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REVIEW

Is over-use of proton pump inhibitors fuelling the current epidemic of *Clostridium difficile*-associated diarrhoea?

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Summary Many developed countries have seen an increase in cases of *Clostridium difficile*-associated diarrhoea (CDAD) in recent years. This has occurred despite heightened awareness of the risks of broad-spectrum antibiotics, overall reduction in antibiotic use and increased focus on hospital hygiene. Some of the increase is due to the introduction of new hypervirulent strains, but it predates the description of these. The epidemic coincides with increased use of proton pump inhibitors (PPIs), much of which is inappropriate according to UK and other national guidelines. Gastric acid is a key host defence against other gastrointestinal infections and epidemiological and animal studies have demonstrated a positive association between incident CDAD and PPI use. An association with recurrence of CDAD after initially successful treatment has also been found. Vegetative *C. difficile* cells are rapidly killed at normal gastric pH, but survive at the pH found in patients taking PPI. It has recently been shown that vegetative organisms survive long enough on moist surfaces for transmission between patients to occur. We conclude that restricting PPI use to patients with an appropriate indication would reduce unnecessary expenditure on these agents, and might be an additional means of controlling the current epidemic of CDAD.

Introduction

The UK, North America and many European countries are undergoing an epidemic of *Clostridium*

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difficile-associated diarrhoea (CDAD). This has occurred despite improvement in hospital hygiene and better control of antibiotic prescribing.

Improved case ascertainment, hypervirulent strains and an ageing population have contributed to this, but may not fully explain the considerable increase in cases seen in recent years.

The epidemic coincides with a major increase in use of proton pump inhibitors (PPIs). Inappropriate use, defined by the National Institute for Health and Clinical Excellence (NICE) guidelines in 2000, has been found in 67% of UK National Health Service (NHS) inpatients.[1,2] Similar results based on their own national guidance have been found in Australia, Ireland and the USA.[3] Gastric acid is a key immune defence against gastrointestinal infection, and a possible association with CDAD was first described in 2003.[4] Since then, numerous studies of hospital and community cases have found an association with PPI use; these have recently been systematically reviewed, with a pooled odds ratio of 1.94 (1.37–2.75).[5] General practioner and hospital prescribers of PPIs may be unaware of this possible adverse effect and, as many prescriptions are unnecessary, an opportunity exists to minimise this risk factor. This could add to conventional control measures and potentially reduce CDAD-associated morbidity and mortality.

Methods

We conducted a literature search of Medline, PubMed and Google Scholar in 2007, using the search terms '*Clostridium difficile*', 'proton pump inhibitor', 'gastric acid'. Relevant references were retrieved and reference lists searched manually. The search was repeated in February 2008.

Epidemiology

Since the early 2000s, CDAD has increased in many developed countries, with well-documented outbreaks in Canada, the USA and many European countries.[6–8] In the UK, a voluntary reporting system between 1990 and 2004, and mandatory reporting of all cases aged >65 years since 2004, has demonstrated a clear increase in notified cases (Figure 1). A report from the Office of National Statistics showed annual increases in mention of *C. difficile* in death certificates between 2000 and 2004.[9]

In the UK, this period has seen an unprecedented focus on infection control and antimicrobial resistance, particularly in the hospital setting. Healthcare Commission standards require all acute hospitals to have a comprehensive antibiotic policy. Inspection teams monitor standards of hospital hygiene and, contrary to public perception, standards of hygiene as assessed by Patient Environment Action Teams (PEAT) have improved in recent years. Overall use of antibiotics in the community has declined substantially since the 1990s.[10]

A novel strain of *C. difficile* (ribotype O27) was first described in outbreaks in Quebec, and subsequently in the USA and UK. This strain usually carries a deletion in a gene regulating toxin production, and increased toxin production has been associated with severe disease in localised outbreaks.[6,11] The relationship between toxin production in vitro and severity of illness is not straightforward, and although hypervirulent strains are the major factor in some outbreaks, increased infection rates predate their description in the UK. Clearly other factors must also be important.

Association between PPI use and CDAD

An association between hypochlorhydria and CDAD was first postulated in 1982, long before PPIs were developed.[12] The association is biologically plausible, is consistent with the increased risk of postpyloric compared with gastric enteral feeding, and may be part of the explanation for increased incidence in the elderly. A retrospective study of hospital inpatients showed a positive association with PPI use in 2003, with an odds ratio (OR) of 2.5 (95% CI: 1.5–4.2).[4] Since then numerous studies have looked at PPI use in hospital and community CDAD, most of which have shown a positive association.[13–19] A systematic review of 12 papers evaluating 2948 patients found a pooled OR of 1.94 (95% CI: 1.28–3.00) for PPI therapy in patients with CDAD.[5] This review also showed a dose–response relationship, as the less potent H2 receptor antagonists showed a similar but lesser trend, OR 1.40 (95% CI: 0.85–2.29). The issue remains controversial; other studies have shown no association between PPIs and CDAD.[20–22] There are a number of possible explanations for this. First, differences in patient populations and prevalent strains might mean that different risk factors are relevant in different locations. These studies included a high proportion of elderly patients, who are often already functionally hypochlorhydric.[23] In such elderly patients, PPI use may not increase the risk of CDAD further. In one study of 293 patients infected with a hypervirulent strain no association with PPI use was