Case report

Flush hypertension during infusion of saline

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Salt-sensitivity is present in approximately half of the population with essential hypertension. Among several methods used to diagnose salt-sensitivity, Weinberger’s saline infusion test is widely accepted; this test compares the blood pressure (BP) measured after infusing 2 l of isotonic saline over 4 h with the BP measured during a salt-restricted diet and administration of three 40-mg doses of oral furosemide. A 10 mmHg or greater difference in mean BP between the salt-loaded and salt-depleted phases of the test is defined salt-sensitivity. In three patients to be described, infusion of isotonic saline induced a surge of BP far in excess to the mild hypertensive effect required to diagnose salt-sensitive hypertension. Such episodes are not well described in the literature.

Cases

Patient 1

A 96-year-old woman was referred with the diagnosis of left lower lobe pneumonia. Amoxicillin/clavulanate intravenous (i.v.) 1 g × 3/day was started. Notable in the patient’s medical history were multi-infarct dementia, dysphagia, grade I arterial hypertension, vitamin B12 and iron deficiency. Her regular medications were simvastatin 20 mg, furosemide 40 mg, vitamin B12 and ferum sulfate 160 mg/day. The patient’s BP readings on the day of admission were 185/90, 139/77, 145/65 mmHg, the heart rate 72 bpm, temperature 38.6°C. The serum creatinine was 0.7 mg/dl, WBC 12 300/mm³, polymorphonuclear leukocytes 79%. Two days later, the temperature returned to normal but the abdomen became distended with no passage of stool or gas and high-pitched bowel sounds suggesting intestinal obstruction or pseudoobstruction. On plain abdominal X-ray, the colon was distended, air visible in all colonic segments including the rectosigmoid and the maximum cecal diameter 7 cm. The BP was 138/70 mmHg. Serum levels of sodium, potassium, calcium and thyrotropin were within the normal range. On surgical consultation, a diagnosis of colonic pseudoobstruction was postulated and conservative management recommended. The patient was kept fasted and i.v. saline was started. Four hours later, she became tachypneic and the BP had increased to 220/107 mmHg. Relief was achieved after administration of furosemide and clonidine. Repeated episodes of intestinal pseudoobstruction followed, characterized by tense abdomen, tympanism, hyperperistalsis and some relief attained by placement of a rectal tube. Another episode of intestinal pseudoobstruction necessitated again i.v. hydration. One liter of normal saline was started slowly, keeping in mind the recent incident. Yet, the patient became dyspneic, with the BP 214/111 mmHg, heart rate 72 bpm and clinical findings consistent with pulmonary edema. The saline infusion was discontinued, furosemide, nitroglycerin and clonidine were administered, briefly followed by hemodynamic stabilization. Subsequently, the administration of saline was avoided; for hydration i.v. glucose 5% was administered. Throughout 12-day hospitalization, the patient received enteral and, repeatedly, parenteral hydration. Only infusion of saline was associated with hypertensive spells, on challenge and, by necessity, on rechallenge. The BP remained in the range 110–138/72–80 mmHg when receiving large quantities of fluids other than saline.
Patient 2
An 81-year-old woman was referred with the diagnosis of right lower lobe pneumonia. Empirical treatment with ceftriaxone and azithromycin was started. Remarkable in her medical history are well controlled arterial hypertension, diabetes mellitus type 2, left bundle branch block and chronic renal failure. The patient’s regular medications comprised insulin mixtard, simvastatin 20 mg/day and clonidine 0.150 mg x 2/day. On admission to our ward, the patient’s temperature was 37.0°C, supine BP 177/70 mmHg, heart rate 60 bpm, oxygen saturation on room air 98%. The chest X-rays showed an alveolar infiltrate with air bronchogram in the right lower lung field. The serum creatinine was 3.5 mg/dl and BUN 84 mg/dl. Acute oliguric renal failure was diagnosed and infusion of isotonic saline, 12 gtt/min was started. Four hours later the patient became tachypneic, the BP had increased to 230/130 mmHg and wet rales were perceived over the lower lung fields. The ECG was unchanged. To this time the patient had received 180 ml of saline. The infusion was discontinued. With 40% oxygen administered by face mask, morphine 10 mg, sublingual clonidine 0.150 mg and 80 mg furosemide i.v. it took about 30 min to observe improvement: the BP decreased to 190/98 mmHg, later 170/60, then 154/76 mmHg and the rales withdraw to the lung bases. During her hospital stay, the patient’s median BP was 134/50 mmHg with furosemide 120 mg/day added and all other medications continued. Control chest X-rays showed no pulmonary congestion. At the time of discharge from the nursing home, the serum creatinine was 3.7 mg/dl and BUN 91 mg/dl.

The severe and unexpected surge of BP in this patient occurred during infusion of merely a small volume of saline. This may be explained by volume-independent direct effects of sodium on the BP, via ouabain-like steroids, angiotensin-mediated central effects and increased sympathetic nervous system activity.3

Patient 3
A 63-year-old usually healthy, normotensive woman underwent elective lumpectomy for carcinoma of the beast. Her preoperative BP was 120/68 mmHg. As part of the post-operative care, she received infusion with 1000 ml of isotonic saline. She made a swift recovery after operation and was in good mood. Unexpectedly, 24 h after surgery her BP was 193/110 mmHg and remained elevated for 24 h. Routine biochemistry and urinalysis were unremarkable. Infusion of saline was discontinued. No antihypertensive medication or sedative was administered. Urinary catecholamines were within the normal range. The patient remained under close observation for another day and had all BP measurements within the normal range. On 24-h ambulatory BP monitoring and during outpatient follow-up the BP remained normal.

The latter case illustrates the unexpected BP surge after saline infusion in a normotensive subject and normalization of the BP after discontinuation of saline infusion. Although hospitalization might be responsible for stress-hypertension, an argument can be made against this possibility in our patient. Indeed, normal BP values were recorded in the hospital before surgery and the BP returned to normal while she was still in the hospital. The rise and fall in BP in this patient is not in line with a psychogenic vasopressor reaction.

Discussion
Studies with intravenous saline loading have shown adaptive responses. In healthy adults, i.v. infusion of 20–30 ml/kg of normal saline over 30 min resulted to increase the pulmonary capillary blood volume by 12% as well as the cardiac output, with concomitant increase of the systolic BP by 7 mmHg, but no significant change in diastolic BP.4 A body of evidence suggests that altered adaptive mechanisms may be operative in salt-sensitive hypertension.

A variety of etiologic factors may be involved in salt-sensitive hypertension. Older age, black race and female sex are associated with an increased frequency of salt-sensitivity.5 Salt-sensitive hypertension may be acquired as a consequence of microvascular and tubulointerstitial renal injury; this is mediated in part by lymphocytes and macrophages infiltrating the tubulointerstitium that produce angiotensin II and stimulate oxidative stress.5 The BP response to changes in salt balance may be genetically determined. The rare, Mendelian, juvenile forms of hypertension involve excessive activation of the epithelial Na+ channel (ENaC), i.e. the final common pathway for reabsorption of sodium from the distal nephron. For example, mutations in the kinases WNK1 and WNK4 have been identified to be responsible for some forms of Gordon’s syndrome; the genetic background of other forms of Gordon’s syndrome remains unclear. A systematic analysis of the genetic mechanisms involved in salt-sensitivity showed contribution of ADD1, ACE, WNK1 and NEDD4L variants to the acute BP response.6 In distinction to the former, a single nuclear polymorphism located in the first introns of PRKG1 gene is associated with surge in BP after acute salt
load by engaging a different pathway: the PRKG1 gene regulates intracellular Ca\(^{2+}\) concentration and by this mechanism it contributes to the control of vascular tone and BP.\(^7\) The BP upsurge induced by the salt load engages genes that regulate contractility of vascular smooth muscle cells.\(^7\)

The mechanisms of hypertension driven by sodium retention include volume-mediated effects of sodium retention, volume-independent direct effects of sodium such as production of ouabain-like steroids, angiotensin-mediated central effects of sodium, increased sympathetic nervous system activity, increase in the production of nuclear factor kappa B and increased expression of the angiotensin 1 receptor in renal tissues.\(^3\)

The medical background of the three patients was remarkably different: normal BP, chronic arterial hypertension without renal failure and chronic hypertension with renal failure. Yet, the patients have in common a transient and severe BP surge during infusion of relatively low volumes of saline, contrasting with the usually mild hypertensive response inducible by infusing large volume of saline which is typical for salt-sensitive hypertension.\(^2\) The pathophysiology of the incidents observed in our patients is obscure. They may stand for an extreme variant of salt-sensitive hypertension, or might be a different syndrome, which has not received emphasis in the literature. Temporality of the association, illustrated by the parallel time course of saline infusion and BP surge, might be an argument supporting the idea of causality. That saline infusion was responsible for flare hypertension in Patient 1 is attested by replication of the reaction on rechallenge, improvement on dechallenge and no placebo response on hydration with i.v. glucose. The clinical implication of these incidents is important and deserves to be acknowledged.

Conclusions

The patients reported here developed flush hypertension under infusion of moderate volumes of isotonic saline. If such was the case, an alert should be added to the patient’s diagnoses. Intravenous administration of salt-free solutions might be tolerated by these patients. When saline is administered for treatment of dehydration, sepsis or worsening renal failure, the BP should be checked frequently as long as the infusion is administered and preferably over the subsequent 24 h. The pathophysiology of the hypertensive spells occurring under infusion of isotonic saline is not well understood and merits to be purposely studied. Assessment of the genetic polymorphism in this context may be instructing.

Conflict of interest: None declared.

References