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Mechanism of paracetamol-induced hypotension in critically ill patients: A prospective observational cross-over study

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ABSTRACT

Objective: To elucidate the mechanism of hypotension following intravenous administration of paracetamol (acetaminophen) to patients on the Intensive Care Unit.
Design: Prospective observational cross-over study.
Setting: Intensive Care Unit, University Hospital Královské Vinohrady, Prague, Czech Republic.
Methods: Ventilated critically ill patients monitored by PiCCO and administered intravenous paracetamol at the same time were eligible for the study. We recorded haemodynamic indices, as well as core and peripheral temperatures, continuously for 3 h after the dose of paracetamol. Ranitidine was then used as a control drug known not to influence haemodynamics.
Results: We included 6 subjects, and recorded 48 cycles of observations after administration of paracetamol, and 35 cycles after administration of the control drug. Haemodynamic parameters were not different at the baseline and administration of control drug did not result in any change in haemodynamics. After intravenous paracetamol, mean arterial pressure (MAP) dropped by 7% ($p < 0.001$) with a nadir at the 19th minute. In 22 measurement cycles (45%) we noted >15% reduction in MAP with paracetamol. Analysis of these cycles suggests that hypotension with paracetamol can be caused by reduction of both cardiac index and systemic vascular resistance. In febrile cycles paracetamol caused narrowing of the gradient between central and peripheral temperatures suggesting skin vasodilation. These changes were not correlated to a change of systemic vascular resistance at any time point.
Conclusion: Hypotension with intravenous paracetamol in critically ill patients is caused by a reduction of both cardiac output and systemic vascular resistance. We did not demonstrate any relation between haemodynamic changes and antipyretic action of paracetamol. A possibility that cardiac output is reduced with paracetamol might be clinically important.

Introduction

Paracetamol is a selective inhibitor of cyclooxygenase-2, which has been in use as an analgesic and antipyretic agent since 1950.[1] Compared to other non-steroidal analgesics, it has an enviable safety profile, and apart from well-known dose-dependent hepatotoxicity, it is generally considered a safe drug.[2] Given the availability of its intravenous form, paracetamol is widely used in the intensive care setting, and administered to patients with varying degrees of circulatory compromise. In this particular subset of patients, any adverse haemodynamic effects of paracetamol would be of concern. Whilst long term use of paracetamol in outpatients may increase the risk of hypertension,[3] its acute administration to critically ill patients may cause hypotension in 10–60% of cases.[4–13] The incidence of hypotension associated with the intravenous administration of paracetamol is well known to ICU nurses and well described in the literature[4–13] but, the mechanism whereby this occurs is not well understood. An early report from 1985 considered paracetamol-induced hypotension as a kind of anaphylactic or anaphylactoid reaction,[4] but subsequent studies suggested such an immune pathogenesis to be less likely,[5–7] as laboratory markers of allergic reactions in hypotensive patients remained within

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normal limits.[7] Other authors have suggested 'centrally mediated' vasodilation due to initiation of physiological mechanisms for heat loss,[13] direct vasodilation effects of paracetamol[14] or a combination of mechanisms.[15]

Hypotension can be caused either by a loss of systemic vascular resistance (i.e. vasodilation) or a decrease in cardiac output (i.e. reduction in stroke volume and/or heart rate). No study has directly measured these key determinants of blood pressure in response to paracetamol. We hypothesized that in the subset of responders paracetamol causes hypotension by the loss of peripheral vascular resistance, particularly in the skin of pyrexial subjects, and that cardiac output remains unchanged or is increased due to the reduction in afterload.

Methods

Study design

We performed a single-centre prospective observational crossover study in ventilated patients who were monitored using a pulse contour cardiac output device (PiCCO – see below) and administered paracetamol at the same time. We continually measured blood pressure, cardiac output and peripheral vascular resistance for 3 h after 1 g of intravenous paracetamol and for 3 subsequent hours after administration of ranitidine, as a control drug known to have no adverse haemodynamic effects.[16] Both drugs were administered in 6 h intervals and 3 h apart from each other and haemodynamic values were recorded continuously. No washout period was allowed between the measurements. A data set obtained during 3 h of measurement after paracetamol or control drug is further referred as a "cycle". These cyclic measurements were stopped when paracetamol or haemodynamic monitoring was no longer clinically indicated. The investigators were not involved in any decisions regarding monitoring and treatment of study subjects. The Královské Vinohrady University Hospital Review Board and Ethical Committee approved the protocol. Given the observational nature of the study, the requirement to provide formal informed consent was waived. Patients' next of kin were informed about the nature and purposes of the study and asked to provide assent.

Setting

22-bed level 3 ICU of the Department of Anaesthesia and Critical Care, Královské Vinohrady University Hospital in Prague, Czech Republic.

Study subjects

Adult (>18 years) patients who were artificially ventilated and administered paracetamol and monitored by PiCCO at the same time were eligible for inclusion in the study. Those patients had to be in sinus rhythm. We excluded subjects who responded by >10% increase in stroke volume during passive leg-raise maneuvers,[17] in order to avoid recruiting patients, who were still fluid responsive. We also excluded patients who were moribund and those with haemodynamic instability (for example, on a varying vasopressor dose or higher than 0.5 $\mu g\,kg^{-1}\,min^{-1}$). We aimed to recruit all eligible patients during the study period and perform as many measurement cycles as possible. Details of the study subjects are given in Table 1.

Administration of drugs

1 g of paracetamol (Perfalgan, Bristol-Myers Squibb), available as a 100 ml solution for infusion, was administered as recommended by the manufacturer over 10 min by infusion pump (BBraun, Austria). The control drug (ranitidine 50 mg, Zentiva, Czech Republic) was administered in the same way. The reasons for paracetamol administration were pain, pyrexia or both. Ranitidine was prescribed as a part of routine stress ulcer prophylaxis.

Haemodynamic monitoring

Invasive pulse pressure analysis was used to assess cardiac output. PiCCO (PiCCO2®, Pulsion Medical Systems AG, USA) uses a mathematical analysis of the area under the curve of arterial pressure wave to calculate the stroke volume (SV).[18] Cardiac output is then calculated by multiplying heart rate by SV, and adjusted to body surface area to give the pulse contour cardiac index (PCCI). Indexed peripheral (systemic) vascular resistance (SVRI) is then calculated by using the pressure gradient across the systemic circulation, as SVRI = [mean arterial pressure (MAP) – central venous pressure (CVP)]/PCCI. The technique uses the Fick principle and transpulmonary thermodilution for calibration (for further details see reference 18). Before each 3 h cycle of measurement, the PiCCO monitor was re-calibrated according to manufacturer's instructions[18] and both invasive pressures (central venous and arterial) were re-zeroed. Haemodynamic indices were recorded continuously, as well as were the doses of vasopressors.

Table 1
Study subject characteristics. *Note*: EF, ejection fraction; STEMI, ST-elevation myocardial infarction; T2DM, type 2 diabetes mellitus; VAP, ventilator-associated pneumonia.

Subject	Age and sex	Diagnosis	Reason for PiCCO monitoring	Noradrenaline dose at baseline [$\mu g\,kg^{-1}\,min^{-1}$]
1	F, 61	Acute renal failure, hyperkalaemic arrest, T2DM, hypertension	Diastolic dysfunction	0.00
2	M, 61	Non-STEMI, EF = 35%, T2DM, hypertension. VAP, septic shock.	Septic and cardiogenic shock	0.34
3	M, 62	Pneumonia, septic shock	Septic and cardiogenic shock	0.42
4	F, 50	STEMI with VF arrest EF = 30%, VAP	Septic and cardiogenic shock	0.16
5	M, 72	Iatrogenic splenic injury, haemorrhagic shock, perioperative non-STEMI	To guide fluid resuscitation	0.04
6	M, 63	Haemorrhagic shock due to GIT bleed, chronic heart failure (EF = 30%)	To guide fluid resuscitation	0.20