Editorial

Paracetamol in intensive care – intravenous, oral or not at all?

Kelly et al. have published a study in this edition of *Anaesthesia* that sought to quantify the hypotensive effect of oral/enteral vs. parenteral paracetamol [1]. In addition, it described the pharmacokinetic (PK) data of parenteral and oral/enteral formulations of paracetamol in critical care patients, as well as its effect on pain and temperature. The results of this study pose some interesting questions over both the choice of prescribing route in critical care and the necessity of paracetamol prescription.

Paracetamol is one of the most widely prescribed medications within critical care, with a large observational trial reporting that 64% of intensive care unit (ICU) patients received paracetamol during their stay [2]. The Guy's and St Thomas' Critical Care Units (54 level 3 beds) use approximately 8500 parenteral doses and 16,000 oral/enteral doses per annum. While it is not a high-cost medication (~£4000-4500 UK, $5500-6000 US, € 5000-5500 per annum), its prescription is ubiquitous. This study by Kelly et al., as well as recent data from the HEAT Trial [3], questions whether the risk–benefit analysis of prescribing paracetamol within critical care should be re-evaluated. In addition, when paracetamol is indicated, is it administered via the correct route?

Kelly et al.'s study was a single-site, open-label, randomised study of oral/enteral vs. parenteral paracetamol. Patients were randomly assigned on a one-to-one basis with 50 patients receiving paracetamol. Prescription was at clinician discretion – 25 patients were randomly allocated to receive 1 g intravenous paracetamol and the remaining 25 received 1 g enteral paracetamol. The primary outcome of the study was hypotensive events after paracetamol administration. Of the 197 doses administered (parenteral or enteral), 16 hypotensive episodes occurred. The vast majority (75%) of hypotensive events were in the parenteral paracetamol arm, despite this group having a significantly higher systolic blood pressure at baseline compared with the enteral group.

Of the 16 hypotensive episodes, just below 70% were clinically significant, necessitating a fluid bolus or commencement or increase in vasopressor infusion. The secondary outcome was the description of paracetamol PK in critical illness. In addition, the effect on temperature and pain/sedation was also assessed. This study describes the potential for significant hypotension in one of the most commonly prescribed medications in critical care. The rate of hypotensive episodes reported by the authors is much greater than the rare incidence rate (1:1000–1:10,000) quoted by the manufacturer [4]. This highlights the difference in physiology between healthy subjects used for PK studies before licensing, and the critically unwell. It raises the question whether parenteral paracetamol-induced hypotension causes patient morbidity.

Paracetamol use within the ICU has become ubiquitous over the years, particularly the parenteral formulation. This is largely due to its perceived superior safety profile compared with non-steroidal anti-inflammatory drugs, as well as its opioid-sparing properties. This opioid-sparing effect is well described outside the ICU [5]. However, data for reduced opioid requirement, improved analgesia and reduced analgesia-related adverse events appear to be lacking within the critical care literature. Within its recommended dose range, paracetamol is generally well tolerated with the rare occurrence of reversible raised hepatic transaminases [4], which is often difficult to interpret in the context of critical illness. The manufacturer also describes a very

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rare incidence (<1:10,000) of thrombocytopenia, leucopenia and neutropenia [4].

Hypotension

The mechanism for paracetamol-induced hypotension is yet to be elucidated [6]. As stated by Kelly et al. in their discussion, paracetamol administration has been associated with decreases in cardiac output and systemic vascular resistance. A reduction in fever or pain may result in reduced sympathetic vascular tone. Of the hypotensive episodes, 43% of patients were in receipt of a vasopressor and ~25% had septic shock. One would assume that these patients are at greater risk of paracetamol-induced hypotension as they may be less likely to be able to autoregulate vascular tone. Additionally, the high C_{max} and rapid time to maximum concentration (T_{max}) may contribute to greater rates of hypotension with parenteral paracetamol.

Previous studies in critically ill patients have similarly reported significant hypotension with parenteral paracetamol administration [6–9]. One such study stated that a third of patients treated with parenteral paracetamol required treatment for hypotensive events [6]. Kelly et al. reported 9 of 12 hypotensive events in the parenteral group. This is a rate of one in eight. Interpreting this into clinical practice: hypotensive events are common following parenteral administration of paracetamol and are most likely under-reported [8]. Parenteral paracetamol is presented as 1 g in 100 ml diluent and is administered over 15 min [4]. One wonders whether slower administration, say over 30–60 min, would minimise hypotension? This is certainly the case with a number of other parenteral medicines which are associated with administration-related adverse effects, including hypotension. These include vancomycin which induces red man syndrome [10] when administered too rapidly, and magnesium sulphate which causes bradycardia and hypotension with rapid administration [11]. Rapid parenteral administration of opioids and sedatives can often induce hypotension. It is perhaps surprising that slower parenteral paracetamol administration has not been previously suggested to limit the risk of hypotension. However, it is possible that the rapid analgesic effect associated with parenteral paracetamol may be compromised if infused more slowly. As one does not usually observe a noted decline in opioid analgesic effect when the parenteral administration is slowed, perhaps this should be investigated for intravenous paracetamol?

Pharmacokinetics

The investigators also sought to describe the PK of enteral vs. parenteral paracetamol in critical care patients. Both groups had similar peak area curve profiles. The parenteral group reported a C_{max} more than double the enteral group (73 vs. 156 μmol.l^{-1}), as well as an increase in volume of distribution (V_d) and clearance. The investigators were unable to calculate the elimination rate constant (k), V_d or clearance in the enteral group, because 5 of the 25 had delayed absorption. The C_{max}, V_d and clearance data in the parenteral group are markedly different from the data in healthy subjects, which emphasises PK variability often observed in critically illness [12]. Interestingly, despite the large difference in C_{max}, there was no reported difference in core temperature or pain/sedation score pre- and post-paracetamol administration in either the enteral or parenteral group. This may be due to sample size or other confounders within this study as neither were the primary endpoint. The increased V_d could be attributed to an increase in extracellular fluid compartment secondary to capillary leakage, as described by the authors, although only 7 of the 25 were reported to have septic shock. The major routes of metabolism of paracetamol are glucuronidation, sulphation and oxidation, accounting for 55%, 30% and 10% of urinary metabolites, respectively [13]. An increase in paracetamol clearance and formation of the major glucuronide metabolite has been previously reported after major surgery [13]. The fact that hepatic enzymes can be induced by extreme stress resulting in an increase in clearance could be a plausible explanation for the increase. Other explanations could include alterations in protein binding.

In contrast, the HEAT Trial reported a modest but statistically significant decrease in core body temperature after parenteral paracetamol administration [3]. The authors also reported that ICU sur-

vivors had greater ICU-free days and non-survivors showed an increased time to death. The hypothesis of the HEAT Trial was that parenteral paracetamol for fever on the ICU would increase mortality. This is because it is unclear whether pyrexia is an unintended consequence of the body's protective response to infection, or is inherently beneficial. It has been suggested that temperatures within the febrile range of 38–40 °C enhance the host response to infection through inhibition of bacterial and viral replication [14]. Proposed mechanisms include augmentation of antibody response, as well as enhanced activation of T cells, lymphocytes, macrophages and neutrophils [15].

Prescribing paracetamol

Prescribers in ICU are frequently requested to change the route of administration from enteral to parenteral for pyrexic patients, as there is often the belief that it is more effective in reducing fever. Rather than changing the route, perhaps the actual prescription needs to be reconsidered. The study by Kelly et al. describes significant hypotension with parenteral paracetamol. The HEAT trial reported that although ICU survivors had an increase in ICU-free days, there was no mortality difference. A previous study did report that administration of paracetamol was associated with decreased in-hospital mortality, but this study did not state the proportion of patients receiving enteral vs. parenteral paracetamol [2]. Therefore, if low-grade pyrexia is not associated with a physiological response such as tachycardia or tachypnoea, perhaps one should consider treating mild fever less aggressively, or not at all. There is the additional consideration that parenteral paracetamol may cause harm in the low body weight patients who may lack sufficient skeletal muscle (glutathione stores) to metabolise the high levels of paracetamol attained from the intravenous formulation. Neonatal, paediatric and low body weight adults, where a fatality has been reported [16], are at particular risk. This resulted in a Medicines and Healthcare Products Regulatory Agency (MHRA) warning highlighting the risk of unintentional overdose with parenteral paracetamol and the need for weight-based dosing [17]. There was no mention of weight range in Kelly et al.'s study or in the HEAT Trial.

In terms of the primary outcome of this publication, does one accept the risk of a reduction in systolic blood pressure for a parenteral dose of paracetamol? We would still say a cautious yes in the cases of moderate to severe pain. Kelly et al. described the opioid-sparing effects of paracetamol in their introduction. In this study, the C_{max} in the parenteral drug was twice as high as the enteral group. In addition, 5 of the 25 patients had delayed absorption. How delayed? Could this mean that 20% of patients prescribed enteral paracetamol do not receive their medicines? It certainly does not fill one with confidence for a parenteral to enteral switch. While the oral/enteral route offers less risk of infection or administration-related adverse events, it remains a preference that the patient actually receives the prescribed dose. The intravenous to oral/enteral switch is often suggested as a cost-effective intervention especially with antimicrobial therapy. As one in five patients experienced delayed absorption in this study, we purport that this switch should be reserved for when there is clear evidence that the patient is absorbing their enteral feed and there is confidence that oral/enteral absorption of the prescribed medication will occur. There are reports that postpyloric administration increases absorption and could be considered when feasible [18].

Future research

The results of Kelly et al. emphasise the need to undertake more PK studies in critical illness, and that we should aspire to routine therapeutic drug monitoring due to the significant variability in PK that critically ill patients experience during the course of their ICU stay [19]. As described earlier, despite the doubling in C_{max}, there were no differences in pain scores before and after administration of paracetamol by either formulation. One ponders why? The authors describe using a numeric pain scale. These are challenging to use in intubated patients and validated pain scales such as the Critical Care Pain Observation Tool are advised in this cohort of patients [20]. There is an alternative and equally valid explanation in that there were only 25 patients in each

group, it was a single-site study and pain/agitation was a secondary outcome. A larger multi-centre study is now required with pain relief as the primary outcome.

What does it all mean for the future of paracetamol prescription in the critically ill? For the time being, if one were to consider for moderate to severe pain, the parenteral formulation is probably still preferred in the haemodynamically stable patient, with dose adjustment in patients weighing less than 50 kg. The enteral/oral route could be considered in the less stable patient, although one may question whether adequate serum levels are achieved. For treating mild fever, what is the value of prescribing either formulation? The parenteral formulation is associated with an increased risk of hypotension and cost (44 times the enteral/oral). The enteral/oral formulation lacks evidence of efficacy. Perhaps, the parenteral route could be considered in fever greater than 39.5 °C, where need exceeds risk of hypotension. Interestingly, temperature is not considered a primary decline response in the latest definition of sepsis [21].

The overall consensus is probably akin to prescribing any medicine in critical illness: consider each and every prescription, including the route, and progress only where benefit exceeds the risk of harm. Ideally, we would like to state 'clearly exceeds any risk' but we recognise that the scientific data are often lacking. Thus, one has to balance the risks and benefits of a given therapy and make a decision that is in the best interests of the patient.

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Editorial

Misuse of anaesthetic gases

Substances with anaesthetic activity when inhaled are available to the public and are abused. The reasons for such abuse are multiple, but include effects such as dysphoria, intoxication, and hallucinations. Legislation has struggled to catch up with abuse of agents with anaesthetic activity, and this has led to increasing reports in the media. The scale of this abuse and long-term effects are unknown, and this editorial will address some examples of abuse, and include simple in-vitro measurements of volumes, pressures, and oxygen levels, performed by the author using equipment found in anaesthetic rooms. Ether, nitrous oxide (N_2O), Norflurane (HFA), chloroform, and trichloro-ethylene may be inhaled to achieve a recreational 'high', and the latter two agents are implicated as sedation agents in robberies and other criminal acts [1, 2] but are not discussed here.

Anaesthetists and other health workers are known to abuse anaesthetic agents, by parenteral and inhaled routes; in the USA, 22% of anesthetic departments reported at least one incident of inhaled agent abuse among trainees, nurse anesthetists, and consultants. Mortality rate was high at 8 out of 31 abusers, five deaths were trainees; the ten abusing N_2O did not die, and only five of the survivors were able to return to practice [3]. Inhaled stupefiants have been ranked in order of popularity of abuse in the USA, namely; gasoline, Freon^{TM} (a chlorofluorocarbon), butane, glue, and N_2O [4]; abusers of these, other aromatic gases, and even helium are described as 'huffers'. Guidelines for determining inhalant deaths to help Medical Examiners, Coroners and Pathologists are published by an independent US body, the National Inhalant Prevention Coalition [5].

Speculating how abusers inhale, in conjunction with measurements, should help to render advice, reduce morbidity, mortality, and increase safety of a pleasure-seeking group of individuals who are unlikely to desist.

Ether

Ether was inhaled in 'ether frolics' in the Victorian period; it may have been discovered much earlier, by Jabiribn Hayyan in the 8th century, and certainly by Valerius Cordus of Germany in 1540. It is produced by adding sulphuric acid to ethyl alcohol creating 'sweet oil of vitriol'. Ether is an orally ingested drug used by the Lemkos peoples of the Carpathian mountains. Flammable diethyl ether in spray canisters is used to start recalcitrant internal combustion engines. No information is available from Government bodies or found by this author about the scale of ether abuse; ether is very good at starting lawn mowers in the spring (personal observation).

Nitrous oxide

Nitrous oxide has been inhaled for recreational purposes since 1799. Deaths from nitrous oxide abuse have been reported [6] (too few to note an increase or decrease), seventeen in England and Wales between the years 2006 to 2012 [7], and there were an estimated 700,000 users in England and Wales between the ages of 16 and 59 years in 2013–2014 [8]. Empty aluminium 8 g cylinders, used to charge whipped cream

