Hypotonia During Amikacin Administration in a Patient Treated with Continuous Ambulatory Peritoneal Dialysis

Maria Wanic–Kossowska,¹ Alicja E. Grzegorzewska,¹ A Tykarski²

In this report we present the history of a patient treated with continuous ambulatory peritoneal dialysis (CAPD) in whom episodes of hypotonia can be related to the administration of amikacin, an antibiotic from the aminoglycosides group.

The 68-year-old female patient was admitted for initiation of renal replacement therapy with CAPD. Her renal failure was probably attributable to hypertension. Three days after catheter implantation, the patient reported dysuric symptoms, and a urine culture showed significant growth of Escherichia coli. Amikacin 250 mg and cefazolin 1.0 g were administered intravenously once daily in accordance with the antibiogram. On the third day of antibiotic administration, the patient fainted, showing an arterial blood pressure of 90/60 mmHg. On the subsequent 2 days, decreases of postural arterial blood pressure to between 90/60 mmHg and 80/50 mmHg were reported two or three times daily. The patient was treated with antibiotics for the next 6 days and felt very bad the entire time, with an arterial blood pressure of 80/50 mmHg. The patient’s condition improved 2 days after discontinuation of treatment with antibiotics, and episodes of hypotonia stopped. The decrease in the arterial blood pressure observed in our patient during intravenous administration of amikacin can, with a high probability, be related to the calcimimetic activity of this aminoglycoside and the resulting inhibition of parathyroid secretion.

Key words
Hypotonia, amikacin, chronic renal failure

Introduction
In clinical practice, hypotonia is related to a number of undesirable clinical symptoms. Because the definition of hypotonia is somewhat arbitrary, the present work assumes that hypotonia refers to systolic pressure below 110 mmHg for men and 100 mmHg for women, and diastolic pressure below 60 mmHg for both sexes (1). Hypotonia may accompany a number of conditions such as depression, dementia, Addison disease, Alzheimer disease, and Down syndrome. The literature reports individual cases of hypotonia caused by innate genetic defects such as deficiency of beta-hydroxylase or monoamine oxidase (2). Life-threatening hypotonia can be provoked by administration of short-acting dihydropyridine derivatives, a situation that primarily concerns patients with renal failure, in whom administration of these derivatives enhances the already-present agitation of the sympathetic system that can lead to cardiac arrhythmia and sudden cardiac death (3).

The occurrence of hypotonia in patients with chronic kidney diseases treated with dialysis reaches a frequency 10% – 12% (4). It has been established that hypotonia in dialyzed patients is related to the appearance of life-threatening cardiovascular complications. In patients subjected to a long-standing hemodialysis program, episodes of hypotonia occurring during dialysis sessions may be the result of hemodynamic disturbances, which are detected in about 30% – 40% of such patients (4). Hypotonia in the period between dialysis sessions is observed in 5% – 10% of patients and typically appears in those who have undergone many years of dialysis therapy.

In patients treated with continuous ambulatory peritoneal dialysis (CAPD), the frequency of hypotonia is similar, reaching 12% (5,6). The pathophysiology of hypotonia in patients treated with CAPD is...
complex and can involve such factors as hypovolemia, hyponatremia, neuropathy of the autonomic nervous system, cardiac insufficiency, reduced sensitivity of blood vessels to pressure factors, overproduction of vasodilatation agents, and hypotension therapy (4–6). For 15% – 20% of cases, the genesis of hypotonia is unknown (5,7).

In this paper, we report the case history of a patient treated with CAPD in whom episodes of hypotonia can be related to the application of the antibiotic amikacin, an aminoglycoside.

**Case report**

A female patient 68 years of age (case history number 7566/05) was admitted for initiation of renal replacement therapy with CAPD. Her renal failure was probably attributable to her 25-year history of hypertension.

On admission, the general condition of the patient was good, with arterial blood pressure (BP) 170/100 mmHg, pulse rate 88, vesicular murmur, abdomen soft and painless, lumbar regions painless, and slight ankle edema. Serum concentration of urea was 220 mg/dL; creatinine, 6.5 mg/dL; uric acid, 7.8 mg/dL; parathormone (PTH), 256 pg/mL; inorganic phosphates, 7.6 mg/dL; total calcium, 8.5 mg/dL. The patient’s Ca×P product was 56.6 mg²/dL². A blood count revealed hemoglobin to be 6.8 mmol/L; hematocrit, 33%; red blood cell count, 2.4 g/L. Urine tests showed specific gravity 1.010, proteinuria 0.5 g/L, and few leukocytes and erythrocytes in urinary sediment. A urine culture was sterile. Creatinine clearance was 15 mL/min/1.73 m² body surface area.

The patient was treated with perindopril 4 mg and furosemide 80 mg once daily, amlodipine 5 mg twice daily, and calcium carbonate 1 g three times daily. In the first week after insertion of the Tenckhoff catheter, the patient reported dysuric symptoms: leukocyturia appeared, and a urine culture showed growth of significant *Escherichia coli*. Amikacin 250 mg and cefazolin 1.0 g daily were administered intravenously in accordance with the antibiogram.

On the third day of antibiotic administration, the patient fainted, showing an arterial blood pressure of 90/60 mmHg. During the subsequent 2 days, decreases in postural arterial blood pressure to between 90/60 mmHg and 80/50 mmHg were reported 2 or 3 times daily. All hypertension medication was withdrawn, but the patient remained weak, suffered from dizziness, and was afraid to move by herself.

Two days after discontinuation of treatment with antibiotics, the patient’s condition improved, and episodes of hypotonia stopped. As blood pressure increased, amlodipine and perindopril were reintroduced at the earlier dosages. Two weeks after implantation of the Tenckhoff catheter, peritoneal dialysis was started—to which the patient responded very well. The technical course of dialysis was good. The patient was released from hospital in good condition.

**Discussion**

In the patient described above, hypotonia was probably related to the introduction of amikacin, an aminoglycoside antibiotic. The mechanism of the hypotensive effect of aminoglycosides has not yet been fully explained. One hypothesis suggests that aminoglycosides resemble ligands that show affinity for the calcium receptor (8,9).

In addition to PTH, the parathyroid glands synthesize the parathyroid hypertension agent PHF, which is partly responsible for development of hypertension—that is, primary hyperparathyroidism (10,11). Results from Pang *et al.* and Benishin *et al.* (12,13) have confirmed this observation. Those authors observed a significant decrease in arterial blood pressure in rats after surgical parathyroidectomy.

Recognition of the properties of the calcium receptor in parathyroid gland cells permitted introduction of a new generation of drugs that inhibit PTH secretion—the so-called calcimimetics. The calcimimetics mimic the activity of extracellular calcium and, by the same mechanism, inhibit secretion of PTH by the main cells of the parathyroid glands even in the absence of extracellular calcium. These substances are called calcium receptor agonists or type I calcimimetics (14). Type I calcimimetics act on the extracellular domain of the calcium receptor; the type II variety act on the intracellular domain (14). Type II calcimimetics enhance the sensitivity of the calcium receptor to extracellular calcium by allosteric modulation (14).

In patients with renal insufficiency and secondary hyperparathyroidism, oral administration of the calcimimetic N-568 led to a fast but reversible decrease in the serum concentration of PTH. Simultaneously, patients revealed aggravation of already-present hypocalcemia (15). In view of considerable interindividual differences in pharmacokinetic response, N-568 was withdrawn from further clinical tests (15).
By activating the calcium receptor, calcimimetics correct the secretion of PTH and affect the secretion of PHF (16). The treatment of patients who have primary hyperparathyroidism and hypertension with the type I calcimimetic R-568 led to a decrease in serum concentration of PTH and a significant decrease in arterial blood pressure (17). The same authors (17) also reported a decrease in arterial blood pressure in spontaneously hypertensive rats (SHR) as a result of administration of this calcimimetic.

The results that Boblewski et al. obtained in SHR and normotensive rats (18) proved that intravenous administration of gentamicin caused hypocalcemia, a decrease in the fractional elimination of phosphates with urine, and a decrease in mean arterial blood pressure by up to 15 mmHg 35 minutes after drug administration. That observation confirms the hypothesis presented earlier: that the affinity of aminoglycosides for the calcium receptor can influence secretion of PTH and PHF. Many experiments have confirmed the agonistic effect of aminoglycosides on the calcium receptor of the parathyroid glands (8,9,19).

McLarnon et al. (9) and Ward et al. (8) compared the effects of a few of the most often used aminoglycoside antibiotics—gentamicin, neomycin, and tobramycin—on the function of the calcium receptor. They showed that the affinity of these drugs for the calcium receptor depend on concentration and the number of amine groups in the drug. Breitwieser et al. (20) and Hagiwara et al. (19) reported that affinity for the calcium receptor is greatest for compounds containing 6 amine groups (neomycin-B, neomycin-C), lower for gentamicin (5 amine groups), and lowest for compounds with 4 amine groups (kanamycin, amikacin).

Conclusions
In view of the foregoing facts, the decrease in arterial blood pressure observed in our patient during intravenous administration of amikacin can, with a high probability, be related to the calcimimetic activity of this aminoglycoside and resulting inhibition of PHF secretion.

References
16 Ryb´czy´nska A, Hoppe A. Calcimimetic and calcilytics: new perspectives of correction of abnor-


19 Hagiwara M, Inagaki M, Kanamura K, Ohta H, Hidaka H. Inhibitory effects of aminoglycosides on renal pro-


Corresponding author: Maria Wanic–Kossowska, Professor, Department of Nephrology, Transplantology and Internal Diseases, University School of Medical Sciences, Przybyszewskiego street 49, Poznań, Poland. E-mail: maewankoss@poczta.onet.pl