Editorial

Unanswered Questions of “ProCon”etic Therapy

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The provision of enteral nutrition shortly after admission to the intensive care unit (ICU) is associated with beneficial outcomes.\(^1\)\(^,\)\(^2\) The development of high residual volumes frequently impedes the delivery of gastric feeding and may be associated with deleterious outcomes.\(^3\) The most common therapeutic option for managing high gastric residual volumes is the initiation of prokinetic therapy with either metoclopramide or erythromycin.\(^4\)\(^,\)\(^5\) Several studies have demonstrated greater gastric motility and feeding tolerance when these agents are used for this indication.\(^4\)\(^,\)\(^7\) However, few data exist that define residual volume that signifies intolerance, delineate the relationship between residual volume and clinical outcomes, or assess the optimal role of prokinetic agents in various patient populations. Moreover, these agents have side effects; metoclopramide may cause extrapyramidal movement disorders, whereas erythromycin is associated with hepatic drug interactions, QT interval prolongation, and possibly microbial resistance.\(^6\)

In this volume of the *Journal of Parenteral and Enteral Nutrition* (JPEN), Dickerson et al demonstrated in trauma patients that: (1) patients with brain injury are approximately 1.8 times more likely to develop feeding intolerance than other trauma patients; (2) metoclopramide frequently fails to maintain residual volume low enough to advance the feeding rate in trauma patients with intolerance; and (3) the presence of brain injury is associated with a 2.9-fold higher rate of metoclopramide therapy failure.\(^8\) These results mandate close monitoring of gastric feeding and aggressive therapy when intolerance is present in this patient population. Although this study was retrospective in design, its strength involves the systematic manner in which nutrition support was provided and gastric residual volumes managed. Others have demonstrated that feeding intolerance is common when neurologic injury is present and that subsequent therapy with metoclopramide may not be effective.\(^9\)\(^,\)\(^14\) The Dickerson study, however, is the first to label traumatic brain injury as an independent predictor of therapy failure, specifically with metoclopramide.

Patients with metoclopramide failure had higher measurements of intracranial pressure, further suggesting that a centrally mediated neurologic insult limits gastric motility. The mechanism may involve the suppression of vagal activity to disturb the migrating motor complex (MMC) that originates in the gastric antrum.\(^4\)\(^,\)\(^5\) Similarly, cardiovascular abnormalities as a result of altered vagal activity may occur after traumatic brain injury. Although Dickerson et al showed similar rates of successful feeding over 7 days regardless of the degree of head injury, whether improved neurologic recovery was associated with greater metoclopramide response was not assessed. One can only speculate that motility dysfunction and therapy failure may be related to unresolving neurologic injury. Other factors known to inhibit gastric emptying include opioid analgesics, exogenous dopamine, calorically dense tube-feeding products, hyperglycemia, fluid and electrolyte abnormalities, and starvation.\(^4\)\(^,\)\(^5\) Additional studies are needed to further define risk factors associated with intolerance and therapy failure so that therapy may be optimized.

Although it was not designed to comparatively assess metoclopramide with erythromycin, this study showed that adding erythromycin to metoclopramide was associated with enhanced prokinetic efficacy and less tachyphylaxis. Others have demonstrated that erythromycin is more effective for promoting gastric motility and less likely to be associated with tachyphylaxis.\(^6\)\(^,\)\(^7\) Combination therapy was even more effective.\(^15\) Another study assessing metoclopramide for preventing aspiration pneumonia showed that the overall rate of pneumonia was similar to placebo, but the onset of pneumonia was delayed, again suggesting that tachyphylaxis may occur.\(^16\) To date, however, studies attributing therapy failure to tachyphylaxis have used only clinical parameters such as residual volumes rather than objective measurements of gastric motility. These data support the recommendation by Dickerson et al that erythromycin is the preferred prokinetic agent. Erythromycin stimulates the MMC greater and more selectively than metoclopramide by augmenting motilin on smooth muscle cells and

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enhancing vagal stimulation, also suggesting from a pathobiologic standpoint that erythromycin is the preferred prokinetic agent.4,5

The use of erythromycin as the preferred prokinetic leads to many unanswered questions regarding the dosage regimen and side effect profile. Effective intravenous (IV) dosages of erythromycin for promoting gastric motility range from 70 mg administered once to 250 mg administered every 6 hours for a prolonged time frame.4-7 Whether the initial dose influences the development of therapy failure or tachyphylaxis over time is unknown, but therapy failure was less likely to occur with an IV dosage regimen of 200 mg twice daily than with 10 mg of metoclopramide administered 4 times daily.7 As mentioned by Dickerson et al, erythromycin therapy may cause side effects that are known and easily monitored in the ICU (eg, hepatic drug interactions, QT prolongation).4,6 Of greatest concern is the possibility that routine use of erythromycin may enhance the emergence of macrolide resistance, particularly Streptococcus species.4,6 This possibility warrants further delineation and emphasizes the importance of short-term therapy.

In addition to defining risk factors of intolerance and therapy failure, several key questions regarding prokinetic therapy warrant further study so that therapy may be optimized. These questions include but are not limited to the residual volume that requires therapy, differential response rates of therapies based on the degree of intolerance, the use of objective surrogate markers of gastric emptying, subsequent steps when the initial therapy fails, and the role of agents in development.4,6 Clearly, all these issues will never be fully addressed. However, studies like the one conducted by Dickerson et al begin to address risk factors for intolerance and predictors of therapy failure, and suggest that response to metoclopramide may be inferior when neurologic injury is present. That tachyphylaxis is the reason for therapy failure seems plausible but requires further investigation.

References


