RESEARCH

Gastro-protective policy and the incidence of upper gastrointestinal bleeding

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ABSTRACT

Objectives In recent years, policies have been proposed in order to guide the safer use of non-steroidal anti-inflammatory drugs (NSAIDs) and antiulcer therapy. We aimed to investigate the incidence of upper gastrointestinal bleeding (UGIB) before and after the introduction of these policies, 2007–2009, in a well-defined population in southwest Scotland.

Methods All patients with non-variceal upper gastrointestinal bleeding (NV-UGIB), diagnosed at a single regional unit, were included. Total drugs prescribed in our population were noted, including antiulcer drugs, antithrombotic drugs and both cyclo-oxygenase-2 enzyme-selective and non-selective inhibiting NSAIDs.

Results The incidence, the number of cases per 100 000 population per annum, of NV-UGIB fell from 134.7 in 2007 to 125.1 in 2008, and to 90.3 cases in 2009 ($p < 0.001$). There was also a significant rise in the use of non-selective NSAIDs, proton pump inhibitors and antithrombotic drugs.

Conclusions Although a cause-and-effect relationship cannot be fully proven, physician education through drug-use policies is associated with a drop in the incidence of NV-UGIB. This is relevant to the prevention of this common condition.

INTRODUCTION

Health and healthcare needs are not static: a health system must respond adaptively to new diseases, changing demographics, scientific discoveries and dynamic technologies in order to remain viable.¹ These aspects can be exemplified by the roles played by drugs in the epidemiology, aetiology and preventative strategies of the common condition of upper gastrointestinal bleeding (UGIB).

UGIB is known to be commonly related to the use of non-steroidal anti-inflammatory drugs (NSAIDs) and antithrombotic drugs, and its prevention is facilitated by the use of antiulcer drugs, particularly proton pump inhibitors.² Rofecoxib, a cyclo-oxygenase-2 enzyme (COX-2) specific inhibitor NSAID, was withdrawn in 2004; this was also followed by a marked drop in the use of other COX-2-specific NSAIDs because of concerns about their cardiovascular side effects.³ On the other hand, both the use of antithrombotic drugs and the incidence of UGIB continued to increase in our region.³ In the face of these challenges, our community physicians were encouraged to implement a gastro-protective policy (See additional supplementary material).² The clinical outcomes have remained unclear. We, therefore, aimed to investigate the incidence of non-variceal upper gastrointestinal bleeding (NV-UGIB) before and after the introduction of gastro-protective policy, 2007–2009, in a well-defined population in southwest Scotland.

METHODS

Design

This is an observational analysis comparing, as a *primary outcome*, the incidence of NV-UGIB preintroduction of the relevant preventative policy for this condition in 2007 with the incidence postintroduction in 2008 and 2009.

As *secondary outcomes*, we assessed the use of NSAIDs, antithrombotic drugs, and antiulcer drugs over the same period.

Definitions

The incidence is defined as the number of cases of NV-UGIB diagnosed per

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100 000 population per annum. The population refers to the inhabitants of North and East Ayrshire, a well-defined geographical region located in southwest Scotland, and served by a single institution, University Hospital Crosshouse. The population receives health-care free of charge under the provisions of the National Health Service—Scotland.

NV-UGIB was diagnosed in patients who presented with UGIB (haematemesis or melaena), and in whom endoscopy showed no evidence of oesophageal or gastric varices, or portal hypertensive gastropathy. Causes of NV-UGIB usually include gastric or duodenal ulcers or erosions, erosive gastritis, Mallory–Weiss lesions, erosive oesophagitis, idiopathic angiodysplasia and upper gastrointestinal tract tumours and malignancies.⁴ Patients with features of portal hypertension, angiodysplasia or tumours were excluded, as such lesions are unlikely to be caused by NSAIDs. We also entered in the analysis of patients who bled while in hospital, and those with a history of UGIB whose bleeding was unwitnessed or with normal endoscopy. The complete Rockall score for acute NV-UGIB, and the Charlson comorbidity index were used as previously described.⁴

The gastro-protective policy involved highlighting the general risks of NSAID and aspirin use, and the need to prevent such risks in line with international guidelines including the option of coprescribing standard agents, such as proton pump inhibitors or H_2 receptor antagonists.²

This policy was disseminated using a dedicated intranet that connects all clinicians in our region and allows exchange of information, educational bulletins, and face-to-face educational meetings delivered by the authors and dedicated pharmacists in 2008. The introduction and dissemination of this policy does not imply that the clinicians concerned were not already aware of its basic principles.

Data sources

As per the standard practice of the community care physicians, all patients with UGIB are referred to our hospital for assessment and management. Patients with NV-UGIB were, therefore, identified from hospital records. Their diagnoses and codes are according to the International Classification of Diseases (ICD-10) for bleeding upper gastrointestinal disorders. Also, all prescriptions issued by the community care physicians are entered into a central database managed by information analysts based at the Medicines Utilization and Business Intelligence Unit of NHS Ayrshire and Arran; they provided us with the prescription data.

Assessments and treatments were according to standard medical care, and no randomisation or allocation to treatment groups took place. Patients' details were anonymised using code numbers. Therefore, no ethical approval or patient's consent were required,

but the work was still approved by the clinical governance team.

Data verification

All records of NV-UGIB were reviewed by a panel of clinicians who confirmed compliance with the definition of this diagnosis as described above.⁴ Awareness of and adherence to the drug-use policy was confirmed by contacting representatives of the community physicians at 6-monthly intervals.

Statistical analysis

Changes in the incidence of NV-UGIB over the time period studied were analysed using the χ^2 test for trend. Changes in the numbers of prescriptions over the time period studied were tested using Poisson regression analysis. SPSS 15.0 for Windows was used for all analyses.

RESULTS

Demography

The demographic characteristics of patients presenting with NV-UGIB are detailed in table 1. This shows increasing proportions of bleeders with cardiovascular and cerebrovascular diseases, although the overall Charlson comorbidity and Rockall scores remained relatively unchanged. There was a trend for fewer alcohol drinkers, but the proportions of bleeders with excess alcohol—more than 20 units per week—or smokers, remained unchanged. Also, there was no change in the prevalence of *Helicobacter pylori* infection among the bleeders: 25.0% in 2007; 27.2% in 2006; and 17.8% in 2009, $p=0.23$ (trend). Nineteen to twenty-nine per cent of bleeders were endoscoped on the same day of presentation and did not require admission. Also, there was no significant change in the 30-day mortality rates in NV-UGIB over the study period.

Incidence data

These are shown in table 2 and illustrated in figure 1. The incidence of NV-UGIB has progressively fallen in 2008 and 2009 following the introduction of the policy on gastro-protection. This fall was noted in all patients and in those subgrouped according to their intake of NSAIDs, low-dose aspirin (75–325 mg per day), or other antithrombotic drugs (clopidogrel, dipyridamole, or warfarin).

Use of NSAIDs, antithrombotic and antiulcer drugs

As shown in table 3, while the use of COX-2 selective NSAIDs has decreased, that of non-selective NSAIDs increased, and this accounts for the overall rise in NSAID use. The use of low-dose aspirin and other antithrombotic drugs has also increased.

As for antiulcer drugs, proton pump inhibitors have remained the main agents prescribed: their use has

Table 1 Characteristics of patients presenting with non-variceal upper gastrointestinal bleeding

	2007 n=344	2008 n=320	2009 n=231	p Value (trend)	p Value (difference)
Age (median, IQR)	63 (46–77)	63 (44–77)	69 (48–79)	0.31	0.22
Males (%)	213/344 (61.9)	187/320 (58.4)	134/231 (58.0)	0.32	0.55
Smoking (%)	123/341 (36.1)	117/319 (36.7)	78/229 (34.1)	0.66	0.81
Alcohol (%)	213/342 (62.3)	178/319 (55.8)	122/230 (53.0)	0.023	0.066
Excess alcohol (%)	82/342 (24.0)	65/319 (20.4)	46/230 (20.0)	0.23	0.41
CVS disease (%)	56/344 (16.3)	58/320 (18.1)	98/231 (42.4)	<0.001	<0.001
CNS disease (%)	4/344 (1.2)	1/320 (0.1)	21/231 (9.1)	<0.001	<0.001
Charlson 0 (%)	61/342 (17.8)	74/318 (23.3)	49/230 (21.3)	0.54	0.036
Charlson 1–2 (%)	170/342 (49.7)	141/318 (44.3)	87/230 (37.8)		
Charlson 3+ (%)	111/342 (32.5)	103/318 (32.4)	94/230 (40.9)		
Rockall 3+ (%)	187/336 (55.7)	180/317 (56.8)	142/231 (61.5)	0.18	0.36
Aspirin (%)	92/344 (26.7)	91/320 (28.4)	66/231 (28.6)	0.61	0.85
Other antithrombotics (%)	70/344 (20.3)	53/320 (16.6)	49/231 (21.2)	0.94	0.31
Aspirin or other antithrombotics (%)	140/344 (40.7)	128/320 (40.0)	97/231 (42.0)	0.79	0.90
NSAIDs (%)	63/344 (18.3)	42/318 (13.2)	34/231 (14.7)	0.18	0.18
Admitted (%)	281/344 (81.7)	227/319 (71.2)	188/231 (81.4)	0.61	0.002
Transfused (%)	112/344 (32.6)	90/303 (29.7)	79/218 (36.2)	0.47	0.29
Death 30 days (%)	11/344 (3.2)	11/317 (3.5)	11/227 (4.8)	0.33	0.57

CNS, cerebrovascular disease; CVS, cardiovascular disease; NSAID, non-steroidal anti-inflammatory drugs.

increased while that of H₂-receptor antagonists decreased.

DISCUSSION

In this analysis, we have observed that the incidence of NV-UGIB has fallen in the 2 years following the introduction of the gastro-protective policy.

The strength of our work relates to the fact that it covers a well-defined population receiving free health-care and served by one single institution.

It could be argued that one possible weakness might be the difficulty in accounting for the use of over-the-counter medications. We believe this is unlikely to have seriously affected our observations or conclusions because of the following: none of the COX-2 selective NSAIDs is available over the counter; with the exception of low-dose aspirin, none of the other antithrombotic drugs—clopidogrel, dipyridamole or warfarin—is available without prescription;

Table 2 Incidence (per 100 000 population per annum) of non-variceal upper gastrointestinal bleeding

	2007	2008	2009	p Value (trend)
Total population	255330	255840	255720	—
Incidence of non-variceal upper gastrointestinal bleeding:				
All patients	134.7	125.1	90.3	<0.001
Low-dose aspirin users	36.0	35.6	25.8	0.043
Aspirin or other antithrombotic users	54.8	50.0	37.9	0.006
NSAID users	24.7	16.4	13.3	0.003

NSAID, non-steroidal anti-inflammatory drugs.

and while some non-selective NSAIDs and some low-dose proton pump inhibitors are sold over the counter, our conclusions are based on the observation that the use of these agents was rising anyway regardless of whether they were prescribed or not.

We accept that proton pump inhibitors could have been prescribed for reasons other than gastro-protection: this was accounted for by our use of Poisson regression analysis for the prescription data as it was not possible to assume that each prescription was for a different member of the population.

It can be extremely difficult to change clinical practice with the publication of clinical guidelines. We addressed this point by regular reminders and by the

Figure 1 Incidence of non-variceal upper gastrointestinal bleeding. There has been a significant fall in the incidence over the period studied, 2007–2009, in all patients with non-variceal bleeding ($p<0.001$) and in patients taking: low-dose aspirin or other antithrombotic drugs ($p=0.006$); low-dose aspirin ($p=0.043$); and in those taking non-steroidal anti-inflammatory drugs ($p=0.003$).

Table 3 Prescriptions of NSAIDs, antithrombotic drugs and antiulcer drugs (per 100 000 population)

	2007	2008	2009	p Value (trend)
Non-selective NSAIDs	31660	32370	33350	<0.001
Selective NSAIDs	15010	14480	14060	<0.001
All NSAIDs	46670	46850	47410	<0.001
Low-dose aspirin	58550	61690	61830	<0.001
All antithrombotic drugs	88110	90850	91310	<0.001
Proton pump inhibitors	75070	81820	86660	<0.001
H ₂ -receptor antagonists	13680	12780	12240	<0.001

NSAID, non-steroidal anti-inflammatory drugs.

repeated presentation of our messages coupled with the verification of data. We believe it was more of a coincidence that the prescription rates of some agents increased while those of others decreased as recommended by the relevant policies.

We also accept that the association between prescription trends and disease incidence are ecological in nature; but despite its relative weakness, such association cannot be ignored and, it may in fact, have therapeutic implications particularly as in the case of NSAIDs.^{2 3}

We have found that the incidence of NV-UGIB has fallen in our region over the same period when there has been a rise in the use of potentially ulcerogenic and proleeding drugs, namely the non-selective NSAIDs and the antithrombotic drugs. The latter might not necessarily cause ulcers by themselves, but can cause bleeding from pre-existing lesions.^{3 5} While it is not possible to exclude the influence of other unknown factors, we believe that a plausible explanation for the fall in the incidence of NV-UGIB in these circumstances is the parallel rise in the use of proton pump inhibitors. These are accepted as the most potent gastro-protective agents.² Some prevention could have also been provided by the smaller numbers of prescriptions of H₂-receptor antagonists given over the same period.^{2 6} Another factor worth considering is that of *H pylori* infection: its incidence in our community is unknown but could not have fallen significantly over a 2-year period; also, its prevalence in our patients with NV-UGIB has remained unchanged. Our findings, particularly with respect to drug use, might help explain the decrease in hospitalisation related to peptic ulcer complications previously reported by other workers.⁷

This work does not claim that general efforts to prevent NV-UGIB did not exist in our region prior to the study period. However, it is worth noting that the incidence of this condition, NV-UGIB, was rising until the introduction of the relevant preventative policy.³

In conclusion, the introduction of drug-use policies, mainly covering gastro-protective drugs, is associated with a drop in the incidence of NV-UGIB in a well-defined population. Although a cause-and-effect

relationship cannot be proven, these policies remain plausible explanations for this drop. This is relevant to the prevention of this condition.

What is already known about this subject

- ▶ Non-variceal upper gastrointestinal bleeding (NV-UGIB) remains a common and serious health challenge.
- ▶ NV-UGIB can complicate the use of non-steroidal anti-inflammatory drugs (NSAIDs).
- ▶ The use of NSAIDs and proton pump inhibitors has been changing, and regulatory policies have been proposed to guide their safer use.

What are the new findings

- ▶ The incidence of NV-UGIB has decreased despite the rise in the use of non-selective NSAIDs and antithrombotic drugs including aspirin. This could be due to the rise in use of proton pump inhibitors.
- ▶ Policies guiding drug use might be relevant to the prevention of NV-UGIB

Contributors AST planned the study and wrote the draft manuscript; all authors helped with data collection and interpretation; WJA carried out the statistical analysis; all authors read and approved the final version of the manuscript.

Competing interests None.

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REFERENCES

- 1 Fineberg HV. A successful and sustainable health system—how to get there from here. *N Engl J Med* 2012;366:1020–7.
- 2 Wilcox CM, Allison J, Benzully K, *et al.* Consensus development conference on the use of non-steroidal antiinflammatory agents, including cyclooxygenase-2 enzyme inhibitors and aspirin. *Clin Gastroenterol Hepatol* 2006;4:1082–9.
- 3 Taha AS, Angerson WJ, Prasad R, *et al.* Upper gastrointestinal bleeding and the changing use of COX-2 non-steroidal anti-inflammatory drugs and low-dose aspirin. *Aliment Pharmacol Ther* 2007;26:1171–8.
- 4 Taha AS, McCloskey C, Craigen T, *et al.* Mortality following blood transfusion for non-variceal upper gastrointestinal bleeding. *Frontline Gastroenterol* 2011;2:218–25.
- 5 Taha AS, McCloskey C, Prasad R, *et al.* Famotidine for the prevention of peptic ulcers and oesophagitis in patients taking low-dose aspirin (FAMOUS): a phase-III, randomised, double-blind, placebo-controlled trial. *Lancet* 2009;374:119–25.
- 6 Taha AS, Hudson N, Hawkey CJ, *et al.* Famotidine for the prevention of gastric and duodenal ulcers caused by nonsteroidal antiinflammatory drugs. *N Engl J Med* 1996;334:1435–9.
- 7 Lanas A, Garcia-Rodriguez LA, Polo-Tomas Md, *et al.* The changing face of hospitalization due to gastrointestinal bleeding and perforation. *Aliment Pharmacol Ther* 2011;33:585–91.