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 intracolonic pressures, secondary to excessive colonic segmentation, and impairment of the mucosal barrier. Calcium channel blockers and antimuscarinics, 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 use of 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.

1 April 1995 and 27 February 2000. These codes were K57.2 (perforation, abscess, or peritonitis of large intestinal diverticula); K57.4 (perforation, abscess, peritonitis, of both the small and large bowel diverticula); and K57.8 (perforation, abscess, or peritonitis of either the small or large bowel diverticula).

The hospital records of all potential cases were reviewed by the principal investigator (CRM) to confirm the diagnoses. A patient was included in the case group if there was evidence of a macroscopic colonic diverticular perforation at either laparotomy or post mortem. In the absence of a macroscopic perforation, patients were included if there was evidence of extracolonic pus or faeces, in the presence of an inflamed diverticulum, and with no other intra-abdominal pathology (implying a sealed perforation). Finally, patients who did not undergo laparotomy were included if there was radiological evidence (computed tomography, ultrasound, or contrast enema) of a colonic diverticular abscess. Patients with the chronic sequelae of perforation such as colonic stricture and fistulae were excluded. These complications may be present for some time before admission to hospital, presenting difficulties in determining whether drug exposures occurred before the onset of the illness.

**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.

**Measurement of exposures**

Data on medication use was obtained for both cases and controls from the general practitioner’s referral letter and medical and nursing records. The primary exposure measures were oral intake of calcium channel blockers and antimuscarinic drugs immediately prior to the onset of symptoms of perforation. For calcium channel blockers, individual drugs were classed as either short acting or modified release. For calcium channel blockers, individual drugs were classed as either short acting or modified release preparations depending on their dosage, frequency of use, and classification in the *British National Formulary*. For antimuscarinic drugs, only those classed as having major systemic effects were included. These were tricyclic antidepressants, phenothiazines, gastrointestinal smooth muscle relaxants, drugs for bladder instability, and antiparkinsonian drugs. To assess whether group differences in the use of calcium channel blockers simply related to differences in comorbidity and overall drug use, data were also recorded on the number of medications used by each patient, the use of all cardiovascular medications, and the prevalence of cardiovascular comorbidity.

**Analysis**

All data were anonymised, coded, and entered into the database of the statistics program STATA 5.0 for Windows 95 (Stata Corporation, Texas, USA). Two separate analyses were performed comparing the prevalence of drug use between the case group and each of the control groups. Conditional logistic regression was used to calculate odds ratios with 95% confidence intervals (95% CI), representing the risk of developing a perforation if taking a drug compared with not taking that drug. These odds ratios were adjusted for the confounding effect of NSAID medication, the only known risk factor for this condition. Primary analyses were undertaken for all calcium channel blockers and antimuscarinics. Further analyses were performed for short acting and modified release calcium channel blockers and tricyclic antidepressants, which accounted for the majority of antimuscarinics. The use of cardiovascular medication and prevalence of cardiovascular comorbidity were also compared using conditional logistic regression. Differences in the number of medications taken by cases and controls were compared using the Wilcoxon signed rank test.

**RESULTS**

**Case group characteristics**

A total of 120 consecutive patients with confirmed PCDD were identified during the study period. The case group consisted of 39 (32.5%) men and 81 (67.5%) women with a median age of 74 years (range 30–95). Prior to hospital admission, 46 people (38%) were known to have colonic diverticular disease from previous radiological or endoscopic investigations. However, only 16 (13%) had previously been admitted to hospital with a complication of diverticular disease. The clinical management was surgical in 107 (89%) cases, the most frequent operative finding being purulent peritonitis (43%) followed by abscess (23%) and faecal peritonitis (22%). The overall mortality rate was 26%, ranging from 14% in patients with an abscess to 48% in those with faecal peritonitis. It was possible to accurately match case group patients so that the age and sex characteristics of cases and controls were identical.

**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 44%).
population survey\(^2\) suggests that these were valid groups to
to the control groups in this study and the UK
Furthermore, the similarity of cardiovascular drug use
hospital records were accurate for the recording of cardio-
This suggests that the
cardiovascular medication use in a large UK population
46%). These rates are also similar to the reported prevalence
contractions, minimising episodes of high intracolonic
cholesterol, 23 particularly in
Clinically, calcium channel blockers have been shown to
smooth muscle
pressure while maintaining basal activity and colonic transit.
beneficial reduction in the strength and duration of slow wave
action potentials generated by colonic pacemaker cells
without affecting their frequency. 22 This may produce a
Clinically, calcium channel blockers have been shown to
suppress the colonic pressure waves normally associated with
eating\(^2\) and parasympathetic stimulation, 23 particularly in
identifying cases of diverticular perforation in a previous
Finally, the selection criteria included only the severe
manifestations of diverticular perforation which are diag-
noses easily confirmed by reviewing hospital records.
Consequently, the selection criteria were not open to
diagnostic interpretation, minimising the chance of misclas-
sification.
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%. 21 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
to diverticular 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%). 20 This suggests that the
hospital records were accurate for the recording of cardio-
vascular 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\(^2\) 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

### Table 1: Comparison of the use of calcium channel blockers between patients with colonic diverticular perforation and two hospital based control groups

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with PCDD (n = 120)</th>
<th>Ophthalmology controls (n = 240)</th>
<th>Dermatology controls (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All calcium channel blockers</td>
<td>(%) use</td>
<td>% use OR (95% CI)*</td>
<td>% use OR (95% CI)*</td>
</tr>
<tr>
<td>Modified release preparations</td>
<td>6.7</td>
<td>14.2</td>
<td>0.4 (0.2–0.9)</td>
</tr>
<tr>
<td>Short acting preparations</td>
<td>2.5</td>
<td>8.3</td>
<td>0.3 (0.1–0.9)</td>
</tr>
</tbody>
</table>
| *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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Patients with PCDD (n = 120)</th>
<th>Ophthalmology controls (n = 240)</th>
<th>Dermatology controls (n = 240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All antimuscarinics</td>
<td>(%) use</td>
<td>% use OR (95% CI)*</td>
<td>% use OR (95% CI)*</td>
</tr>
<tr>
<td>Tricyclic antidepressants</td>
<td>11.7</td>
<td>9.2</td>
<td>1.3 (0.6–2.8)</td>
</tr>
<tr>
<td></td>
<td>(%) use</td>
<td>% use OR (95% CI)*</td>
<td>% use OR (95% CI)*</td>
</tr>
<tr>
<td></td>
<td>3.3</td>
<td>5.0</td>
<td>0.7 (0.2–2.1)</td>
</tr>
</tbody>
</table>

*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. Antimuscarinic drugs have similar effects in blocking extrinsic stimuli but do not affect slow wave activity. 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. 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.

ACKNOWLEDGEMENTS
Funding for this study was from the Directorate of Health and Social Care, Department of Health, UK, and the Norfolk and Norwich Hospitals Bicentenary Trust.

We would like to acknowledge the help and cooperation of staff in the departments of clinical coding and medical records as well as all consultant general surgeons, ophthalmologists, dermatologists, and plastic surgeons at the Norfolk and Norwich University Hospital NHS Trust and the James Paget Hospital NHS Trust.

Authors’ affiliations
C R Morris, School of Medicine Health Policy and Practice, University of East Anglia, Norwich, UK
I M Harvey, School of Medicine Health Policy and Practice, University of East Anglia, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK
W S L Stebbings, C T M Speakman, Department of General Surgery, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK
H J Kennedy, Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK
A R Hart, School of Medicine Health Policy and Practice, University of East Anglia, and Department of Gastroenterology, Norfolk and Norwich University Hospital NHS Trust, Norwich, UK

REFERENCES