The implications of the PEPTIC trial for clinical practice

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Proton pump inhibitors (PPIs) are among the most widely prescribed drugs in the intensive care unit (ICU). Many, if not most, prescriptions of PPIs in the ICU are for stress ulcer prophylaxis. Although PPIs are used most widely for this indication, histamine-2 receptor blockers (H_2RBs) are used in preference to PPIs in some ICUs.[1,2] This practice variation, which appears to be largely dependent on clinician preference rather than based on patient-specific factors,[2,3] has continued for decades.

The PPIs versus H_2RBs for Ulcer Prophylaxis Therapy in the Intensive Care Unit (PEPTIC) trial[4] was an international, randomised, open label, cluster crossover, registry-embedded trial which compared strategies of stress ulcer prophylaxis in mechanically ventilated adults implemented at the level of the ICU. One approach was to use PPIs as the default treatment and the other was to use H_2RBs as the default treatment when stress ulcer prophylaxis was prescribed. Irrespective of the treatment being implemented in the ICU, clinicians could use either a PPI or an H_2RB for individual patients where they considered this indicated. The primary outcome was in-hospital all-cause mortality up to 90 days. Secondary outcomes were clinically significant upper gastrointestinal (GI) bleeding, *Clostridioides difficile* infection, and ICU and hospital length of stay. With 26 828 participants, the PEPTIC trial is the largest clinical trial ever conducted in intensive care medicine and provides very precise estimates of the likely range of possible treatment effects associated with PPIs versus H_2RBs. For the first time, we now have clinically directive data on the comparative efficacy and safety of using these classes of drugs for stress ulcer prophylaxis in the ICU.[5]

The clinical implications of the PEPTIC trial results are best assessed by considering which approach to stress ulcer prophylaxis provides the best balance of risks and benefits in terms of clinically important outcomes for patients. Since these are established therapies with similar costs, even if it is only slightly more likely that one treatment is better for patients overall, then it is logical that this treatment should be preferred.

A total of 18.3% of patients admitted to the ICU when PPIs were used as the default stress ulcer prophylaxis and 17.5% of patients admitted when H_2RBs were used died in hospital by Day 90 (risk ratio, 1.05; 95% CI, 1.00–1.10; $P = 0.05$).[5] While rates of *C. difficile* infection and ICU and hospital length of stay were similar by treatment group, clinically significant upper GI bleeding occurred less frequently in patients in the PPI group (risk ratio, 0.73; 95% CI, 0.57–0.92; $P = 0.009$).[5]

Overall, for every 1000 mechanically ventilated patients admitted when PPIs were the default stress ulcer prophylaxis, five fewer patients had a clinically significant upper GI bleed compared with when H_2RBs were the default.[5] Extrapolating from the intervention rates seen in the Stress Ulcer Prophylaxis in ICU (SUP-ICU) trial,[6] this would equate to three fewer patients getting a blood transfusion and two fewer patients getting an upper GI endoscopy. Based on the findings of the SUP-ICU trial[6] and the PEPTIC trial,[5] we now have very strong evidence that PPIs do what they are supposed to do when administered for stress ulcer prophylaxis in the ICU: they prevent upper GI bleeding. While it appears that such upper GI bleeding events do not generally result in death, they presumably cause anxiety for families and for patients who are awake. They also complicate management decisions for clinicians in relation to whether or not to perform investigations such as upper GI endoscopy, what to do with deep vein thrombosis prophylaxis, and what to do with medicines such as aspirin and warfarin.

In order to avoid dealing with upper GI bleeds in five out of every 1000 ventilated patients, choosing to use PPIs is appealing. However, there are additional complexities to consider in interpreting the data. First, in cardiac surgery patients, the observed rate of clinically significant GI bleeding was 0.7% irrespective of the strategy of stress ulcer prophylaxis chosen.[5] In the more than 6500 cardiac surgical patients in the PEPTIC trial, the observed risk of death was statistically significantly higher in the PPI group (2.5%) than in the H_2RB group (1.9%), corresponding to a risk ratio of 1.27 (95% CI, 1.04–1.57).[5] While the increased risk of death with the PPI strategy observed in cardiac surgical patients may be a chance finding, there seems to be little to lose by adopting an H_2RB strategy as the default for this group of patients where clinically significant upper GI bleeding is so rare. Second, the overall findings in relation to mortality are consistent with a treatment effect that ranges from no effect to a 10% relative increase in mortality using the PPI strategy.[5] While it is now vanishingly unlikely that the default PPI strategy reduces mortality by

a clinically important degree, the possibility of increased mortality risk with this strategy is not excluded. In ventilated ICU patients, the number of Gram-negative bacilli in gastric aspirates increases as the gastric pH increases. Because PPIs cause more profound acid suppression than H_2RBs, they result in greater bacterial overgrowth in the stomach.[7] Such bacterial overgrowth may contribute to the pathogenesis of ventilator-associated pneumonia. We did not collect data on rates of ventilator-associated pneumonia in the PEPTIC study, so our data do not exclude the possibility that mortality attributable to ventilator-associated pneumonia is increased by using PPIs. Moreover, PPIs appear to exert a range of immunosuppressive effects[8] that could potentially increase the risk of death from infection-related complications that commonly arise in ICU patients. These effects include inhibition of natural killer cell activity,[9] neutrophil chemotaxis and superoxide generation.[10] The magnitude of the potential increase in mortality with PPIs suggested by the point estimate of treatment effect is clinically important[5] and globally could account for tens of thousands of deaths per year in developed countries alone.

Weighing a potential increased risk of death with PPIs against what is essentially, on the basis of the entirety of the evidence,[3,5,6] an unequivocal reduction in the risk of clinically significant upper GI bleeding is not simple and clinicians will not necessarily all come to the same conclusion about how to do this. However, the PEPTIC study suggests that the number needed to treat with a default PPI strategy to prevent clinically significant upper GI bleeding compared with a default H_2RB strategy is 200.[5] Our view is that mortality has primacy and, although there is still uncertainty about whether PPIs do in fact increase mortality risk, most patients would rather not be exposed to a therapy that might kill them in order to have a one in 200 chance of being prevented from having an upper GI bleed that probably will not.

Competing interests

None declared.

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