

Vaptans for edematous and hyponatremic disorders in childhood: a systematic literature review

Running title: Vaptans in childhood

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What is already known about this subject:

- Vaptans produce an increase of the electrolyte-free water, which tends to correct hyponatremia and edema.
- In adults, vaptans are effective in raising circulating sodium of hyponatremic patients affected among others by chronic heart failure or advanced liver disease.

What this study adds:

- Vaptans have been used in >200 children, most of whom were affected by heart disease.
- Also in children, vaptans are effective in increasing diuresis, and in raising circulating sodium of hyponatremic patients.

Abstract

Aims: To systematically review the use of vaptans (nonpeptide vasopressin receptor antagonists) in children.

Methods: Through a database search (Web of Science, the National Library of Medicine, Excerpta Medica), we identified case series and case reports and extracted clinical and laboratory data.

Results: Twenty-six articles, published since 2008, reported on 226 patients. Among 115 children with hyponatremic (n=63) and edematous disorders (n=52), a 48h course of tolvaptan with an initial dose of 0.38 ± 0.27 mg/kg was administered in 106, while intravenous conivaptan was reported in 9 cases. An increase ($p < 0.02$) in urine output was shown in both edematous (from 3.2 ± 2.0 to 5.3 ± 6.7 mL/kg/day) and hyponatraemic (from 3.0 ± 1.5 to 4.4 ± 2.3 mL/kg/day) patients. In these latter, sodium increased from 125 ± 6 to 133 ± 6 mmol/L ($p < 0.0001$). The increase in sodium level correlated with its basal value, but not with the administered vaptan dose.

Among 111 children undergoing cardiac surgery, after tolvaptan 0.21 ± 0.01 mg/kg/day, mostly combined with conventional diuretics, an increase in diuresis by $41 \pm 4\%$ was seen within 24h ($p < 0.0001$). Similarly, a single add-on dose of tolvaptan 0.45 mg/kg allowed a reduced additional intravenous furosemide administration (0.26 ± 0.23 versus 0.62 ± 0.48 mg/kg, $p < 0.005$). Side effects were rarely reported, and included excessive thirst and xerostomia in seven, skin rash in one and elevated aminotransferases in one patient(s).

Conclusion: Vaptans appear to be safe for edematous and hyponatremic disorders also in children. Although they increase diuresis and natremia, no superiority to traditional diuretics and sodium supplements has been demonstrated. Reported side effects are rare and non-serious.

1. Introduction

Vasopressin, also known as antidiuretic hormone, is implicated in fluid homeostasis and in the pathogenesis of edematous and hyponatremic disorders [1-3]. Over the past two decades, the development of nonpeptide vasopressin receptor antagonists for the management of edematous and hyponatremic disorders has nearly exploded. These drugs, known as vaptans, antagonize the effect of vasopressin by binding to the type 2 vasopressin receptor in the kidney collecting ducts, therefore increasing water excretion. It has been therefore proposed that vaptans might be a valuable new tool for the management of some types of edematous and hyponatremic disorders, like for example the syndrome of inappropriate vasopressin secretion, cardiorenal syndrome and nephrotic syndrome [1-3]. Finally, fluid management, a crucial task following cardiac surgery, is a further possible indication for vaptans [4].

The main side effects of vaptans are thirst and dry mouth, which may limit the rise in sodium concentration. Furthermore, the use of tolvaptan has been occasionally associated with increased aminotransferase levels [5].

Information on vaptans in infants and children is very limited. This review aims at analyzing the literature dealing with vaptans in this age group.

2. Methods

2.1. Search Strategy

We conducted this review following the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations [6]. Searches were performed in three databases (Web of Science, the National Library of Medicine, and Excerpta Medica) to January, 2022. Original reports with

no date or language limits were considered. The search strategy incorporated the terms (conivaptan OR tolvaptan OR vaptans) AND (childhood OR child OR pediatrics) AND (anasarca OR edema OR hyponatremia). References listed within bibliographies of the retrieved records and publications already known to us were also considered.

Two authors independently screened the identified titles and abstracts in an unblinded fashion. Upon retrieval of candidate reports, full-text publications were reviewed for eligibility. During the entire process, uncertainties were solved through discussions and consensus. Institutional Review Board approval was not required for this literature review.

2.2. Eligibility criteria

We included original articles and letters reporting humans 18 years or less of age with an edematous or hyponatremic disorder, who were treated with a vaptan. Children managed with a vaptan after heart surgery were also retained. Reports addressing the use of vaptans in polycystic kidney disease, in which a different mechanism of action is exploited, were not included [7].

2.3. Data Extraction

Data were collected using a checklist and transcribed into a spreadsheet. The data extracted for reports meeting inclusion criteria were demographics, underlying condition, comedication (including supplementation with salt), laboratory values, diuresis, chosen vaptan (and mode of administration), duration of vaptan treatment and possible side effects (including excessive thirst, dry mouth, and elevated aminotransferase levels). When needed, attempts were made to contact authors of the original reports to obtain missing data.

2.4. Completeness of reporting

Completeness of reporting was judged for each included case using the following three components [8]: 1. description of history, physical examination and previous treatment; 2. information on dosage and treatment duration; and 3. information on laboratory values and urine output. Each component was rated as 0, 1, 2, or 3 and the reporting quality was graded according to the sum of each item as excellent (9), good (6 to 8), or acceptable (3 to 5).

2.5. Analysis

Categorical data are given as counts and were analyzed using the Fisher exact test. Continuous data are presented as mean and standard deviation and were compared using analysis of variance with the Tukey post-test. The formulas recommended by Hozo et al. were used to estimate mean and standard deviation from median, range and size of a sample [9]. Two-sided P-values of <0.05 were considered statistically significant.

3. Results

3.1. Search Results

The literature search process is summarized in Figure 1. For the final analysis, we retained 26 reports published since 2008 [10-35]: 10 from Asia (Japan, N=7; Turkey, N=3), 8 from Europe (United Kingdom, N=3; Germany, N=2; France, N=1; Italy, N=1; Spain, N=1) and 8 from the United States of America. The included articles described 226 patients. Reporting completeness was excellent in 34, good in 191 and acceptable in the remaining case.

3.2. Findings

3.2.1. Hyponatremic and edematous disorders

3.2.1.1. Basal data

Four articles included a total of 93 cases, which were analyzed retrospectively. The remaining 20 reports included 22 cases: 19 single case reports and one article describing 3 cases. The main indication for treatment was edema in 63 (52% males and 48% females) and hyponatremia in 52 (56% females and 44% males) patients, as depicted in table 1. Eighty-five percent of cases were affected by a congenital heart disease. Nervous system diseases, kidney diseases and oncological diseases accounted for most of the remaining cases. All edematous children and the great majority (80%) of hyponatremic children were on treatment with at least one diuretic. The management rather often also included sodium supplementation, fluid restriction and glucocorticosteroids (more frequently in hyponatremic than in edematous patients).

3.2.1.2. Treatment with vaptans for 48 hours

An initial oral tolvaptan dose of 0.38 ± 0.27 mg/kg body weight was given in 106 cases [10-24, 26-33, 35]. An identical tolvaptan dose was administered 24 hours later in 92 cases [10-13, 15, 17-24, 26-28, 31-33]. The tolvaptan dose was increased (from 0.33 to 0.66 mg/kg body weight) respectively decreased (from 0.28 to 0.14 mg/kg body weight) in each one case [27,28]. A second dose of tolvaptan was not administered in the remaining 12 cases [14, 16, 29, 30, 35]. Intravenous conivaptan was administered in 9 cases: an initial bolus of 0.34 ± 0.15 mg/kg body weight [10-13], followed by maintenance of 0.34 ± 0.13 mg/kg body weight per day in eight cases [10-

12]. A second bolus of 0.20 mg/kg body weight was administered 12 hours later in the remaining case [13].

Sodium values and urine output immediately before and 48 hours after tolvaptan or conivaptan were assessed (figure 2). The basal urine output was similar in edematous and hyponatremic patients before vaptans ($p=ns$), while the blood sodium level was significantly lower in hyponatremic than in edematous patients ($p<0.0001$). Medication with vaptans was followed by a significant increase in urine output in both groups of patients (edematous: from 3.2 ± 2.0 to 5.3 ± 6.7 mL/kg body weight daily, $p<0.02$; hyponatremic: from 3.0 ± 1.5 to 4.4 ± 2.3 mL/kg body weight daily, $p<0.01$). Sodium was almost identical before and after vaptans in edematous patients (from 132 ± 8 to 134 ± 5 mmol/L, $p=ns$) but significantly increased in hyponatremic patients (from 125 ± 6 to 133 ± 6 mmol/L, $p<0.0001$). The urine output and the sodium level were similar in the two study groups after vaptans ($p=ns$).

The correlation between basal sodium and increase induced by vaptans was studied in 22 hyponatremic cases [10-13, 15, 17-23, 27, 28, 31-33]. In these patients, the increase in sodium level after 48 hours significantly ($p<0.01$) correlated with its basal value (figure 3). On the contrary, no significant correlation was noted between the vaptan dose and the increase in sodium level ($p=ns$).

3.2.1.3. Treatment with vaptans for one week

In 26 edematous and two hyponatremic cases, oral tolvaptan (0.5 ± 0.3 mg/kg body weight per day) was given for about one week [17, 28, 31, 33]. The urine output, which was 3.9 ± 2.4 mL/kg body weight daily before treatment, was 5.3 ± 2.3 mL/kg ($p=0.10$) body weight daily three days later and 6.7 ± 4.1 mL/kg body weight daily ($p<0.01$) one week later.

3.2.1.4. Treatment with vaptans for 6 months or more

In seven hyponatremic patients, tolvaptan was given for 6 months or more [15, 19, 22, 26, 27]. Circulating sodium, which was 128 ± 4 mmol/L before tolvaptan, was found to be 134 ± 4 mmol/L ($p < 0.05$) two days later and 138 ± 4 mmol/L ($p < 0.005$) one month later (0.2 ± 0.1 mg/kg body weight per day). Six months after starting tolvaptan, sodium was ≥ 135 mmol/L in all cases.

3.2.1.5. Speed of correction

Individual sodium levels before and 48 hours respectively 10 days after tolvaptan or conivaptan were documented in the cases presented in figure 4. A correction of sodium of more than 16 mmol/L in 48 hours was observed in 5 out of 22 cases [13, 16, 28, 30, 35].

3.2.1.6. Side effects

A skin rash was observed in one [23], excessive thirst and dry mouth in seven cases [10,21]. Information on aminotransferase levels before and after treatment with tolvaptan was provided for 69 cases [17, 19, 20, 21, 26-27, 30-32, 35]. The mentioned parameters were within normal ranges both before and on treatment in 68 cases. Slightly increased aminotransferase levels were observed on tolvaptan in one Japanese child [21].

3.2.2. After heart surgery

Two retrospective studies analyzed the effect of oral tolvaptan in children undergoing open heart surgery.

Eighty-six infants 1.2 ± 0.2 years of age were given tolvaptan 0.21 ± 0.01 mg/kg body weight daily, mostly (N=84) combined with conventional diuretics [34]. This treatment regimen was followed by

a significant increase in diuresis by $41 \pm 4\%$ 24 hours later ($p < 0.0001$) and by $52 \pm 6\%$ 7 days later ($p < 0.0001$). This treatment strategy was associated with a tendency to correct hyponatremia in cases with this dyselectrolytemia (no detailed corresponding information was provided). Transient self-remitting hypernatremia (151 mmol/L) was observed in one of the 86 cases.

In a second study with 43 children (2.3 ± 3.2 years of age), a single add-on dose of tolvaptan (0.45 mg/kg body weight) was given in 25 cases [25]. As compared with the remaining 18 cases, this treatment strategy allowed a reduced additional intravenous furosemide administration (0.26 ± 0.23 versus 0.62 ± 0.48 mg/kg body weight; $p < 0.005$) without any deleterious effect on central venous pressure and urine output. In this study, the circulating sodium level was normal both before and after tolvaptan.

4. Discussion

Vaptans produce a selective water diuresis without affecting sodium and potassium excretion [1,3]. The ensuing loss of electrolyte-free water tends to correct hyponatremia and edema [1,3]. The results of the present literature review indicate that oral tolvaptan and intravenous conivaptan have so far been prescribed in more than 200 children. The majority of them were affected by a chronic heart disease, presented with apparently refractory hyponatremia or edema and were prescribed a vasopressin antagonist for compassionate use.

Despite the obvious limitations of the present systematic review, the results generally confirm those reported in adulthood. In the latter age group, well-designed studies have shown that oral (tolvaptan or lixivaptan) or intravenous (conivaptan) vaptans are effective in raising circulating sodium of hyponatremic patients affected among others by chronic heart failure or advanced liver disease both in and out of the hospital. Most patients had asymptomatic or mildly

symptomatic hyponatremia and a sodium concentration close to normal. The increase in sodium level in these studies ranged on the average between 2 and 7 mmol/L in 24 hours [1-3]. Furthermore, a correction of hyponatremia exceeding 8 mmol/L in 24 hours was observed in about every fifth case (mostly in patients with more severe hyponatremia at baseline). Finally, thirst, often associated with dry mouth, increases substantially with these drugs, which may limit the rise in blood sodium level [1-3]. Finally, an increase in aminotransferase level sometimes occurs while on tolvaptan [5].

It is currently unclear whether vaptans have added a new tool to the treatment armamentarium of chronic edema and hyponatremia [36, 37]. In adult patients with edema resistant to typically effective doses of loop diuretics, concurrent administration of thiazide-diuretics, which block distal sodium chloride reabsorption, is usually advised [36, 37]. Furthermore, recent results provide a rationale for the concurrent use of glifozins, which inhibit the proximal tubular sodium-glucose transporter [37, 38]. On the contrary, there is presently no clear-cut role for vaptans in resistant edema [37]. Although several therapeutic approaches are available for chronic hyponatremia including urea, fluid restriction and salt tablets, vaptans provide a simplified and appealing approach in this setting [39-41]. A further case for vaptan therapy is hyponatremia in subjects awaiting liver transplantation [39-41].

Recently, tolvaptan has also been shown to slow the progression of cyst development and kidney failure in adult patients with autosomal dominant polycystic kidney disease, the most common inherited disorder of the kidney [5]. A trial in pediatric patients is currently underway [7].

5. Conclusions

Vaptans appear to be safe for edematous and hyponatremic disorders in childhood. They might therefore be considered as part of the therapeutic armamentarium for these conditions. However, despite a solid pathophysiological rationale, vaptans have so far not dramatically changed the treatment of edematous and hyponatremic disorders in adults [39]. Additional clinical trials with selected populations including among others children may be warranted.

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CONFLICT OF INTEREST STATEMENT

There are no competing interests to declare.

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DATA AVAILABILITY STATEMENT

The data presented in this study is available from the corresponding author upon reasonable request.

CONTRIBUTORS

Dr. Bianchetti and Dr. Lava conceived the study design, and wrote the draft of manuscript. Dr. Piffer and Dr. Milani conducted the literature search and performed article selection, data extraction and analysis, and reporting quality. Dr. Leoni-Foglia and Dr. Simonetti corrected the draft of the manuscript. All authors contributed to revising the manuscript and approved the final version.

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Table 1: Basal clinical data in 115 pediatric patients included in this review of the literature. Data are given as mean \pm SD or as frequency.

	All	Edema	Hyponatremia	P-value
N	115	63	52	
Age, years	4.1 \pm 5.4	2.9 \pm 4.6	5.6 \pm 5.4	
Underlying condition				
Heart disease	98	62	36	<0.001*
Nervous system disease	7	0	7	
Kidney disease	4	1	3	
Cancer	3	0	3	
Further conditions	3	0	3	
Management				
Diuretics	105	63	42	<0.001
Sodium supplementation	13	0	13	<0.001
Fluid restriction	12	1	11	<0.005
Corticosteroids	10	2	8	<0.05
Further drugs	6	0	6	<0.005

* versus further underlying conditions.

Figures - Legends

Figure 1

Vaptans in childhood. Flowchart of the literature search.

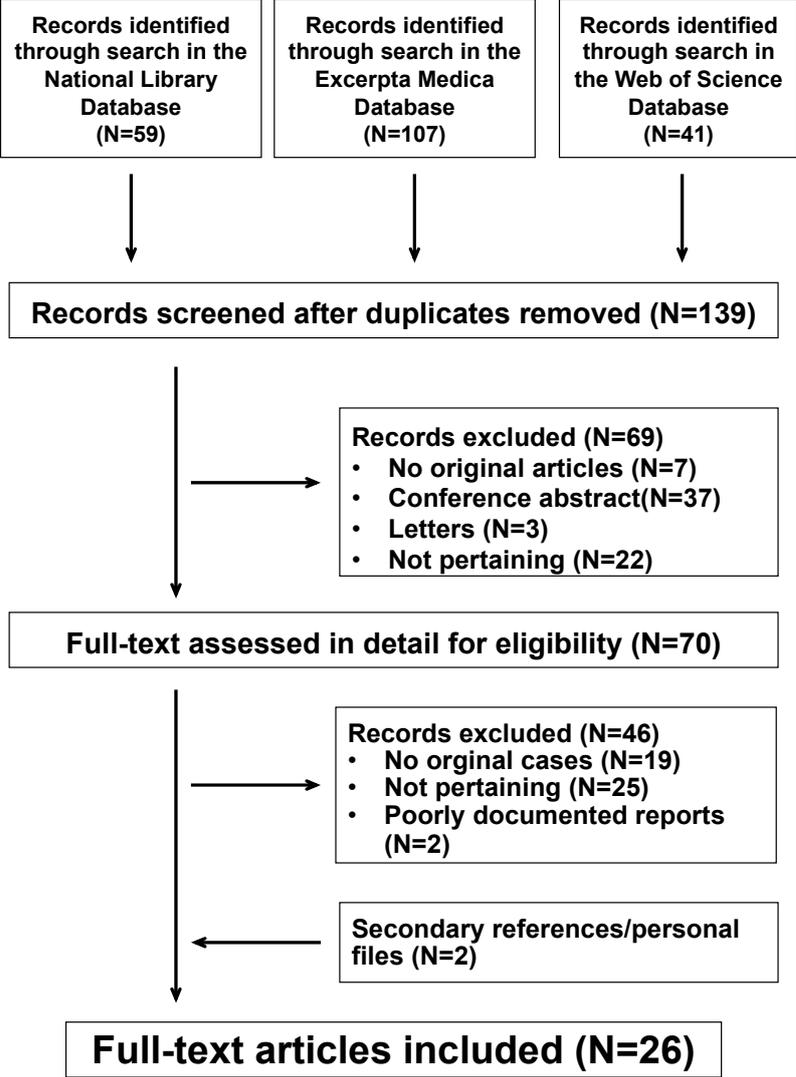


Figure 1

Figure 2

Sodium blood values and urine output immediately before and 48 hours after tolvaptan or conivaptan in children with

hyponatremic or edematous disorders.

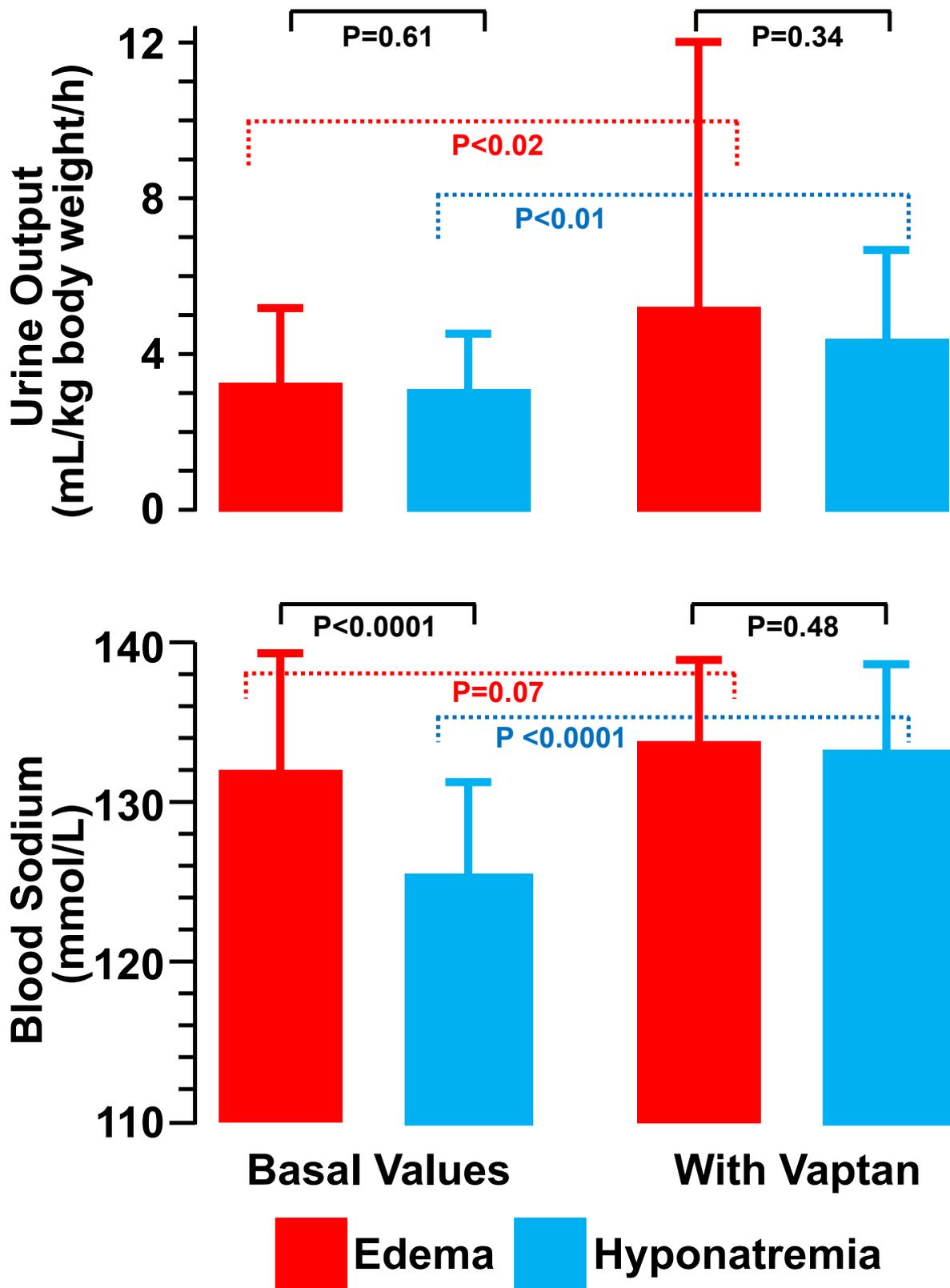


Figure 2

Figure 3

Relationship between basal sodium and increase in sodium after treatment with a vaptan for 48 hours in 22 hyponatremic children for whom this information was available. No significant correlation was noted between the vaptan dose and the increase in sodium level.

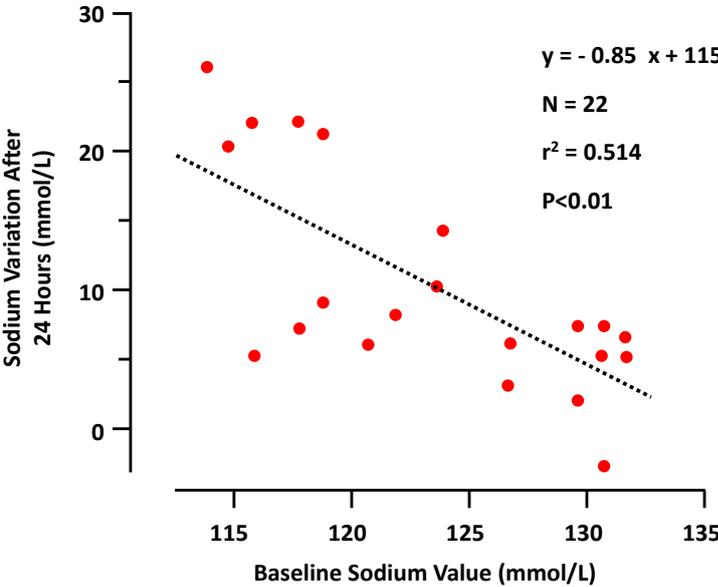


Figure 3

Figure 4

Individual sodium blood values before and 48 hours,
respectively 10 days, after tolvaptan or conivaptan.

Sodium Correction

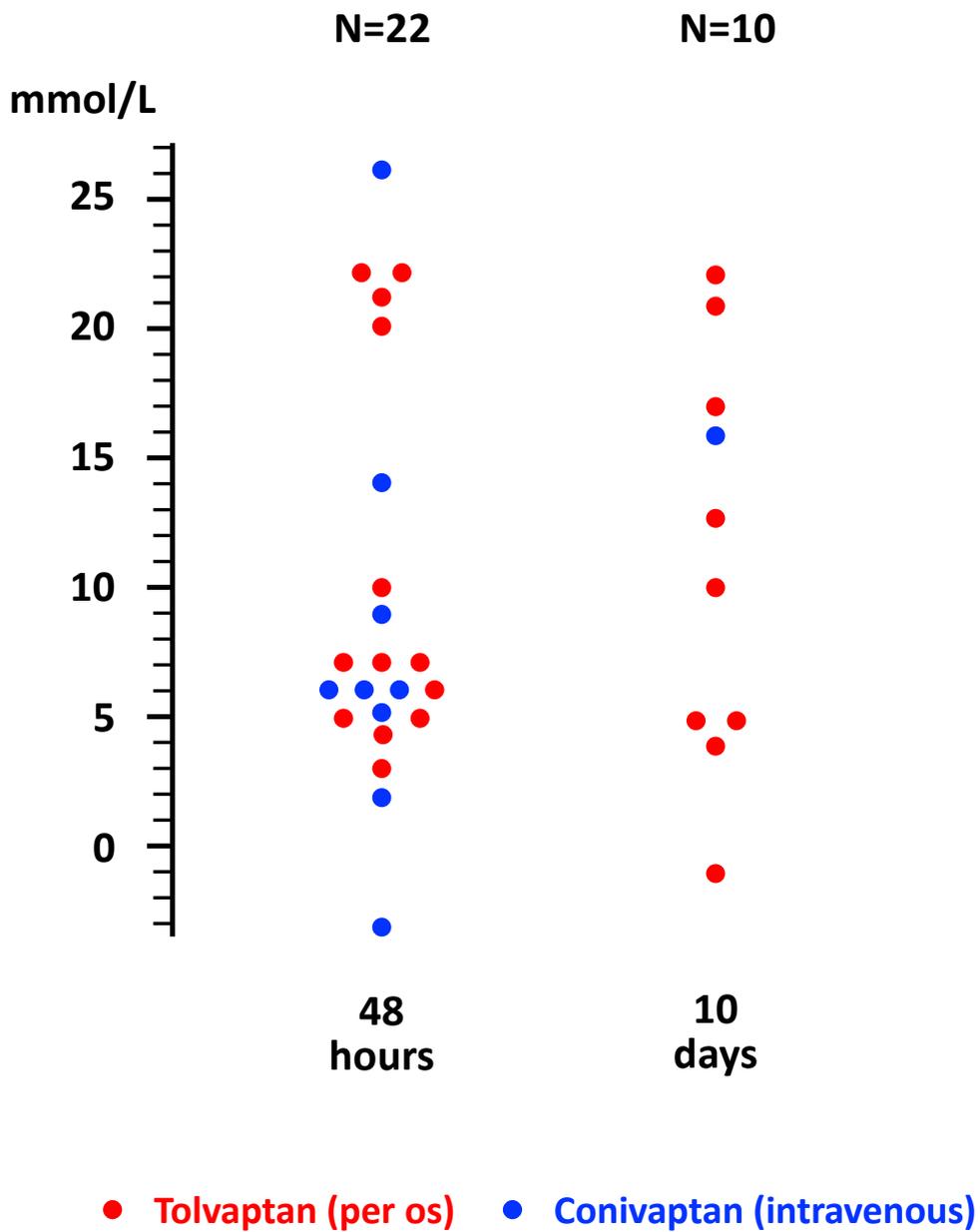


Figure 4