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Haemodynamic changes with paracetamol in critically-ill children

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ABSTRACT

Purpose: Paracetamol has been associated with a reduction in blood pressure, especially in febrile, critically-ill adults. We hypothesised that blood pressure would fall following administration of paracetamol in critically-ill children and this effect would be greater during fever and among children with a high body surface area to weight ratio.
Methods: A 12-month prospective observational study of children (0–16 years) admitted to paediatric intensive care, who underwent pulse contour analysis and received paracetamol concurrently.
Results: Mean arterial blood pressure decreased significantly by 4.7% from baseline (95% CI 1.75–8.07%) in 31 children following 148 doses of paracetamol. The nadir was 2-hour post-dose. The effect was pronounced in children with fever at baseline (6.4%, 95% CI 2.8–10%), although this was not statistically significant. There was no simple relationship between this effect and body surface area to weight ratio. The association between a change in blood pressure and changes in heart rate or measured stroke volume was poor; therefore it was likely that a change in the systemic vascular resistance contributes most to this effect.
Conclusion: There is a significant but modest reduction in blood pressure post-paracetamol in critically-ill children. This is likely related to a change in systemic vascular resistance.

1. Introduction

Paracetamol is associated with a reduction in blood pressure in critically-ill adults [1-5]. The reported decrease ranges between 7 and 15% from baseline and occurs over the first 2 h. The haemodynamic mechanism for this blood pressure decrease has been explored using various methods. Some authors have reported a reduction in cardiac output - either due to a reduction in heart rate [6], or due to the diuretic effect of mannitol present in intravenous paracetamol preparations [7]. However, there is also evidence to suggest that the reduction in blood pressure is related to a decrease in the systemic vascular resistance (SVR): (a) peripheral blood flow increases when measured using laser Doppler flowmetry in febrile patients [8]; and (b) a reduction in SVR has been observed following paracetamol administration when measured in a randomised controlled trial of healthy volunteers, but not after an equivalent dose of mannitol alone was given [7].

Although the use of paracetamol has been associated with a modest reduction in mean blood pressure in neonates [9], the haemodynamic effects have not been evaluated in critically-ill children. If the phenomenon is based on a reduction in SVR, this effect may be greater in children, because they have a larger body surface area to weight (BSA-to-weight) ratio than adults.

The hypotensive effect of paracetamol has been most studied during fever [1,2,8]. Fever is an increase in the hypothalamic temperature 'set-point' following pathogen invasion or tissue damage. The hyperthermia of fever is produced by an increase in metabolic rate, and a reduction in surface heat loss, through peripheral vasoconstriction. Paracetamol resets this central 'set-point': this opposes heat-conserving vasoconstriction, explaining a fall in both SVR and blood pressure. However the haemodynamic impact of paracetamol may be complex given that heart rate also increases with temperature [10].

We hypothesise that (a) critically-ill children will show a significant reduction in blood pressure following paracetamol administration with a reduction in SVR, and (b) this effect will be greatest in children with fever, and those with higher BSA-to-weight ratio.

2. Methods

We conducted a prospective observational study of children admitted to our paediatric intensive care unit between October 2014 and October 2015, who (a) underwent cardiac output monitoring via pulse

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contour analysis (Lidco Rapid, LiDCO Ltd., U.K.) and (b) received one or more dose of paracetamol by any route.

The decision to use cardiac output monitoring was made by the treating clinical team. Mean arterial blood pressure (MABP), heart rate (HR) and stroke volume index (SVI) data were recorded every 3–8 s by the cardiac output monitor (variable frequency as data automatically compressed for longer recordings). Data points with an inferior signal (as identified by the monitor - for example when the arterial line was being sampled) were excluded. The pulse contour measurements were calibrated using non-invasive (supra-sternal) continuous wave Doppler ultrasound (USCOM Ltd., Australia) at the start of recording, and every 24 h.

Haemodynamic data from the hour before paracetamol was given, the hour paracetamol was given and four hour post-paracetamol administration, were compared. As a summary measure, we used the mean of 200 consecutive values of MABP, HR and SVI centred around the hour mark i.e. if data were recorded every 3 s, mean values between 5 min before (3 s × 100 readings) and 5 min after the hour were used. In addition, we collected data on the following confounders from the electronic health record: vasoactive drug doses; fluid administered as a bolus of ≥5 ml/kg; sedation changes, furosemide, mean airway pressure changes (all expressed as increase, decrease or no change) and physiotherapy (expressed as a binary variable).

The data were analysed using multi-level linear regression modelling, with (a) either MABP, HR or SVI as outcome variables; (b) time, expressed as hours from the paracetamol dose (i.e. −1, 0, 1, 2, 3, 4), along with the above confounders as fixed effect variables, and (c) each dose administration and patient as random effect variables. This enabled us to evaluate changes in MABP, HR and SVI in relation to the time from the paracetamol dose, evaluating the effect per dose, per patient. This controlled for the assumption that each patient may not have the same haemodynamic effect with paracetamol as another, and the effect may vary between doses in the same patient. Each patient therefore was their own control, with a comparison made before and after paracetamol.

Change in MABP is either due to HR, SV or SVR (pressure = flow x resistance). Although SVR is calculated by the Lidco Rapid pulse contour analyser, a static central venous pressure is assumed. We do not routinely measure or target central venous pressure in our intensive care unit, especially as femoral venous liens are used preferentially to internal jugular or subclavian venous lines. Therefore we used linear regression to examine the effect of HR and SVI on MABP: from the coefficient of determination (adjusted R^2, the proportion of change in MABP explained by the changes in HR and SVI) we inferred the relative effect of SVR on MABP (i.e. 1-R^2).

To test our two a priori hypotheses we added temperature to our model, and analysed children separately according to whether they had a fever (defined as a temperature > 38 °C) at baseline. We similarly analysed children separately according to BSA-to-weight ratio quartiles. Analyses were carried out using Microsoft Excel (Microsoft Corp, WA, USA) and r (ww.cran.r-project.org).

Data were collected as a part of a locally registered service evaluation. Informed consent was not required as only non-identifiable, routinely collected clinical data were used.

3. Results

Thirty-one children received 148 paracetamol doses during cardiac output monitoring. Median age was 37 months (IQR 18–109 months). One hundred and twenty seven (85%) doses were intravenous (Table 1). Doses ranged from 10 to 15 mg/kg. MABP decreased post-paracetamol, with the nadir at 2 h (2 hour post intravenous dose; 3 hour post enteral dose). The mean reduction in blood pressure was small – from 68 to 65 mm Hg; the median reduction was from 67 mm Hg to 64 mm Hg. However the top quartile decrease ranged from 9 mm Hg to 32 mm Hg, a percentage change between 12.5 and

Table 1
Characteristics of children with cardiac output monitoring given doses of paracetamol. Weight was either measured or estimated. Body surface area was calculated using weight and height data (as calculated by the Lidco Rapid pulse contour analyser).

Patient number	Weight (kg)	Body surface area (m^2)	Fever (baseline temperature ≥ 38 °C)	Age (months)	Diagnosis	Intra-venous doses of paracetamol	Total paracetamol doses
1	13.3	0.58	Yes	38	RSV bronchiolitis	6	11
2	10.5	0.48	No	26	Pneumonia	1	1
3	11.4	0.48	No	26	CMV pneumonitis	4	4
4	18	0.74	Yes	64	Septic shock, acute appendicitis	7	7
5	4	0.24	No	1	Bronchiolitis	0	2
6	15	0.64	Yes	49	Streptococcal pneumonia	9	9
7	28.5	1.05	Yes	123	Staphylococcal pneumonia	4	4
8	8	0.36	No	6	Bronchiolitis	0	3
9	8.8	0.41	Yes	15	Pneumonia	2	2
10	65	1.71	No	156	Status asthmaticus	3	3
11	9	0.33	Yes	35	Septic shock	10	10
12	28	0.97	Yes	89	Post cardiac arrest, primary cardiac arrhythmia	0	1
13	8.5	0.31	No	8	Pneumonia	5	5
14	10	0.47	No	14	Empyema	1	5
15	29.3	0.88	No	41	Influenza pneumonitis	0	1
16	3.6	0.22	No	1	Group B Streptococcal sepsis	0	3
17	12	0.54	Yes	30	Toxic shock syndrome	3	3
18	65	1.69	Yes	167	ARDS	11	11
19	14	0.57	Yes	37	Aspiration pneumonia	2	2
20	11.2	0.48	No	31	Influenza pneumonitis, aplastic anaemia	11	11
21	60	1.6	No	141	Renal cell carcinoma	6	6
22	11.11	0.52	No	22	Propionic acidaemia	3	3
23	8.1	0.35	Yes	18	Metapneumovirus bronchiolitis	0	2
24	56	1.71	No	180	Subdural empyema	2	2
25	72	1.86	Yes	181	Crohn's disease	3	3
26	45	1.27	Yes	147	Post cardiac arrest	1	1
27	22	0.83	Yes	95	Staphylococcal pneumonia	2	2
28	10	0.49	No	23	Neutropenic sepsis	9	9
29	17	0.76	Yes	75	Haemophagocytic lymphohistiocytosis	10	10
30	5.3	0.26	Yes	2	Sepsis, congenital hyperinsulinism	1	1
31	58	1.57	No	114	Septic shock	11	11