The effect of acetaminophen on temperature in critically-ill children: a retrospective analysis of over 50000 doses

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Abstract

Objective: Acetaminophen is widely used in paediatric intensive care units (PICU). While randomised controlled trials suggest acetaminophen significantly reduces body temperature in adults, the effect of acetaminophen on temperature in critically ill children has not been previously quantified.

Design: Retrospective observational cohort study

Setting: Single centre general and cardiac paediatric intensive care unit in a specialist children's hospital

Patients: All children who received acetaminophen or had a fever (temperature >=38^{o}C) while on the intensive care unit over a 40-month period (September 2012 to December 2015)

Interventions: none

Measurements and Main Results: In total 58177 doses of acetaminophen were administered, with temperature data available for analysis for 54084 doses. Temperature decreased by 0.11^{o}C (95% CI 0.09-0.14^{o}C) 4-hours post acetaminophen dose, after adjustment for weight and illness severity. In children who had a fever and were given acetaminophen, temperature decreased by 0.78^{o}C (95%CI 0.74-0.82^{o}C). Temperature decreased by 0.88^{o}C (95%CI 0.85-0.92^{o}C) in children who had fever but did not receive acetaminophen. The change in temperature associated with fever was significantly different between those who did and did not receive acetaminophen (likelihood ratio statistic 246.06, $p<2.2 \times 10^{-16}$).

Conclusions: Acetaminophen is associated with a significant decrease in temperature in children with fever. However, temperature may decrease following fever without acetaminophen in the PICU. The threshold to use acetaminophen must be understood to determine the true effect on temperature in any future trials.

Introduction

Acetaminophen is the most commonly used anti-pyretic in intensive care units (ICU) (1). This anti-pyretic effect is mediated through the inhibition of cyclo-oxygenase-3, and therefore prostaglandin synthesis. Prostaglandin re-sets the hypothalamic set-point to generate a fever: inhibition of prostaglandin synthesis returns the set-point back towards normal (2).

Fever is associated with improved case-mix adjusted ICU survival in adults with infection (3,4). The recent HEAT trial, comparing acetaminophen with placebo for fever management in ICU did not show any effect on the number of ICU free days (5). However, the temperature separation between the arms was modest, with the mean daily peak body temperature being slightly lower in the acetaminophen group (38.4+/-1.0^{o}C vs 38.6+/-0.8^{o}C) and a lower mean daily average body temperature (37.0+/-0.6^{o}C vs 37.3+/-0.6^{o}C).

Subsequent randomised controlled trials have demonstrated the anti-pyretic effects of acetaminophen against placebo (6-8). A recent meta-analysis of these data suggested a pooled estimate of temperature reduction by 0.38^{o}C (0.13-0.63^{o}C) (9). There are no paediatric ICU trials exploring the effect of acetaminophen against placebo on temperature. Several trials explore the comparative effects of anti-pyretic agents in non-ICU settings. The mean reported temperature reduction from acetaminophen is between 1.1-1.9^{o}C (10-13).

Large automated observational datasets offer an opportunity to explore the real-world associations of temperature and acetaminophen usage in children. We aimed to (a) measure the temperature effects of acetaminophen on children in ICU through a retrospective observational analysis of all acetaminophen doses (Group P) given in a single centre paediatric ICU over a 40-month period; (b) as acetaminophen is often used for analgesia and comfort rather than fever, to specifically analyse the sub-group of children who had acetaminophen and fever (Group P|F) ; (c) analyse the temperature changes in children who had a fever (temperature >38^{o}C) who did ***not*** receive acetaminophen over the same time-period (Group F).

Methods

We conducted a retrospective observational study using data from a single, tertiary level children's hospital. The hospital has 42 intensive care beds, divided into general paediatric, neonatal surgical and cardiac intensive care units. Acetaminophen is the first line agent for temperature management, with or without environmental measures, such as bedside fans, or ice-packs (post cardiac surgery). Servo-controlled cooling mattresses are used as a second line therapy, or earlier in specific cases where aggressive temperature control is desirable (for example, in a previously conducted audit of children with post-cardiac low cardiac output state, 8.5% of children on the cardiac ICU were cooled (14)). Non-steroidal anti-inflammatory agents are used infrequently; extra-corporeal circuits for renal replacement and ECMO allow for temperature control. Acetaminophen is prescribed regularly for analgesia in all post-surgical patients, which forms the predominant population in cardiac ICU. Acetaminophen is given in the operating room only in children if extubation is expected soon after admission to ICU.

Data were collected from electronic health records (Philips Intellivue Critical Care and Anaesthesia, Philips Electronics, Netherlands) for patients admitted between September 2012 and December 2015. Data are recorded typically at hourly intervals. All acetaminophen doses were included, regardless of route of administration (enteral or intravenous). Temperature data were collected for 6 hours in relation to each acetaminophen dose (Group P): the hour before the dose was given (time-point -1), the hour of the dose (time-point 0), and 4 hours following the dose (time-points 1-4). As not all acetaminophen doses were given for fever, the sub-group of patients who received acetaminophen and had a temperature >38^{o}C at time-points -1 or 0 were analysed separately (Group P|F). In addition, incidences of fever (temperature >=38^{o}C) were identified where acetaminophen was ***not*** given 6 hours before or after the recorded temperature (Group F). Temperature data an hour before, and 4 hours after such an incidence were collected.

The site of temperature measurement (axillary, tympanic, oesophageal or rectal) was not differentiated, apart from peripheral or skin temperatures measured as part of a core-toe gap. This was to reflect normal clinical practice. Temperatures recorded below 32^{o}C were excluded, as these were likely to be either due to external cooling, or mis-labelled peripheral or skin temperatures. Temperature values with no accompanying site were also excluded to avoid inclusion of peripheral or skin temperature measurements. Data regarding other temperature control measures, such as environmental measures or surface cooling were not collected, as the aim was to quantify the effect of acetaminophen in the 'real-world' setting i.e. the effect of acetaminophen within the context of other temperature mechanisms.

Acetaminophen dose data as well as the weight of patient, Paediatric Index of Mortality (PIM) score and unit (cardiac or general paediatric/neonatal ICU) were collected. Mann-Whitney U tests were used to compare weight and PIM score for children in Groups P|F and F to identify indication bias for acetaminophen use in fever. A chi-squared test was used to compare the units, i.e. cardiac versus general paediatric and neonatal ICU, where the doses were given.

Temperature data were analysed using multi-level linear regression, with temperature as the dependent variable, time in relation to acetaminophen (in Groups P and P|F) or fever (in Group F), weight and PIM score as the fixed effect variables and dose identifier, year and unique patient identifier as the random effect variable. This allowed for the evaluation of the mean change in temperature for each hour from time-point 0 for four hours, despite missing temperature values, while accounting for weight and PIM (as a marker of severity of illness). Inclusion of the individual patient identifier accounted for individual patient effects. Subgroup analyses for intravenous and enteral doses of paracetamol were separately undertaken. The effect of the dose of paracetamol was analysed, using the dose per kilogram of paracetamol given in an interaction term with time as the fixed effect variable, in children who received paracetamol. Models with and without the interaction term were compared using the likelihood-ratio test statistic. Similarly, To compare the

temperature changes following fever with or without acetaminophen, the likelihood-ratio test statistic was calculated, comparing (a) a multi-level regression model for all children with fever, i.e. groups P|F and F combined, with temperature as the dependent variable, time in relation to acetaminophen (in Group P|F) or fever (in Group F), weight and PIM score as the fixed effect variables and dose and unique patient identifier as the random effect variable; and (b) the same model, including an interaction term for acetaminophen use and time as a fixed effect variable. Accepting the null hypothesis, i.e. a likelihood ratio test statistic close to 0, would suggest that acetaminophen has a non-significant effect on change in temperature in children with fever. All data were analysed using Microsoft Excel (Microsoft Corp., WA, USA) and r (www.r-cran.org).

Individual patient consent was not sought as this is a retrospective observational study and no patient identifiable data is reported. The study was reviewed and approved by the institutional audit department (ref 2013).

Results

Over the 40-month time period there were 6002 admissions across the intensive care units. A total of 58177 acetaminophen doses were administered, to 4076 children (median weight 7.7kg, inter-quartile range 3.8-16.0kg) over 4681 admissions (median PIM 0.017, inter-quartile range 0.009-0.050). Therefore acetaminophen was given during 4681/6002 i.e. 78% of all admissions. Of the acetaminophen doses, 16605 (28.5%) of the doses were given intravenously, the remainder given enterally. The median dose was 15.5 mg/kg (inter-quartile range 14.7-19.4 mg/kg). Most of the doses (34107/58177, 58.6%) were given in the cardiac ICU. Temperature data were available for 54084 (92.9%) of the total acetaminophen doses in 3779 children (median weight 7.1kg, median PIM 0.017), and were used for subsequent analyses (Figure 1).

Effect of acetaminophen on temperature: Figure 2 shows the distribution of temperature for each hour in relation to the acetaminophen dose (Group P). Following multi-level linear regression, the mean difference in temperature each hour is statistically significant: the mean decrease in temperature 4-hours post acetaminophen dose was 0.11°C (95% CI 0.09-0.14°C) from baseline (time-point 0) (Table 1).

As the temperature effect of acetaminophen is due to inhibition of prostaglandin action on the hypothalamus in fever, we analysed the sub-group of doses where the baseline temperature was >=38°C (at time-point -1 or 0) (Group P|F). Acetaminophen was given when the baseline temperature was >=38°C in 4849/54084 doses (9.0%) in 1463 children. The median weight for this cohort was 12.8kg (inter-quartile range 7.0-27.0kg), and median PIM score was 0.030 (inter-quartile range 0.01-0.06). Two-thirds of these doses (3229/4849, 66.6%) were given on the general paediatric and neonatal ICUs. Following multi-linear regression as above, the temperature decrease in fever was greater 4 hours post acetaminophen dose, with a mean decrease in temperature 0.78°C (95%CI 0.74-0.82°C) from baseline. (Table 1)

Effect of route of administration: The temperature effect of acetaminophen was tested separately according to the route of administration. With both intravenous and enteral paracetamol doses the nadir of the temperature effect occurred 4 hours post administration (decrease in temperature 4 hours post intravenous dose 0.78°C, 95% CI 0.71-0.84°C; post enteral dose 0.78°C, 95% CI 0.74-0.84°C). The decrease in temperature however occurred sooner following intravenous administration (decrease in temperature 1 hour post intravenous dose 0.41°C, 95% CI 0.34-0.47°C; post enteral dose 0.37°C, 95% CI0.32-0.42°C).

Effect of the dose administered: The dose of acetaminophen given, expressed as milligrams per kilogram, was included in an interaction term with time in relation to the dose. When models with and without this interaction term were compared using the likelihood-ratio test, the effect of the

size of dose was found to be significant (Chi-square value=37.04, p-value=1.7 x 10^{-6} in Group P; chi-square value=16.57, p-value=0.01 in Group P|F).

Temperature profiles in fever without acetaminophen administration: There were 6439 episodes, in 1508 children (median weight 7.4kg, inter-quartile 3.4-15.5kg; median PIM score 0.037, inter-quartile range 0.014-0.085), when a temperature of >=38^{o}C was not treated with acetaminophen (Group F). Three quarters of these episodes (4745/6439, 73.7%) were in the general paediatric and neonatal ICUs. Following Mann-Whitney U Test, both weight and PIM scores were statistically significantly different between Groups P|F and F (p-value<2.2 x 10^{-16} for both). The unit distribution (cardiac versus general paediatric and neonatal ICU) was also significantly different between groups P|F and F following chi-square test (chi-squared=67, p-value=2.9 x 10^{-16}) (Table 2).

Following multi-level regression as described above, the mean temperature decrease following fever without acetaminophen was 0.88^{o}C (95%CI 0.85-0.92^{o}C).

The difference in temperature distributions following fever, with or without acetaminophen treatment, were compared (Figure 3). When the multi-level linear regression models with or without the interaction term for acetaminophen use and time were compared for children with fever, the likelihood ratio test statistic was 246.06. This suggests that the change in temperature with or without acetaminophen use is significantly different (p-value <2.2 x 10^{-16}). While the average temperature decrease seems to be marginally greater in Group F, the temperature is higher, for a longer duration, at baseline in the children in Group P|F.

Discussion

In this study, we aimed to demonstrate the temperature changes in relation to acetaminophen administration in children in ICU. Our data demonstrate that while the temperature changes post

acetaminophen administration (Group P) are statistically significant, this are unlikely to be clinically significant - individual body temperatures have been described to show diurnal variation greater than this (15). However, when acetaminophen is given with a fever (Group P|F), the mean decrease in temperature 4-hours post acetaminophen is 0.78^{o}C. Enteral and intravenous doses had similar effect sizes, although the decrease in temperature occurred sooner following intravenous administration. The size of the dose had a significant impact on the change in temperature. In the group of children who had fever but were not given acetaminophen (Group F), the temperature decrease was similar, if not slightly greater (maximum mean decrease in temperature of 0.88^{o}C).

Based on these data, acetaminophen does not change fever grade temperature any more than if not given: temperature change is greater in children who did not receive acetaminophen. However, the indication for giving acetaminophen (or not giving acetaminophen) may be relevant. In a retrospective observational study, this is difficult to determine. Acetaminophen is used commonly in our centre – only 9.0% of doses were given with a fever. More children with a fever were not given acetaminophen. Although in a previous survey of practice within the UK (including staff from our centre) staff reported to treat a temperature of >=38^{o}C (16), it is possible that the threshold temperature for giving acetaminophen may be higher and context dependent. Children with fever who received acetaminophen weighed more and had lower PIM scores, compared to those who did not receive acetaminophen. It is possible that the temperature changes in children in Group F reflect an increased lability in temperature in smaller, sicker children. However, weight and PIM were both included in the multi-variate models: despite this, there was a significant difference in the temperature profiles between groups F and P|F. Children with fever were more likely to be given acetaminophen if they were on cardiac ICU. This may be due to 2 reasons: (i) children in cardiac ICU are more likely to receive acetaminophen routinely for post-operative analgesia, and (ii) temperature is managed more aggressively post bypass to reduce the risk of tachy-arrhythmias, and reduce the temperature induced increase in heart rate to improve diastolic filling and stroke volume.

We did not collect data on other interventions such as environmental cooling. It is possible that acetaminophen was given only if other measures were unsuccessful in decreasing temperature. To this extent, it is notable that the temperatures are higher at baseline, for longer, in group P|F compared to Group F: nearly 80% of children have fever at time-point -1 in Group P|F, compared to just under 50% in Group F (Figure 3). This could be a definitional artefact: in group P|F, fever was defined as a temperature >=38^{o}C in the hour of the acetaminophen dose (time-point 0), or the hour before (time-point -1). Children in group F were identified by the presence of a temperature >=38^{o}C, which was labelled time-point 0 (some children had a temperature >=38^{o}C at time point -1 in Group F if they had acetaminophen within the previous 6 hours). To test this further, we re-defined fever in group P|F as only those with a temperature >=38^{o}C at time-point 0 and repeated the analysis. The median temperature at time-point -1 was 38.0, and the temperature distribution remained different from those not given acetaminophen (comparing models as previously described, the likelihood ratio test statistic was 68.72, $p<7.5 \times 10^{-13}$). It is possible that acetaminophen is likelier to be administered if fever is persistent beyond a single reading, with or without other temperature control mechanisms. When designing a trial to understand the temperature changes in children on ICU following acetaminophen, it may be necessary to enrich the population by selecting only these children.

Our results suggest that the temperature effect size of acetaminophen may be more modest than previously reported in children (0.78^{o}C versus >1^{o}C). This should be considered when designing a trial to demonstrate the temperature effects of acetaminophen in children on ICU. However, similar retrospective study in adults showed similar results (8), only for subsequent randomised trials to suggest a greater effect size of acetaminophen on temperature (6,7). It would also be useful to compare the effectiveness of acetaminophen against other temperature management interventions. We did not account for acetaminophen given just prior to admission – however only 706/6441 (11.0%) episodes of fever in Group F were within the first 6 hours of admission. We did not account for mode of temperature measurement. However, post-hoc analysis of the subgroup with only core

temperature measurements (oesophageal, rectal or bladder) showed a decrease in temperature of 0.72°C (95% CI 0.64-0.80°C) 4 hours post acetaminophen in Group P|F, and 0.89°C (95% CI 0.80-0.98°C) 4 hours post fever in Group F. Finally, we do not describe clinical outcomes or adverse events: this would be best demonstrated prospectively through a randomised trial, as there are too many confounders to adequately control for retrospectively.

These data quantify the temperature change following acetaminophen in children admitted to ICU. However, the retrospective nature of this study raises questions regarding the indication to use acetaminophen in children with fever on the ICU. The ongoing REACTOR trial will shed more light on temperature management interventions in adult ICU patients (17), as will the current prospective multi-centre observational component of the FEVER study (NIHR Health Technology Assessment Project 15/44/01 https://njl-admin.nihr.ac.uk/document/download/2009621). It will also be interesting to note the degree of separation between the liberal and conservative arms in the upcoming FEVER pilot trial (comparison of a liberal threshold of 37.5°C or a conservative threshold of 39.5°C for treating fever in children on ICU) given these data. Until then, the question must remain whether children with fever will benefit from acetaminophen for temperature management.

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Figure 1: Flow diagram showing the number of acetaminophen doses given in the 40-month study period, as well as the number of episodes of fever when acetaminophen was not given. Acetaminophen doses were excluded from the analysis if no temperature were available (temperature data were only considered if the site of measurement were labelled, and the sites were not 'peripheral' or 'skin' temperatures). Fever was defined as a temperature≥38^{o}C. Fever at baseline was defined as a temperature≥38^{o}C in the hour of or the hour before the acetaminophen dose was given.

Figure 2: Beanplots showing temperature distribution in relation to (a) all acetaminophen doses given (Group P, n=54084), (b) doses given with a fever at baseline (Group P|F, n=4849), and (c) incidence of fever when no acetaminophen was given (Group F, n=6439). The time-points are defined in relation to the acetaminophen dose, or incidence of fever in (c): time-point -1 is the hour before the acetaminophen dose/fever; time-point 0 the hour of the acetaminophen dose/fever; time-points 1-4 are 1 to 4 hours after the acetaminophen dose or fever. Fever is defined as a temperature >=38^{o}C - hence the skewed distributions for time-points -1 and 0 in (b) and time-point 0 in (c). The dotted line represents the overall median value for the population. Temperature decreases over time: in Group P this is statistically although not clinically significant following multi-level linear regression (mean temperature difference 0.11^{o}C at time-point 4). The temperature changes are more marked following fever: mean temperature difference 0.78^{o}C at time-point 4 in Group P|F and 0.87^{o}C in Group F.

Figure 3: Median and interquartile ranges of temperature for children with fever given acetaminophen (Group P|F, solid line, hatch shading) and not given acetaminophen (Group F, dashed line, smooth shading). The temperature falls following hour 0 in both groups, with a slightly greater drop in Group F. The temperature is elevated for longer at baseline in Group P|F compared to Group F.

Table 1: Mean temperature changes following all doses of acetaminophen given (Group P), only those doses given following a fever (Group P|F), and temperature changes with a fever when no acetaminophen is given (Group F). Time-points are defined in relation to the acetaminophen dose: -1 = the hour before acetaminophen is given, 1-4 = hours 1 to 4 after the acetaminophen is given (for the group where acetaminophen is not given, defined in relation to an incidence of temperature >=38^{o}C). Temperature changes are calculated following multi-level linear regression analysis, including weight and PIM scores as fixed effects variables, with individual patients and doses as random effects variables.

Table 2: Table showing the characteristics of the patients and unit location for children with fever. Weight and Paediatric Index of Mortality (PIM-score) are expressed as median (inter-quartile range), and were compared using the Mann-Whitney U test. Those given acetaminophen (Group P|F) were likely to be heavier and had a lower PIM-score compared to those not given acetaminophen (Group F). A greater proportion of episodes of fever were treated with acetaminophen on the cardiac ICU compared to the general paediatric and neonatal ICU (chi-squared value 67, p=2.9 x 10^{-16}).