

## Commentary

# Dantrolene and heatstroke: a good molecule applied in an unsuitable situation

Pierre Hausfater

MD, Service d'accueil des urgences, Centre Hospitalier Universitaire Pitié-Salpêtrière, Assistance Publique-Hôpitaux de Paris, Université Pierre et Marie Curie, Paris, France

Corresponding author: Dr Pierre Hausfater, [pierre.hausfater@psl.ap-hop-paris.fr](mailto:pierre.hausfater@psl.ap-hop-paris.fr)

Published online: 3 September 2004

This article is online at <http://ccforum.com/content/9/1/23>

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*Critical Care* 2005, **9**:23-24 (DOI 10.1186/cc2939)

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## Abstract

Because they share one pathognomonic sign (major hyperthermia), classic or environmental heatstroke and malignant hyperthermia have often been confronted from the therapeutic point of view. As expected and according to major physiopathological discrepancies between both syndromes, analysis of published data does not support effectiveness of dantrolene in heatstroke despite its significant reduction in mortality in malignant hyperthermia. If cooling methods still represent the cornerstone of the heatstroke therapeutic approach, the magnitude of heat-related deaths and the morbidity associated with the August 2003 French heatwave have highlighted the need for more ambitious methods of treatment.

**Keywords** dantrolene, health care, heatstroke, heatwave, malignant hyperthermia

The magnitude of heat-related deaths during the August 2003 heatwave in France and conflicting discussions about Earth's global warming consequences have forced physicians to revisit an up to now rare disease: classic or environmental heatstroke (CHS) [1,2]. Indeed, most reported cases of CHS are sporadic except for a few previously published epidemics linked to unusual heatwaves [3,4]. The CHS therapeutic approach to date has therefore been limited to human case reports or experimental data on animal models.

CHS is often compared with other extreme hyperthermia syndromes such as malignant hyperthermia and neuroleptic malignant syndrome, two situations where dantrolene administration has proved to reduce mortality. It therefore seemed superficially attractive to study the usefulness of dantrolene in CHS. The review by Hadad and colleagues aims to summarize previously published data on dantrolene use in CHS [5]. Overall, although there are conflicting results, analysis does not support the use of dantrolene in this situation. Notably, the few case reports that exhibited a beneficial effect were not confirmed in controlled studies.

Moreover, heterogeneous study designs make data interpretation difficult, as dantrolene was used either as a preventive or curative therapeutic, either on humans or animals, and either in CHS or exertional heatstroke.

The temptation to use dantrolene in CHS is the result of a misjudgement about pathophysiology. Dantrolene effectiveness in malignant hyperthermia does not result from direct action on the hypothalamic setpoint, but from reducing muscular heat production. Indeed, as discussed by Hadad and colleagues, malignant hyperthermia/neuroleptic malignant syndrome and CHS represent two clinical hyperthermia entities with quite different heat-generating pathophysiology: although muscular rigidity is the cornerstone of heat production in the former, massive thermoregulatory failure related to prolonged environmental heat exposure seems to be predominant in CHS [5,6]. So, although they share a pathognomonic sign (major hyperthermia), CHS and malignant hyperthermia/neuroleptic malignant syndrome are two distinct entities with only a few overlaps concerning heat production mechanisms.

Moreover, there are some arguments against dantrolene use in CHS. First, dantrolene is known to cause potential hepatic injury. This is of major concern in the context of CHS, a disease frequently associated with hepatic failure and/or disseminated intravascular coagulation [6]. Second, there are some experimental animal studies reporting negative inotropic effects of dantrolene on myocardium and diaphragm muscle [7,8]. As CHS predominantly affects elderly patients, a population with frequent cardiac impairment, dantrolene could theoretically be detrimental in this situation.

After the August 2003 French experience, we were able to draw several lessons from CHS care. In the first place, the health care structure appeared to be the cornerstone of epidemic management and effectiveness. As a delay to benefit from efficient cooling therapeutics dramatically influences the immediate prognosis, the most useful action is undoubtedly to put the patient into the hands of an expert 'cooling team' as quickly as possible. In order to initiate patient cooling earlier, prehospital emergency care (Service d'Aide Médicale d'Urgence; SAMU) and rescue teams began to apply ice to the skin of CHS-suffering patients immediately at the site of care (nursing homes, apartments, public thoroughfares) until they reached the Emergency Department. Interestingly, in the study of Bouchama and colleagues, no difference in the cooling rate could be demonstrated between the group of patients receiving dantrolene and the group of patients who did not [9]. However, both treatment groups achieved satisfactory cooling in less than 1 hour using a body-cooling unit, which was obviously the key therapeutic procedure in this study [9].

Does that mean that we should only focus on improving our cooling methods instead of studying adjunctive therapies in CHS? The answer rests in the mortality rate (20–50%) attributed to CHS despite active cooling procedures [6].

CHS therapeutic care may benefit from advances in sepsis management, in that both syndromes share some pathophysiological similarities: cytokine and acute-phase protein production, coagulation disorders and, finally, multiorgan dysfunction [6]. Notably, treatment with corticosteroids improves prognosis in animal models of heatstroke, as was reported in patients with septic shock using low doses of hydrocortisone [10,11]. Similarly, improvement in knowledge of coagulation disorders observed in CHS may lead to the indication of replacement therapy with recombinant activated protein C, as reported in severe sepsis [12].

Overall, the traumatic experience shared by French emergency physicians during the August 2003 heatwave, along with the severe outcome still associated with CHS, justifies ambitious therapeutic trials. Undoubtedly, Earth's global warming will especially expose urban populations to

future heatwaves and thereby to the risk of CHS. If preventive procedures and identification of vulnerable populations are crucial, emergency and critical care physicians must take up the challenge for reducing CHS morbidity and mortality.

## Competing interests

The author(s) declare that they have no competing interests.

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