Do calcium channel blockers and antimuscarinics protect against perforated colonic diverticular disease? A case control study

C R Morris, I M Harvey, W S L Stebbings, C T M Speakman, H J Kennedy, A R Hart

Background: The aetiology of perforated colonic diverticular disease (PCDD) remains largely unknown. Perforation may result from a combination of high intracolic pressures, secondary to excessive colonic segmentation, and impairment of the mucosal barrier. Calcium channel blockers and antimuscarinics, drugs which reduce colonic contractility and tone, could potentially protect against perforation. The aim of this study was to test this hypothesis using a case control design.

Methods: All cases of acute PCDD were identified over a five year period in two hospitals in Norfolk, UK. Each case was matched for age, sex, and date of admission to two controls groups: (1) patients undergoing cataract surgery and (2) patients with basal cell carcinoma. Data on drug use prior to hospital admission were obtained from medical and nursing records and compared between cases and controls.

Results: A total of 120 cases of PCDD were identified and matched to 240 controls in each group. A statistically significant protective association was seen between calcium channel blocker use and PCDD using both control groups. The odds ratios were 0.41 (95% confidence interval (CI) 0.18–0.93) using the ophthalmology control group and 0.36 (95% CI 0.16–0.82) using the dermatology control group.

Conclusions: This study has shown for the first time that a protective association exists between calcium channel blockers and PCDD. The validity of this association is supported by the consistent finding in both control groups and the plausible biological mechanisms. Further studies are required to confirm this association but calcium channel blockers may represent a potential preventive therapy in PCDD.

METHODS
Identification and confirmation of case group
Hospital inpatient data were used to identify patients with PCDD admitted to two hospitals, which serve a population of approximately 750,000 people (Norfolk and Norwich University Hospital NHS Trust, Norwich and James Paget Hospital, Great Yarmouth, Norfolk, UK). A computer search of the international classification of disease (ICD-10) codes was used to identify patients admitted to hospital between

Abbreviations: PCDD, perforated colonic diverticular disease; NSAIDs, non-steroidal anti-inflammatory drugs
developing a perforation if taking a drug compared with confidence intervals (95% CI), representing the risk of logistic regression was used to calculate odds ratios with 95% case group and each of the control groups. Conditional (Stata Corporation, Texas, USA). Two separate analyses were database of the statistics program STATA 5.0 for Windows 95 cardiovascular comorbidity.

comorbidity and overall drug use, data were also recorded on depressants, phenothiazines, gastrointestinal smooth muscle systemic effects were included. These were tricyclic anti-muscarinic drugs, only those classed as having major preparations depending on their dosage, frequency of use, were classed as either short acting or modified release medical and nursing records. The primary exposure measures controls from the general practitioner’s referral letter and Data on medication use was obtained for both cases and Measurement of exposures

Selection of the control groups

Two control groups were used, with each case matched for age (within one year), sex, and hospital of admission to two patients from each control group. The first control group were patients admitted for cataract surgery within three months of the case admission (ophthalmology control group). The second control group were outpatients who had attended for excision of non-melanotic skin tumours within three months of the case admission (dermatology control group). These two control groups were chosen because patients with these diagnoses were likely to use calcium channel blockers and antimuscarinic drugs with similar rates to that of the general population and were likely to be within a similar age range as the case group.

Use of calcium channel blockers

Calcium channel blockers were used by only 6.7% (n = 8) of patients in the case group compared with 14.2% (n = 34, p = 0.03) of the ophthalmology control group and 15.8% (n = 38, p = 0.01) of the dermatology group. The specific drugs used by patients in the case group were nifedipine (n = 3), amlodipine (n = 2), verapamil (n = 2), and diltiazem (n = 1). In the ophthalmology control group, nifedipine (n = 13) and diltiazem (n = 14) were most frequently used, while in the dermatology group nifedipine (n = 18) and amlodipine (n = 12) were most commonly consumed. Overall use of calcium channel blockers showed a strong protective association against diverticular perforation in both control group analyses (table 1). All of this association appeared attributable to the use of modified release preparations. Adjustment for the use of NSAIDs had no effect on these protective odds ratios.

Use of antimuscarinic drugs

Antimuscarinic drugs were used by 11.7% (n = 14) of patients in the case group compared with 9.2% (n = 22) in the ophthalmology group and 10.0% (n = 24) in the dermatology group. These differences were not statistically significant (table 2). The most commonly prescribed drugs with antimuscarinic properties were tricyclic antidepressants and although these were more frequently used by control group patients, this difference was not statistically significant (table 2).

Overall drug use and comorbidity

Although calcium channel blockers were more commonly used by patients in the control groups compared with the case group, there were no differences in the use of all types of cardiovascular medication (case group 41%, ophthalmology control group 44%, and dermatology control group 46%). Rates of cardiovascular disease were also similar (case group 33%, ophthalmology group 38%, and dermatology group
36%). The number of drugs (all types) taken per patient was higher in the case group (median = 3) than in both the ophthalmology control group (median = 2, p<0.01) and the dermatology control group (median = 1, p<0.01).

**DISCUSSION**

This case control study has shown for the first time that a protective association exists between calcium channel blocking drugs and PCDD. This association appears to be solely attributable to the modified release preparations of these drugs. No protective effect against perforation was found for antimuscarinic drugs.

The main potential source of bias in this study is likely to arise from inaccuracies in the recording of drug use in hospital records. Bias could arise if the completeness of medication histories differed between cases and controls. The increased use of calcium channel blockers in the control groups might reflect a more thorough drug history or a better recall of medication in a group of healthier patients. However, this explanation is unlikely as patients admitted with perforation were recorded as taking more medications than either of the two control groups and the prevalence of cardiovascular medication use was similar for all groups (41–46%). These rates are also similar to the reported prevalence of cardiovascular medication use in a large UK population survey of older people (38–47%). This suggests that the hospital records were accurate for the recording of cardiovascular medication for both cases and controls. Furthermore, the similarity of cardiovascular drug use between the control groups in this study and the UK population survey suggests that these were valid groups to use.

Selection bias is unlikely to have influenced the findings of this study as all patients with a diverticular perforation who were eligible for inclusion in this study should have been identified. Patients with an abscess or peritonitis secondary to diverticular perforation nearly always require hospital admission. Furthermore, the ICD-10 codes used in this investigation were shown to have a high sensitivity for identifying cases of diverticular perforation in a previous study. Finally, the selection criteria included only the severe manifestations of diverticular perforation which are diagnosed easily confirmed by reviewing hospital records. Consequently, the selection criteria were not open to diagnostic interpretation, minimising the chance of misclassification.

The use of hospital control groups can be problematic but in this study we used two different groups of patients with conditions that have no known link with the use of calcium channel blockers. All patients with a previous history of complicated diverticular disease were excluded from the control groups but the exact prevalence of asymptomatic or mildly symptomatic diverticular disease in these groups was unknown. Previous studies however have suggested that in a population with a median age of 74 years (as in the control groups), the prevalence of diverticular disease will be as high as 65%. This supports the conclusion that the protective effect of calcium channel blockers is associated with the perforation of a diverticulum rather than its initial formation.

The consistency of the findings between cases and both control groups greatly strengthens the observation that calcium channel blocker use is lower in patients with colonic diverticular perforation. Furthermore, the strength of the protective effect of calcium channel blockers and plausible biological mechanisms for this effect suggests that the association is real. Calcium channels are involved in the generation of myoelectrical activity and smooth muscle contraction throughout the colon. L-type calcium channel blockers, which include most of the drugs in clinical use, selectively reduce the amplitude and duration of slow wave action potentials generated by colonic pacemaker cells without affecting their frequency. This may produce a beneficial reduction in the strength and duration of colonic contractions, minimising episodes of high intracolonic pressure while maintaining basal activity and colonic transit. Clinically, calcium channel blockers have been shown to suppress the colonic pressure waves normally associated with eating and parasympathetic stimulation, particularly in

| Table 1 | Comparison of the use of calcium channel blockers between patients with colonic diverticular perforation and two hospital based control groups |
|-----------------|-----------------|-----------------|-----------------|
| Drug            | Patients with PCDD (n = 120) (% use) | Ophthalmology controls (n = 240) % | Dermatology controls (n = 240) % |
| All calcium channel blockers | 6.7 | 14.2 | 0.4 (0.2–0.9) | 15.8 | 0.4 (0.2–0.8) |
| Modified release preparations | 2.5 | 8.3 | 0.3 (0.1–0.9) | 11.7 | 0.2 (0.1–0.6) |
| Short acting preparations | 4.2 | 5.9 | 0.7 (0.2–2.0) | 4.6 | 0.9 (0.3–2.7) |

PCDD, perforated colonic diverticular disease.
*Odds ratio (OR) (with 95% confidence interval (CI)) of developing PCDD if taking a drug compared with not taking a drug.

| Table 2 | Comparison of the use of antimuscarinic drugs between patients with colonic diverticular perforation and two hospital based control groups |
|-----------------|-----------------|-----------------|-----------------|
| Drug            | Patients with PCDD (n = 120) (% use) | Ophthalmology controls (n = 240) | Dermatology controls (n = 240) |
| All antimuscarinics | 11.7 | 9.2 | 1.3 (0.6–2.8) | 10.0 | 1.2 (0.6–2.4) |
| Tricyclic antidepressants | 3.3 | 5.0 | 0.7 (0.2–2.1) | 7.1 | 0.5 (0.2–1.4) |

PCDD, perforated colonic diverticular disease.
*Odds ratio (OR) (with 95% confidence interval (CI)) of developing PCDD if taking a drug compared with not taking a drug.
patients with excessive colonic contractility.\textsuperscript{24, 25} Antimuscarinic drugs have similar effects in blocking extrinsic stimuli but do not affect slow wave activity.\textsuperscript{19} The lack of a protective effect for antimuscarinics may indicate that suppression of slow wave amplitude and duration is important in protecting against perforation. Alternatively, calcium channel blockers may be acting through other mechanisms such as increasing gastrointestinal mucosal blood flow, helping to promote cytoprotective activity and repair in the diverticular mucosa.\textsuperscript{14} A further possibility is that the duration of action of a drug is important as the protective association of calcium channel blockers was attributable to modified release drugs. Modified release preparations are likely to produce more gradual and sustained effects on motility, which may explain why no association was seen for shorter acting calcium channel blockers and antimuscarinics.

In view of the findings of this investigation, further aetiological studies are required to confirm the protective association between calcium channel blockers and perforated colonic diverticular disease. These studies should ideally involve community control groups and use interviews with patients to obtain more detailed data, particularly on the duration of use of medications. Confirmation of a causal relationship would support therapeutic trials of calcium channel blockers in patients at high risk of developing complications secondary to diverticular perforation. Such a group might include those who have had two or more episodes of inflammation and who would currently be advised to undergo surgical resection. This study has also shed light on possible mechanisms through which diverticular perforation may be prevented. Future investigations should examine other pharmacological factors that reduce colonic motility or augment mucosal blood flow. Identification of an effective drug treatment for preventing perforation would be a major advance in the management of patients with known colonic diverticular disease. As well as preventing perforation, drugs such as calcium channel blockers might also help to reduce the abdominal symptoms attributed to colonic spasm. Such a measure could potentially improve the quality of life of patients as well as reducing the healthcare resources required to treat them.

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