

## DIURETIC EFFECT OF SODIUM ARTESUNATE IN PATIENTS WITH MALARIA

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**Abstract.** Previously, we described a direct inhibitory effect of sodium artesunate on sodium chloride transport in the thick ascending limb of Henle's loop, indicating that artesunate acts as a diuretic agent. Here we present 2 cases of falciparum malaria treated with 4 intravenous 60-mg doses of sodium artesunate. Neither diuretics nor vasoactive drugs were administered. A rise in diuresis (6 L/24 hours) was accompanied by an increase in natriuresis, and both declined at the end of the treatment. This diuretic effect has not been reported previously in patients and may modify the course of renal failure and respiratory distress syndrome, both of which complicate severe malaria.

### INTRODUCTION

Artesunate and other artemisin derivatives are drugs obtained from the Chinese medicinal herb, qinghao. Sodium artesunate currently is used in malaria treatment; it is more potent than quinine and decreases parasite counts dramatically.<sup>1</sup> Previously, we described a direct inhibitory effect of sodium artesunate on sodium chloride transport in the thick ascending limb of Henle's loop (TALH), indicating that this drug may act as a diuretic agent.<sup>2</sup> Here we report this effect in 2 patients with severe malaria who were treated with intravenous sodium artesunate (Guilin no.2 Pharmaceutical Factory, Guangxi, China).

### CASE REPORTS

**Case 1.** A 32-year-old man was admitted to the hospital with a 4-day history of fever, headache, and vomiting. He came from Tocantins (Amazon Region), Brazil. Positive parasitemia for *Plasmodium vivax* (20 parasites/field) was detected in a blood smear, and a positive ParaSight F test (Becton and Dickinson, Sparks, MD) confirmed a coinfection with *Plasmodium falciparum*. The patient was started on mefloquine therapy.

On the second day of hospitalization, the patient developed acute respiratory failure. He was moved to the intensive care unit (ICU) with dyspnea, bilateral diffuse lung crackles, and hypoxemia (pO<sub>2</sub> 37.9 mm Hg, breathing oxygen at 5 L/min). Chest radiography revealed bilateral pulmonary alveolar infiltrates. He was intubated and placed on mechanical ventilation. Blood pressure was 120/80 mm Hg and pulse was 100 beats/min. Arterial blood gases (obtained after intubation and mechanical ventilation on 80% fraction of inspired oxygen and 15 CmH<sub>2</sub>O of positive end-expiratory pressure) showed a pH of 7.54, pO<sub>2</sub> of 124 mm Hg, pCO<sub>2</sub> of 24 mm Hg, and HCO<sub>3</sub> of 20 mmol/L. Blood tests indicated a hemoglobin level of 12.3 g/dl, a white blood cell count of 10.1 × 10<sup>9</sup>/L, and a platelet count of 35,000 mm<sup>3</sup>. Liver and kidney function were within normal limits. Neither diuretics nor vasoactive drugs were administered. Medication was switched to sodium artesunate, which was given intravenously in 60-mg doses at 0, 4, 24, and 48 hours. Sodium and potassium concentrations were measured by flame photometry (model 143; Instrumentation Laboratory, Lexington, MA). Chloride concentration was determined by a chloridometer (model 4-2000; Buchler Instruments, Fort Lee, NJ). Before administration of the antimalarial, urine flow rate was 37.3 ml/h, and urinary excretion of sodium, potassium, and chloride was 1.6, 1.1, and 1.8

mmol/h. On day 2 of treatment, urine volume increased progressively to 270 ml/h, and urinary excretion of sodium, potassium, and chloride increased to 31.9, 7.1, and 31.6 mmol/h. Two days after discontinuing the drug, urine volume decreased to 79.2 ml/h, and urinary excretion of sodium, potassium, and chloride decreased to 3.3, 3.5, and 2.9 mmol/h (Figure 1). Serum creatinine was 1.1 mg/dl at ICU admission and did not change during artesunate treatment. Respiratory function improved progressively. Three days after the initial administration of artesunate, the patient was extubated, and his chest radiograph was clear. Parasitemia for *P. vivax* and the ParaSight F test were negative 2 days after the end of artesunate therapy. On day 8, the patient was discharged from the ICU.

**Case 2.** A 16-year-old boy was admitted with fever, asthenia, anorexia, and consciousness disturbance. He had returned from a trip to Thailand 18 days before admission. His blood pressure was 130/80 mm Hg, and his pulse rate was 108 beats/min. Hemoglobin was 7.2 g/dl, white blood cell count was 5 × 10<sup>9</sup>/L, and platelet count was 13,000 mm<sup>3</sup>. *P. falciparum* parasite count was 40,080/mm<sup>3</sup>. Analysis of arterial blood gases revealed pH of 7.4, pO<sub>2</sub> of 130 mm Hg, pCO<sub>2</sub> of 27 mm Hg, and HCO<sub>3</sub> of 19 mmol/L. Hepatic and renal function remained within normal values throughout hospitalization. Intravenous 60-mg doses of sodium artesunate were given at 0, 4, 24, and 48 hours. On day 4 of artesunate treatment, diuresis was 260.4 ml/h, and urinary excretion of sodium, potassium, and chloride was 24.8, 5.8, and 26.1 mmol/h. Four days after the artesunate was discontinued, urine volume decreased to 83 ml/h. Urinary excretion of sodium, potassium, and chloride also decreased to 5.5, 2.0, and 5.9 mmol/h. A blood transfusion was given on the second day of artesunate therapy. Parasite count cleared 4 days after artesunate introduction. The patient showed progressive improvement and was discharged from the hospital on day 18.

### DISCUSSION

In these 2 cases, diuresis and natriuresis began to rise immediately after artesunate administration and declined at the end of the treatment. In malaria patients whose symptoms do not include renal failure, severe volume depletion and increased secretion of antidiuretic hormone are responsible for the oliguria commonly observed in these cases.<sup>3,4</sup> We can verify that the increased diuresis is due to artesunate rather than to plasmodial infection in the kidneys by referring to case 1. This patient presented with normal urinary volume in the control period, when he had malaria but had not yet received artesunate. As we have shown previously, artesunate

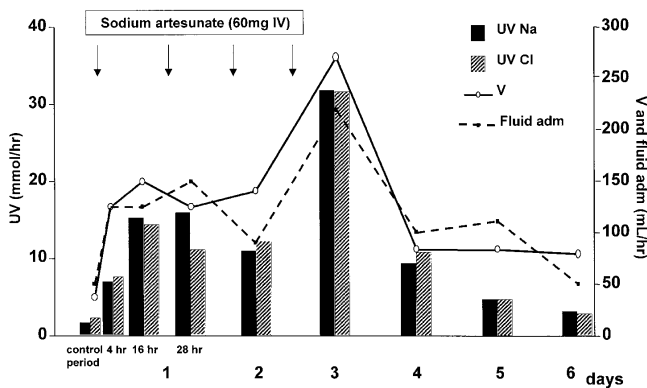


FIGURE 1. Urine flow rate (V), fluid administered (fluid adm), and urinary excretion (UV) of sodium (Na) and chloride (Cl) in control period and after artesunate administration.

exerts its diuretic effect by reducing chloride lumen-bath fluid in the rabbit TALH in the peritubular membrane.<sup>2</sup> The molar concentration used in this *in vitro* study was comparable to the drug's therapeutic range because the maximum concentration of artesunate after a 2–4 mg/kg intravenous dose in humans was 2.64–5.30 mg/L, approximately  $10^{-5}$  mol/L.<sup>5</sup>

Our experimental study showed that intravenous administration of artesunate increases the urinary excretion of nitrites and nitrates, which are metabolites of nitric oxide, suggesting that the drug can stimulate the renal production of nitric oxide. We also verified that L-nitro-arginine-methyl ester (L-NAME), an inhibitor of nitric oxide synthase, blocked the effect of sodium artesunate on TALH, suggesting that artesunate stimulates nitric oxide in this nephron segment. This may be one of the mechanisms that contributes to its diuretic and natriuretic effect.

Studies suggest that nitric oxide can have a protective effect in malaria.<sup>6</sup> Febrifugine, another antimalarial drug, reduces mortality and parasitemia in mice infected with *Plasmodium berghei* NH65.<sup>7</sup> These effects are associated with an increase in nitrate ( $\text{NO}_3$ ) and were reduced by nitric oxide blockers, indicating that the increased production of nitric oxide by febrifugine plays an important role in host defense against malaria infection in mice.

The rapid improvement in pulmonary function observed in case 1 may be due in part to the diuretic effect of artesunate. It is also possible that an increase in nitric oxide production in the lungs induced by this antimalarial drug played a part be-

cause endogenously produced nitric oxide has been reported to be protective against lung injury.<sup>8</sup>

The diuretic effect of artesunate can modify the course of acute renal failure, which frequently accompanies severe malaria. In the case of patients who lose water from high fever and tachypnea, the increase in urinary sodium and water can worsen hypovolemia and aggravate renal failure. Administration of a drug that inhibits sodium chloride transport in the TALH (e.g., furosemide) can convert a case of renal failure from oliguric to nonoliguric, however, facilitating the management of patients with fluid overload.<sup>9</sup> Future studies with malaria patients are necessary to verify whether artesunate modifies the outcome of renal failure and adult respiratory distress syndrome in this disease.

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