

COMMENTARY

A new way of thinking: hydrocortisone in traumatic brain-injured patients

Antoine Roquilly, Mickael Vourc'h, Raphael Cinotti and Karim Asehnoune*

See related research by Chen et al., <http://ccforum.com/content/17/5/R241>

Abstract

Data suggest that treatment of critical illness-related corticosteroid insufficiency after traumatic brain injury (TBI) with a stress dose of hydrocortisone may improve the neurological outcome and the mortality rate. The mineralocorticoid properties of hydrocortisone may reduce the rate of hyponatremia and of brain swelling. The exaggerated inflammatory response may cause critical illness-related corticosteroid insufficiency by altering the function of the hypothalamic–pituitary–adrenal axis, and hydrocortisone is able to restore a balanced inflammatory response rather than inducing immunosuppression. Hydrocortisone could also prevent neuronal apoptosis. Considering side effects, corticosteroids are not equal; when a high dose of synthetic corticosteroids seems detrimental, a strategy using a stress dose of hydrocortisone seems attractive. Finally, results from a large multicenter study are needed to close the debate regarding the use of hydrocortisone in TBI patients.

In the previous issue of *Critical Care*, Chen and colleagues investigate whether hydrocortisone influences the neurological outcome and mortality in a rat model of traumatic brain injury (TBI)-induced critical illness-related corticosteroid insufficiency (CIRCI) [1]. Up to 30 to 80% of TBI patients develop pituitary hormone impairment [2]. Growth hormone as well as the thyroid and gonadal axis have been extensively studied. CIRCI has been studied in sepsis but received much less attention after TBI, despite the fact that its incidence seems high [3]. The authors postulated that early recognition of CIRCI after TBI and treatment with corticosteroids may improve neurological outcome. This may prove

important since Bombardier and colleagues have shown that 51.3% of patients met the criteria for major depressive disorders during the first year after TBI [4].

In the present study, Chen and colleagues nicely demonstrate in a rat model of TBI that treating CIRCI with hydrocortisone improves neurological recovery by blocking neuronal apoptosis, and reducing damage of the tight junction. Interestingly, the authors also show that a synthetic glucocorticoid (methylprednisolone) did not alter neurological outcomes or mortality.

Several mechanisms may explain a beneficial effect of hydrocortisone. First, hydrocortisone may improve the cerebral perfusion pressure through a mineralocorticoid effect. Hydrocortisone displays a four times better affinity than methylprednisolone for the mineralocorticoid receptor. Hyponatremia is frequent after TBI, and recent evidence showed that mild hypernatremia could decrease the intracranial pressure, improving the cerebral perfusion pressure [5]. Hydrocortisone may therefore reduce the rate of hyponatremia and of brain swelling.

Second, after initial TBI, the exaggerated inflammatory response may cause CIRCI by altering the function of the hypothalamic–pituitary–adrenal axis. Tumour necrosis factor and interleukin (IL)-6 are increased in TBI or septic shock associated with CIRCI [3,6]. In particular, Hoen and colleagues have shown that blood IL-6 was significantly higher in severe trauma patients with CIRCI as compared with patients without CIRCI [7]. It is well known that hydrocortisone decreases the production of these inflammatory cytokines, but recent evidence permits a reappraisal of the properties of hydrocortisone regarding the inflammatory response. In septic patients, hydrocortisone decreased the blood level of the anti-inflammatory cytokines (IL-10) and increased the blood levels of IL-12 (cytokine-enhancing immune response against bacterial infection) without inducing immunosuppression. These data suggest that hydrocortisone is able to restore a balanced inflammatory response rather than inducing immunosuppression [8].

* Correspondence: karim.asehnoune@gmail.com
Service d'Anesthésie réanimation, CHU de Nantes, 1 place Alexis Ricordeau, 44093 Nantes Cedex 1, France

Third, corticosteroids are believed to be potent inducers of apoptosis mainly by a shutdown of the inflammatory response through inhibition of the NF- κ B pathway [9], which promotes survival of cells generally. These data were provided mainly with a high dose of synthetic glucocorticoids in patients with cancer or solid organ transplantation, but few data were published with hydrocortisone.

Chen and colleagues show that hydrocortisone prevents neuronal apoptosis even if the exact mechanism for this novel property of the drug remains largely unknown. The authors also demonstrate that hydrocortisone but not methylprednisolone improves neurological outcomes and prevents mortality in TBI rats [1]. However, the benefit of corticosteroids in TBI patients remains controversial. In the CRASH study, a high dose of methylprednisolone worsened mortality as compared with placebo, and it was also speculated that hydrocortisone might increase the rate of secondary infections [10]. In a recent COCHRANE systematic review, a stress dose of hydrocortisone (200 to 300 mg/day) did not increase the rate of infection as compared with placebo in septic shock patients [11]. In the HYPOLYTE study involving severe trauma patients, including 65% TBI patients, no safety issue was raised with the use of hydrocortisone [12]. Of note, the results obtained with hydrocortisone were spectacular in CIRCI patients, whereas in the *a priori* planned subgroup analysis the treatment was particularly efficient in the TBI patients [12].

Conclusion

Answering the question of whether we should use hydrocortisone in TBI patients remains a subject of hard debate. Detecting CIRCI to select patients eligible for hydrocortisone treatment shows promise. The results of a large randomized multicenter study (CORTI-TC) will provide valuable data on the effects of hydrocortisone in severe TBI patients [13].

Abbreviations

CIRCI: Critical illness-related corticosteroid insufficiency; IL: Interleukin;
TBI: Traumatic brain injury.

Competing interests

The authors declare that they have no competing interests.

Published: 04 Dec 2013

References

1. Chen X, Zhao Z, Chan Y, Luo L, Jiang R, Dong J, Zhang J: **Stress-dose hydrocortisone reduces critical illness-related corticosteroid insufficiency associated with severe traumatic brain injury in rats.** *Crit Care* 2013, 17:R241.
2. Dimopoulou I, Tsagarakis S, Kouyialis AT, Roussou P, Assithianakis G, Christoforaki M, Ilias I, Sakas DE, Thalassinou N, Roussos C: **Hypothalamic-pituitary-adrenal axis dysfunction in critically ill patients with traumatic brain injury: incidence, pathophysiology, and relationship to vasopressor**

- dependence and peripheral interleukin-6 levels. *Crit Care Med* 2004, 32:404–408.
3. Benvenega S, Campenni A, Ruggeri RM, Trimarchi F: **Clinical review 113: hypopituitarism secondary to head trauma.** *J Clin Endocrinol Metab* 2000, 85:1353–1361.
4. Bombardier CH, Fann JR, Temkin NR, Esselman PC, Barber J, Dikmen SS: **Rates of major depressive disorder and clinical outcomes following traumatic brain injury.** *JAMA* 2010, 303:1938–1945.
5. Roquilly A, Mahe PJ, Latte DDD, Loutrel O, Champin P, Di Falco C, Courbe A, Buffenoir K, Hamel O, Lejus C, Sébille V, Asehnoune K: **Continuous controlled-infusion of hypertonic saline solution in traumatic brain-injured patients: a 9-year retrospective study.** *Crit Care* 2011, 15:R260.
6. Kwon YS, Suh GY, Jeon K, Park SY, Lim SY, Koh W-J, Chung MP, Kim H, Kwon OJ: **Serum cytokines and critical illness-related corticosteroid insufficiency.** *Intensive Care Med* 2010, 36:1845–1851.
7. Hoen S, Asehnoune K, Brailly-Tabard S, Mazoit J-X, Benhamou D, Moine P, Edouard AR: **Cortisol response to corticotropin stimulation in trauma patients: influence of hemorrhagic shock.** *Anesthesiology* 2002, 97:807–813.
8. Keh D, Boehnke T, Weber-Cartens S, Schulz C, Ahlers O, Bercker S, Volk H-D, Doecke W-D, Falke KJ, Gerlach H: **Immunologic and hemodynamic effects of 'low-dose' hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study.** *Am J Respir Crit Care Med* 2003, 167:512–520.
9. Ling J, Kumar R: **Crosstalk between NF κ B and glucocorticoid signaling: a potential target of breast cancer therapy.** *Cancer Lett* 2012, 322:119–126.
10. Roberts I, Yates D, Sandercock P, Farrell B, Wasserberg J, Lomas G, Cottingham R, Svoboda P, Brayley N, Mazairac G, Laloë V, Muñoz-Sánchez A, Arango M, Hartzenberg B, Khamis H, Yuthakasemsunt S, Komolafe E, Ollidashi F, Yadav Y, Murillo-Cabezas F, Shakur H, Edwards P, CRASH Trial Collaborators: **Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial.** *Lancet* 2004, 364:1321–1328.
11. Annane D, Bellissant E, Bollaert P-E, Briegel J, Confalonieri M, De Gaudio R, Keh D, Kupfer Y, Oppert M, Meduri GU: **Corticosteroids in the treatment of severe sepsis and septic shock in adults: a systematic review.** *JAMA* 2009, 301:2362–2375.
12. Roquilly A, Mahe PJ, Seguin P, Guitton C, Floch H, Tellier AC, Merson L, Renard B, Mallédant Y, Flet L, Sébille V, Volteau C, Masson D, Nguyen JM, Lejus C, Asehnoune K: **Hydrocortisone therapy for patients with multiple trauma: the randomized controlled HYPOLYTE study.** *JAMA* 2011, 305:1201–1209.
13. Asehnoune K, Roquilly A, Sébille V, Corti-TC Trial Group: **Corticotherapy for traumatic brain-injured patients – the Corti-TC trial: study protocol for a randomized controlled trial.** *Trials* 2011, 12:228.

10.1186/cc13138

Cite this article as: Roquilly et al.: A new way of thinking: hydrocortisone in traumatic brain-injured patients. *Critical Care* 2013, 17:1016