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Acetaminophen Has Limited Antipyretic Activity in Critically Ill Patients

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Abstract

Purpose—Fever occurs commonly in the critically ill patients and may adversely affect outcome. Acetaminophen is one of the most commonly utilized antipyretic agents in the intensive care unit; however, there is little evidence that it is effective in this population. The objective of this study was to analyze the antipyretic activity of acetaminophen in critically ill patients.

Materials/Methods—We performed a retrospective study of MICU and SICU patients with Systemic Inflammatory Response Syndrome (SIRS) and compared the resolution of fever in the presence and absence of acetaminophen treatment by comparing the absolute reduction in body temperature and the rate of cooling over comparable time frames in fevers that were untreated and those treated with acetaminophen.

Results—We analyzed 166 febrile episodes (body temperature $>38^{\circ}\text{C}$) in 59 patients with SIRS without cancer, neurologic disease, or liver disease. Acetaminophen was administered for 88 of 166 fevers. Febrile episodes in which other antipyretic drugs or external cooling were administered were excluded. The response to acetaminophen was variable, but the absolute temperature reduction was slightly higher (mean 0.86 vs. 0.56°C ; $p = 0.0362$) and the cooling rate slightly more rapid (mean 0.20 vs. 0.13°C per h; $p = 0.0152$) in acetaminophen-treated vs. untreated fevers. There were no obvious differences between the most and least responsive patients.

Conclusions—We conclude that acetaminophen has significant albeit modest antipyretic activity in critically ill patients.

Keywords

Fever; Acetaminophen; Antipyretic; Systemic Inflammatory Response Syndrome; Critically ill

Introduction

Fever is a common occurrence in critically ill patients and is one of the criteria for the systemic inflammatory response syndrome (SIRS) [1]. Retrospective studies suggest that the presence

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of fever is associated with improved survival in patients with serious bacterial infections. However, a reanalysis of several retrospective studies by our group suggests that the association between fever and improved survival is lost and it may even be harmful in patients with higher acuity [2]. Epidemiological studies indicate that fever after acute neurological injury is associated with significantly increased mortality and impairment of functional outcome [3,4].

A prospective study of ibuprofen in patients with sepsis failed to show an effect of therapy on survival [5]; however, this study was not designed to test the antipyretic effects of ibuprofen as 33% of the treatment group and 29% of control patients also received acetaminophen during the study. A more recent study of antipyretic therapy in patients with non-neurologic trauma compared aggressive fever management comprising regularly dosed acetaminophen for temperature exceeding 38.5°C and cooling blanket for fever exceeding 39.5°C vs. more permissive management with acetaminophen and cooling blankets for fever exceeding 40°C [6]. This study was stopped early because survival was reduced in the aggressive fever treatment group (7 vs. 1 death; $p = 0.06$). There was no difference in maximal daily temperature (38.3 ± 0.8 vs. $38.3 \pm 0.7^\circ\text{C}$, mean $\pm$ SD) and only a slight difference in mean of all body temperatures (37.71 ± 0.82 vs. $37.8 \pm 0.72^\circ\text{C}$) between the aggressive and permissive groups. The percent of patients subjected to external cooling and the potential consequences of external cooling (tachycardia, shivering, increased metabolic rate) were not mentioned. However, it is noteworthy that 4 of the 7 deaths in the aggressive treatment group occurred in patients that were at least 73 years old.

Animal and *in vitro* studies suggest that febrile-range hyperthermia may increase lung [7-9] and brain [10,11] injury, in part through increased neutrophil recruitment and endothelial and epithelial injury [7,9]. In addition to the proinflammatory effects of fever, global metabolism increases approximately 10% for each degree Centigrade increase in core temperature [12], which may be particularly problematic in patients with impaired pulmonary or cardiovascular function. Considering the potential adverse effects of fever in critically ill patients, it may be beneficial to minimize fever in certain critically ill patients.

Acetaminophen is commonly used to treat fever in intensive care units [13], but few studies directly address its efficacy in the critically ill. A prospective study of acetaminophen found it to have no effect on fever in 30 critically ill patients [14], while a retrospective study found it to have very modest antipyretic activity [15]. Two additional studies found the acetaminophen prodrug, propacetamol [16,17], to be ineffective as an antipyretic agent in critically ill patients. The purpose of this study was to analyze the effectiveness of acetaminophen as an antipyretic agent in critically ill patients in a surgical and a medical intensive care unit. Our hypothesis that acetaminophen was an ineffective antipyretic in critically ill patients was tested by comparing two measures of antipyresis, absolute reduction in body temperature and cooling rate during untreated fevers and those treated with acetaminophen.

Materials and Methods

With approval of the University of Maryland Institutional Review Board, patient logs from the medical and surgical intensive care units at the University of Maryland Medical Center (Baltimore, MD) were reviewed to identify patients admitted between September 2008 through December 2008. Inclusion criteria included age > 18 years of age, admission to either the surgical or medical intensive care units, exhibit criteria for the Systemic Inflammatory Response Syndrome (SIRS) (two or more of the following: heart rate greater than 90; core temperature less than 36°C or greater than 38°C, respiratory rate greater than 20 breaths/min or PaCO₂ less than 32 mm Hg; white blood cell count less than 4000 or greater than 12,000 or at least 10% immature forms), experience at least one episode of fever (temperature >38°C

independent of route of measurement) [1], and have temperature measurements no less frequently than every 2 hours during the febrile episodes. Exclusion criteria included acute neurologic injury, underlying malignancy, and liver disease. The charts of eligible patients were then reviewed for qualifying febrile episodes. Only fevers that were untreated or treated with acetaminophen were included. Those treated with other medications having thermomodulatory activity, including major tranquilizers, nonsteroidal anti-inflammatory agents, corticosteroids, and paralytics or with external cooling were excluded. Each febrile episode was treated as a discrete event and assigned to the acetaminophen-treated fever or untreated fever groups. Multiple episodes and both treated and untreated episodes from individual patients were included in the analysis. Fevers were counted as discrete febrile episodes when separated by at least 6h of normothermia (temperature < 38°C). For each episode, the time of acetaminophen administration was assigned as time 0 and the changes in body temperature were analyzed over the subsequent 5h. Since we found that the mean delay from onset of fever (temperature >38°C) until administration of acetaminophen was 3.4h, we assigned time 0 for untreated (control) fever episodes as close to 3.4h after onset of fever as the data allowed. For all episodes of fever, we analyzed the maximal reduction in temperature between time 0 and 5h and the cooling rate. To adjust the temperature reduction for the magnitude of fever, we also expressed the temperature drop as the percent normalization of temperature (37°C), which was calculated using the equation:

$$\% \text{ normalization} = 100\% \times (\text{maximal temperature reduction}) / (\text{time 0 temperature} - 37^{\circ}\text{C}).$$

The cooling rate was defined as the slope of the linear regression temperature vs. time plot calculated using Deltagraph™ (SPSS; Chicago, IL). To account for having multiple febrile episodes per patient, a linear mixed regression model [18] was used for testing the effect of acetaminophen treatment on each of the three measures of cooling. For each of the outcomes, the model includes age, gender and acetaminophen effect as fixed effect and patients as random effect. Means, the 95% confidence interval for the difference between the treated and untreated groups, and p values are shown. To compare the characteristics of the three patient groups (never treated, always treated with acetaminophen or sometimes treated), continuous data were expressed as mean ± SE and were compared between two groups by unpaired two-tailed Student t test and among three groups by applying a Tukey Honestly Significant Difference test to a one-way ANOVA. Ordinal data were compared by Pearson Chi Square. P-values less than 0.05 were considered significant.

Results

Of 408 patient charts screened, 227 met inclusion criteria for SIRS and had at least one febrile episode with adequate temperature monitoring. Of these, 84 were excluded because of an underlying malignancy, 37 because of liver disease, 29 because of an acute neurological injury, 21 because other antipyretic/thermoregulatory drugs were administered, and 3 because external cooling was used (some patients had more than one exclusion criteria). One hundred and sixty six qualifying febrile episodes occurred in the remaining 59 patients. 88 of which were treated with acetaminophen and 78 were not. Fifty two percent of the temperature measurements were axillary, 25% were oral, 23% were core, but the same route was consistently used for each febrile episode. The number of febrile episodes per patient ranged between 1 and 17. Twenty-four patients never received acetaminophen, 17 received acetaminophen for all qualifying febrile episodes, and 18 received acetaminophen for some of their qualifying fevers. The three groups were similar in age and disease acuity (Table 1). The group that always received acetaminophen had a much higher proportion of men and the group that sometimes received

acetaminophen had a higher proportion of patients receiving mechanical ventilation and a greater number of febrile episodes.

Acetaminophen was given an average of 3.4h after the febrile episode began, when temperature first exceeded 38°C. With the exception of three acetaminophen doses of 325 mg, one of 500 mg, and one of 975 mg, 650 mg acetaminophen was administered. Except for two acetaminophen doses administered per rectum, acetaminophen was administered per os or via gastric feeding tube. About three fourths of the patients receiving acetaminophen were receiving nutrition at >30% goal, indicating adequate gastrointestinal function.

For each patient, the mean maximal temperature drop, %-normalization, and cooling rate were calculated for acetaminophen-treated and untreated fevers. The response to acetaminophen was quite variable (Fig. 1-3), but the absolute temperature reduction was modestly greater (Fig. 1; mean 0.86 vs. 0.56°C for treated vs. untreated; 95% confidence interval of the difference -0.4344, -0.01467; $p = 0.0362$) and the cooling rate slightly more rapid (Fig. 3; mean 0.20 vs. 0.13°C per h; 95% confidence interval of the difference -0.1107, -0.01204; $p = 0.0152$) in acetaminophen-treated fevers than control fevers, but there was no statistical difference in temperature reduction when expressed as percent return to basal temperature (Fig. 2; mean 56% vs. 43.5%; 95% confidence interval of the difference -24.18, 8.69; $p = 0.352$). In two patients with multiple febrile episodes, we compared the fever resolution time courses between acetaminophen-treated and untreated episodes. In the first patient there were no differences in maximum temperature drop ($0.87 \pm 0.57^\circ\text{C}$ vs. $0.84 \pm 0.69^\circ\text{C}$), % normalization ($64.9 \pm 50.4\%$ vs. $66.9 \pm 48.9\%$), or cooling rate (0.22 ± 0.15 vs. 0.19 ± 0.18 °C per hour) between the 10 acetaminophen-treated and 7 untreated febrile episodes. In the second patient there were no differences in maximum temperature drop ($0.17 \pm .25^\circ\text{C}$ vs. $0.40 \pm 0.60^\circ\text{C}$), % normalization ($12 \pm 20.2.4\%$ vs. 23.8 ± 28.6), or cooling rate (0.04 ± 0.06 vs. $0.11 \pm 0.14^\circ\text{C}$ per hour) between the 10 acetaminophen-treated and 4 untreated febrile episodes. As demonstrated in figure 1, responsiveness to acetaminophen was very variable in the study population. To determine whether the intra-individual responsiveness to acetaminophen was also variable, we analyzed the range of temperature drop following each administration of acetaminophen in four subjects who had at least 6 acetaminophen-treated fevers. The ranges of post-acetaminophen temperature drop in these five patients were 1.35°C, 1.375°C, 0.55°C, and 1.05°C. To try to determine whether acetaminophen responsiveness could be predicted by clinical criteria, we compared the 5 patients with the greatest response to acetaminophen (mean $\pm$ SE drop in temperature $1.66 \pm 0.05^\circ\text{C}$ after acetaminophen) and the 5 least responsive patients ($0.21 \pm 0.05^\circ\text{C}$ drop). The groups were similar in age, gender composition, and disease acuity (Table 2).

Discussion

Although acetaminophen is one of the most commonly prescribed antipyretic agents in hospitalized patients [13], there is little information about its use and efficacy in the intensive care unit. We found that 59% of patients in medical and surgical intensive care units had orders for acetaminophen. We analyzed the efficacy of acetaminophen as antipyretic therapy in patients who met criteria for SIRS. We used a commonly accepted definition of fever as a regulated increase in body temperature that exceeds 38°C [19,20.] Because the mechanisms causing fever in patients with cancer and neurologic disease may be different from those with infection and trauma, we excluded such patients. Because acetaminophen therapy may be disproportionately withheld from patients at risk for hepatotoxicity, we excluded patients with pre-existing liver disease. Since acetaminophen dosing frequency is 4-6 hours, we analyzed three measures of defervescence between 0 and 5 hours after administration of acetaminophen, including the maximal temperature drop, the cooling rate, and the percent normalization (to 37°C.) The latter parameter is intended to correct for the magnitude of fever. A similar approach was utilized by Mackenzie *et al.* [15] who expressed the reduction in temperature as a percent

of the pre-treatment febrile temperature. Percent normalization also takes into account the magnitude of the fever and therefore the absolute potential for temperature reduction. Since fever is self-limited, we compared the change in fever following acetaminophen dosing with fevers that were untreated. However, while the time period analyzed for acetaminophen-treated fevers was well-defined as beginning with administration of acetaminophen, there was no discrete time zero for the untreated febrile episodes. To allow for the mean 3.4h delay between first onset of fever and administration of acetaminophen, we defined time zero for untreated fevers as 3-4 hours after the first temperature $> 38^{\circ}\text{C}$. That there was no difference in time zero temperature between treated and untreated fevers validates this analysis. However, the delay in administration of acetaminophen for fever demonstrates the nonrigorous approach that is usually used in treating fever. It is likely that the lack of rigor in treating fever extended to documentation of external cooling. Although commonly used in our intensive care units, external cooling was only documented in the patient record in 3 excluded patients. Therefore, we acknowledge that external cooling was likely used without documentation in some of the patients included in this analysis. However, this is an unavoidable limitation of these retrospective data.

The majority of the temperature measurements were axillary. Since the relationship among axillary, oral and core measurements are complex and controversial [21], we elected to utilize the raw temperature data rather than to utilize a transformation algorithm. Since the same route was used to monitor all temperatures during each individual febrile episode, the effect on the change in temperature and rate of cooling are not likely affected. However, since the criterion for fever is based on an absolute temperature threshold of 38°C and the formula used to calculate percent normalization utilizes 37°C as the target temperature, the site of temperature measurement may have introduced systemic errors in these parameters.

We found a modest difference in absolute temperature drop and cooling rate between acetaminophen-treated and untreated fevers, but did not find a difference in the percent normalization. Even with acetaminophen treatment, only half the fever was eliminated. Furthermore, if the use of axillary temperature measurements underestimated the actual core temperature, then the actual percent normalization may have been even less. The temperature reduction after acetaminophen administration in a retrospective study of critically ill patients by Mackenzie and colleagues [15] found a similar effect of acetaminophen on fever, 1.3% or 0.5°C reduction over 3h compared with no change in the untreated control group. However, the starting temperature in the control group in that study was only 37.6°C vs. 38.3°C in the acetaminophen-treated group. Henker *et al.* [14] found that the core temperature of 5 critically ill febrile patients increased from 39.2°C to 39.4°C following acetaminophen administration. Two studies analyzed the antipyretic efficacy of the acetaminophen prodrug, propacetamol, in critically ill febrile patients [16,17]. One study [17] found no effect of propacetamol on fever while the second [16] reported a 0.5°C reduction in temperature after propacetamol, but the latter study did not include an untreated control group. As our data demonstrate, fever abates in the absence of specific antipyretic therapy, underscoring the importance of an untreated control group.

We found a high degree of variability among patients, in responsiveness to the antipyretic effects of acetaminophen, but could not identify any clinical differences between the responders and nonresponders. Moreover, individual patients exhibited highly variable responsiveness to acetaminophen. These results suggest that acetaminophen exerts only modest and unpredictable antipyretic effects.

Since acetaminophen achieves incomplete antipyresis in the critically ill, adequate antipyresis in this patient population will require alternative approaches to cooling. Two studies of regularly dosed ibuprofen in patients with sepsis, [5,22] showed ibuprofen to be effective in

mitigating fever and failed to find the expected renal or gastrointestinal toxicity, reducing mean core temperature to 37°C in both studies. External cooling is frequently used as primary or adjuvant cooling therapy, but studies of external cooling have shown it to be only partially effective in establishing normothermia, especially when shivering occurs [16,23]. Furthermore, provoking a shivering response can profoundly increase energy expenditure [16,23,24], with negative consequences in patients with critical cardiovascular or pulmonary disease. Many agents with anti-shivering activity have been studied as adjuvant therapy in combination with external cooling, but have been found to have limited effectiveness or serious toxicity [25-29]. Although acetaminophen is often used in combination with external cooling, we can find no published study of its capacity to block the shivering response and increase in energy expenditure caused by external cooling in critically ill patients.

Although acute hepatic injury is a known complication of acute acetaminophen overdose, there are several case reports of hepatic injury in patients chronically using acetaminophen within prescribing guidelines [30,31]. While critically ill patients tend to have reduced levels of antioxidants [32], a key protection against acetaminophen toxicity, there have been no studies of its toxicity in critically ill patients. In developing protocols for fever management in the critically ill, the small theoretical risk of acetaminophen-induced hepatotoxicity must be weighed against its quite modest antipyretic activity.

In conclusion, we have shown that acetaminophen has significant albeit modest antipyretic activity in the critically ill, raising questions about its use as first line antipyretic therapy in this patient population. However, its potential as an adjuvant with other antipyretic agents or with external cooling has yet to be evaluated.

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Figure 1. Comparison of Temperature Drop in Untreated Fevers and Fevers Treated with Acetaminophen

The maximum drop in temperature within 5 hours of acetaminophen administration (B) or equivalent time period in untreated fevers (A) is compared. The distributions, means, and the 95% confidence interval (95% CI) for the difference between the 88 treated and 78 untreated febrile episodes and p-value are shown.

Figure 2. Comparison of Temperature Normalization in Untreated Fevers and Fevers Treated with Acetaminophen

The percent resolution of fever, defined as return to 37°C within 5 hours of acetaminophen administration (B) or equivalent time period in untreated fevers (A) is compared. The distributions, means, and the 95% confidence interval (95% CI) for the difference between the 88 treated and 78 untreated febrile episodes and p-value are shown.

Figure 3. Comparison of Cooling Rate in Untreated Fevers and Fevers Treated with Acetaminophen

The cooling rate during the 5 hours after acetaminophen administration (B) or equivalent time period in untreated fevers (A) is compared. The cooling rate is defined as the slope of the linear regression of temperature vs. time for each febrile episode. The distributions, means, and the 95% confidence interval (95% CI) for the difference between the 88 treated and 78 untreated febrile episodes and p-value are shown.

TABLE 1
Characteristics of the three groups of patients

	Never	Always	Sometimes
Age (years)	56.8±13.7 ¹	50.8±22.3	49.1±16.1 ⁴
Male/Female	12/12	14/3	10/8
Apache II	13.1±31.9 ¹	12.2±22.5	12.7±24.1 ⁴
% on Mechanical Ventilation	42	53	72 ²
Number of Febrile	1.92±1.07 ¹	1.94±1.36	5.78±4.7 ⁵
Episodes			
Length of Stay (days)	22.25±15.9	19.7±25.1	22.3±17.9
Primary Diagnosis			
Septic Shock	3 (12.5%)	3 (16.7%)	1 (5.9%)
Other infections	7 (29.2%)	6 (33.3%)	6 (35.3%)
Cardiovascular	3 (12.5%)	3 (16.7%)	1 (5.9%)
Gastrointestinal	4 (16.7%)	1 (5%)	2 (11.8%)
Pulmonary	2 (8.3%)	1 (5%)	3 (17.6%)
Other	4 (16.7%)	3 (16.7%)	4 (23.5%)
Nutritional support			
Tube feeds/po @ goal	19 (79.2%)	10 (55.6%)	11 (64.7%)
Feeds @ 30-50% goal	2 (8.3%)	4 (22.2%)	1 (5.9%)
NPO or trophic feeds	3 (12.5%)	4 (22.2%)	5 (29.4%)

¹ mean±SD

² p = 0.02 difference among three groups

³ p = 0.0486 difference among three groups

⁴ not significant

⁵ p<0.05 vs. Never and Always groups

Table 2
Characteristics of Patients with the highest and lowest responsiveness to acetaminophen

Acetaminophen responsiveness	Temperature drop (°C)	Age (years)	Male/female	Apache II	mechanical ventilation
Unresponsive	0.21±0.11 ¹	58.8±15.2 ¹	4/1	11.6±3.8 ¹	4/5
Responsive	1.66±0.16 ²	46.6±22.8 ²	3/2 ²	12.4±3.1 ²	2/5 ²

¹ mean±SD

² not significant