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Original Article

Copeptin Response to Clonidine Stimulation in Healthy Children

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ABSTRACT

Aim: The aim of this study was to evaluate whether clonidine, a centrally acting alpha-2-adrenergic agonist widely used in pediatric endocrinology for growth hormone (GH) stimulation testing, also induces copeptin release in children. Since copeptin is a stable, easily measurable marker of vasopressin, its stimulation could offer a practical diagnostic approach for distinguishing diabetes insipidus (DI) from primary polydipsia.

Materials and Methods: We conducted a prospective diagnostic pilot study including ten otherwise healthy children (age 3-14 years) undergoing standardized clonidine stimulation testing for suspected GH deficiency. Following oral administration of clonidine, serial blood samples were collected at predefined intervals in order to measure plasma GH and copeptin concentrations. Additionally, blood pressure and heart rate were continuously monitored in order to assess hemodynamic effects and overall tolerability. Adverse events and subjective tolerability were documented systematically.

Results: Administration of clonidine led to a significant reduction in systolic and diastolic blood pressure in all participants. However, contrary to expectations, copeptin levels decreased significantly in all subjects (p=0.013). No serious adverse events occurred, and overall tolerability of the test was rated as high, in line with clinical experience.

Conclusion: Contrary to the initial hypothesis, clonidine does not stimulate copeptin secretion in children and is unsuitable as a diagnostic tool for DI. Nevertheless, its high tolerability and consistent copeptin suppression warrant further exploration of its neuroendocrine effects.

Keywords: Copeptin, clonidine, diabetes insipidus, vasopressin, children

Introduction

Diabetes insipidus (DI) is a rare endocrine disorder characterized by excessive urine output (polyuria) and increased thirst (polydipsia), resulting from either insufficient production of or an inadequate response to vasopressin (1). Central DI is due to deficient vasopressin secretion, while nephrogenic DI arises from renal insensitivity to vasopressin (1,2). Primary polydipsia, on the other hand, is characterized by excessive fluid intake and, consequently, excessive diuresis (3). Discriminating between these subcategories is crucial as treatment for each condition differs considerably (3). Until recently, the indirect water deprivation test was the accepted diagnostic gold standard for differentiating between polyuric states, even though its diagnostic criteria were based on data from only 36 patients (4,5) and yielded a poor overall diagnostic accuracy of 70% (3). Additional measurements of plasma

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vasopressin concentrations to enhance the sensitivity of the water deprivation test did not overcome the test's limitations, mainly due to technical restrictions of the vasopressin assay (6). Copeptin, on the other hand, the C-terminal part of the vasopressin precursor, is released in equal amounts with vasopressin and provides a stable and easily measurable alternative (7). Several alternative tests for diagnosing DI based on copeptin measurements have been proposed (7,8). Measuring plasma copeptin after hypertonic saline infusion has been suggested as the most reliable method; however, it may lead to side effects such as thirst, nausea, dizziness, and headaches (6,9) due to the hypernatremia it causes. It also requires careful monitoring of plasma sodium concentrations (6).

Recently, the arginine stimulation test was developed (6). This test is based on the fact that arginine, as an alpha-receptor agonist, stimulates various anterior pituitary hormones, such as prolactin and growth hormone, and it is widely used as a simple and well-tolerated method for diagnosing growth hormone (GH) deficiency (6,10). Arginine-stimulated copeptin measurements are an accurate test for DI and are recommended as the first choice for distinguishing DI from other causes of polydipsia and/or polyuria (6). It is a simple and safe test which rarely causes side effects (6). Similar to arginine, glucagon, also an alpha-receptor agonist, can stimulate the secretion of GH and affect the neurohypophysis (10,11). Glucagon-induced increases in plasma copeptin have the potential to be used as a safe and precise test for the differential diagnosis of polyuria–polydipsia syndromes (11).

Clonidine is a centrally acting medication which functions as an agonist on alpha-adrenergic and imidazoline receptors (12). By stimulating alpha-receptors in the depressor area of the vasomotor center in the medulla oblongata and hypothalamus, clonidine lowers blood pressure, heart rate, total peripheral resistance, plasma renin activity, and the excretion of aldosterone and catecholamines in urine, with minimal effect on resting cardiac output, exercise response, or changes in kidney function (13). Furthermore, clonidine is used to treat a range of conditions, including attention deficit hyperactivity disorder, tics, cancer pain, neonatal opioid withdrawal, and symptoms linked to sympathetic overactivity, such as hot flashes, migraines, and restless leg (13,14). It is also used off-label for managing withdrawal, anxiety, insomnia, and post-traumatic stress disorder (14), as well as in the diagnosis of pheochromocytoma through a suppression test based on measuring catecholamine levels before and after clonidine administration (15). Additionally, clonidine is recognized as a stimulant of pituitary hormone secretion and it is used as a well-tolerated, straightforward tool for diagnosing GH deficiency. Clonidine affects GH secretion through selective activation of alpha-2-adrenergic receptors in the hypothalamus (10).

Alpha-adrenergic activation in the hypothalamus stimulates the secretion of GH-releasing hormone, leading to an increase in GH levels in plasma (10). At the same time, clonidine is believed to inhibit the endogenous release of somatostatin, which also contributes to increased GH release (10). However, the effect of clonidine on vasopressin secretion is poorly investigated.

The purpose of this study was to investigate whether clonidine, as a pituitary-stimulating agent, can also affect the release of vasopressin/copeptin. This investigation aimed to clarify whether the clonidine test can serve as a diagnostic method for DI and potentially for other conditions where copeptin may function as a diagnostic marker.

Materials and Methods

Study Design and Participants

This prospective diagnostic pilot study was conducted at the Pediatric Department of Sørlandet Hospital in Arendal, Norway, from August 2024 to April 2025. Ten children (5 males, 5 females) aged 3-14 years [mean 7.9 years, standard deviation (SD) 3.84] undergoing routine evaluation for short stature were enrolled. Table I presents the participants' age, gender, weight, and height data. Inclusion criteria included general good health and no history of DI, polyuria, or polydipsia. Exclusion criteria included acute illness, known endocrine disorders, and medications which affect vasopressin levels.

Ethical Considerations

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (approval number: 602201, date: 15.11.2023) and the Institutional Board at Sørlandet Hospital HF, Norway. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). Informed consent was obtained from both parents of each participant. The children received age-appropriate information and provided assent where applicable.

Procedures

Participants fasted overnight and arrived at the clinic at 08:00. Baseline measurements included height, weight, blood pressure, and urine osmolality. A peripheral venous catheter (PVC) was inserted for serial blood sampling.

Clonidine was administered orally at a dose of 0.10 mg/m² body surface area.

Blood samples were collected at baseline, as well as at 30, 60, 90, and 120 minutes after clonidine administration for the analysis of copeptin and GH. Blood pressure was measured at each time point. Subjective tolerability was assessed using a Visual Analog Scale (VAS) for symptoms such as nausea, dizziness, and fatigue.

Laboratory Analysis

GH was measured using an immunoluminometric assay (Immulite 2000xpi, Siemens Healthineers). Copeptin levels were measured via TRACE technology (Time Resolved Amplified Cryptate Emission) with the BRAHMS KRYPTOR system. The samples were analyzed at the Hormone Laboratory, Oslo University Hospital.

Statistical Analysis

Descriptive statistics were calculated. Changes in blood pressure, GH, and copeptin levels were analyzed using Friedman's test and the Wilcoxon signed-rank test. A p value of less than 0.05 was considered statistically significant. IBM SPSS Statistics version 21.0 was utilized.

Results

Blood Pressure Effects

Clonidine significantly reduced both systolic and diastolic blood pressure across all time points (p=0.006 and p=0.019, respectively) (Figure 1A and 1B).

Copeptin Response

The participants' copeptin levels are shown in Table II. Data were missing (N/A) for the baseline copeptin value for one participant (no. 4) due to technical issues. Significant differences were observed between the baseline copeptin values. The lowest measured value was 5.1 pmol/L, while the highest value was 37 pmol/L (M=13.03; SD=10.43).

Table I. Demographic characteristics of the study population: age, gender, weight, and height of participants

Participant no.	Age (years)	Gender	Weight (kg)	Height (cm)
1	11	M	26.0	135.5
2	3	M	11.4	89.5
3	10	F	31.3	135.4
4	8	F	20.6	120.1
5	8	F	18.2	116.0
6	3	F	12.2	90.6
7	3	F	14.4	96.0
8	8	M	23.2	124.5
9	11	M	23.7	135.0
10	14	M	42.7	148.6

Table II. Participants' copeptin levels at baseline and at 30, 60, 90, and 120 minutes during the clonidine test. Values in pmol/L

Participant no.	0 min	30 min	60 min	90 min	120 min
1	5.2	11.0	7.6	5.7	4.6
2	9.7	7.5	7.4	30.0	19.0
3	5.1	4.0	3.6	4.3	3.8
4	N/A	5.8	5.2	4.8	5.1
5	5.5	4.9	4.8	4.7	4.9
6	5.8	5.0	5.0	4.8	4.1
7	19.0	16.0	15.0	14.0	16.0
8	17.0	13.0	13.0	13.0	14.0
9	13.0	12.0	8.0	8.0	6.0
10	37.0	21.0	14.0	10.0	9.8

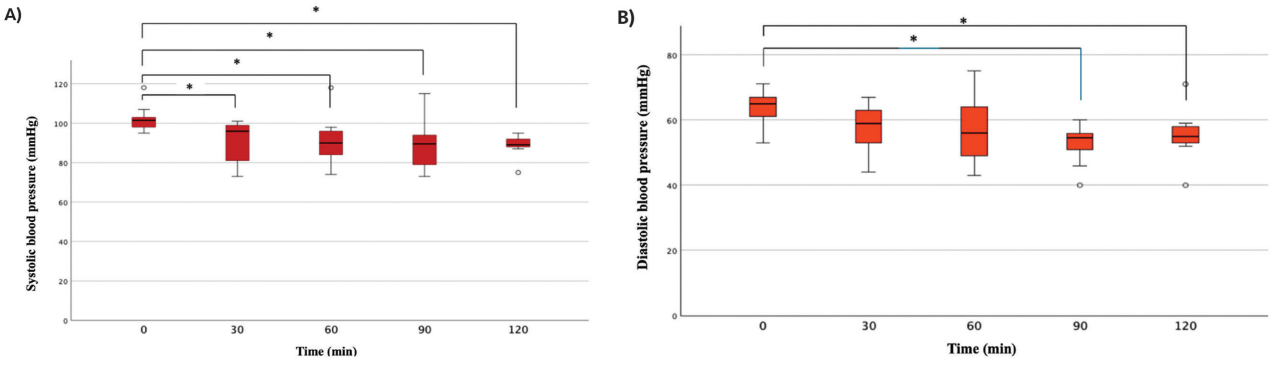

Figure 1. Blood pressure during the clonidine test. **A)** Changes in systolic blood pressure during the clonidine test. The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates statistically significant changes from time 0 ($p<0.05$) in systolic blood pressure values. **B)** Changes in diastolic blood pressure during the clonidine test. The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates the instances of diastolic blood pressure, between 0 minutes and 90 or 120 minutes, respectively, where the lowest level of statistical significance was achieved

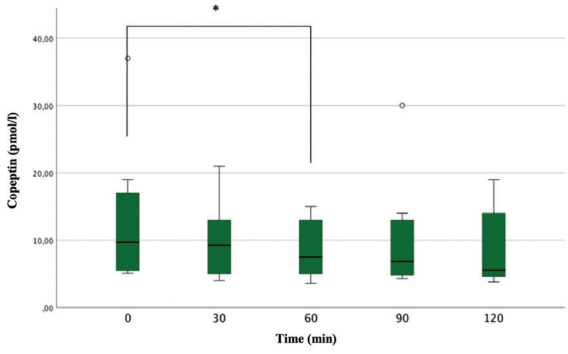

Figure 2. Distribution of copeptin values over time during the clonidine test. The vertical axis represents copeptin value (pmol/L), while the horizontal axis indicates time (minutes). The median (Q2) is shown as a black horizontal line within each box. The first quartile (Q1) is the lower edge of the box, while the third quartile (Q3) is the upper edge. The minimum and maximum values are illustrated by the lower and upper horizontal lines extending from the box, respectively. Outlier values are marked with "°". The symbol "*" indicates a statistically significant decrease in copeptin value between 0 and 60 minutes ($p=0.038$; Wilcoxon signed-rank test)

The distribution of the copeptin values over time for all participants combined is presented in Figure 2. Contrary to the initial hypothesis, all participants showed a statistically significant decrease in plasma copeptin levels after clonidine administration ($p=0.013$; Friedman's test) (Figure 2). No increases were seen at any time point.

Growth Hormone Response

GH levels increased significantly in four participants, confirming the expected stimulation. GH deficiency was indicated in six participants, consistent with their clinical evaluation (GH<10 µg/L) (10).

Test Tolerability

VAS scores showed high tolerability. The most common symptoms were mild fatigue and dizziness, which resolved spontaneously. No participant withdrew from the test.

Discussion

The aim of this study was to investigate whether clonidine, acting as a pituitary-stimulating agent, influenced the release of vasopressin/copeptin. This study involved children aged 3-14 years who underwent a clonidine stimulation test as part of the diagnostic evaluation for GH deficiency.

Copeptin, a stable byproduct of vasopressin synthesis, can be reliably measured in plasma and serves as a surrogate marker for vasopressin release (17). Copeptin levels respond rapidly to changes in osmolality, non-specific stress, and reductions in blood pressure (8). In our study, high baseline copeptin levels were observed, which may potentially be attributable to elevated osmolality or stress-related factors. Osmolality changes are known to significantly affect copeptin concentrations, which rise during dehydration and decline rapidly following fluid intake (18). In this context, we found that participants 4, 7,

8, and 9 had urine osmolality values exceeding the reference range, which may explain the higher baseline copeptin levels observed in participants 7, 8, and 9. Data were missing for the baseline copeptin value for participant no. 4 due to technical issues. These elevated urine osmolality values may be due to the fluid restriction for at least eight hours prior to testing, as per the study protocol. Furthermore, in the GH stimulation test, since the patient is kept fasting and without fluids overnight, elevated baseline copeptin levels should be expected. In this test, ten hours of dehydration have already occurred, and increased copeptin secretion is likely. However, in the hypertonic saline infusion test, the patient is not yet dehydrated because fluid intake has not been stopped. Therefore, the baseline copeptin measurements may have lost their diagnostic significance in the current study. Performing the clonidine-stimulated copeptin test without dehydration may yield different results. Additionally, psychological and procedural stress may have contributed to high copeptin levels. Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, leading to the secretion of adrenocorticotropic hormone, cortisol, and vasopressin (17). This could explain the elevated copeptin values in participants 2, 8, and 10, who also exhibited the highest cortisol levels. Participant 10 had both the highest cortisol and baseline copeptin levels. It is likely that PVC insertion and general hospital procedures induce stress, especially in young children. Furthermore, participants with higher baseline copeptin levels showed a more significant decrease over time. This decline, observed between baseline and the end of the test, was statistically significant, particularly between baseline and 60 minutes after clonidine administration. A further decline was noted at 120 minutes, though this was not statistically significant. Given the small sample size, these findings should be interpreted cautiously, as the observed copeptin changes may have been coincidental.

It is well established that a drop in blood pressure triggers the release of vasopressin (and thus copeptin), helping to maintain circulatory homeostasis through several mechanisms: vasoconstriction (via V1a and V1b receptors), water reabsorption (via V2 receptor activation), and sodium retention (through the activation of the renin-angiotensin system) (19,20). Clonidine, a centrally acting agent, stimulates alpha-adrenergic and imidazoline receptors (13). This suppresses sympathetic nervous system activity, resulting in reduced blood pressure (13). In our study, a statistically significant decrease in both systolic and diastolic pressure was observed in all participants. The most significant change was recorded at 90 minutes post-administration, confirming clonidine's hypotensive effect. This drop in blood pressure would typically be expected to stimulate the release of vasopressin/copeptin (19,20). Moreover, clonidine activates alpha-2-adrenergic receptors in the hypothalamus, promoting the release of GH from the pituitary gland (10). This is the rationale behind its use in GH stimulation testing, reflecting its similar impact on other pituitary hormones, as observed with arginine and glucagon (10). Based on this physiological background, we hypothesized that clonidine-induced hypotension and pituitary stimulation would result in increased vasopressin/copeptin secretion. However, our observations revealed a paradoxical outcome: while clonidine effectively reduced blood pressure, copeptin levels decreased instead of increasing. This result may be explained by clonidine's central inhibition of sympathetic tone. By reducing adrenaline and noradrenaline levels, clonidine lowers stress responses and decreases HPA signaling (14). The reduced sympathetic drive likely suppresses vasopressin/copeptin secretion, even in the presence of hypotension. The interplay between fluid balance systems and baroreceptor feedback may involve biphasic regulation of vasopressin, depending on physiological needs (14). In this case, central sympathetic suppression appears to dominate, overriding baroreceptor-induced vasopressin release. As a result, copeptin levels fell during clonidine administration. This finding is in concordance with two reported studies (20,21) which also reported a decrease in copeptin levels during clonidine stimulation, consistent with our findings.

Furthermore, the test was well tolerated with the participants reporting minimal discomfort, and all of the participants completing the test. Toward the end of the procedure, most participants became tired or fell asleep, which is a common side effect of clonidine. Mild reactions, such as fatigue, hypotension, and gastrointestinal symptoms, were observed, consistent with the existing literature (10,20,21).

Study Limitations

This study's small sample size limits its generalizability. Furthermore, the absence of a comparator group, such as participants undergoing arginine or hypertonic saline stimulation, represents a limitation. As this was designed as a pilot study, the primary objective was to explore clonidine's potential as a copeptin stimulant. However, this objective was not achieved, and further investigation in this direction will not be pursued.

Conclusion

This study confirms clonidine's established effects on GH stimulation and blood pressure reduction in children. However, contrary to expectations, clonidine did not stimulate copeptin release. Instead, it caused a paradoxical decrease in copeptin levels, likely due to its central suppression of sympathetic tone. These findings suggest that clonidine's inhibitory effects on the sympathetic nervous system may override vasopressinergic activation, despite hypotensive conditions. While clonidine remains a valuable and well-tolerated agent for GH stimulation testing, it cannot be recommended as a diagnostic stimulant for copeptin-based evaluation in DI or similar conditions.

Ethics

Ethics Committee Approval: This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics (approval number: 602201, date: 15.11.2023) and the Institutional Board at Sørlandet Hospital HF, Norway.

Informed Consent: They were included in the study after obtaining informed consent from their legal guardians.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.R.P., K.H., Concept: N.R.P., Design: N.R.P., Data Collection or Processing: N.R.P., J.K., K.H., Analysis or Interpretation: N.R.P., J.K., Literature Search: N.R.P., J.K., Writing: N.R.P., J.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

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