Syndrome of Inadequate Antidiuretic Hormone Secretion in Pulmonary Tuberculosis – a Therapeutic Challenge

Case Report and Review of the Literature

Syndrom der inadäquaten ADH-Sekretion bei Lungentuberkulose – eine therapeutische Herausforderung
Fallbericht und Literaturübersicht

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Abstract

A forty-nine-year-old female patient with pulmonary tuberculosis developed syndrome of inadequate antidiuretic hormone secretion. Consequent restriction of fluid intake as a therapeutic measure was just as ineffective as a medication with tolvaptan which was performed later on. A probable explanation for the inefficacy of the aquaretic drug is an interaction of rifampicine and tolvaptan. This case report gives a short summary of SIADH in pulmonary TB and discusses possible reasons for the difficult antituberculous treatment in this patient.

Introduction

Tuberculosis remains a worldwide infectious problem [1]. Treatment should follow recently published recommendations [2]. SIADH is a possible cause of hyponatremia in patients with pulmonary diseases – especially in granulomatous diseases. However, the number of case reports on patients with a SIADH exclusively related to pulmonary TB is low and the mechanism poorly understood. Hypoxia, decreased vascular volume [3] and ectopic ADH production have been discussed as possible causes [4].

The case

A forty-nine-year-old cachectic woman (height 1.60 m, weight 30.4 kg, BMI 11.9 kg/m²) was admitted to our hospital due to strong suspicion of pulmonary tuberculosis (TB) (● Fig. 1 a, b). The patient was an active smoker (17 pack-years) until the day of admission to our hospital. For a

Zusammenfassung

Eine 49-jährige Patientin mit ansteckungsfähiger Lungentuberkulose entwickelte ein Syndrom der inadäquaten ADH-Sekretion. Eine konsequente Beschränkung der Flüssigkeitszufuhr als erster therapeutischer Schritt zeigte keinen Erfolg – ebenso wenig wie die als weiterer Ansatz durchgeführte Behandlung mit Tolvaptan. Eine mögliche Erklärung für die fehlende Wirksamkeit von Tolvaptan stellt eine Arzneimittelinteraktion zwischen dem oralen V₂-Rezeptorantagonisten und Rifampicin dar. Dieser Fallbericht gibt eine kurze Übersicht über SIADH im Rahmen von Lungentuberkulosen und diskutiert mögliche Ursachen für die schwierige antituberkulotische Therapie bei dieser Patientin.

couple of years, she had been abstinent from alcohol abuse.

Initial microbiological examination revealed acid-fast bacilli in auramine staining, confirmed by Ziehl-Neelsen stain. Antituberculous treatment with isoniazide (H), rifampicine (R), ethambutole (E) and pyrazinamide (Z) was initiated following approved protocols [2, 5]. Later on, cultural results showed mycobacterium tuberculosis (MTB) sensitive to H and R.

From the day of her admission, we observed hyponatremia. Later on, the patient developed severe hypokalemia (● Table 1). Clinically, these electrolyte imbalances caused no specific symptoms. For treatment of hyponatremia, fluid intake was consequently restricted to a total of 1000 ml per day. Oral potassium substitution was started but did not result in normalization of hypokalemia. Therefore, continuous parenteral potassium administration via a central line was initiated, again without sustained success.

Fig. 1 Chest radiographs, day after admission 0 (a, b) and 133 (c, d). Features of extensive lung emphysema and variable sized nodular areas of consolidation within the upper parts of both lungs. Moreover, an area of low density visible in the left upper lobe (a, b). Marked decrease of consolidation with only minor parenchymal scarring in both upper lobes (c, d).

Table 1 Evolution of laboratory parameters

Day after admission	0	17	20	35	57	78	101	118	134	239	Laboratory reference range
Serum Na ⁺	125	125	126	125	130	136	136	140	138	139	135 – 145 mmol/L
Serum K ⁺	4.8	4.1	3.5	2.3	4.0	4.9	5.1	4.1	3.8	4	3.5 – 5 mmol/L
Serum Osmolality		244	244	258	260	296				295	280 – 295 mos/kg
Urine Osmolality		317		272		426				248	50 – 1200 mos/kg
Urine Na ⁺		48		40		<10				77	80 – 164 mmol/L
Urine K ⁺		53		37		94				17	32 – 74 mmol/L
CRP	1809	161.8	76.1	238.0	161.8	209.4	114.2	57.1	123.8	28.6	0 – 95 nmol/L
ADH			30.5							<0.5	0.7 – 4.2 pmol/L
SUSPUP		33.66		50.27						7.67	3.6 – 22.6
SUSPPUP		8.21		21.86						1.92	0.6 – 5.3
ACTH					0.4	11.9					2 – 11.4 pmol/L
Cortisol					504.9	1594.7					193 – 689.8 nmol/L
Renin					3.0						0.1 – 0.36 pmol/L
Aldosterone					0.59						0 – 0.42 nmol/L
H through level				<1.5	<1.5	<1.5	<1.5	5.1	18.2 ¹		1.5 – 7.3 μmol/L
R through level				2.9	3.9	<0.1	0.5	2.1	2.2		0.1 – 12.2 μmol/L

Day 20: Start intravenous antituberculous treatment, Day 28–35: tolvapatan administration

¹ H peak level (laboratory reference range 10.9–72.9 μmol/l); H through level controlled on day 135 after admission: 4.4 μmol/l

Biochemical analysis revealed serum osmolality being reduced, urine osmolality normal and sodium urine concentration reduced, fulfilling formal criteria for syndrome of inadequate antidiuretic hormone secretion (SIADH) with hyposmolar hyponatremia. Reduced sodium urine concentrations with consecutively elevated SUSPUP (serum sodium to urinary sodium to serum potassium to urinary potassium ratio) and SUSPPUP (serum sodium to urinary sodium to [serum potassium]² to urinary potassium ratio) [6] suggested reactive hyperaldosteronism as a compensatory mechanism. There were no clinical hints for an extrarenal sodium loss. Renal function was slightly reduced during the whole in-hospital stay, thyroid gland function normal. In the absence of oedema, there were no signs of heart failure. Hemodynamically, the patient was stable at all times.

Further laboratory evaluations revealed antidiuretic hormone (ADH) being markedly increased as well as serum renin and aldosterone levels, while aldosterone-renin ratio was normal. These findings confirmed our diagnosis of SIADH with secondary hyperaldosteronism as a compensatory mechanism for hyponatremia. With regard to etiology of the SIADH, there were no hints for medication-related effects or a possible malignant disease. Also, no central nervous affections were found, so we had reason to assume the SIADH to be due to the pulmonary TB. At no point of hospitalization, we had clues for extrapulmonary tuberculosis. Despite antituberculous treatment using directly observed therapy (DOT) from the very beginning, sputum analyzes revealed still significant smear-positive TB and cultural results MTB being furthermore multi-sensitive to first-line antituberculous medication. We excluded interaction with co-medication and reconfirmed alcohol and tobacco-smoke abstinence. Additionally and pragmatically, we switched antituberculous treatment from oral to intravenous administration at this point of the hospitalization to exclude malabsorption as a reason for treatment failure.

Due to persisting hyponatremia we started treatment with tolvaptan. Consequently, hydration restriction was stopped. Surprisingly, tolvaptan remained ineffective and was stopped after eight days of unsuccessful treatment.

After five weeks of intravenous antituberculous therapy, sodium and potassium levels increased and normalized finally in parallel with clinical and radiologic response to the antituberculous treatment (● Fig. 1 c, d). Moreover, several consecutive sputum samples were negative for MTB. As a further effect of successful treatment, the patient gained weight (39.4 kg at the end of hospitalization).

The reason for the difficult antituberculous treatment despite proven multi-sensitivity of MTB may be seen in sub-therapeutic H-levels measured repeatedly during treatment and necessitating dose adjustments. Probably, the patient belongs to a group of fast-acetylators (polymorphism of the *NAT2*-gene). Written consent for further genetic testing was denied.

In view of the clinical course, we are convinced that the SIADH was directly attributable to pulmonary TB. As part of follow-up, the patient presented at our hospital three months after discharge, i.e. 7.5 months after first admission. Under continued antituberculous treatment, there were no signs of infectious pulmonary TB. Sodium and potassium levels were normal without substitution or further specific therapy.

Discussion

Tolvaptan is a nonpeptide, vasopressin V₂ receptor antagonist, a new class of pharmaceuticals for treatment of hyponatremia, especially when SIADH-induced [7]. These aquaretics selectively antagonize the antidiuretic effect of vasopressin by competitively binding to renal V₂ receptors.

The mechanism of TB-related SIADH is poorly understood. Notably, a correlation between floridity of TB and severity of SIADH has not been examined so far. Thus, it is difficult to conclude unambiguously, why tolvaptan remained ineffective in this case. A probable explanation is drug-interaction of R and tolvaptan. R is a strong inducer of cytochrome P450-dependent monooxygenases (CYP), notably CYP3A4, 1A2, 2C9, 2C8 and 2C18/19 in intestinal epithelium and liver [8]. Tolvaptan is a sensitive CYP3A4 substrate with no inhibitory activity. In healthy subjects, mean maximum concentration C_{max} and AUC of tolvaptan were reduced when co-administered with R [9].

Gene polymorphisms of *N-acetyltransferase2* (*NAT2*) are known to cause individual variation in N-acetylation capacity of H. In a study of H pharmacokinetics and pharmacodynamics most homozygous fast acetylators needed a dose twice as high as homozygous slow acetylators to achieve equivalent AUC and 2-hours H serum concentration [10].

Acetylation status has not been described to influence the metabolism of tolvaptan, and CYP3A4 has previously been identified as the only enzyme to be involved in the metabolism of this aquaretic drug [9]. Therefore, it seems unlikely that the reduced effectiveness of tolvaptan is caused by a polymorphism of *NAT2*.

Conclusion

In this case of TB-related SIADH, tolvaptan remained ineffective. A probable reason is seen in a clinically relevant drug-interaction of rifampicine and tolvaptan. Consequently, dose adjustments of tolvaptan may be necessary when co-administered with R. This would be in agreement with results of a previous trial in healthy volunteers [9]. Further studies on the mechanisms of TB-related SIADH and interactions of antituberculous and aquaretic drugs in this population are necessary.

Author contributions

All authors planned the work and interpreted the results. H. Knoop, U. Knoop, J.W. Dietrich and J. Behr wrote the article. C.M. Heyer, S. Kuert, D. Roggenland and M. Suermann made substantive suggestions for revision. All authors approved the final version.

Conflict of interest

The authors have no conflict of interest.

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References

- 1 World Health Organization. WHO report global tuberculosis control. Geneva/ Switzerland: World Health Organization, WHO; 2011: 10
- 2 Schaberg T, Bauer T, Castell S et al. Recommendations for therapy, chemoprevention and chemoprophylaxis of tuberculosis in adults and children [German Central Committee against Tuberculosis (DZK), German Respiratory Society (DGP)]. *Pneumologie* 2012; 66: 133–171
- 3 Ellison DH, Berl T. Clinical practice. The syndrome of inappropriate antidiuresis. *N Engl J Med* 2007; 356: 2064–2072
- 4 Lee P, Ho KKY. Hyponatremia in Pulmonary TB: Evidence of Ectopic Antidiuretic Hormone Production. *Chest* 2010; 137: 207–208
- 5 World Health Organization. Treatment of tuberculosis: guidelines. 4th. Edn.; Geneva/ Switzerland: World Health Organization, WHO; 2009: 1–160
- 6 Willenberg HS, Kolentini C, Quinkler M et al. The serum sodium to urinary sodium to (serum potassium)² to urinary potassium (SUSPPUP) ratio in patients with primary aldosteronism. *Eur J Clin Invest* 2009; 39: 43–50
- 7 Verbalis JG, Adler S, Schrier RW et al. Efficacy and safety of oral tolvaptan therapy in patients with the syndrome of inappropriate antidiuretic hormone secretion. *Eur J Endocrinol* 2011; 164: 725–732
- 8 Sousa M, Pozniak A, Boffito M. Pharmacokinetics and pharmacodynamics of drug interactions involving rifampicine, rifabutin and antimalarial drugs. *J Antimicrob Chemother* 2008; 62: 872–878
- 9 Shoaf SE, Bricmont P, Mallikaarjun S. Effects of CYP3A4 inhibition and induction on the pharmacokinetics and pharmacodynamics of tolvaptan, a non-peptide AVP antagonist in healthy subjects. *Br J Clin Pharmacol* 2012; 73: 579–587
- 10 Donald PR, Parkin DP, Seifart HI et al. The influence of dose and N-acetyltransferase-2 (NAT2) genotype and phenotype on the pharmacokinetics and pharmacodynamics of isoniazid. *Eur J Clin Pharmacol* 2007; 63: 633–639