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Thiazide-Associated Hyponatremia: A Retrospective Cohort Study Comparing Hydrochlorothiazide Versus Indapamide Versus Chlorthalidone

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ABSTRACT

Hyponatremia is a crucial complication of therapy with thiazide diuretics. This study compares the epidemiological and biochemical profiles and hospital course of patients using hydrochlorothiazide (HCTZ), indapamide (INDA), and chlorthalidone (CTD) admitted with thiazide-associated hyponatremia (TAH). Data were obtained retrospectively from the hospital's digital registries. The epidemiological and biochemical parameters between the HCTZ, INDA, and CTD groups were compared. The correlation between dose and biochemical parameters in each group was performed. The thiazide groups without diuretic co-medication were compared (HCTZ vs. INDA), and the correlation between dose and biochemical parameters in each group was examined. A comparison of the HCTZ ($n = 135$), INDA ($n = 125$), and CTD ($n = 27$) groups identified differences in serum potassium (s-K; $p = 0.03$). The hyponatremia correction rate was slower in the CTD group at 96 h after admission ($p < 0.001$). After the exclusion of diuretic co-medication, the HCTZ group ($n = 64/135$) showed a higher prevalence of ARBs, s-K (both $p < 0.001$), and a lower median (IQR) equipotent dose (12.5 (o) mg vs. 2.5 (1.2) mg), prevalence of ACE-I ($p < 0.001$), and eGFR ($p = 0.03$), when compared to the INDA group ($n = 109/125$). In conclusion, except for s-K, we observed no significant difference in biochemical and epidemiological profiles between HCTZ, INDA, and CTD. After excluding the influence of other diuretics, we observed higher s-K in the HCTZ group compared to the INDA group, potentially explained by the lower equipotent dose of HCTZ. The CTD group showed a statistically significant trend of slower hyponatremia correction.

1 | Introduction

The term thiazide diuretics refers to a heterogeneous group of sulfur-containing compounds, which could be subdivided into compounds containing the benzothiadiazine ring (*thiazide* or sometimes called *thiazide-type*) and those lacking this chemical structure, which are called *thiazide-like* [1]. Both groups share the inhibition of thiazide-sensitive Na/Cl−cotransporter (NCC) in the proximal segment of the distal tubule of the nephron as their principal mechanism of action. However, it is essential to distinguish between thiazide and thiazide-like diuretics beyond their chemical structure due to differences in their pleiotropic effects,

pharmacokinetic parameters, and available evidence-based trials [1, 2].

Both thiazide and thiazide-like diuretics, even 60 years after their introduction to clinical practice, have been a mainstay in the therapy of primary hypertension [3]. The trend of preferring thiazide-like diuretics such as indapamide (INDA) or chlorthalidone (CTD) over thiazide diuretics such as hydrochlorothiazide (HCTZ) is notable at present, mainly due to their greater antihypertensive efficacy and better cardiovascular morbidity and mortality data [2, 4, 5]. However, the superiority of thiazide-like diuretics has not been confirmed in large population trials [6–8].

Compelling contraindications of use of thiazide or thiazide-like diuretics are hyponatremia, chronic kidney disease due to obstructive uropathy, and sulfonamide allergies. Caution is needed in gout, glucose intolerance, pregnancy, hypercalcemia, hypokalemia, and cancer patients with bone metastasis [9]. In terms of incidence, commonly labeled side effects include hypersensitivity reaction, maculopapular rash, and hypokalemia [10]. Hyponatremia, a well-known and clinically important complication in the therapy with both thiazide and thiazide-like diuretics, is often labeled as an uncommon adverse reaction [11]. If we considered only hyponatremia requiring hospitalization, we could be satisfied with this labeled frequency [12], but a more recent study suggests a more substantial excess risk for hyponatremia [11]. Generally, taking low doses of thiazide or thiazide-like diuretics is considered a rational strategy to prevent adverse outcomes without substantially compromising the benefits of their use [1]. However, even relatively low doses are observed to cause severe adverse events such as hypotonic hyponatremia.

Hyponatremia is defined as a decrease in the serum sodium concentration. The threshold for hyponatremia can vary slightly depending on the source and context, usually below 135–136mmol/L [13, 14]. If we based the threshold for hyponatremia on population distribution and defined hyponatremia as a value below the 2.5th percentile, we would get a value of 136.7 mmol/L [15]. The range between 130 and 135 mmol/L is sometimes considered controversial as it may not always correlate with significant clinical manifestations. The correlation between even mild chronic hyponatremia and mortality is well-established. However, it is uncertain whether chronic mild hyponatremia is the cause of increased mortality or simply correlates with the severity of the disease that raises the risk of mortality [16].

In connection with hypotonic hyponatremia and thiazides, usually two terms are used: thiazide-induced hyponatremia (TIH) and thiazide-associated hyponatremia (TAH) [17, 18]. TIH refers to hyponatremia caused clearly by thiazide or thiazide-like diuretics. TIH is dose-independent, affecting only susceptible populations, and shows great re-challenge potential [19]. The more extensive term TAH encompasses the hyponatremia that occurs when taking thiazide or thiazide-like diuretics. Since diagnosing TIH is highly challenging in actual clinical practice, the term TAH is more widely used [17, 18].

We have limited and partially conflicting results from head-to-head trials comparing the incidence of TAH among patients using thiazide or thiazide-like diuretics [8, 20–22]. Contrary to TIH, the incidence of TAH seems dose-dependent [23]. The half-life is assumed to play a key role in the risk of TAH development [21]. It is essential to state that the pathophysiology of TAH is a complex process, including the increase in fluid intake, impaired free-water excretion, and osmotic inactivation of sodium [17]. Moreover, genetic factors could be crucial in specific populations. These genetic factors include polymorphism in the renal outer medullary potassium channel (ROMK) [17] or the apical prostaglandin transporter of the distal nephron [18]. Therefore, determining the role the different pleiotropic effects of individual thiazides may have, besides different half-lives, would be of interest.

Despite the high prevalence of TAH among patients admitted for hypotonic hyponatremia, comparative studies on individual thiazides or thiazide-like diuretics regarding their impact on the course of hospitalization, severity of hyponatremia, and biochemical profile are sparse. This study aims to compare epidemiological and biochemical profiles and the course of hospitalization of patients using HCTZ, INDA, and CTD admitted for TAH. Further, this study aims to analyze the effect of dose on admission biochemical parameters and evaluate the eventual dose-dependent relationship.

2 | Method

The study design was set according to our previous studies with the extension of the enrollment period [26, 27]. The design was purposely set to reflect actual clinical practice, in which thiazide diuretics are commonly combined with other antihypertensive and diuretic therapies.

2.1 | Inclusion and Exclusion Criteria

Patients admitted to the Internal Medicine Department of the Tomas Bata Hospital Zlin during the period between 1.1.2016 and 31.12.2022 with a diagnosis of hypotonic hyponatremia (defined as serum sodium ≤135 mmol/L and serum osmolality <280 mmol/kg) and thiazide use were enrolled. Serum osmolality was calculated by the formula: serum osmolality = (2× serum Na [mmol/L]) + serum urea [mmol/L] + serum glucose [mmol/L] [28] and/or directly measured. Exclusion criteria were: one of the measured or calculated serum osmolality ≥280 mmol/kg, the need for dialysis, age under 18 years, and combination therapy of ≥2 thiazides. Further, patients with continued use of thiazide were excluded from the analysis of the course of hospitalization.

2.2 | Patient Enrollment

Patients were identified by retrospective data analysis of the hospital's digital registries. All patients were hospitalized in the Internal Medicine Department during the inclusion period for the diagnosis of E87.1 (hypo-osmolality and hyponatremia) and/or E22.2 (SIADH) according to the International Statistical Classification of Diseases and Related Health Problems, the 10th revision (ICD-10). The study assembly is shown in Figure 1.

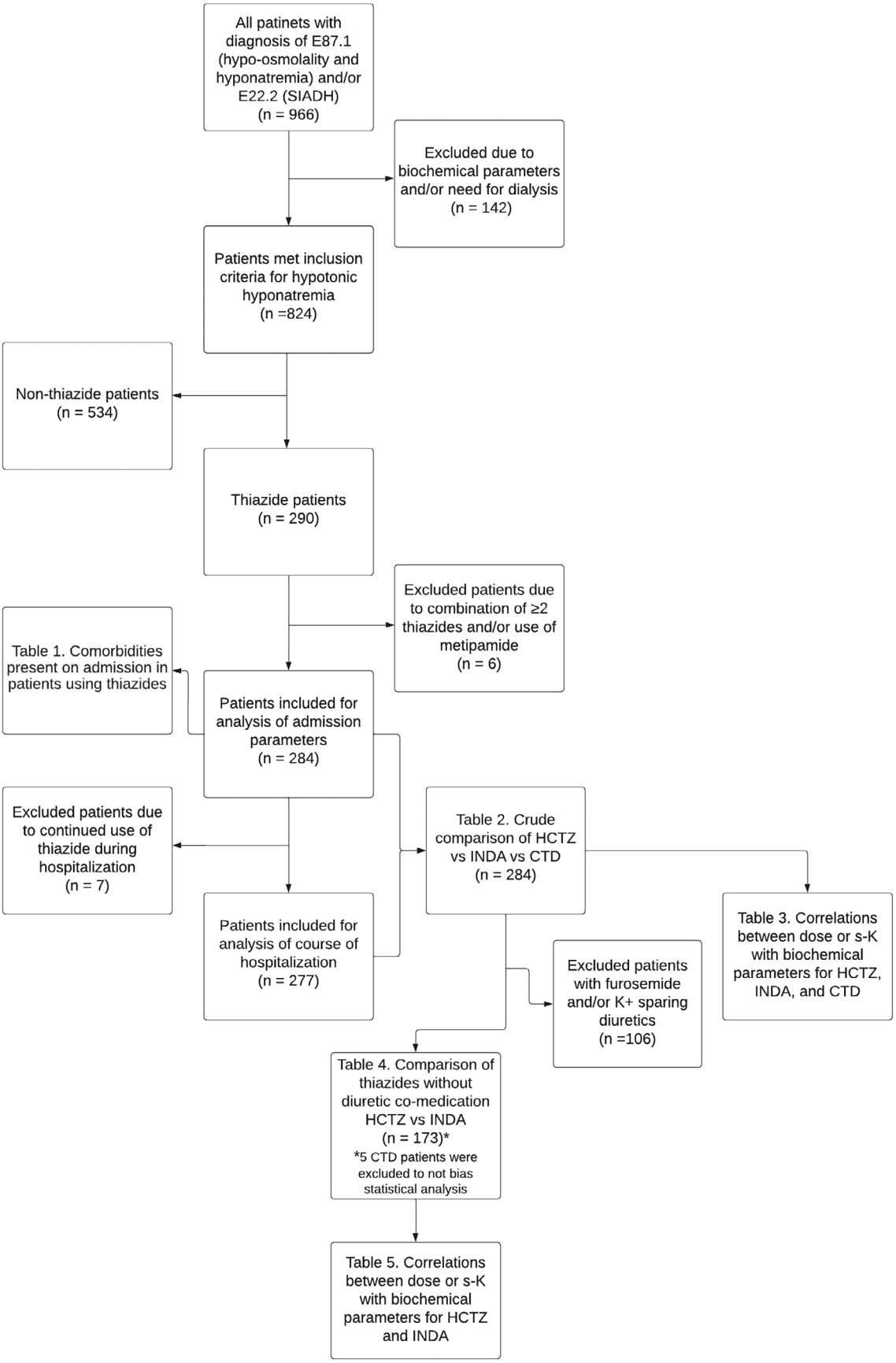

FIGURE 1 | Flowchart of study assembly.

TABLE 1 | Comorbidities present on admission in patients using thiazides.

	HCTZ ($n = 135$)		INDA ($n = 122$)		CTD ($n = 27$)		
	Number	**%**	**Number**	**%**	**Number**	**%**	***p* value**
Hypertension	131	97.0	119	97.5	26	96.3	0.998
Diabetes	51	37.8	47	38.5	15	55.6	0.39
GIT losses	55	40.7	40	32.8	12	44.4	0.49
Acute infection	40	29.6	34	27.9	4	14.8	0.40
Hepatic disease/cirrhosis	29	21.5	26	21.3	4	14.8	0.77
Chronic kidney disease	20	14.8	19	15.6	4	14.8	0.89
Alcohol abuse	11	8.1	15	12.3	5	18.5	0.18
Chronic heart failure	17	12.6	12	9.8	0	0.0	0.23
Active cancer	13	9.6	11	9.0	2	7.4	0.80
Ascites	3	2.2	1	0.8	0	0.0	—

2.3 | Data Collection

Blood samples and urine spots were obtained at admission. The biochemical analysis of blood samples included serum Na (s-Na), K (s-K), Cl (s-Cl), osmolality (s-osmolality), urea (s-urea), creatinine (s-creatinine), uric acid (s-UA), and glucose (s-glucose). Urine spots were biochemically analyzed for urine osmolality (u-osmolality), Na (u-Na), K (u-K), Cl (u-Cl), and creatinine (u-creatinine). The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI formula based on s-creatinine. Fractional excretions (FE) of Na, K, Cl, and uric acid (UA) were calculated by the formula FE = (u-Ion × s-creatinine)/(s-Ion × u-creatinine)*100.

Clinical symptoms and medication history were recorded as part of the admission protocol or obtained during the hospital stay by the patient or their caretakers if the patient was not conscious at admission. Mortality was obtained directly from the hospital's digital register. All data were analyzed retrospectively. Written informed consent was obtained from all the patients as part of the informed consent to hospital admission. The study design was approved by the Ethics Committee of The Tomas Bata Hospital (2023-22).

2.4 | Statistical Analysis

Normal distribution was tested using the Shapiro–Wilk test. Since almost all parameters are not normally distributed, we used non-parametric tests for further processing. Group comparisons of categorical variables were done with a chi-square test. For group comparisons of quantitative variables, the Mann-Whitney test for two medians and the Kruskal-Wallis test for three medians were done. Correlations were assessed using Spearman's rank correlation analysis. The statistical analyses were performed with SOFA Statistics version 1.5.3 (Paton-Simpson & Associates Ltd, Auckland, New Zealand) and *R* Statistical Software (R Core Team; 2021).

2.5 | Laboratory Methods

Sodium, potassium, and chloride concentrations in both serum and urine were measured by indirect ion-selective electrodes on an Abbott ci 16 200 Architect analyzer (Abbott Laboratories, Illinois, USA). Urea, creatinine (sarcosine oxidase-based enzymatic method), and UA in both serum and urine were measured on Abbott ci 16 200 Architect analyzer (Abbott Laboratories, Illinois, USA). Osmolality was measured by the freezing point depression method on Arkray Osmostation OM-6050 analyzer (Arkray Inc., Kyoto, Japan). Serum indices, including hemolytic, lipemic, and icteric indices, were measured to exclude the possibility of pseudohyponatremia.

3 | Results

The inclusion criteria for the analysis of admission parameters were met by 284 patients (HCTZ, $n = 135$; INDA, $n = 122$; CTD, $n = 27$). Inclusion criteria for analysis of the course of hospitalization were met by 277 patients (HCTZ, $n = 133$; INDA, $n = 118$; CTD, $n = 26$). The comorbidities present on admission in patients using thiazides are listed in Table 1. A crude comparison of HCTZ versus INDA versus CTD groups is shown in Table 2. It established differences in the prevalence of potassium-sparing diuretics ($p < 0.001$), angiotensin II receptor antagonists (ARBs; $p < 0.001$), angiotensin-converting enzyme inhibitors (ACE-I; $p < 0.001$), and s-K ($p = 0.03$). Also, a difference in the correction rate of hyponatremia at 96 h after admission was observed ($p < 0.001$). The correction rate of hyponatremia is shown in Figure 2.

No statistically significant difference was observed for the rest of the monitored parameters, including s-Na ($p = 0.83$) and mortality ($p = 0.11$). The median daily dose (interquartile range; IQR) was found to be 25 (12.5) mg in the HCTZ group, 2.5 (1.25) mg in the INDA group, and 12.5 (12.5) mg in the CTD group. Five patients were taking INDA 1.5 mg in a slow-release formulation.

Table 3 shows the correlations between dose or s-K and biochemical parameters. They revealed no statistically significant results.

Further, patients using thiazides with another diuretic co-medication were excluded ($n = 106$). The remaining five CTD patients were excluded to avoid biasing the statistical analysis. A comparison of patients using thiazide without diuretic co-

TABLE 2 | Crude comparison of HCTZ versus INDA versus CTD.

Admission parameters											
		HCTZ ($n = 135$)			INDA ($n = 122$)			CTD ($n = 27$)			
	Unit	Number	Median (IQR)	%	Number	Median (IQR)	%	Number	Median (IQR)	%	*p* value
Age	years	135	79 (11)		122	77 (14)		27	81 (9)		0.21
Female gender	—	98		72.6	92		75.4	22		81.5	0.61
ACE-I		41		30.4	100		82	9		33.3	<0.001
ARB		62		45.9	12		9.8	9		33.3	<0.001
Potassium-sparing diuretics	—	67		49.6	5		4.1	20		74.1	<0.001
Dose	mg	124	25 (12.5)		115	2.5 (1.25)		27	12.5 (12.5)		—
Serum											
Na	mmol/L	135	119 (8)		122	120 (10)		27	120 (11)		0.83
K	mmol/L	122	3.8 (0.9)		108	3.6 (0.9)		22	3.7 (0.7)		0.03
Cl	mmol/L	135	85 (9)		122	85 (12)		27	86 (9)		0.46
eGFR (CKD-EPI)	mL/min/ 1.73 m^2	135	68 (34)		122	76 (33)		27	76 (36)		0.07
Urine											
Osmolality	mmol/kg	83	353 (265)		82	345 (191)		16	324 (183)		0.71
Na	mmol/L	83	58 (52)		81	64 (50)		16	60.5 (32)		0.44
K	mmol/L	83	29 (33)		81	32 (34)		16	22 (30)		0.72
Cl	mmol/L	83	63 (60)		81	67 (54)		16	54 (50.5)		0.29
Fractional excretion											
Na	%	32	1.13 (1.27)		42	1.06 (1.19)		9	1.12 (0.58)		0.80
K	%	37	13.1 (13.1)		38	14.0 (11.3)		9	18.0 (21)		0.86
Cl	%	34	1.36 (1.93)		43	1.4 (1.45)		10	1.36 (0.7)		0.91
Uric acid	%	36	11.6 (11.5)		35	10.0 (6.45)		8	9.9 (4.6)		0.84
H_2O	%	44	1.86 (2.07)		42	1.59 (1.49)		10	1.83 (1.3)		0.61
Course of hospitalization											
		HCTZ ($n = 133$)			INDA ($n = 118$)			CTD ($n = 26$)			
	Unit	Number	Median (IQR)	%	Number	Median (IQR)	%	Number	Median (IQR)	%	*p* value
In-hospital mortality	—	12		9.0	5		4.2	0		0	0.11
Na morning after admission	mmol/L	122	126 (7)		116	126 (8)		25	123 (6)		0.63
Na + 24 h	mmol/L	117	130 (6.5)		98	129 (7)		23	128 (9)		0.78
Na + 48 h	mmol/L	104	132 (5)		93	131 (7.5)		23	131 (7)		0.47
Na + 72 h	mmol/L	81	134 (5)		75	133 (7)		14	134 (4)		0.052
Na + 96 h	mmol/L	74	135 (4)		64	135 (6)		16	133 (4.5)		<0.001

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonist; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

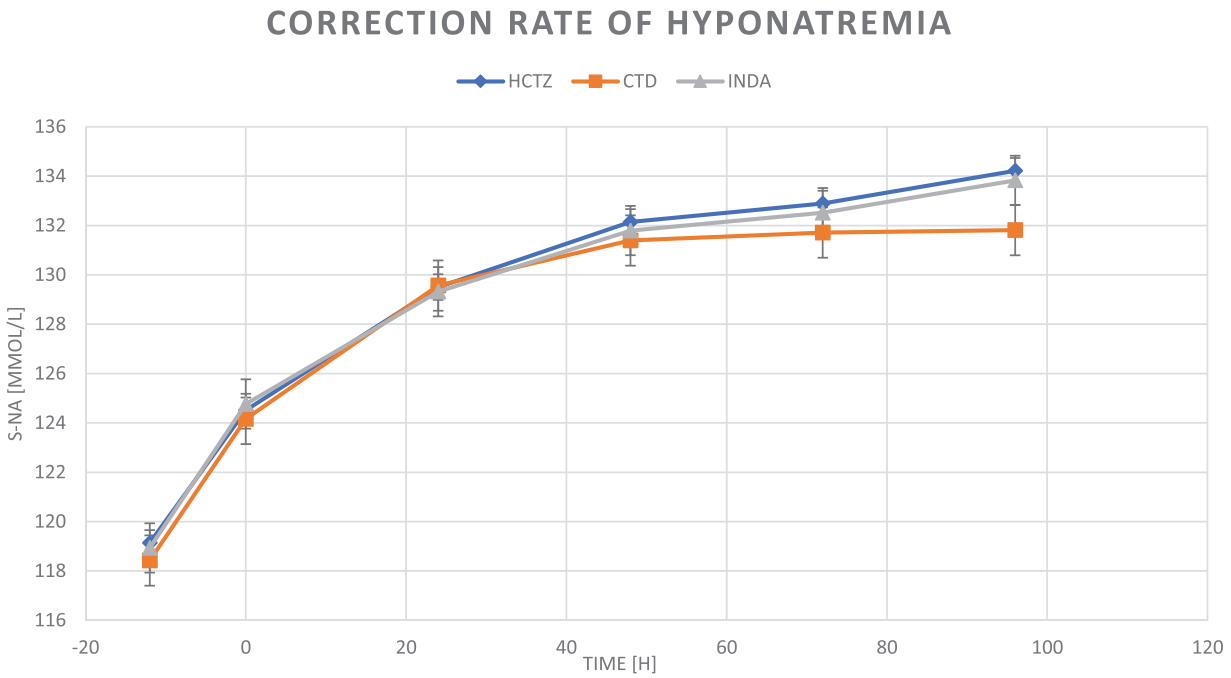

FIGURE 2 | Correction rate of hyponatremia. *shown as means with SD.

medication (HCTZ, $n = 64$; INDA, $n = 109$) is shown in Table 4. It shows a lower prevalence of female gender ($p = 0.03$), eGFR ($p = 0.03$), and higher s-K ($p < 0.001$) in the HCTZ group, when compared to the INDA group. The median daily dose (IQR) was found to be 12.5 (0) mg in the HCTZ group and 2.5 (1.2) mg in the INDA group.

The correlations between dose or s-K with biochemical parameters in patients using thiazide without diuretic co-medication are shown in Table 5. They revealed a negative correlation between HCTZ dose and s-K (rs = −0.32; $p = 0.03$), U-K (rs = −0.43; $p = 0.01$), and U-osm (rs = −0.36; $p = 0.03$). In the INDA group, a positive correlation between s-K and FE-K was observed (rs = 0.29; $p = 0.02$). For the rest of the observed parameters in Table 5, we did not find any significant correlation. Extended results are shown in Tables S1–S4.

4 | Discussion

This study compares the epidemiological and biochemical profiles and hospital course of patients using HCTZ, INDA, and CTD admitted with TAH. Despite different half-lives and pleiotropic effects of individual thiazides, we determined no significant difference in biochemical and epidemiological profiles between HCTZ, INDA, and CTD, except for s-K. After excluding the influence of other diuretics, we identified higher s-K in the HCTZ group compared to the INDA group, potentially explained by the lower equipotent dose of HCTZ compared to INDA. Further, we observed a statistically significant trend of slower hyponatremia correction in the CTD group.

Characteristics of TAH, in addition to hypotonic hyponatremia itself, usually include slightly lower s-K, higher FE-K, FE-UA, prevalence of female gender, and advanced age [17, 18, 29, 30]. As shown in Table 2, a crude comparison of HCTZ, INDA, and CTD shows almost identical biochemical and epidemiological profiles of each molecule, consistent with the previous description of TAH. This depicts TAH, regardless of associated thiazide, as a biochemically well-described phenomenon mostly affecting a relatively narrow group of patients. Notably, the median daily doses (IQR) of HCTZ, INDA, and CTD shown in crude comparison (Table 2) could be considered as equipotent: 25 (12.5) mg versus 2.5 (1.25) mg versus 12.5 (12.5) mg, respectively. It is unknown whether the doses of thiazides shown in the study are equivalent to those used in the general population.

However, a crude comparison of HCTZ, INDA, and CTD groups established differences in the prevalence of potassium-sparing diuretics, ARBs, ACE-I (all $p < 0.001$), and s-K ($p = 0.03$). The different prevalence of potassium-sparing diuretics is plausibly due to the various availability of fixed combination products on the market. In Czechia, CTD is available only as a fixed combination with amiloride or atenolol. HCTZ is available both alone and in fixed combination with amiloride or other antihypertensives. INDA is not available in fixed combination with potassium-sparing diuretics at all, only as a single drug or in combination with other antihypertensives. The availability of individual fixed combinations on the market is shown in Table S5 in the supplement.

The incidence of TAH is considered to be a dose-dependent side effect [23]. This relationship does not apply to the severity of hyponatremia as we did not find a significant correlation between dose and s-Na in any thiazide group (Table 3). Also, considering the absence of difference in s-Na between the HCTZ, INDA, and CTD groups ($p = 0.83$; Table 2), a plausible explanation could be the necessity of reaching a certain hyponatremia level, which leads to the manifestation of clinical symptoms and is subsequently the reason for hospital admission. In our previous

TABLE 3 | Correlations between dose or s-K with biochemical parameters for HCTZ, INDA, and CTD.

	HCTZ			INDA			CTD		
	Dose			Dose			Dose		
	N	**R(s)**	***p* value**	***N***	**R(s)**	***p* value**	***N***	**R(s)**	***p* value**
Serum									
Na	123	−0.002	0.98	114	−0.025	0.79	27	−0.003	0.99
K	111	−0.13	0.16	100	0.003	0.98	22	−0.046	0.84
Cl	123	−0.015	0.87	114	−0.056	0.56	27	−0.096	0.64
eGFR (CKD-EPI)	123	0.121	0.18	114	0.082	0.39	27	−0.058	0.77
Urine									
Osmolality	77	0.000	0.10	77	0.041	0.72	16	−0.27	0.32
Na	77	0.087	0.45	76	0.23	0.05	16	−0.15	0.58
K	77	−0.090	0.44	76	0.10	0.37	16	−0.086	0.75
Cl	77	0.086	0.46	76	0.25	0.03	16	−0.33	0.22
FE									
Na	29	0.079	0.68	38	0.16	0.34	9	0.14	0.73
K	34	−0.19	0.30	34	0.20	0.25	9	0.046	0.91
Cl	31	−0.066	0.73	39	0.21	0.20	10	0.087	0.81
Uric acid	34	−0.055	0.76	32	0.18	0.32	8	0.68	0.07
H2O	41	0.014	0.93	38	0.027	0.87	10	0.30	0.41
	HCTZ			**INDA**			**CTD**		
	s-K			**s-K**			**s-K**		
	N	**R(s)**	***p* value**	***N***	**R(s)**	***p* value**	***N***	**R(s)**	***p* value**
eGFR	121	−0.16	0.08	107	−0.15	0.11	22	0.038	0.87
U-K	74	0.16	0.18	71	0.19	0.11	12	−0.36	0.25
FE-K	35	−0.092	0.60	38	−0.19	0.26	8	−0.67	0.07

Note: R(s): Spearman's correlation coefficient.

study, this threshold level in patients admitted for TAH was lower compared to other etiologies of hyponatremia but without a difference in in-hospital mortality [26].

Table 2 shows that we observed no differences in mortality ($p = 0.11$); on the other hand, the absolute mortality numbers are low. Therefore, further studies are warranted to rule out a Type II error, as the trend of increasing mortality with shorter thiazide half-life is evident. We found no difference in the rate of hyponatremia correction between HCTZ, INDA, and CTD groups the next morning, 24 h, and 48 h after admission ($p = 0.63$; 0.78; 0.47, respectively). However, at 72 and 96 h after admission, a statistically significant trend of slower rate of hyponatremia correction is notable in the CTD group (approaching a statistical significance at 72 h, $p = 0.052$; highly significant at 96 h, $p < 0.001$), compared to the HCTZ and INDA groups (see Figure 2). This may be attributed to the longer CTD half-life (40–60 h) compared to HCTZ and INDA (6 and 14 h, respectively) [1]. A plausible explanation for the statistically similar initial increase in s-Na could be the admission of patients to the intensive care unit (ICU), where different half-lives of each thiazide are effectively blunted.

Of the patients, 37% (106/284) were taking another diuretic medication besides thiazide, potentially modifying their biochemical profile or even causing the hyponatremia itself [31]. Hence, we excluded patients with concomitant diuretic medication. Subsequently, we excluded the remaining five patients in the CTD group to avoid biasing the statistical analysis. Comparison of thiazides without diuretic co-medication (Table 4) shows a lower prevalence of female gender ($p = 0.03$), eGFR ($p = 0.03$), and higher s-K ($p < 0.001$) in the HCTZ group, when compared to the INDA group. Also, a median daily dose of the HCTZ group (12.5; IQR: 0 mg) could be considered lower when compared to the INDA group (2.5; IQR: 1.2 mg).

Part of the explanation for the lower equipotent dose in the HCTZ group compared to the INDA group after the exclusion of patients taking another diuretic co-medication can be again demonstrated in the different range of products on the market.

TABLE 4 | Comparison of thiazides without diuretic co-medication.

Admission parameters								
		HCTZ ($n = 64$)			INDA ($n = 109$)			
	Unit	Number	Median (IQR)	%	Number	Median (IQR)	%	p value
Age	years	64	79 (10)		109	77 (14.5)		0.27
Female gender	—	40		62.5	85		78	0.03
ACE-I		18		28.1	84		77.1	<0.001
ARB		44		68.8	11		10.1	<0.001
Dose	mg	56	12.5 (0)		102	2.5 (1.2)		—
Serum								
Na	mmol/L	64	118 (9.5)		109	120 (10)		0.56
K	mmol/L	54	4.0 (1)		96	3.6 (0.9)		<0.001
Cl	mmol/L	64	85 (8.5)		109	84 (12.5)		0.47
eGFR (CKD-EPI)	mL/min/1.73 m^2	64	68 (31)		109	80 (29)		0.03
Urine								
Osmolality	mmol/kg	42	338 (286)		74	360 (209)		0.52
Na	mmol/L	42	58 (58)		73	67 (53)		0.18
K	mmol/L	42	31 (32)		73	37 (36.5)		0.53
Cl	mmol/L	42	61.5 (60)		73	72 (54.5)		0.15
Fractional excretion								
Na	%	15	0.91 (1.01)		38	1.06 (1.21)		0.82
K	%	17	12.7 (13.2)		35	14 (11.7)		0.87
Cl	%	17	1.25 (1.36)		39	1.4 (1.47)		0.76
Uric acid	%	19	12.1 (18)		32	9.87 (6.34)		0.24
H_2O	%	22	1.78 (1.61)		38	1.55 (1.16)		0.40

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin II receptor antagonist; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

The fixed HCTZ/amiloride combination is only available in strengths of 25/2.5 or 50/5 mg, respectively. HCTZ is also available in other fixed preparations, including strengths of 12.5 mg even in combination with maximum daily doses of telmisartan (80 mg), candesartan (32 mg), irbesartan (300 mg), losartan (100 mg), and valsartan (320 mg), as well as in combination HCTZ/bisoprolol 6.25/10 mg, respectively. We revealed that 54.1% (20/37) of patients in the HCTZ group without diuretic co-medication using ARBs were taking 12.5 mg of HCTZ in combination with maximum daily doses of ARBs. INDA is available in fixed combination predominantly as INDA/perindopril, always in ratio 2.5/0.625, 5/1.25, or 10/2.5 mg, respectively, and is registered as a combination INDA/telmisartan 2.5/80 mg, respectively. Thus, prescribers may aim to add substantially reduced doses of thiazide diuretic to the current antihypertensive medication, preferably in a single, more compound-containing pill. With HCTZ, this goal is easier to achieve.

The lower eGFR in the HCTZ, compared to the INDA group, may also explain the higher s-K in the HCTZ group when compared to the INDA group ($p < 0.001$), as a negative correlation between eGFR and s-K is well-known [32]. Nevertheless, we identified no correlation between s-K and eGFR in either the HCTZ or INDA groups (Table 5). Since we observed a negative correlation between HCTZ dose and s-K (rs = −0.32; $p = 0.03$), and the negative correlation between the thiazide dose and s-K is well-documented [33], one plausible explanation for the higher s-K in the HCTZ group compared to the INDA group is the lower equipotent dose of HCTZ. Remarkably, we identified a negative correlation between HCTZ dose and U-K (rs = −0.43; $p = 0.01$) and U-osm (rs = −0.36; $p = 0.03$).

4.1 | Strengths and Weaknesses

This is the first study directly comparing individual thiazides regarding their biochemical profile, including their FE. The study's design reflects the real use of thiazide diuretics in common clinical practice, where thiazides are routinely combined with other antihypertensive and diuretic therapy.

On the other hand, the results of this work must be considered in the light of serious limitations. Firstly, the observational retrospective design of the study is a major limitation, which prevents

TABLE 5 | Correlations between dose or s-K with biochemical parameters for HCTZ and INDA without diuretic co-medication.

	HCTZ			INDA		
	Dose			Dose		
	Number	R(s)	*p* value	Number	R(s)	*p* value
Na	55	0.025	0.86	101	−0.088	0.38
K	45	−0.32	0.03	88	0.02	0.85
Cl	55	0.046	0.74	101	−0.097	0.34
eGFR (CKD-EPI)	55	0.14	0.31	101	0.11	0.26
Urine						
Osmolality	36	−0.36	0.03	69	−0.004	0.97
Na	36	−0.094	0.59	68	0.16	0.21
K	36	−0.43	0.01	68	0.048	0.70
Cl	36	−0.063	0.71	68	0.19	0.12
Fractional excretion						
Na	12	0.032	0.92	34	0.19	0.29
K	14	−0.40	0.16	31	0.19	0.31
Cl	14	−0.23	0.43	35	0.24	0.17
Uric acid	17	0.35	0.17	29	0.19	0.32
H2O	19	0.084	0.73	34	0.14	0.45
	HCTZ			**INDA**		
	s-K			**s-K**		
	Number	**R(s)**	***p* value**	**Number**	**R(s)**	***p* value**
eGFR	53	0.017	0.91	95	−0.079	0.45
U-K	35	0.27	0.11	35	−0.17	0.32
FE-K	15	−0.13	0.65	64	0.29	0.02

Note: R(s): Spearman's correlation coefficient.

us from following proper patient adherence and establishing a standardized procedure for the re-evaluation of biochemical measurements during hospitalization. Due to the study design, we are also unable to fully rule out that different ranges of individual thiazides in fixed combinations could significantly affect their biochemical profiles and obscure their pharmacological effects. Secondly, some measurements are partially absent. Thirdly, we have no data on therapeutic measures during hospitalization. Fourthly, the number of patients in the CTD group was comparatively minor. Fifthly, we are not able to determine the duration of thiazide treatment before hospital admission. Sixth, for variables with low frequencies, such as mortality, a larger data set is required to confirm non-inferiority.

5 | Conclusion

Except for s-K, we discovered no significant difference in biochemical and epidemiological profiles between HCTZ, INDA, and CTD. After excluding the influence of other diuretics, we identified higher s-K in the HCTZ group compared to the INDA group, which was potentially explained by the lower equipotent dose of HCTZ. Further, the CTD group showed a statistically significant trend of slower hyponatremia correction.

1. TAH, regardless of associated thiazide, is a biochemically well-described phenomenon that mostly affects a relatively narrow group of patients. In particular, hypokalemia remains a real adverse effect even under TAH conditions.
2. The different availability of fixed combination products could be a crucial factor in modifying the biochemical profile and daily dose of each thiazide.
3. The daily dose of any thiazide did not correlate with the severity of hyponatremia on admission.
4. In a real-world setting, the half-life of thiazide could be a clinically relevant factor modifying the correction rate of hyponatremia. However, prospective studies are desirable to confirm the observed findings.

Ethics Statement

The study design was approved by the Ethics Committee of The Tomas Bata Hospital (2023-22).

Consent

Written informed consent was obtained from all the patients as part of the informed consent to hospital admission.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data were submitted to the journal.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.