

What is already known on this topic

Several published studies, principally in the United States, have used statistical modelling to predict the future risk of hospital admission in individual patients

What this study adds

A reasonably sensitive and specific algorithm has been developed to identify patients at high risk of readmission to hospital in the next 12 months

The algorithm can be used to provide a “business case” that shows the potential costs and impact of an intervention to reduce hospital admissions

The factors that were most influential in predicting future admissions for reference conditions in the NHS included age, sex, previous admission, and clinical condition

understanding of the range of their needs. This information could then be incorporated into efforts to design interventions, whether the services are ultimately “made” or “bought” by the primary care trust or strategic health authority; in the second case, the information would be used in developing the specifications to tender proposals for delivery of services from

potential providers. Once the intervention has begun, primary care trusts and strategic health authorities could also consider randomising patients into intervention and non-intervention arms to learn as much as possible about the effectiveness and costs of the intervention.

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Competing interests: DW is the president and chief operating officer of a private company, Health Dialog Analytic Solutions, which has developed similar algorithms in the United States.

Ethical approval: Not needed.

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Spironolactone and risk of upper gastrointestinal events: population based case-control study

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Abstract

Objective To confirm and quantify any association between spironolactone and upper gastrointestinal bleeding and ulcers.

Design Population based case-control study.

Setting A primary care information database in the Netherlands.

Participants All people on the database who were aged 18 or more between 1 January 1996 and 30 September 2003. Patients with a history of alcoholism or gastrointestinal cancer were excluded. Ten controls were matched to each case of gastroduodenal ulcer or upper gastrointestinal bleeding by age (year of birth), sex, and index date.

Main outcome measures The occurrence of an upper gastrointestinal event (bleeding or ulcers), adjusted for potential confounders with conditional logistic regression analysis.

Results Within the source population of 306 645 patients, 523 cases of gastric or duodenal ulcer or upper gastrointestinal bleeding were identified and matched to 5230 controls. Current use of

spironolactone was associated with a 2.7-fold (95% confidence interval 1.2 to 6.0) increased risk of a gastrointestinal event.

Conclusion The risk of gastroduodenal ulcers or upper gastrointestinal bleeding is significantly increased in patients using spironolactone.

Introduction

Case reports indicate a possible association between spironolactone, an aldosterone receptor antagonist, and upper gastrointestinal bleeding and ulcers.^{1 2} One study found that spironolactone may inhibit the healing of ulcers when combined with carbenoxolone, an established ulcer healing drug.³ Ulcer healing was not impaired in patients treated with loop diuretics and carbenoxolone, although in another trial, ulcer healing was impaired when amiloride was added to carbenoxolone.⁴



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The mechanism behind the association between spironolactone and upper gastrointestinal events is not well understood, and the association has never been quantified. We therefore conducted a case-control study in the general population to examine the association between spironolactone and upper gastrointestinal events (bleeding and ulcers).

Patients and methods

Setting

Our study was conducted within the integrated primary care information project in the Netherlands. This electronic database contains information on more than 500 000 patients registered with 150 general practitioners. See bmj.com for details. The demographic characteristics of this population are similar to those in the national registry held by the Central Bureau of Statistics (www.cbs.nl).

Source population

The source population comprised all people aged 18 or more with at least one year's valid database history. Follow-up started on 1 January 1996 or the date that one year of valid history was obtained, whichever was latest. We excluded patients with a history of alcohol misuse or gastric cancer. All participants were followed from study entry until the first event (gastric or duodenal ulcer or upper gastrointestinal bleeding), the end of the study period (September 2003), exclusion, transfer from the practice, or death, whichever occurred first.

Identification and validation of cases

The primary outcome was upper gastrointestinal bleeding or a symptomatic peptic or duodenal ulcer, confirmed by endoscopy. The computerised medical records of all potential cases were manually evaluated by two doctors to exclude false positive records and to assess the earliest date of onset of each of the events (index date). Each case was classified as definite (patient with an upper gastrointestinal event confirmed by endoscopy) or possible (patient with signs of an upper gastrointestinal event not confirmed by endoscopy), or was excluded. Doctors were blinded to exposure to drugs throughout the validation process.

Controls

Up to 10 controls were obtained for each case from the source population. Controls were followed up at the same time as the case and we matched them for sex, age (year of birth), and calendar date (index date).

Definition of drug exposure

We retrieved all prescriptions for aldosterone antagonists, loop diuretics, and amiloride before the index date. Exposure was classified as "current" if the last prescription covered the index date or ended within one month before the index date; exposure was "past" if the period covered by the last prescription ended between the start of our study and one month before the index date. We classified participants with no prescription within this period as non-users. For current users, we studied the effects of daily dose. Daily doses were expressed as defined daily dose equivalents.

Covariates

We considered the following conditions as potential confounders: a history of smoking, ischaemic heart disease (angina pectoris and myocardial infarction), stroke (cerebral bleeding, ischaemic events, and transient ischaemic attacks), peripheral artery disease, hypertension, diabetes mellitus, heart failure, previous upper gastrointestinal events (ulcers or bleeding), and previous gastritis or oesophagitis.

The following concomitant drugs were taken into account as covariates: non-steroidal anti-inflammatory drugs, systemic corticosteroids, platelet aggregation inhibitors (including acetylsalicylic acid), anticoagulants, antidepressants, proton pump inhibitors or histamine 2 receptor antagonists, antacids, and cardiovascular drugs (digoxin, angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers, α blockers, β blockers, and other diuretics).

Statistical analysis

We calculated the incidence of upper gastrointestinal events and the incidence of first time use of spironolactone by dividing the number of upper gastrointestinal events and first time users of spironolactone by the number of person years accumulated by the study population.

We used conditional logistic regression analysis to assess the matched unadjusted and adjusted estimates of risk for the association between risk factors and upper gastrointestinal events and exposure to diuretics and the occurrence of an upper gastrointestinal event. In the adjusted model we included, one by one, all covariates that were univariately associated with outcome ($P < 0.05$). Risk factors that changed the relative risk of an upper gastrointestinal event during current use of diuretics by more than 5% were maintained in the final model. We also calculated the population attributable risk (population attributable risk = attributable risk \times proportion exposed in the population). See bmj.com.

Results

Our source population consisted of 306 645 patients who contributed 1 003 053 person years. We identified 523 definite upper gastrointestinal events (209 gastroduodenal ulcers and 314 cases of upper gastrointestinal bleeding). We randomly selected 5230 controls, matched on index date, age, and sex. The mean age of the cases was 63.4 years (standard deviation 17.5). Cases had a higher prevalence of previous gastrointestinal bleeding, gastric and duodenal ulcers, oesophagitis, heart failure, and peripheral artery disease (table 1). Current use of other drugs was also higher among cases than controls (table 1). During the study period 1717 patients started taking spironolactone for the first time. The incidence rate of first time use of spironolactone increased from 0.7 per 1000 person years in 1996 to 3.1 per 1000 person years in 2003.

Current use of spironolactone was associated with a 2.7-fold increase (95% confidence interval 1.2 to 6.0) in upper gastrointestinal events (table 2). The association was strongest in patients taking the higher

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Table 1 Risk of upper gastrointestinal events according to patient characteristics.* Values are numbers (%) unless stated otherwise

Characteristic	Cases (n=523)	Controls (n=5230)	Adjusted odds ratio (95% CI)
Comorbidity			
History of upper gastrointestinal bleeding	10 (1.9)	19 (0.4)	5.39 (2.48 to 11.7)
History of gastric or duodenal ulcer	25 (4.8)	55 (1.1)	4.79 (2.95 to 7.80)
History of oesophagitis	88 (16.8)	378 (7.2)	2.61 (2.02 to 3.36)
Heart failure	53 (10.1)	246 (4.7)	2.54 (1.81 to 3.56)
Peripheral artery disease	21 (4.0)	102 (2.0)	2.13 (1.31 to 3.46)
Current use of other drugs			
Non-steroidal anti-inflammatory drugs	75 (14.3)	261 (5.0)	3.32 (2.49 to 4.42)
Systemic corticosteroids	22 (4.2)	61 (1.2)	3.91 (2.36 to 6.47)
Platelet aggregation inhibitors	111 (21.2)	714 (13.7)	2.16 (1.68 to 2.78)
Anticoagulants	26 (5.0)	132 (2.5)	2.16 (1.40 to 3.33)
Proton pump inhibitors or histamine 2 antagonists	66 (12.6)	303 (5.8)	2.83 (2.11 to 3.78)
Antacids	7 (1.3)	20 (0.4)	3.52 (1.49 to 8.33)
Diuretics	79 (15.1)	558 (10.7)	1.73 (1.31 to 2.94)

*Only variables with an odds ratio ≥ 2 shown, except for use of diuretics.

doses of the drug. Increasing dosages of loop diuretics or amiloride were not associated with upper gastrointestinal bleeding (see bmj.com).

When we stratified patients into those with or without heart failure, an association was seen between current use of spironolactone and upper gastrointestinal events in patients without heart failure. However, when fully adjusted the association was not statistically significant because of the low numbers (adjusted odds ratio 4.0, 0.99 to 16.6).

We studied effect modification by ulcerogenic drugs such as non-steroidal anti-inflammatory drugs, platelet aggregation inhibitors, corticosteroids, and anticoagulants. As expected, the association with upper gastrointestinal events was highest for patients currently taking spironolactone and an ulcerogenic drug (7.3, 2.9 to 18.7) (see bmj.com). Effect modification was not seen in patients taking loop diuretics and ulcerogenic drugs.

On the basis of an incidence rate of upper gastrointestinal events of 25.9 per 10 000 person years among the exposed source population and 9.6 per 10 000 person years among the unexposed source population, we calculated a population attributable risk of 9.3/10⁶/year. Using demographic data from the Dutch Central Bureau of Statistics and on the basis of an overall incidence rate of upper gastrointestinal events of 9.7 per 10 000 person years, we calculated that 1% of upper gastrointestinal events in 2000 could be attributed to the current use of spironolactone.

Table 2 Risk of upper gastrointestinal events according to use of spironolactone. Values are number (%) unless stated otherwise

Spiro lactone	Cases (n=523)	Controls (n=5230)	Odds ratio	Adjusted odds ratio* (95% CI)
Never used	506 (96.7)	5176 (99.0)	1.0	1.0
Currently used	13 (2.5)	30 (0.6)	4.6	2.7 (1.2 to 6.0)
<0.5 defined daily dose	7 (1.3)	21 (0.4)	3.5	1.9 (0.7 to 5.1)
≥ 0.5 defined daily dose	6 (1.1)	9 (0.2)	7.3	5.1 (1.5 to 17.1)
Used in the past	4 (0.8)	24 (0.5)	1.8	0.99 (0.3 to 3.1)

*Adjusted for ischaemic heart disease, history of gastric ulcer, heart failure, and use of angiotensin converting enzyme inhibitors, nitrates, platelet aggregation inhibitors, proton pump inhibitors or histamine 2 antagonists, anticoagulants, and other diuretics.

What is already known on this topic

Individual case reports indicate an association between spironolactone and upper gastrointestinal events

What this study adds

This population based, case-control study found that spironolactone was associated with a 2.7-fold increased risk of upper gastrointestinal events (bleeding or ulcers)

The association increased proportionally with dosage and was most pronounced when combined with ulcerogenic drugs

Discussion

Spironolactone was associated with an increased risk of upper gastrointestinal events. This association was stronger as the dosage increased and was most pronounced when spironolactone was combined with ulcerogenic drugs.

Possible mechanism of action

Aldosterone promotes the formation of fibrous tissue in the heart and in various other organs by binding to mineralocorticosteroid receptors; the effect is modulated by 11 β hydroxysteroid dehydrogenase enzymes.⁵ Compounds with mineralocorticosteroid-like activity also promote tissue repair, whereas spironolactone inhibits the formation of fibrous tissue.^{3 5 6} This inhibition is beneficial in patients with heart failure and arterial hypertension, as it prevents cardiac fibrosis. The stomach, and to a lesser extent, the duodenum express mineralocorticosteroid receptors and 11 β hydroxysteroid dehydrogenase enzymes, so fibrous tissue formation—via binding of aldosterone to the mineralocorticosteroid receptors—is probably important in the healing of gastric or duodenal erosions and ulcers.⁷ Thus, aldosterone receptor antagonists, such as spironolactone, could impair the healing of gastric or duodenal erosions and result in the formation of gastroduodenal ulcers, with or without bleeding. This could explain why the association between current use of spironolactone and upper gastrointestinal events is highest in patients also taking an ulcerogenic drug.

Strengths and limitations of our study

Our study had a population based design, so selection bias is unlikely. Information bias is also unlikely, as data were gathered prospectively without knowledge of the hypothesis studied. Misclassification of the outcome is probably minimal as we manually validated all cases and only analysed definite cases, doctors who classified the cases were blinded to the patient's drug exposure, and known risk factors for upper gastrointestinal events appeared as risk factors in our analysis as well. To control for confounding by indication we adjusted for heart failure, as one study identified heart failure as a risk factor for bleeding of peptic ulcers.⁸

Confounding by severity is also possible. Patients with more severe heart failure are more likely to be treated with spironolactone than those with less severe

disease, but they might also have an inherently higher risk of upper gastrointestinal events. Increasing dosages of loop diuretics, however, were not associated with increased risk of upper gastrointestinal events, but a strong dose-response relation was seen for increasing dosages of spironolactone. Thus, confounding by severity appears unlikely. In contrast to a previous study, we found no association or dose relation between amiloride and upper gastrointestinal events.⁴

Conclusions

A Canadian study reported a large increase in prescriptions for spironolactone after publication of the randomised aldactone evaluation study, which showed that spironolactone significantly improves outcomes in patients with severe heart failure.⁹ We also found such an increase. On the basis of these observations, we believe doctors and patients should be informed about the potential of upper gastrointestinal events when using spironolactone.

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Competing interests: None declared by KMCV, GM, JPD, and BHChS. MCJMS is leader of the IPCI database, a general practice database used for research by pharmaceutical companies. She has received several research grants in cardiovascular

disease from Pfizer (license holder of Aldactone), but none was related to the topic of this paper. She has also received travel reimbursement from Pfizer for participation in conferences.

Ethical approval: internal review board of the integrated primary care information project database.

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Foundation (nursery) schools

After a long day as a surgical houseman and a glass of red wine, I was all set to blank out comfortably, if surreptitiously, in a chair near the back at an event held by my son's nursery school (no need to be awake as Will was at home with the babysitter). But when the head teacher began outlining a "foundation programme," I sat up, worried that I was acutely confused.

It turns out Will and I have more in common than genes and a love of Julia Donaldson's verse.¹ We're both on foundation programmes, one of us on the wards, the other in a sandpit.

After a year-long paper trail of DOP (directly observed procedure), Cbd (case-based discussion), CEX (clinical evaluation exercise), and MSF (multi-source feedback), I worried that 4 year old Will was being asked a bit early to think about his public accountability and personal development.² Surely he was just being left alone in said sandpit "to see the World in a grain of sand," just so long as he wasn't throwing the stuff in his friends' faces?

Not so. On one occasion, the teacher told the children to line up by a climbing frame and made a careful note of their alpine skills—a nursery DOP. During an expedition to find interesting shapes and patterns in the streets around the nursery, the teacher asked the children: "Who remembers what self appraisal is?"

I thought guiltily of my own personal development plan and self appraisal forms yet to be filled in. Will piped up, saying that he thought he had "eaten well," guzzling cold pizza, during a picnic at the end of a trip. Then, as instructed, he twisted round to give himself a pat on the back. At least his paperwork only involves potato shapes and saucers of paint.

The government introduced the foundation stage for 3-4 year old children in 2000 with six "early learning goals" (a sense of déjà vu here, with the 2002 foundation programme's "seven principles"). Although

the Department of Education promises that "most children see it as just fun and play," the foundation stage sees Will tested on everything from his knowledge of the world to his communication skills.³ All this will be assessed in a "foundation stage profile," a bit like my own foundation portfolio.

"Re-inventing the wheel," grumbled a consultant recently at a presentation on Modernising Medical Careers at my hospital. Given the existence of a preschool foundation programme two years before the medical one, he might be right.

Meanwhile, with concerns about the limited number of school places for certain catchment areas echoing fears over numbers of medical posts available after foundation year 2, I hope Will is grateful for his recent offer of an "F1" placement at the local primary school. But if, by some mishap Will and I mix up our foundation placements, I suggest you don't get ill in August.

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We welcome articles up to 600 words on topics such as *A memorable patient*, *A paper that changed my practice*, *My most unfortunate mistake*, or any other piece conveying instruction, pathos, or humour. Please submit the article on <http://submit.bmj.com> Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.