J Anesth (2009) 23:266–269
DOI 10.1007/s00540-008-0725-0

Journal of
Anesthesia

Successful treatment with hydrocortisone for heat stroke with critical illness-related corticosteroid insufficiency: transitional changes in serum cytokine and cortisol concentrations

Takashi Miyauchi, Ryosuke Tsuruta, Satoshi Kutsuna, Takashi Nakahara, Motoki Fujita, Shunji Kasaoka, and Tsuyoshi Maekawa

Advanced Medical Emergency And Critical Care Center, Yamaguchi University Hospital, 1-1-1 Minami-Kogushi, Ube 755-8505, Japan

Abstract
A 37-year-old man was transferred to our emergency center because of heat stroke with circulatory shock. Despite aggressive body cooling, massive intravenous transfusion, and supply of inotropic agents, shock was persistent. To evaluate adrenal function, an adrenocorticotropic hormone stimulation test was conducted and the results indicated that he had critical illness-related corticosteroid insufficiency (CIRCI) as a result of adrenal insufficiency. Continuous hydorocortisone administration was started and he recovered from shock within a few hours. He was discharged on the thirty-seventh hospital day. Serum cortisol and cytokine concentrations were initially high and the cytokines decreased subsequent to hydrocortisone administration. It is speculated that CIRCI is an exacerbating factor in heat stroke, and hydrocortisone may be a potential therapeutic approach in such patients.

Key words Heat stroke · Adrenocorticotropic hormone · Cortisol · Cytokine

Introduction

Recently, air temperature around the world has been rising because of global warming. Since the 1990s, many people have suffered from heat stroke during severe heat waves in the United States and Europe, in 1995 and 2003, respectively [1,2]. We collected the data from all cases of heat illness for 1 year in our prefecture and reported the results in 2007 [3]. The tendency in Japan has also been the same.

Heat illness is caused by exposure to a hot environment or by excessive exertion. Heat stroke is defined as the most severe form of heat illness and is characterized by a high body temperature, of more than 40° Celsius and by central nervous system dysfunction, such as delirium, convulsions, and coma [4]. It can be a fatal illness, and its incidence will increase in the near future.

We report a patient with heat stroke with circulatory shock. He was treated with hydrocortisone and had a good outcome. We measured his serum cortisol and cytokine concentrations and in this report we discuss the therapeutic efficacy of hydrocortisone in heat stroke.

Case report

A 37-year-old man suffered a consciousness disturbance while working in scorching heat in August. The maximum air temperature was 34.8° Celsius and humidity was 51%. His colleagues moved him to a shaded area and cooled down his body with water; however, his consciousness disturbance was not alleviated. He was transported to a hospital by ambulance 1 h after the onset. When he arrived there, his Glasgow Coma Scale (GCS) level was 3 (E1V1M1). His blood pressure, heart rate, and respiratory rate were 118/79 mmHg, 142 bpm, and 28 breaths·min^{-1}, respectively. His body temperature (axillary) was 41.8° Celsius. Immediately, body cooling and massive fluid transfusion were started. But his blood pressure gradually decreased and a blood gas analysis showed hypercapnea and metabolic acidosis (fractional inspired oxygen [$F_{I_{O_2}}$], 1.0; pH, 7.14; Pa_{O_2}, 91.5 mmHg; Pa_{CO_2}, 56.7 mmHg; base excess [BE], –9.2 mmol·l^{-1}; HCO_3^-, 15.9 mmol·l^{-1}). After tracheal intubation, he was transferred to our medical emergency center.

On admission, his GCS, blood pressure, heart rate, respiratory rate, and body temperature (bladder) were: 3 (E1V1M1), 110/40 mmHg, 140 bpm, 24 breaths·min^{-1}, and 39.8° Celsius, respectively. On head computed tomography (CT), there was no significant finding which

Address correspondence to: T. Miyauchi
Received: September 5, 2008 / Accepted: November 22, 2008

Table 1. ACTH stimulation test in the patient

	Before ACTH	After 30 min	After 60 min
ICU day 3 ($\mu g \cdot dl^{-1}$)	32.1	37.0	37.9
ICU day 28 ($\mu g \cdot dl^{-1}$)	15.7	30.7	40.7
Normal range ($\mu g \cdot dl^{-1}$)	(4.0–18.3)		

ACTH, adrenocorticotropic hormone; ICU, intensive care unit

indicated any cause of the consciousness disturbance. From the physiological findings and laboratory data, he was diagnosed as having heat stroke associated with respiratory failure, disseminated intravascular coagulopathy, and acute renal failure. The amount of crystalloid transfusion reached 20000 ml during the first 24 h after admission. Mechanical ventilation ($F_{I_{O_2}}$, 1.0; positive end-expiratory pressure [PEEP], 8 cmH_2O) and continuous hemodiafiltration were performed. His core body temperature (bladder) cooled down to 36° Celsius within 8 h after the onset. Despite massive intravenous transfusion and inotropic agents such as dopamine, dobutamine, and norepinephrine, he was in persistent circulatory shock (blood pressure decreased to 50/30 mmHg and heart rate increased to 150 bpm). The circulatory parameters, measured with a pulmonary artery catheter (Swan-Ganz CCOmbo Pulmonary Artery Catheter; Edwards Lifescience, Irvine, CA, USA), showed decreased somatic vascular resistance of 800–1100 $dyne \cdot s \cdot cm^5 \cdot m^2$ and an increased cardiac index of 6.5 $l \cdot min^{-1} \cdot m^2$. In order to search for a site of infection, we repeatedly checked cultures of blood, sputum, and urine, and X-ray and CT scans, but there were no data indicating the existence of any infections during the clinical course.

We conducted an adrenocorticotropic hormone (ACTH; tetracosactide acetate) stimulation test to evaluate adrenal function on his third day in the intensive care unit (ICU). Synthetic ACTH 0.25 mg was intravenously injected. Serum cortisol concentrations were measured before and 30 and 60 min after the ACTH injection (Table 1). He was diagnosed as having critical illness-related corticosteroid insufficiency (CIRCI) as a result of adrenal insufficiency, which has been defined in previous reports as the condition of a less than 9 $\mu g \cdot dl^{-1}$ maximum increment of serum cortisol concentration after ACTH injection [5,6]. After this diagnosis, continuous hydrocortisone infusion of 200 $mg \cdot day^{-1}$ was started, from the third ICU day. A few hours after the first injection, his blood pressure gradually increased (Fig. 1). Consequently, he recovered from circulatory shock and the inotropic agents could be tapered off on the fifth ICU day. Hydrocortisone administration of 200 $mg \cdot day^{-1}$ was continued for 7 days. The dose was reduced to 100 $mg \cdot day^{-1}$ on the tenth ICU day, and reduced to 50 $mg \cdot day^{-1}$ on ICU day 11, and then discontinued on ICU day 12. When the hydrocortisone administration was stopped, his general condition, including circulation and respiration, was still stable and we found no adverse effects of the hydrocortisone therapy. Mechanical ventilation was discontinued on ICU day 15. Reevaluation of adrenal function by the ACTH stimulation test on ICU day 28 showed a normal response (Table 1). There were no serious complications except for speech and gait disorders that were caused by central nervous injury caused by high core temperature. He was discharged from our hospital on hospital day 37.

After obtaining informed consent from his wife, we had obtained arterial blood samples on ICU days 2, 3, 4, and 8. These samples were separately injected into sterile tubes. After being left for at least 30 min at 4° Celsius, the tubes were centrifuged at 3000 rpm for 10 min. The supernatant liquid (serum) was aspirated and separately injected into sterile tubes and these tubes were frozen at –80° Celsius for preservation. Serum cortisol concentrations were measured by an enzyme-linked immunosorbent assay (ELISA; Cortisol ELISA; IBL, Hamburg, Germany). Serum cytokines were analyzed by the Bio-Plex Cytokine Human 8-Plex panel (Bio-Rad Laboratories, Hercules, CA, USA). The transitional changes in serum cortisol and cytokine levels in the early phase are shown in Fig. 2.

Discussion

Heat stroke is a life-threatening illness characterized by an excessive elevation of body temperature with central nervous system disturbance. Exposure to a hot environment and disorder of thermoregulatory function generate heat stroke. In order to prevent organ failure, effective core body cooling in the early phase is essential [4]. However, once heat stroke develops, cooling is not enough to alleviate the pathophysiological manifestations of the thermoregulatory function disorder.

The main pathophysiology of heat stroke is endothelial injury caused by heat exposure. Endothelial injury induces the release of inflammatory cytokines, and the cytokine cascade causes further endothelial injury, vascular dilatation, and organ dysfunction, which is a similar condition to sepsis. Excessive stress and inflam-

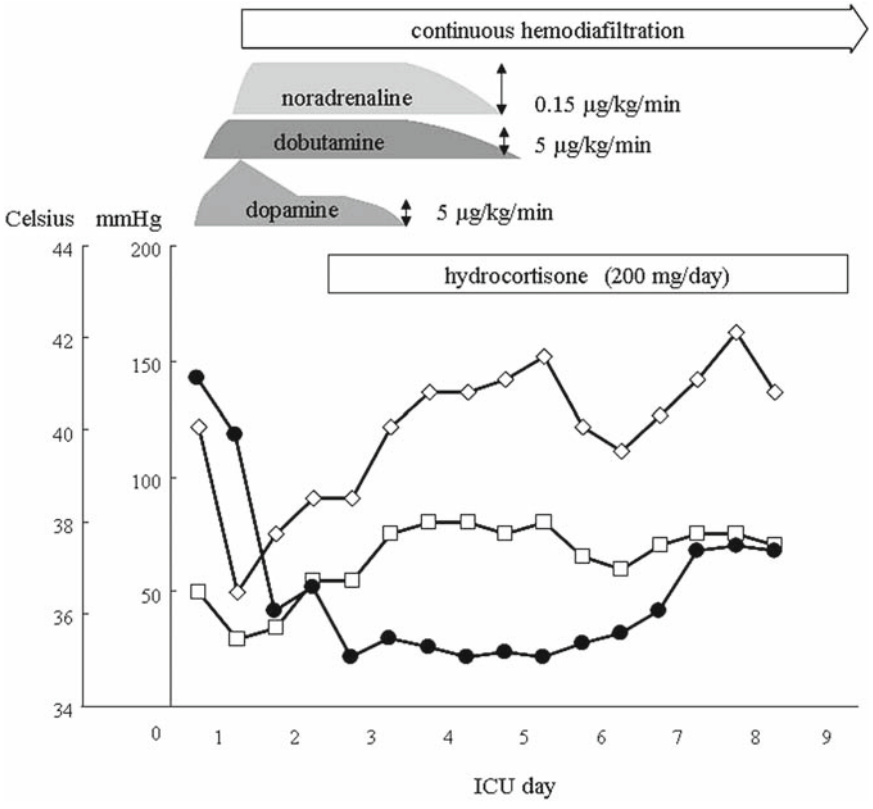

Fig. 1. Clinical course of the patient. Although his initial core body temperature (*circles*) was more than 40° Celsius, he was cooled down to 36° Celsius within 8 h after onset. Despite massive intravenous transfusion, inotropic agents, and continuous hemodiafiltration, he was still in shock. After hydrocortisone was started, his blood pressure (systolic, *diamonds*; diastolic, *squares*) gradually increased. Hydrocortisone at 200 mg·day^{-1} was continued for 7 days. There were no complications during the clinical course

matory cytokines lead to a decrease in adrenal steroid production (adrenal insufficiency) and/or tissue resistance to glucocorticoid. CIRCI, which is a novel pathophysiological condition, is defined as inadequate cellular corticosteroid activity for the severity of the patient's illness, and it occurs as a result of adrenal insufficiency [6,7].

In our patient, the standard therapeutic approach against shock, including massive transfusion, vasopressors, mechanical ventilation, and continuous hemodiafiltration, was not sufficient to stabilize his circulatory condition. We diagnosed him as having CIRCI as a result of adrenal insufficiency by the ACTH stimulation test. Serum cytokines, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α, IL-6, and interferon (IFN)-γ are involved in the pathophysiological development of heat stroke [8,9]. It is noteworthy that the serum IL-6 level correlates with the severity of heat stroke [9]. In our patient, initial serum IL-6, TNF-α, and IFN-γ levels were 10753 pg·ml^{-1}, 96.5 pg·ml^{-1}, and 196 pg·ml^{-1}, respectively (Fig. 2). Hydrocortisone was reported to be effective for refractory shock with adrenal insufficiency; therefore, he was given hydrocortisone [4,7,10]. Soon after the start of the hydrocortisone administration, his circulatory condition became steady, which indicated that hydrocortisone was effective for CIRCI. Although the International guidelines for management of severe sepsis and septic shock 2008 [11] do not recommend the ACTH stimulation test to identify the patients who should receive hydrocortisone, we think that hydrocortisone therapy is still potentially useful because of its strong anti-inflammatory activity.

Despite the initial serum cortisol concentration being physiologically high in our patient, inflammatory cytokine concentrations were also high. Serum cortisol had increased and inflammatory cytokines had decreased on ICU day 8 (Fig. 2). The transitional changes in these mediators indicate that the initial serum cortisol level may have been "relatively" insufficient. The recovery of adrenal response by the second ACTH stimulation on ICU day 28 indicates that CIRCI is reversible.

In animal experiments, a cytokine antagonist and glucocorticoid therapy were confirmed to be effective for heat stroke [12,13]. In contrast, an experiment in a baboon heat stroke model suggested that glucocorticoid did not reduce mortality [14]. Although there are no available data in humans, we think that hydrocortisone was effective to improve an inflammatory imbalance in our patient. However, we also think that the effective dose, timing, and duration of glucocorticoid therapy are different in each case, and this may be an explanation of the discrepancy in animal experiments. We should strictly determine the candidates for glucocorticoid therapy.

CIRCI is not a specific condition in septic shock, and it is also found in heat stroke. The present report sug-

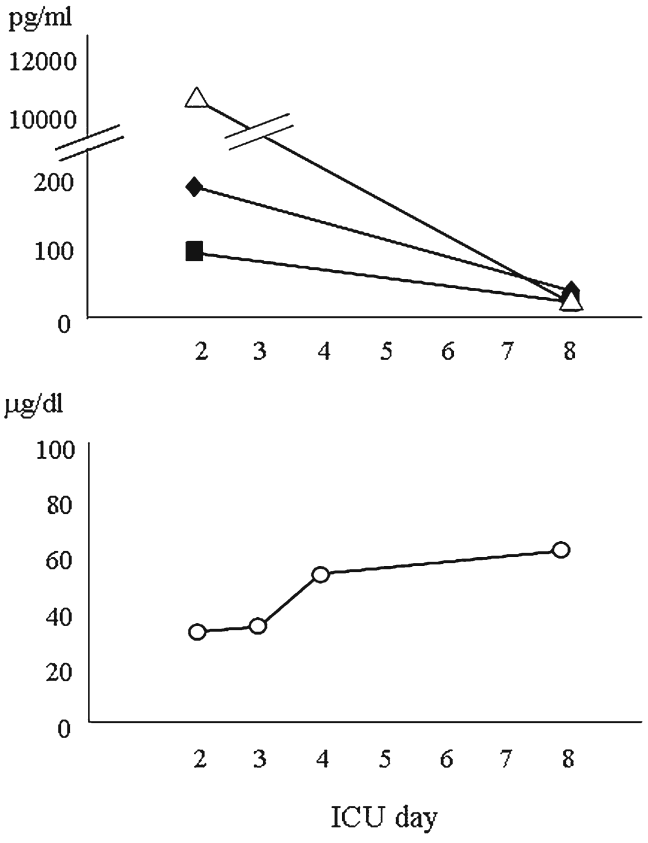

Fig. 2. Transitional changes in serum cortisol and cytokines. The *upper figure* shows the changes in serum cytokines. Initial serum interleukin-6 (*IL-6; triangles*), tumor necrosis factor-α (*TNF-α; squares*), and interferon-γ (*IFN-γ; diamonds*) levels were high, but they had decreased on intensive care unit (*ICU*) day 8. *The lower figure* shows the changes in serum cortisol (*circles*). The initial serum cortisol level was above the normal limit and it increased with hydrocortisone administration

gests that CIRCI is an exacerbating factor in heat stroke and that hydrocortisone therapy may be an additional and special treatment for patients with heat stroke and circulatory shock.

Conclusions

Hydrocortisone was successfully used to treat heat stroke with circulatory shock. We confirmed that heat stroke is sometimes associated with CIRCI. Even when the serum cortisol level is physiologically high, hydrocortisone may be effective in heat stroke, because the cortisol level is sometimes relatively insufficient during an excessive inflammatory response.

References

1. Dematte JE, O'Mara K, Buescher J, Whitney CG, Forsythe S, McNamee T, Adiga RB, Ndukwu M. Near-fatal heat stroke during the 1995 heat wave in Chicago. Ann Intern Med. 1998;129:173–81.
2. Vandentorren S, Bretin P, Zeghnoun A, Mandereau-Bruno L, Croisier A, Cochet C, Ribéron J, Siberan I, Declercq, Ledrans M. August 2003 heat wave in France: risk factors for death of elderly people living at home. Eur J Public Health. 2006;16:583–91.
3. Tsuruta R, Hitaka Y, Inoue T, Oda Y, Kaneda K, Kasaoka S, Maekawa T. Epidemiologic investigation of the severity in patients transported by ambulance suffering from heat illness in Yamaguchi prefecture (in Japanese with English abstract). JJAAM (Journal of Japanese Association for Acute Medicine). 2007;18:694–700.
4. Bouchama A, Knochel JP. Medical progress: heat stroke. N Engl J Med. 2002;346:1978–88.
5. Annane D, Sébille V, Troché G, Raphaël JC, Gajdos P, Bellissant E. A three-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. JAMA. 2000;283:1038–45.
6. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh Didier, Briegel J, Beishizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. Crit Care Med. 2008;36:1937–49.
7. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. Crit Care Med. 2003;31:141–5.
8. Lu KC, Wang JY, Lin SH, Chu P, Lin YF. Role of circulating cytokines and chemokines in exertional heatstroke. Crit Care Med. 2004;32:399–403.
9. Bouchama A, Al-Sedairy S, Siddiqui S, Shail E, Rezeig M. Elevated pyrogenic cytokines in heatstroke. Chest. 1993; 104:1498–502.
10. Gonzalez H, Nardi O, Annane D. Relative adrenal failure in the ICU: an identifiable problem requiring treatment. Crit Care Clin. 2006;22:105–18.
11. Dellinger RP, Levy MM, Carlet JM, Bion J, Parker MM, Jaeschke R, Reinhart K, Angus DC, Brun-Buisson C, Beale R, Calamdra T, Dhainaut JF, Gerlach H, Harvey M, Marini JJ, Marshall J, Ranieri M, Ramsay G, Sevransky J, Thompson BT, Townsend S, Vender JS, Zimmerman JL, Vincent JL. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. Intensive Care Med. 2008;34:17–60.
12. Lin MT, Liu HH, Yang YL. Involvement of interleukin-1 receptor mechanisms in development of arterial hypotension in rat heatstroke. Am J Physiol. 1997;273:H2072–7.
13. Liu CC, Chien CH, Lin MT. Glucocorticoids reduce interleukin-1 concentration and result in neutroprotective effects in rat heatstroke. J Physiol. 2000;27:333–43.
14. Bouchama A, Kwaasi A, Dehbi M, Mohanna FA, Eldali A, El-Sayed R, Tbakhi A, Alzahrani AS, Roberts G. Glucocorticoids do not protect against the lethal effects of experimental heatstroke in baboons. Shock. 2007;27:578–83.