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(Accepted 28 September 1993)

Recent treatment with H₂ antagonists and antibiotics and gastric surgery as risk factors for salmonella infection

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BMJ 1994;308:176

Experimental evidence shows that gastric acid protects against enteric infections,^{1,2} and patients who have had gastric surgery seem to be more susceptible to salmonella infection.^{3,4} Whether H₂ antagonists are also associated with salmonella infection is not known, although diarrhoea is a recognised side effect. Statutory notifications of salmonella infection have increased in recent years and the use of H₂ antagonists has become widespread, suggesting that suppression of acid by these drugs may have been contributory. We conducted a case-control study to assess whether H₂ antagonists are associated with salmonella infection.

Patients, methods, and results

From March 1990 to September 1992, 218 notified cases of salmonella infection, confirmed by faecal culture, occurred in people aged ≥ 45 in the Nottingham area. Thirty cases were excluded because the patient was non-resident (4), the patient's general practitioner declined to participate (19), or the notes were unobtainable (7). Thus 188 cases (86 in men) were studied. Controls were identified as the next two patients in the practice records system matched for age (within five years) and sex.

Data on previous gastric surgery; drugs prescribed in the preceding year; and whether H₂ antagonists, hydroxocobalamin, antibiotics, and corticosteroids had ever been prescribed were extracted from the patients' records. Only drugs that the patients had

begun taking before the onset of salmonella infection were noted. Data were analysed by conditional logistic regression with the EGRET package, and relative risks were approximated by odds ratios. The number of attributable cases was calculated from the adjusted relative risks.

Treatment with H₂ antagonists in the past month was associated with a twofold increased risk of salmonella infection, and recent antibiotic treatment was associated with a 50% increased risk; previous gastric surgery was associated with a fivefold increased risk (table). Much of this increased risk was in patients aged over 65. In three cases and one control gastric surgery had been performed in the five years before infection. Analyses by sex showed the same associations. No associations were seen with corticosteroid or hydroxocobalamin treatment or any other class of prescription drug. The total estimated number of notified cases attributable to an iatrogenic cause was 32 (gastric surgery 15, H₂ antagonists 9, antibiotics 8).

Comment

Our results confirm that gastric surgery predisposes to clinical salmonella infection⁴ and show the same for H₂ antagonists. Our finding that current users, but not former users, of H₂ antagonists were at increased risk suggests that the relation is causal. The severity of infection has been related to the size of the infecting dose. These risk factors are likely to increase the severity of infection by reducing the gastric killing of ingested organisms because of reduced acidity and more rapid transit after gastric surgery.

Salmonella infection has been reported anecdotally in people taking proton pump inhibitors, but none of the cases or controls had taken these drugs during the study period. We used treatment with hydroxocobalamin as a proxy for the achlorhydria associated with pernicious anaemia, but as only three cases and three controls had taken hydroxocobalamin, no definitive comment on a causal link can be made.

Our results also suggest that antibiotics increase the risk, or possibly the severity, of salmonella infection, especially in elderly people, as was reported from the United States.⁵ Antibiotics may predispose to infection by changing the flora in the bowel. More work is needed to determine how long the risk persists after treatment with antibiotics.

Our data suggest that the above factors are most important in people over 65. This may reflect the reduction in the secretion of gastric acid that occurs with age interacting with other predisposing factors.²

We thank Mrs G Campion for her help in collecting data.

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(Accepted 28 October 1993)

Relative risks for associations with salmonella infection*

Exposure	Cases (n=188)	Controls (n=376)	Relative risk (95% confidence interval)				
			All ages		Ages 45-64 (124 cases) adjusted	Age 65 + (64 cases) adjusted	
			Unadjusted	Adjusted			
Gastric surgery	18	7	5.6 (2.1-15.2)†	4.5	9-11(0)‡	2.0 (0.5-8.3)	8.8 (2.4-32.3)‡
H ₂ receptor antagonists:							
In past month	16	14	2.4 (1.1 to 5.4)§	1.9 (0.9 to 4.0)	1.1 (0.4 to 3.0)	4.6 (1.1 to 19.3)§	
In past year	19	22	1.8 (0.9 to 3.6)	1.5 (0.8 to 2.9)	1.0 (0.4 to 2.6)	2.6 (0.8 to 8.7)	
Ever	27	38	1.5 (0.9 to 2.6)	1.3 (0.8 to 2.2)	1.1 (0.5 to 2.2)	1.6 (0.7 to 4.0)	
Ever (excluding past month)	11	24	1.0 (0.4 to 2.1)	0.9 (0.4 to 2.0)	1.1 (0.4 to 2.9)	0.8 (0.2 to 3.0)	
Antibiotics:							
In past month	17	20	1.8 (0.9 to 3.7)	1.8 (0.9 to 3.8)	1.7 (0.9 to 2.4)	6.3 (1.1 to 34.8)§	
In past year	74	116	1.5 (1.0 to 2.1)§	1.4 (1.0 to 2.1)	1.5 (0.9 to 2.4)	1.3 (0.6 to 2.7)	
In past year (excluding past month)	57	96	1.4 (0.9 to 2.1)	1.5 (1.0 to 2.3)	1.8 (1.0 to 3.1)§	1.0 (0.5 to 2.3)	
Ever (excluding past month)	148	309	1.0 (0.6 to 1.7)	0.9 (0.5 to 1.7)	1.1 (0.6 to 2.2)	0.3 (0.1 to 1.4)	

*Adjusted for gastric surgery, H₂ antagonist treatment, antibiotic treatment, and other drug use.

†P=0.00003.

‡P=0.001.

§P<0.05.