Commentary

Erythromycin for prokinesis: imprudent prescribing?

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Abstract

Problems with antibiotic resistant bacteria are increasing in the hospital and particularly in the intensive care unit. Methicillin-resistant *Staphylococcus aureus*, *Acinetobacter baumanii* and extended spectrum beta-lactamase producing Gram-negative bacilli constitute a therapeutic and infection control challenge. Early enteral feeding improves survival in patients in the intensive care unit. Prokinetic agents are routinely used in patients with inappropriate gastrointestinal motility. The use of erythromycin at sub-therapeutic doses as a prokinetic agent is a cause of concern for the following reasons: it can increase the emergence and spread of antibiotic resistance and the likelihood of *Clostridium difficile* disease. The use of an antibiotic as a prokinetic agent does not constitute prudent antimicrobial prescribing and should be avoided. Alternative agents, whenever possible, should be used.

There are increasing problems with antimicrobial resistant bacteria in intensive care. Some examples include *Clostridium difficile*, methicillin-resistant *Staphylococcus aureus* (MRSA), extended spectrum beta-lactamase producing Gram-negative bacilli and *Acinetobacter baumanii*. There is overwhelming evidence that the use of antibiotics is a driving factor for the emergence of resistance [1]. This problem is particularly severe in intensive care areas where antibiotic use is high. Does the current practice of prescribing of erythromycin for prokinesis constitute prudent use of antimicrobials [2]?

The mechanisms by which antibiotic use can increase antibiotic resistance have been reviewed by Lipsitch and Samore [3] and include: selecting in favour of resistant strains; creating colonization opportunities for resistant strains (assuming competition between resistant and susceptible strains); and encouraging an increased colonisation 'load'. In addition, antibiotic use can more rarely select in favour of the emergence of *de novo* resistance.

The predominant MRSA strains in the UK are resistant to erythromycin. We recently conducted an observational carriage study that supported the view that MRSA and methicillin-susceptible *S. aureus* strains compete for colonisation space in the anterior nares [4]. Thus, exposure to macrolides has the potential to alter the composition of the resident bacterial microbiota in the anterior nares, leading to selection of MRSA. In support of this, treatment with slow release clarithromycin has been shown to eliminate nasal carriage of *S. aureus* [5]. This would leave patients more susceptible to colonisation and infection with MRSA.

Berg and co-workers [5] also showed that treatment with a macrolide increased macrolide resistance in the oro-pharyngeal flora. This effect was still present at an eight weeks follow up.

Erythromycin as a prokinetic agent is used at sub-therapeutic doses, which particularly promotes selection of mutational resistance [1,6].

Hospitals in North America and Europe are experiencing a rise in *C. difficile* infections in the inpatient population caused by a strain (NAP1/027) that is characterized by increased toxin production [7]. *C. difficile* strains isolated from UK hospitals are resistant to several antibiotics, including erythromycin [8]. In addition, the transfer of erythromycin resistance to sensitive *C. difficile* strains has been linked to simultaneous acquisition of a gene homologous to *C. difficile* toxin A in nontoxigenic strains of *C. difficile* (9).

Early enteral feeding improves outcome in critically ill patients by increasing gut blood flow and gut function, improving wound healing and reducing septic complications. Early

nutrient intake (within 24 to 48 hours of admission) is now recommended [10]. Inappropriate gastrointestinal motility may cause macro- or micro-aspiration of the gastric contents into the lower respiratory tract, which may act as a risk factor for ventilator-associated pneumonia. Motility agents are routinely prescribed in patients with high gastric content, identified by high volume of fluids aspirated from the nasogastric tube [11]. The prokinetic agents available have been reviewed [12], although a subsequent commentary highlighted the lack of any large methodological studies on which to base treatment recommendations [10]. In addition, there is little evidence from clinical trials that erythromycin used as a prokinetic agent improves the outcome of patients in intensive care.

Although benefits of early enteral nutrition are evident, there is lack of evidence to support the use of erythromycin. Other prokinetic agents like metoclopramide are available, and new agents are under investigation [13]. Metoclopramide is recommended by the Canadian Critical Care Society [11].

Prudent use of antibiotics is an essential component of any strategy aimed at reducing the spread of antimicrobial resistance and health care associated infections [14].

The use of sub-inhibitory concentrations of erythromycin as a prokinetic agent contributes to the antibiotic burden, is likely to lead to the spread of antimicrobial resistance in the intensive care unit and may increase the likelihood of *C. difficile*-associated disease.

This practice is incompatible with the principle of 'prudent antimicrobial prescribing' and should be reserved only for patients in whom alternative agents are contraindicated.

Competing interests

The author(s) declare that they have no competing interests.

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