

# Poison/Potion/Placebo?

## Paracetamol for non-neurogenic fever;

### *Hot or Not?*

*Nepean WTET summary 24/11/2020*

#### **Background and Rationale**

- Fever is associated with an increase in metabolic rate (increased oxygen consumption and CO<sub>2</sub> production) with associated increased myocardial work and potential for vasodilatory effects. Very high fevers inhibit neutrophil and immune function
- On the other-hand animal studies have shown that suppressing fever increased rate of bacterial growth (and viral replication/ shedding), prolonging duration of illness. This suggests that fever may be an appropriate physiological host response to attenuate infection and actually confer a benefit
- Paracetamol is a cheap, readily available, relatively harmless antipyretic agent (COX-3 inhibitor) that avoids some of the concerns associated with the other main group of antipyretic agents – the non-selective COX1/2 inhibitors (NSAIDs) namely renal dysfunction, peptic ulceration and bleeding risk which are already prevalent amongst the critically ill

#### **Advantages and Disadvantages**

- Advantages
  - Fever is associated with tachycardia, tachypnoea (increased minute ventilation and therefore potential for ventilator dyssynchrony) and patient discomfort – paracetamol is both an analgesic and an antipyretic
  - Reduced metabolic rate, myocardial work and vasodilation may prevent decompensation in those with limited physiological reserve
  - Less intensive than non-pharmacological cooling approaches, does not risk shivering
  - Cheap, readily available, familiar. May reduce need for other analgesics (opioids) and S/E
- Disadvantages
  - Microbial activity may be enhanced by fever suppression
  - Only small reduction in temperature likely to be seen with paracetamol; ?defervescence of fever may for the most part be part of the natural course rather than drug effect per se?
  - Drug reactions (hypotension when given IV) and interactions (pyroglutamic acidosis risk)
  - Expensive when given regularly IV for prolonged periods
  - Many causes of fever exist (to include many non-infective), some may benefit, others not, a one size-fits-all approach to treatment of fever is unlikely to be beneficial to ICU all-comers

#### **Key studies**

- Young 2012 Intens Care Med
  - Retrospective observational study 2005-2009 (ANZICS & ICNARC) excluded cardiac arrest (hypothermia) and those with omissions in key data. Separated into infective and non-infective based on APACHE3 admission diagnosis. N=636, 051 (20.8% with infective cause)

- Primary outcome; illness-severity adjusted in-hospital mortality associated with peak documented temperature in first 24h of ICU admission
  - ANZ; adjusted in-hospital mortality risk progressively decreased in patients with infection when temperature increased (lowest risk 39-39.4°C, adjusted OR 0.56, 95% CI 0.48-0.66; relative to risk at 36-36.5°C). UK similar; adjusted OR 0.77 (95% CI 0.71-0.85)
  - ANZ; in those without infection, adjusted mortality progressively increased above 39°C (adjusted OR 2.07 at  $\geq$ 40°C). UK correlated; adjusted OR 1.92 (95% CI 1.60-2.34)
- Suzuki 2015 Crit Care
  - Retrospective observational study over 4 AU ICUs; Paracetamol more likely to be given to post-operative patients, patients with higher fever (mean highest temperature 37.8 compared to 37.4°C in non-paracetamol group,  $P < 0.001$ ) and patients admitted with primary diagnosis of infection. N=15,818 (10,046 received  $\geq$  single dose of paracetamol)
  - Primary outcome; in-hospital mortality with paracetamol use compared to non-paracetamol use; survivors had a lower maximum temperature, were less likely to have had a temperature  $>38^\circ\text{C}$  and were also more likely to receive paracetamol. Paracetamol use had a significant independent association with reduced in-hospital mortality (adjusted for co-variables) OR=0.60 (95% CI 0.53-0.68,  $P < 0.001$ ). Upheld even with exclusion of surgical pop.
- HEAT 2015 NEJM
  - MC blinded RCT; Patients with temperature  $\geq 38^\circ\text{C}$  within 12h enrollment, receiving antimicrobial therapy for known or suspected infection (excluded brain disorders, liver dysfunction that contraindicated paracetamol use). Randomly assigned to 1g paracetamol versus placebo (5% dextrose) 6hrly. Continued til d28 or discharge from ICU / resolution of fever / cessation of antimicrobial therapy / new contraindication to drug / death. Rescue strategy (physical cooling) if  $T \geq 39.5^\circ\text{C}$ . N=700
  - Primary outcome; ICU-free days to d28 (composite of mortality and ICU LOS); 23d vs 22d ( $P=0.07$ ). At 90d, there was no difference in mortality
  - Of survivors, those who received paracetamol had a shorter ICU LOS; 3.5d vs 4.3s,  $P=0.01$
  - Paracetamol group had lower mean daily peak body temperature 38.4 vs 38.6 (absolute difference  $-0.25^\circ\text{C}$ , 95% CI  $-0.38$  to  $-0.11$ ,  $P < 0.001$ ) and lower mean body temperature ( $P < 0.001$ )

### Summary (my practice and additional information)

- For general ICU patients (to include infective aetiologies) my approach is to treat fever (use paracetamol early as part of this, unless contraindicated -relatively benign) only if it is causing patient discomfort or reaching  $\geq 39.5^\circ\text{C}$ ; if continuing to rise despite paracetamol I will also add in other active cooling strategies  $\geq 40.0^\circ\text{C}$  (risk harm  $>$  benefit on multi-organ level with very high-grade fevers)
- Exceptions to this approach being patients presenting with hyperthermic emergencies (e.g. toxidromes) where temperature management is a key part of supportive care and appropriateness of paracetamol use will be dependent on individual circumstances
- If there is another indication to use of paracetamol (e.g. as part of a multimodal approach to analgesia) however I do so – I do not actively avoid paracetamol in patients with a fever of likely infective aetiology
- Paracetamol reduces temperature by  $0.25^\circ\text{C}$ . Fever (presence/severity) may impact clinician decision making with regards to timing of ICU discharge