 March 2015
Available online 21 May 2015

Summary

Introduction/Background
Many recent treatment guidelines have advocated the importance of a full noninvasive medical evaluation. To individualize treatment, special emphasis must be put on recording of the maximum voided volume (MVV) and nocturnal diuresis in a diary or frequency/volume chart.

Objective
The aim of this study was to identify any possible predictive factors to desmopressin response.

Study design
This study is a re-analysis of a prospective, open-label, multinational, phase-IV study evaluating ≤6 months of treatment with desmopressin tablets for children with primary nocturnal enuresis. The children were enrolled between April 2002 and December 2004 from 86 centers in four countries: UK, Canada, Germany and France. A total of 936 children were screened; 744 children aged 5–15 years participated in the study. Of these, 471 children completed the study with 6 months follow-up and recording in a frequency/volume chart. All children experienced six or more wet nights during the 14-day screening period. Exclusion criteria were: organic pathology, treatment for enuresis within the past year, previous treatment for enuresis for >4 weeks, diurnal symptoms, renal or central diabetes insipidus and the use of systemic antibiotics or other drugs known to affect desmopressin activity.

The predictive value of number of wet nights a week, fluid intake, daytime voiding frequency and diuresis was investigated by performing a multinomial logistic regression.

Results
Of the demographic variables, age was the only significant predictor for response to desmopressin. Controlling for age, the significant predictive variables were: number of wet nights a week, average voided volume daytime, maximum voided volume daytime, total daytime diuresis, nocturnal diuresis (see Figure), maximum voided volume 24 h and total 24 h diuresis. More than 80% of the children had no nocturnal polyuria and a low maximum voided volume.

Discussion
Performing a secondary analysis is a limitation because the original study was not designed for that. A new prospective study is ethically hardly defendable for children if data are available from previous literature [1]; therefore, a re-analysis was the appropriate choice. The study confirms the predictive value of age, number of wet nights a week and nocturnal diuresis [1,2].

Conclusions
The study demonstrates that desmopressin response rates are higher in children with greater age, limited number of wet nights a week and nocturnal polyuria.

Only a minority of a primary nocturnal enuresis population, based on history alone, had nocturnal polyuria. The majority had a low maximum voided volume. The results clearly stress the importance of a frequency/volume chart for individualizing therapy to the characteristics, thereby resulting in elevated success rates.

Registration number of clinical trial: Clinical Trials.gov NCT00245479.

http://dx.doi.org/10.1016/j.jpurol.2015.03.007

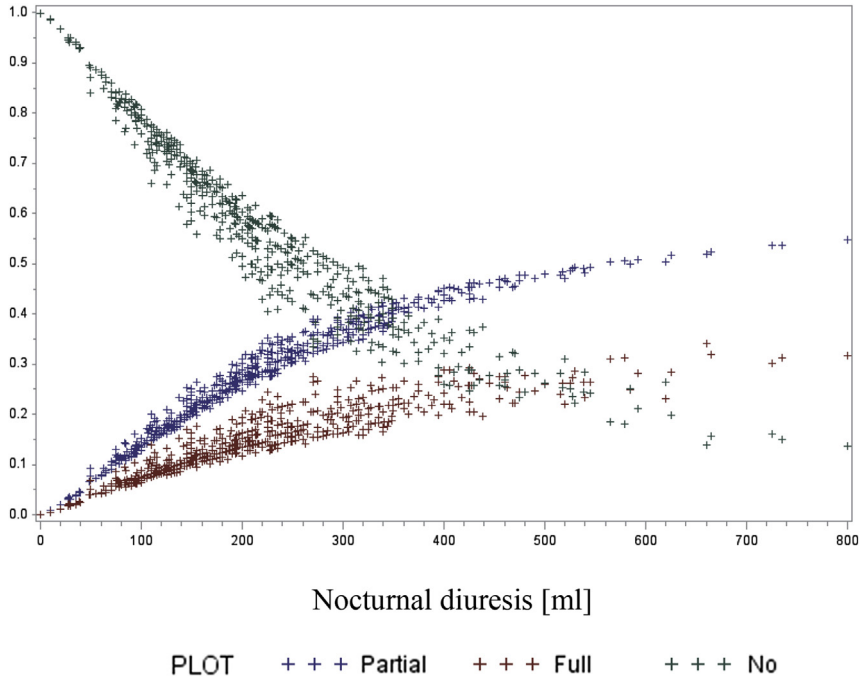

Figure Model-based predicted probabilities (y-axis) of partial, full and no response versus nocturnal diuresis (x-axis).

Introduction

A mismatch between the bladder capacity and nocturnal urine production plays a major role in the pathogenesis of nocturnal enuresis [3]. If the nocturnal urine production exceeds the bladder capacity, nocturia or enuresis occurs. The latter occurs if the child has a deficient arousal mechanism and cannot appropriately respond to the signals of a full bladder. Many recent guidelines have incorporated this, advocating the importance of a full noninvasive evaluation to individualize treatment, with special emphasis on recording the maximum voided volume (MVV) and the nocturnal diuresis in a diary or frequency/volume chart [4—6].

There are two evidence-based first-line treatments. One is the alarm therapy, which has a proven effect on the arousal mechanism and the MVV [7]. The other is desmopressin, which is an analogue of the naturally produced vasopressin and reduces nocturnal urine production [3]. International guidelines defend a rationalized strategy: the alarm should be the treatment of choice for children with reduced MVV without nocturnal polyuria and desmopressin is indicated in children with nocturnal polyuria and normal MVV.

A good frequency/volume chart provides information about diurnal and nocturnal diuresis, MVV, voiding frequency, incontinence, fluid intake and bowel habits. A nuanced and integrated diagnoses and an appropriate choice of therapy are only achievable by a global interpretation of these parameters [4]. The major parameters that need to be defined are MVV and nocturnal diuresis. Literature has failed, so far, to document the beneficial effects of the evaluation parameters in individualizing therapy leading to higher success rates. The discrepancy between the high response rate to desmopressin in initial studies [8—11] and the lower success rates to desmopressin in later Cochrane analysis [12] remains unexplained.

The aim of this study was to investigate which parameters of the frequency/volume chart are the best predictors for desmopressin therapy. Based on the original study [1] and previous literature, it was hypothesized that nocturnal diuresis predicts response to desmopressin. Furthermore, because of the limited response rate in the original study [1], it was hypothesized that only a minority of the children with primary enuresis have nocturnal polyuria.

Material and methods

This study is a re-analysis of a prospective, international, open-label, phase-IV study evaluating $\leq$6 months treatment of children with primary nocturnal enuresis using desmopressin tablets (desmopressin response in primary enuresis study, DRIP-study) [1]. Further details of this intention-to-treat study can be found elsewhere [1].

The children were enrolled between April 2002 and December 2004 from 86 centers in four countries: UK, Canada, Germany and France. A total of 936 children were screened; 744 children aged 5—15 years participated in the study. Of these, 471 children completed the study with 6-months of follow-up and recording a frequency/volume chart. The 531 boys (71%) and 213 girls (29%) had no organic pathology and experienced six or more wet nights during the 14-day screening period. Exclusion criteria were: organic pathology, treatment for enuresis within the past year, previous treatment for enuresis for $>$4 weeks, diurnal symptoms, renal or central diabetes insipidus and the use of systemic antibiotics or other drugs known to affect desmopressin activity. The children were considered to have monosymptomatic nocturnal enuresis, although the