

ORIGINAL ARTICLE

Risk of Barrett's oesophagus, oesophageal adenocarcinoma and reflux oesophagitis and the use of nitrates and asthma medications

TODD C. LADANCHUK^{1*}, BRIAN T. JOHNSTON^{2*}, LIAM J. MURRAY¹ & LESLEY A. ANDERSON¹ ON BEHALF OF THE FINBAR STUDY GROUP

¹Centre for Public Health, Queen's University, Belfast, Northern Ireland, UK, and ²Royal Group of Hospitals, Belfast, Northern Ireland, UK

Abstract

Objective. To investigate the relationship between use of asthma medication and nitrates and risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma. **Material and methods.** Data were collected on use of asthma medication and nitrates at least 1 year before interview from patients with reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma. Associations between use of asthma medications and nitrates and the risk of reflux oesophagitis, Barrett's oesophagus and oesophageal adenocarcinoma were estimated using multiple logistic regression. **Results.** Nine hundred and forty-one subjects were recruited: 230 reflux oesophagitis, 224 Barrett's oesophagus, 227 oesophageal adenocarcinoma patients and 260 population controls. Barrett's oesophagus patients were more likely than controls to have had a diagnosis of asthma (odds ratio 2.15, 95% confidence interval 1.15–4.03) and to have used asthma medications (odds ratio 2.13, 95% confidence interval 1.09–4.16). No significant associations were observed between use of asthma medication or nitrates and reflux oesophagitis or oesophageal adenocarcinoma. **Conclusions.** Gastro-oesophageal reflux symptoms appear to confound the association between asthma medication use and Barrett's oesophagus. However, it is possible that asthma medications may increase the risk of Barrett's oesophagus by other mechanisms.

Key Words: Anti-asthmatic agents, asthma, Barrett's oesophagus, oesophageal adenocarcinoma, oesophageal disorders, nitric oxide donors, nitrates, reflux oesophagitis

Introduction

Prolonged exposure of the oesophagus to gastric acid may lead to metaplastic changes of the normal squamous epithelial lining into columnar epithelium. Both prolonged gastro-oesophageal reflux (GOR) and Barrett's oesophagus (BO) have been identified as significant risk factors in the development of oesophageal adenocarcinoma (OAC) [1–8], a cancer that has been increasing in incidence over recent decades [9–15].

GOR is promoted by relaxation of the lower oesophageal sphincter (LOS). The effect of various medications on LOS tone has been described in several clinical studies. These medications include: nitrates [16], calcium channel blockers [17], β -agonists [18] and benzodiazepines [19]. Several epidemiological studies have linked these medications to an increased risk of BO [20] and OAC [21–23]. However, there is some debate about the strength of these relationships. Lagergren et al. [22] conducted a case-control study of oesophageal and gastric cardia

Correspondence: Lesley A. Anderson, Centre for Public Health, Queen's University, Belfast, Institute of Clinical Sciences, Block B, Grosvenor Road, Belfast BT12 6BA, Northern Ireland, UK. Tel: +44 28 9063 5046. Fax: +44 28 9024 8017. E-mail: l.anderson@qub.ac.uk

*Joint first authors.

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adenocarcinoma. They found an elevated incidence rate ratio in users of lower oesophageal sphincter-relaxing medications (incidence rate ratio 3.8, 95% confidence interval (CI), 2.2–6.4) for use greater than 5 years. By contrast, a study by Corley et al. [20] only detected an association between BO and asthma medications (odds ratio (OR) 5.8; 95% CI 2.2, 14.9) and not nitrates or calcium channel blockers.

Studies comparing risk factors for reflux oesophagitis (RO), BO and OAC provide the opportunity to examine whether these risk factors are important in the development of RO and/or BO or in its progression to OAC. We set out to investigate the relationship between the use of asthma medications and nitrates and risk of RO, BO and OAC using an all-Ireland case-control study the Factors INfluencing the Barrett's Adenocarcinoma Relationship (FINBAR) study.

Methods

The FINBAR study (March 2002 to December 2004) methods have been described in detail elsewhere [24]. Briefly, the study included (1) patients with histologically confirmed OAC, (2) patients with long-segment BO (≥ 3 cm of typical Barrett's mucosa seen at endoscopy and specialised intestinal metaplasia confirmed by histological examination), and (3) normal population controls. OAC patients, BO patients and controls were recruited from throughout Ireland. RO patients (macroscopically visible erosive oesophagitis at upper gastrointestinal endoscopy) were recruited in a separate oesophagitis study in Northern Ireland only (September 2004 to July 2005). BO subjects, RO subjects and controls were frequency matched (within 5 year age and sex strata) to the distribution of OAC subjects with a maximum age of 85 years.

Northern Ireland OAC cases were identified from electronic pathology records from all pathology laboratories within the province. Republic of Ireland cases were identified from the main hospitals involved in the diagnosis and treatment of oesophageal cancer and through the National Cancer Registry Ireland, Cork. Subjects with BO were identified from electronic pathology records from all pathology laboratories in Northern Ireland and from large teaching hospitals in the Dublin and Cork areas. In Northern Ireland controls were selected at random from the General Practice Master Index (a province-wide database of all persons registered with a General Practitioner). Controls in the Republic of Ireland were selected at random from four general practices (two urban and two rural) in the Dublin and Cork areas to represent the urban/rural distribution of the OAC

patients. RO patients were identified through electronic pathology records from all pathology laboratories within the province. BO patients, RO patients and controls were all frequency matched to the location (Northern Ireland/Republic of Ireland), age (5-year age band) and gender distribution of the OAC cases. Subjects with a prior history of gastrointestinal tract cancers were excluded.

All subjects underwent a structured computerised interview with trained interviewers. Information was collected on medication use more than 1 year before the interview date, and was defined as any use "at least once per week for 6 months or longer". Short- and long-term use of asthma medication (< 7 years and ≥ 7 years) and nitrates (< 6 years and ≥ 6 years) and frequency of use of these medications was also recorded. Asthma medications included salbutamol, terbutaline, theophylline and aminophylline. Nitrate medications included glyceryl trinitrate, isosorbide dinitrate and isosorbide mononitrate. Additionally, information was collected on symptoms of GOR, relevant medical history, weight, smoking history, education, occupational type (manual/non-manual) and alcohol consumption. Height was measured at the time of interview.

Statistical methods

Statistical analyses were performed using STATA 8.0 (StataCorp, College Station, TX, USA). In bivariable analyses, chi-square tests were used to examine differences in categorical variables between groups. ANOVA was used to compare continuous variables for the BO/OAC/control comparisons with a *post hoc* Dunnett *t*-test. T-tests were used to compare continuous variables for the RO/control comparisons. Unconditional maximum-likelihood multinomial (polytomous) logistic regression analyses were undertaken to examine the associations between case status (BO and OAC) and the use of asthma medication and nitrates and case/control status adjusting for potential confounders included in Table I. Frequency and duration of asthma medication and nitrates were categorised above and below the median frequency and duration of use among all controls. RO patients were compared to Northern Ireland controls only since medication usage may differ between Northern Ireland and the Republic of Ireland.

Ethical committee approval for the FINBAR study was obtained from the Research Ethics Committee of the Queen's University Belfast, the Clinical Research Ethics Committee of the Cork Teaching Hospitals and the Research Ethics Committee Board of St. James's Hospital, Dublin.

Table I. Characteristics of controls, Barrett's oesophagus, oesophageal adenocarcinoma and reflux oesophagitis patients.

Variables	FINBAR study				Oesophagitis study		
	Controls	BO	p-Value (BO vs. controls)	OAC	p-Value (OAC vs. controls)	Northern Ireland controls	RO
Sex, n (%)							
Male	220 (84.6%)	185 (82.6%)	0.548	192 (84.6%)	0.992	85 (70.1%)	189 (82.2%)
Female	40 (15.4%)	39 (17.4%)		35 (15.4%)		36 (29.8%)	41 (17.8%)
Age							
Mean years	63.0	62.4	0.782	64.2	0.446	68.1	61.7
Education							
Years	12.0	11.3	0.017	10.7	<0.001	11.1	10.8
Job type							
Manual	119 (48.0%)	130 (59.1%)	0.016	128 (59.5%)	0.013	54 (47.0)	107 (48.2)
Non-manual	129 (52.0%)	90 (40.9%)		87 (40.5%)		61 (53.0)	115 (51.8)
Smoking status							
Never	102 (40.2%)	87 (39.2%)	0.400	45 (20.4%)	<0.001	54 (42.9%)	109 (48.4%)
Ex-smoker	107 (42.1%)	85 (38.3%)		99 (44.8%)		45 (37.8%)	68 (30.2%)
Current	45 (17.7%)	50 (22.5%)		77 (34.8%)		23 (19.3%)	48 (21.3%)
Alcohol, n (%)							
Never	69 (26.5%)	57 (25.6%)	0.135	65 (28.9%)	0.004	45 (37.2%)	57 (26.0%)
Ever	191 (73.5%)	166 (74.4%)		160 (71.1%)		76 (62.8%)	162 (74.0%)
Body mass index							
Mean (kg/m ²)	27.0	27.0	0.989	28.7	<0.001	27.3	27.8
<i>Helicobacter pylori</i>							
Seronegative	96 (37.9%)	122 (56.7)	<0.001	100 (48.1%)	0.03	36 (30.3%)	132 (57.6%)
Seropositive	157 (62.1%)	93 (43.3)		108 (51.9%)		83 (69.8%)	91 (42.4%)
Location							
Northern Ireland	121 (46.5%)	152 (67.9%)	<0.001	115 (50.7%)	0.364	121 (100%)	230 (100%)
Republic of Ireland	139 (53.5%)	72 (32.1%)		112 (49.3%)		0	0
GOR symptoms ^a							
Never	211 (81.2%)	60 (26.8%)	<0.001	117 (51.5%)	<0.001	93 (76.9%)	140 (60.9%)
Ever	49 (18.8%)	164 (73.2%)		110 (48.5%)		28 (23.1%)	90 (39.1%)

Abbreviations: BO = Barrett's oesophagus; OAC = oesophageal adenocarcinoma; RO = reflux oesophagitis; GOR = gastro-oesophageal reflux.

^aSymptoms of heartburn or acid reflux experienced at least once per week or more than 50 times per year, more than 5 years prior to the interview date.

Results

In total 224 BO patients, 227 OAC patients, 230 RO patients and 260 controls were included in the study. The characteristics of patients and controls used in the subsequent analyses are shown in Table I. The participation rates for BO patients, OAC patients, RO patients and controls were 82.4%, 74.2%, 68.7% and 41.8%, respectively.

An asthma diagnosis was reported more commonly by BO patients than controls (OR, 95% CI: 2.15, 1.15–4.03). No association was observed between an asthma diagnosis and OAC or RO (ORs, 95% CIs: 0.78, 0.36–1.68 and 1.06, 0.42–2.69, respectively). The use of asthma medications, without adjustment for GOR symptoms, was also more common in BO patients than controls (OR, 95% CI: 2.13, 1.09–4.16) (Table II). When use of asthma medication was adjusted for GOR symptoms, the OR was attenuated (OR, 95% CI: 1.88, 0.89–3.98). The OR for the highest frequency of asthma medication use without adjustment for GOR symptoms was borderline higher in patients with BO compared to controls (OR, 95% CI: 2.42, 1.00–5.88) and there was a significant dose–response relationship ($p = 0.028$) (Table II). Asthma medications were not significantly associated with OAC (Table II) or RO (Table III). However, the OR for the highest frequency of asthma medication

use was elevated in RO patients (OR 2.31, 95% CI 0.90–5.91).

There were no significant associations between nitrate-containing medications and RO, BO or OAC (Tables II and III). When we adjusted for GOR the OR's were attenuated. There were no significant associations between the duration or frequency of nitrate medication use and risk of BO and OAC (Table II) or RO (Table III).

Discussion

This study has shown that a self-reported diagnosis of asthma and previous use of asthma medications is higher among patients with BO compared to controls. In particular, BO patients appeared to be more likely to have frequent asthma medication use compared to controls, and there was a significant dose–response relationship. However, adjustment for frequent GOR symptoms results in a non-significant elevated OR. Conversely, nitrate-containing medications were not significantly associated with BO, OAC or RO.

Our study concurs with previous work that investigated lower oesophageal sphincter-relaxing medications and their relationship with BO [20]. Corley et al. reported that users of asthma medications had an increased risk of BO (OR, 95% CI: 4.0, 1.5–10.4)

Table II. Asthma medication and nitrate-containing medication use in Barrett's oesophagus and oesophageal adenocarcinoma cases compared to controls.

	Controls		Barrett's oesophagus		Oesophageal adenocarcinoma		
	<i>n</i>	<i>n</i>	Adjusted ^a , OR (95% CI)	Adjusted ^a + GOR, OR (95% CI)	<i>n</i>	Adjusted ^a , OR (95% CI)	Adjusted ^a + GOR, OR (95% CI)
Asthma medication							
Never	236	189	1.00	1.00	204	1.00	1.00
Ever ^b	22	35	2.13 (1.09–4.16)	1.88 (0.89–3.98)	22	1.35 (0.64–2.83)	1.25 (0.58–2.67)
Short-term use ^c	11	9	2.31 (0.89–6.01)	1.65 (0.58–4.65)	6	1.73 (0.62–4.84)	1.42 (0.50–4.01)
Long-term use ^d	11	6	1.97 (0.80–4.86)	2.27 (0.80–6.48)	6	0.85 (0.28–2.58)	0.90 (0.28–2.83)
<2 daily	11	14	1.80 (0.69–4.71)	1.76 (0.57–5.43)	7	1.09 (0.35–3.33)	1.11 (0.35–3.52)
≥2 daily	12	21	2.42 (1.00–5.88)	2.01 (0.76–5.31)	14	1.41 (0.52–3.77)	1.22 (0.45–3.33)
Nitrates							
Never	245	204	1.00	1.00	209	1.00	1.00
Ever ^b	13	18	1.96 (0.82–4.69)	1.08 (0.41–2.71)	15	1.44 (0.60–3.46)	1.07 (0.43–2.70)
Short-term use ^c	5	9	3.10 (0.87–11.07)	2.04 (0.49–8.42)	6	1.95 (0.51–7.48)	1.57 (0.38–6.50)
Long-term use ^f	6	6	1.16 (0.29–4.58)	0.58 (0.12–2.70)	6	0.85 (0.22–3.29)	0.62 (0.15–2.58)
<2 daily	5	8	2.28 (0.60–8.62)	1.45 (0.33–6.35)	5	1.19 (0.29–4.90)	0.94 (0.21–4.14)
≥2 daily	8	11	2.08 (0.69–6.26)	1.02 (0.30–3.39)	10	1.67 (0.56–4.96)	1.17 (0.38–3.64)

Abbreviations: GOR = gastro-oesophageal reflux; OR = odds ratio; CI = confidence interval. Figures in bold represent a significant association with a p -value < 0.05.

^aAdjusted for gender (male is reference group), age at time of interview (years), years of education, occupation (manual vs. non-manual), smoking status (never, former, current), alcohol consumption, body mass index 5 years before interview date, *Helicobacter pylori* status and location (Northern Ireland or Republic of Ireland).

^bDefined as medication use more than 1 year before the interview date which was “at least once per week for 6 months or longer”.

^c<7 years.

^d≥7 years.

^e<6 years.

^f≥6 years.

Table III. Asthma medication and nitrate-containing medication use in reflux oesophagitis cases compared to Northern Ireland controls.

	Northern Ireland controls		Reflux oesophagitis	
	<i>n</i>	<i>n</i>	Adjusted ^a , OR (95% CI)	Adjusted ^a + GOR, OR (95% CI)
Asthma medication				
Never	108	204	1.00	1.00
Ever ^b	11	26	1.55 (0.75–3.20)	1.41 (0.67–2.97)
Short-term use ^c	7	13	1.37 (0.48–3.92)	1.32 (0.45–3.88)
Long-term use ^d	4	13	0.80 (0.44–1.46)	1.48 (0.55–4.01)
<2 daily	5	7	0.79 (0.24–2.64)	0.77 (0.23–2.65)
≥2 daily	7	19	2.31 (0.90–5.91)	2.02 (0.77–5.27)
Nitrates				
Never	113	211	1.00	1.00
Ever ^b	6	18	1.43 (0.57–3.60)	1.28 (0.49–3.33)
Short-term use ^c	2	11	2.70 (0.45–16.0)	3.01 (0.50–18.1)
Long-term use ^f	3	6	1.42 (0.25–7.97)	1.08 (0.18–6.35)
<2 daily	3	0	–	–
≥2 daily	3	18	2.35 (0.81–6.82)	2.21 (0.73–6.68)

Abbreviations: GOR = gastro-oesophageal reflux; OR = odds ratio; CI = confidence interval.

^aAdjusted for gender (male is reference group), age at time of interview (years), years of education, occupation (manual vs. non-manual), smoking status (never, former, current), alcohol consumption, body mass index 5 years before interview date and *Helicobacter pylori* status.

^bDefined as medication use more than 1 year before the interview date which was “at least once per week for 6 months or longer”.

^c<7 years.

^d≥7 years.

^e<6 years.

^f≥6 years.

and suggested that the association may be confounded by GOR [20]. GOR is common in patients with asthma and has been described as a potential trigger for asthma symptoms [25–27]. There are two potential aetiologies for reflux-induced asthma: aspiration of gastric contents causing irritation and subsequent bronchoconstriction [28–31] and reflux-induced activation of a vago-vagal reflex arc from the oesophagus to the lung causing bronchoconstriction [32]. Self-reported GOR symptoms were therefore included as a potential confounder in the regression models. This attenuated the association suggesting that asthma medications may not be independently associated with BO risk, but rather that GOR is associated with an increase both in asthma medication use and BO. Although the associations did not remain statistically significant the persisting elevated ORs do not exclude the possibility that asthma medications increase the risk of BO by inducing GOR. Respiratory symptoms have been reported to be increased among GOR patients [33], with 30–90% of asthma patients experiencing reflux symptoms [34,35].

Corley et al. also investigated the relationship between nitrate-containing medications and BO and found a highly elevated, albeit not significant, association between longer term nitrate medication use and BO (OR, 95% CI: 7.3, 0.9–60.3) [20]. We did not find a significant association between nitrate medication use and BO (OR, 95% CI: 1.96,

0.82–4.69), suggesting that relaxation of the lower oesophageal sphincter may not be an explanation for the association between asthma medication use and BO since nitrates would be expected to exert a similar effect. Indeed, although lower oesophageal sphincter pressure may result in GOR in some patients, transient lower oesophageal sphincter relaxations are thought to induce GOR episodes in the majority of patients with GORD [36].

We found no significant associations between asthma or nitrate medication use and risk of RO or OAC. In keeping with our findings, a large population-based prospective multi-centre study of RO and a cohort study of patients with erosive reflux disease found no significant associations with asthma medications or nitrates [37,38]. However, our data suggest the possibility that a high frequency of asthma medication use could increase the risk of developing RO. Unfortunately, since our analyses were limited to comparison only with Northern Ireland controls we did not have sufficient power to detect a significant association. A recent study using data from the pharmacy records of two healthcare systems in Seattle and Detroit also found no significant associations between asthma and nitrate medications and OAC, although the ORs were elevated [23]. By contrast, a population-based study of three areas of the north-eastern United States [21] found a significant increase in OAC risk among theophylline users (OR, 95% CI: 2.5, 1.1–5.6).

The strengths of the FINBAR study are its population-based design and the inclusion of RO, BO and OAC patients under strict criteria. Additionally, information was collected on several potential confounders which were controlled for in the statistical analyses.

There are also potential weaknesses of the study. Firstly, recall bias is a possibility within this study, as data on asthma medication and nitrate use were collected by interview with study participants rather than from pharmacy or medical records. However, we included a question on paracetamol use as a control question within the questionnaire and the responses did not differ between the case groups and controls (data not shown), suggesting that there was no differential recall bias. Secondly, the low response rate among controls may have led to selection bias. People who are in regular contact with health services, for example with cardiovascular disease or respiratory diseases, may be more likely to participate as controls in medical research such as the FINBAR study, and may have higher medication use. However, such a bias would tend to reduce any association noted between patient groups and medication use. Finally, the power of the study to detect a significant association was limited by the number of cases and controls using nitrate and asthma medications. We therefore cannot exclude the possibility that an association exists between asthma and/or nitrate medications and RO, BO and/or OAC.

In conclusion, these findings suggest that there is an association between both the diagnosis of asthma and frequent asthma medication use and BO. This finding appears to be partially explained by confounding by GOR as it is associated with both BO and asthma. However, it is possible that asthma medications may increase the risk of BO by other mechanisms.

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