Editorial Comments

Thiazides: do they kill?

Peter Gross and Catrin Palm

Nephrology, Medizinische Klinik III, Universitätsklinikum C.G. Carus, Dresden, Germany

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Introduction

In 2000 and 2002 after the ALLHAT-study had been published [1,2] there was a paradigm shift in the use of thiazides. ALLHAT was a study of cardiovascular endpoints in relation to different antihypertensive treatments in 33 357 hypertensive patients observed over an average of 4.9 years. The study [1,2] found no differences between the three treatment groups [diuretics in the form of chlorthalidone vs calcium antagonists (amlodipine) vs ACEI (lisinopril)]. Consequently, after ALLHAT, it was emphasized that thiazides ought to be an integral part of the hypertensive patient’s prescription sooner or later—and health policy makers clearly favoured ‘sooner’ over ‘later’ because of their low cost. Indeed, the sale of thiazide-like agents has more than doubled between 2001 and 2004 in Germany alone. In the meantime, quite a few articles have dealt with the pros and cons of thiazides [3], when prescribed on such an extended basis. However, there appears to be yet another important side-effect of thiazides that is frequently missed—even though it may kill patients. This will be discussed herein.

Why is the lady comatose?

The clinical manifestation to be discussed is almost always stereotype: an elderly lady will have been admitted to hospital a short while ago in an unexplained comatose state. The major discernible abnormality detected in the ICU will be severe hyponatraemia (110–116 mmol/l) associated with mild hypokalaemia (3.0–3.4 mmol/l). The constellation of laboratory results will not quite fit that of classical SIADH (with euvalaemia) nor that of hypovolaemic hyponatraemia. Euvolaemia is usually characterized by low or below normal levels of uric acid, urea and creatinine in the absence of major hyperglycaemia; there will be normal blood pressure and no signs of dehydration. Hypovolaemia, in contrast, would show mildly elevated plasma concentrations of urea, creatinine and uric acid; low blood pressure and clinical signs of volume loss; absence of edema. The patients with thiazide-induced hyponatraemia seem to be in between such euvalaemia and hypovolaemia. Meanwhile in the ICU it will usually take about 48 h of more or less heated discussions with the house staff about the best mode and particularly about the rate of corrective treatment of the hyponatraemia, plus discontinuation of thiazides if they are a known prescription at that time, fluid restriction and possibly other measures (such as infusions of normal or hypertonic saline) until the serum sodium rises towards near normal levels, making the patient more awake and communicative. It will then be revealed that thiazides had been prescribed for the first time about 1–4 weeks earlier, usually for hypertension and sometimes for congestive cardiac failure. Occasionally, one will find a neighbour who had noticed the patient often drinking a lot of fluids.

Thiazide-hyponatraemia: do they die?

Thiazide-induced hyponatraemia is fully reversible once the diuretic is stopped. Re-exposure is very likely to produce the same consequences should it be enacted. A seminal report on seven index patients with thiazide-hyponatraemia by Ashraf et al. [4] appeared in 1981, almost 25 years ago. All seven patients were elderly ladies who had first been started on thiazides on average <16 days before severe hyponatraemia (105 ± 6 mmol/l) ensued. The serum creatinine was normal in all and urinary sodium excretion rate was somewhat high (on average 100 mmol/l). Plasma ADH was low, but measurable. The patients in the report [4] suffered from CNS changes such as generalized seizures, stupor,
 coma, death or permanent paralysis—supposedly all related to the associated brain edema and its consequences. Subsequent reports have confirmed all essential features of this syndrome, including the preferential occurrence in elderly women, the associated hypokalaemia and the preceding polydipsia [5–8]. The causative agents were not limited to hydrochlorothiazide (HCTZ) per se but metolazone, indapamide, and combinations of HCTZ with amiloride or with triamterene have also been incriminated. Chow et al. [9] analysed 223 cases of thiazide-hyponatraemia in their hospital: they were able to identify old age, low body weight and low serum potassium concentrations as specific risk factors.

What is wrong with summer?

Why does the syndrome preferentially occur in summer? For instance we observed over the last 4 years in our own (university) hospital that the daily incidence of all hyponatraemias increased by 100–200% in a hot summer (P. Gross, unpublished observations).

Hyponatraemia is usually the result of relative water overload. To generate body water overload a reduced renal water excretion is necessary and this is usually related to failure to suppress ADH. In that situation, drinking (hypotonic) fluid will make the problem worse. In hot summers most people drink many more hypotonic fluids than normal. The system works like a bath tub. The water level in the tub rises too high (hyponatraemia) if the outflow is too narrow (renal antidiuresis from too much ADH), which will be made a lot worse if there happens to be an increased inflow (thirst and increased drinking in summertime).

Indeed, excessive drinking has been noted in reports of thiazide-hyponatraemia. Given this baseline fact it is more than likely that high temperatures in hot summer lead to increased thirst and fluid intake and further worsening of hyponatraemia. This then appears to be the chain of events linking hot summer to coma (in thiazide users, that is), although admittedly this aspect has never been studied in a systematic fashion.

Any new kids on the block?

So what is the point of thiazide-hyponatraemia at this particular point in time? Is there anything new?

Clinically—as mentioned before—when prescribing thiazides more frequently, as is now widely observed, we must direct more awareness to the hyponatraemic risk occurring in elderly thin ladies; we ought to measure their serum sodium concentration perhaps 2 and 8 weeks after the start of a thiazide to protect them from the occasional severe symptomatic hyponatraemia.

A new publication has very recently indicated a potential explanation for—hitherto unexplained—thiazide-hyponatraemia [10]. In this paper, Kim et al. [10] present evidence obtained in rats to show that thiazides may upregulate aquaporin-2 in the collecting duct. The authors suggest that by this mechanism the common practice of using thiazides to improve nephrogenic diabetes insipidus may also be explained. To be sure, many issues remain to be explained, including the mechanism of this effect of thiazides in the collecting duct (principal) cell, any potential effects of sex hormones on the upregulation of aquaporin-2 after thiazide, the apparent lack of feedback of aquaporin-2 upregulation on ADH-secretion and the dysregulated thirst in thiazide-hyponatraemia. However, a new starting point has been set and further observations will undoubtedly follow.

The imminent introduction of oral V1/V2 vasopressin antagonists into clinical practice scheduled for early 2006 (Conivaptan of Astellas) will soon make the treatment of thiazide-hyponatraemia more specific and hopefully easier. These agents promise to allow better fine-tuning of the treatment of any hyponatraemia especially when severe.

Conclusions

After ALLHAT, there has been a widespread surge in the use of thiazides primarily for the treatment of hypertension, but also of congestive cardiac failure. Several important side-effects of thiazides such as hypokalaemia and arrhythmias, hyperglycaemia and hyperuricaemia triggering acute attacks of gout are well known; in contrast, thiazide-hyponatraemia is usually missed. It is not extremely rare, it manifests in the first 4 weeks after the start of thiazides, it affects primarily elderly thin women, it manifests a severe symptomatic hyponatraemia (comatose state; 110–116 mmol/l) and the laboratory constellation is somewhat reminiscent of that in SIADH, however, associated with mild hypokalaemia. The best mode of treatment is discontinuation of thiazides (if known), fluid restriction to <1 l/day all fluids included and other measures (infusions of isotonic or hypertonic saline) to increase the serum sodium concentration at a rate of <0.5 mmol/l/h. The best present explanation of thiazide-hyponatraemia is thiazide-induced over-expression of aquaporin-2 in the collecting duct in susceptible individuals. The causes of this particular susceptibility remain to be elucidated. The literature has described patients that have died from thiazide-hyponatraemia.

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References

Efficacy of antihypertensive treatment: which endpoints should be considered?

Giuseppe Mancia and Guido Grassi

Clinica Medica, Dipartimento di Medicina Clinica, Prevenzione e Biotecnologie Sanitarie, Università Milano-Bicocca, Centro Auxologico Italiano and Centro Interuniversitario di Fisiologia Clinica e Ipertensione, IRCCS Policlinico, Milano, Italy

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Knowledge on the benefit of antihypertensive treatment owes a great deal to antihypertensive drug trials based on incidence of morbidity and mortality [1]. These trials have demonstrated that antihypertensive drugs reduce cardiovascular morbid and fatal events of hypertensive individuals, counteracting their increased cardiovascular risk. They also demonstrated that this reduction occurs in males and females of different ages, ethnicities and clinical conditions and that thus the protection is virtually universal across the demographic and pathophysiological spectrum that characterizes an elevated blood pressure. They have finally demonstrated that drugs capable of lowering blood pressure protect hypertensive patients via sizes and designs that exclude even the remote possibility of 'chance' results as well as of errors due to selection bias, investigators' and patients' expectations, and inappropriate or unbalanced identification of events.

The above has generated the widespread opinion that information provided by morbidity/mortality trials is the most important one in a hypothetical scale of scientific soundness [2], and the only one on which Guidelines on antihypertensive treatment should be based on. This, however, overlooks the fact that morbidity/mortality trials on antihypertensive treatment are not devoid of limitations and that failure to appreciate them can endanger proper interpretation of available data and make it more difficult to devise studies that allow further progress to be made [3].

First limitation of clinical trials — selection bias

One of the limitations of morbidity/mortality trials derives from the need to ensure, through a stringent selection process, that the population under study is relatively homogeneous and compliant to treatment, in order to minimize confounders that can make interpretation of the data more difficult. This, however, makes the study population different from that seen