lighted by patients in this study. If it is agreed that these are important and desirable tasks, then the dimensions of care discussed in this paper should feature more prominently in assessments of outcome after stroke.

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Topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation: a record linkage case-control study

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Abstract

Objective—To evaluate the relation between topically applied non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding and perforation.

Design—A case-control study with 1103 patients admitted to hospital for upper gastrointestinal bleeding or perforation between January 1990 and December 1992 (cases). Two different control groups were used, with six community controls and with two hospital controls for each case. Previous exposure to topical and oral non-steroidal anti-inflammatory drugs and ulcer healing drugs was assessed. **Study population**—The population of 319465 people who were resident in Tayside and were registered with a Tayside general practitioner between January 1989 and October 1994. A record linkage database containing all data on hospital events and dispensed drugs between 1989 and 1992 was used for this population.

Main outcome measures—Unadjusted and adjusted odds ratios of exposure in those admitted to hospital compared with controls.

Results—Significant unadjusted associations were detected between all three classes of drug and upper gastrointestinal complications. The significant association detected for topical non-steroidal anti-inflammatory drugs was no longer evident in analyses which adjusted for the confounding effect of concomitant exposure to oral anti-inflammatories and ulcer healing drugs (odds ratio=1.45; 95% confidence interval 0.84 to 2.50 with community controls; 1.06; 0.60 to 1.88 with hospital controls).

Conclusion—In this study topical non-steroidal anti-inflammatory drugs were not significantly asso-

ciated with upper gastrointestinal bleeding and perforation after adjustment for the confounding effects of concomitant use of oral anti-inflammatories and ulcer healing drugs.

Introduction

The use of oral non-steroidal anti-inflammatory drugs is associated with upper gastrointestinal complications, particularly perforated and bleeding peptic ulcer.¹ Meta-analyses suggest that the relative risk is about 3.0.² Recent studies have shown this risk to be dose related.^{3,4} This is one reason why the use of topically applied non-steroidal anti-inflammatory drugs is advocated as plasma concentrations of the drugs remain relatively low after topical application. Despite this, spontaneous reporting data from the "yellow card" system of the Medicines Control Agency⁵ suggest that the risks of topical anti-inflammatory drugs may not be negligible. For example, since July 1963 there have been seven reports of adverse events in the gastrointestinal tract after topical application of diclofenac, four with ibuprofen, one with ketoprofen, 25 with piroxicam, and 47 with felbinac (an active metabolite of fenbufen) (Committee on Safety of Medicines, personal communication).

Furthermore, in a post-marketing study of 23590 patients exposed to topical felbinac 3% gel (Traxam), 327 patients experienced 331 adverse events, of which 24 were related to the gastrointestinal tract.⁶ This study may have been confounded by the use of other drugs as 17 of these patients were taking additional medication. Nevertheless, six cases were judged to be "definitely" or "probably" related to the use of topical non-steroidal anti-inflammatory drugs.

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To clarify the risks associated with these topically applied preparations we carried out a case-control study with multiple control groups by using a record linkage database containing data for a population of 319 465 people that was purpose built for carrying out such pharmacoepidemiological research.

Subjects and methods

The study was carried out with the record linkage database of the medicines monitoring unit at the University of Dundee. This database contains prospectively gathered information on all dispensed community prescriptions for non-steroidal anti-inflammatory drugs and ulcer healing drugs in Tayside from 1 January 1989 and diagnostic and demographic data on all patients admitted to hospital in Tayside from 1980 (Scottish Morbidity Record 1). These data can be linked by a unique 10 digit number, the community health number. The methods of data collection for this database have been described in detail elsewhere.⁷ In brief, prescriptions encashed at Tayside pharmacies are sent to the medicines monitoring unit after dispensing. The patient's name, address, and other prescription details are used to find the unique community health number by using purpose written software to search the community health index for Tayside. This is a list of all patients registered with a general practitioner, which is maintained by Tayside Health Board. Dispensed prescribing details are entered on the prescription database with the community health number.

When patients in Tayside are discharged from hospital, codes for their diagnoses (*International Classification of Diseases*, ninth revision (ICD-9)) and codes for their operations (Office of Population Censuses and Surveys, fourth revision) are entered on the Tayside section of the Scottish Morbidity Record database with the community health number as an identifier. Copies of these data are held within the medicines monitoring unit.

The community health number allows the temporal linking of data on dispensed prescriptions and admissions. In addition, as the unit has lists of every patient registered with a general practitioner in Tayside and every person admitted to hospital in Tayside, both community and hospital controls can be generated.

Calculation of sample size—In a preliminary analysis the extent of prescribing of topical non-steroidal anti-inflammatory drugs and the preparations most commonly prescribed were investigated for the population of Tayside between 1989 and 1992. With this information we calculated the minimum odds ratios which could be detected with the sample sizes used in the case-control study.

The study population comprised 319 465 people who were resident in Tayside and were registered with a Tayside general practitioner in January 1989 and were either still resident in October 1994 or had died in Tayside during this period.

A case was defined as any patient within the study population who had an ICD-9 code for upper gastrointestinal bleeding or perforation in their computerised discharge summary for an episode of admission to hospital between 1 January 1990 and 31 December 1992. The codes used were for acute, chronic, or unspecified gastric ulcer, duodenal ulcer, or gastrojejunal ulcer with haemorrhage, with haemorrhage and perforation, or with perforation. Codes for haematemesis and melaena were also used. The first admission with such an episode was taken to be the case episode.

Validation of case identification—A validation study was carried out to estimate the sensitivity and

specificity of the computerised ICD-9 codes to identify cases in this study. Hospital episodes containing any gastrointestinal code were identified for all patients over 50 years of age who had cashed a prescription for a non-steroidal anti-inflammatory drug between 1989 and 1991. The original case records were then reviewed by seven medically qualified staff and a further sample audited by two consultant physicians, one a gastroenterologist (FEM). The separate events that the episodes represented were assessed and by using predetermined criteria were judged to be acute bleeds or perforations, or otherwise. It was thus possible to determine how many "true cases" (that is, acute bleeds and perforations) would be missed and how many "non-cases" would be incorrectly selected if case identification was based on the ICD-9 codes alone.

Community controls—From the study population up to six community controls matched for sex and age (within 30 days) were generated randomly for each case. These controls were all still alive in September 1992. The index date of the case and its matched control was the date of the patient's first admission to hospital.

Hospital controls—Up to two hospital controls matched for sex, age (within 365 days), and hospital of admission were generated randomly for each case. They could have been admitted to hospital with any diagnosis other than gastrointestinal bleeding and perforation within 90 days of the case. The index date of the hospital control was the date of admission.

Analyses—Previous exposure to three classes of drugs was investigated: oral and topical non-steroidal anti-inflammatory drugs (excluding aspirin) and ulcer healing drugs. Odds ratios were calculated for two predefined exposure variables for each and modelling by using conditional logistic regression.^{8,9} These were 45 day exposure—one or more prescriptions dispensed during a 45 day period before the index date—and ever exposure—one or more prescriptions dispensed at any time from 1 January 1989 to the index date. The more significant exposure variable for each drug was included in the final model. If neither variable was significant or they were equally significant ever exposure was modelled. Thus the results for each drug are given with the confounding effects of the other drugs removed. The analyses were also carried out for bleeding and perforation separately.

Results

CALCULATION OF SAMPLE SIZE

Table I shows the use of topical preparations in the study population between 1989 and 1992. The expo-

TABLE I—Use of topical non-steroidal anti-inflammatory drugs in study population, 1989-92

Preparation	No of prescriptions	No of patients
Diethylamine salicylate (Algesal)	92	25
Glycol salicylate (Algipan)	93	73
Ammonium salicylate (Aspellin)	53	30
Methyl salicylate (Balmosa)	28	17
Benzylamine hydrochloride (Diffam)	9 500	4 848
Piroxicam (Feldene)	16 357	9 925
Ibuprofen (Ibugel)	432	330
Ibuprofen (Ibuleve)	54	41
Salicylamide (Intralgine)	138	103
Salicylic acid (Movelat)	1 869	1 089
Ketoprofen (Oruvail)	815	677
Ibuprofen (Proflex)	2 486	1 405
Tetrahydrofurfuryl salicylate (Transvasin)	332	200
Felbinac (Traxam)	5 358	3 314
Diclofenac (Voltarol)	6 624	3 983
Total	43 831	23 103
1989	4 409	3 207
1990	7 788	5 361
1991	11 961	7 767
1992	19 822	11 745

sure during the time of the study was 7%. As the study included 1103 cases the minimum odds ratio which could have been detected at the 5% level of significance with 80% power and with six controls per case was 1.4 (n=1081). With only two controls per case the minimum odds ratio was 1.5 (n=958).¹⁰

CASES AND VALIDATION OF CASES

There were 1103 patients admitted to hospital for upper gastrointestinal bleeding and perforation between 1 January 1990 and 31 December 1992. Of these, 569 were men and 534 were women; 860 were aged over 50 years.

The validation study examined 3078 admission-discharge events that contained at least one diagnostic code for an upper gastrointestinal event; 542 were acute bleeding events and 75 were perforations. The

sensitivity of the diagnostic codes used for this study to identify cases was calculated to be 68% for acute bleeds and 79% for perforations. The specificity was 98%.

CONTROLS

A total of 6593 suitable community controls and 2184 suitable hospital controls were found for these cases. No suitable community controls could be found for two cases, which were therefore excluded from the relevant analyses. No suitable hospital controls could be found for seven cases, which were also excluded.

RESULTS OF CASE-CONTROL STUDIES

When we used community controls oral and topical non-steroidal anti-inflammatory drugs and ulcer healing drugs were significantly associated with upper gastrointestinal bleeding and perforation, whether the variables of 45 day exposure or ever exposure were used (table II). With hospital controls, both the exposure variables were significant for ulcer healing drugs but only 45 day exposure was significant for oral non-steroidal anti-inflammatory drugs. Neither exposure variable was significant for topical preparations (table III).

Tables IV and V show the results of the conditional regression analyses which adjusted for the effects of exposure to the other drugs simultaneously and also investigated the separate end points of bleeding and perforation. The few cases which had both bleeding and perforation were excluded. Oral non-steroidal anti-inflammatory drugs and ulcer healing drugs were significantly associated with an increased risk of gastrointestinal complications in all cases. There were no significant associations between topical preparations and gastrointestinal events after adjustment for confounding by oral preparations and ulcer healing drugs.

The effects of confounding were investigated in further conditional regression analyses. With community controls, topical non-steroidal anti-inflammatory drugs were still associated with upper gastrointestinal complications after adjustment for oral preparations alone, suggesting that there was further confounding from ulcer healing drugs. Similarly, there was confounding from ulcer healing drugs after adjustment for oral non-steroidal anti-inflammatory drugs. With hospital controls, however, it was enough to adjust for just one class of drug to remove all the confounding effects. This was because most of the excess risk associated with topical non-steroidal anti-inflammatory drugs among cases compared with hospital controls was among patients exposed to oral preparations and ulcer healing drugs simultaneously. The excess risk with community controls, however, seemed to be more evenly distributed among patients on different combinations of these drugs.

To investigate further the validity of the result for topical non-steroidal anti-inflammatory drugs, the analyses were recalculated by using a repeated technique for the random selection of controls. Ten further hospital and 10 further community control groups were assembled and the analyses repeated for each. The figure shows the adjusted results for 45 day exposure and ever exposure to topical non-steroidal anti-inflammatory drugs.

Discussion

Our results show that while there are associations between the use of topical non-steroidal anti-inflammatory drugs and upper gastrointestinal complications in unadjusted analyses these associations are mainly due to confounding by concomitant use of oral non-steroidal anti-inflammatory drugs and ulcer healing drugs. In analyses which adjusted for the effects of all the three classes of drug simultaneously

TABLE II—Crude odds ratios for exposure variables (community controls)

Drug	No (%) of cases (n=1101)	No (%) of controls (n=6593)	Unadjusted odds ratio (95% confidence interval)	P value
Oral non-steroidal anti-inflammatory drugs:				
45 Day exposure	186 (16.9)	457 (6.9)	2.81 (2.33 to 3.40)	<0.001
Ever exposure	457 (41.5)	2131 (32.3)	1.53 (1.33 to 1.75)	<0.001
Topical non-steroidal anti-inflammatory drugs:				
45 Day exposure	23 (2.1)	54 (0.8)	2.59 (1.58 to 4.23)	<0.001
Ever exposure	98 (8.9)	415 (6.3)	1.48 (1.17 to 1.88)	<0.001
Ulcer healing drugs:				
45 Day exposure	243 (22.1)	393 (6.0)	4.61 (3.85 to 5.52)	<0.001
Ever exposure	421 (38.2)	849 (12.9)	4.33 (3.74 to 5.01)	<0.001

TABLE III—Crude odds ratios for exposure variables (hospital controls)

Drug	No (%) of cases (n=1096)	No (%) of controls (n=2184)	Unadjusted odds ratio (95% confidence interval)	P value
Oral non-steroidal anti-inflammatory drugs:				
45 Day exposure	186 (17.0)	206 (9.4)	1.98 (1.60 to 2.46)	<0.001
Ever exposure	457 (41.7)	909 (41.6)	1.00 (0.86 to 1.17)	0.970
Topical non-steroidal anti-inflammatory drugs:				
45 Day exposure	23 (2.1)	29 (1.3)	1.59 (0.92 to 2.74)	0.099
Ever exposure	97 (8.9)	192 (8.8)	1.00 (0.78 to 1.30)	0.983
Ulcer healing drugs:				
45 Day exposure	242 (22.1)	288 (13.2)	1.88 (1.55 to 2.28)	<0.001
Ever exposure	417 (38.0)	569 (26.1)	1.75 (1.50 to 2.05)	<0.001

TABLE IV—Final conditional logistic regression analysis (community controls)

Exposure variable	Adjusted odds ratio (95% confidence interval)	P value
All cases:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	2.59 (2.12 to 3.16)	<0.001
45 Day exposure—topical non-steroidal anti-inflammatory drugs	1.45 (0.84 to 2.50)	0.184
Ever exposure—ulcer healing drugs	4.21 (3.63 to 4.88)	<0.001
Bleeding:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	2.18 (1.75 to 2.71)	<0.001
Ever exposure—topical non-steroidal anti-inflammatory drugs	1.43 (0.81 to 2.54)	0.221
Ever exposure—ulcer healing drugs	4.30 (3.67 to 5.03)	<0.001
Perforation:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	8.75 (4.77 to 16.06)	<0.001
Ever exposure—topical non-steroidal anti-inflammatory drugs	5.50 (0.70 to 44.40)	0.106
Ever exposure—ulcer healing drugs	3.51 (2.13 to 5.79)	<0.001

TABLE V—Final conditional logistic regression analysis (hospital controls)

Exposure variable	Adjusted odds ratio (95% confidence interval)	P value
All cases:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	2.00 (1.60 to 2.50)	<0.001
45 Day exposure—topical non-steroidal anti-inflammatory drugs	1.06 (0.60 to 1.88)	0.851
Ever exposure—ulcer healing drugs	1.76 (1.51 to 2.07)	<0.001
Bleeding:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	1.74 (1.37 to 2.22)	<0.001
45 Day exposure—topical non-steroidal anti-inflammatory drugs	1.05 (0.57 to 1.92)	0.875
Ever exposure—ulcer healing drugs	1.74 (1.47 to 2.05)	<0.001
Perforation:		
45 Day exposure—oral non-steroidal anti-inflammatory drugs	4.84 (2.49 to 9.39)	<0.001
45 Day exposure—topical non-steroidal anti-inflammatory drugs	0.86 (0.10 to 7.28)	0.892
Ever exposure—ulcer healing drugs	1.87 (1.07 to 3.27)	0.028

Odds ratios for topical non-steroidal anti-inflammatory drugs with 95% confidence intervals adjusted for exposure to oral non-steroidal anti-inflammatory drugs and aspirin. Calculated for cases with 10 sets of hospital and community control groups

there were no significant associations between topical non-steroidal anti-inflammatory drugs and upper gastrointestinal complications.

There was some disparity between the results obtained by using the different control groups. Assessing the validity of different control groups is often a difficult problem in case-control studies. Irrespective of the source of controls, however, the final results were similar in that topical non-steroidal anti-inflammatory drugs did not carry a significant independent risk of gastrointestinal complications.

One possible weakness of our study may relate to statistical power. The original power calculations were based on 7% exposure to topical non-steroidal anti-inflammatory drugs. This, however, was appropriate only for the ever exposure analyses. Based on 45 day exposure to topical preparations, to which 2% of cases and controls were exposed, the minimum odds ratios which could have been detected were nearer 2.0.¹⁰ An adjusted odds ratio of 1.45 was found for 45 day exposure to topical non-steroidal anti-inflammatory drugs by using community controls. This was not significant, but this may have been due to lack of power. Indeed, the plot of 45 day exposure with community controls suggests that a very small risk associated with use of topical preparations might be present. This may not represent a true toxic effect but may be evident because patients already at high risk from upper gastrointestinal complications are prescribed topical drugs in an effort to avoid the toxicity of oral drugs.

An independent estimated relative risk of 2.6 (2.1 to 3.2) was found for oral non-steroidal anti-inflammatory drugs with community controls and 2.0 (1.6 to 2.5) with hospital controls. These figures are consistent with those reported previously.² We also found an independent increased risk associated with ulcer healing drugs. This is unlikely to be a causal association but probably arises because people known to be at high risk from gastrointestinal bleeding and perforation, or who have symptoms already, are prescribed ulcer healing drugs.

MISCLASSIFICATION AND BIAS

The importance of misclassification and bias must be considered.

Misclassification of disease—Concerns have been expressed as to the accuracy of the ICD-9 codes which were used to identify cases in this study. For example, a review of 150 case records for discharges from medicine and paediatrics in the Tayside region suggested that these diagnostic codes in Scottish Morbidity Record data were unacceptable in 21%.¹¹ Our validation of case records showed that the sensitivity of identifying cases is indeed quite low but that the specificity is higher, albeit in a particular group of patients. So although a proportion of the cases will have been missed, possibly even 30%, there will be few cases incorrectly identified. This is acceptable for a case-control study.

Misclassification of exposure is also a possible source of bias. We assigned prescriptions to individual patients by looking up their community health number on computer from details of name and address recorded on their prescriptions. A small proportion of community health numbers could not be identified, and others may have been assigned wrongly. From internal quality control systems the error rate of misclassification is known to be less than 2%. In any case, such misclassification will be similar in cases and controls which would tend to mask any associations.¹² We do not think a significant exposure bias exists as the well described association between oral non-steroidal anti-inflammatory drugs and gastrointestinal bleeding and perforation is evident.

Selection bias occurs if criteria for selecting subjects into a study are not consistent. The only difference in inclusion criteria between cases and community controls in our study was because of a computing technicality which meant that community controls were still alive in September 1992 whereas death after admission to hospital could have occurred in cases. This could mean that controls were healthier than cases and therefore less likely to be exposed to drugs. This bias would tend to increase the odds ratio, however, rather than mask a significant association. There were no differences in selection criteria between cases and hospital controls. This might explain some of the disparity between the results with the different control groups.

Recall bias—One of the strengths of our study is that it did not rely on patient recall of exposure thereby eliminating recall bias. We know that the prescriptions were dispensed, which is an important factor,¹³ although we could not control for patients who were non-compliant.

FURTHER LIMITATIONS

There are some limitations of the design. No information was available on confounding factors such as smoking and alcohol. Medical history of gastrointestinal events was not controlled for, and the

Key messages

- Topical non-steroidal anti-inflammatory drugs are widely used in general practice, often in an attempt to avoid the gastrointestinal toxicity of oral anti-inflammatories
- Recent case reports have queried the safety of these topical drugs
- This study suggests that the independent risk of gastrointestinal complications is minimal
- An automated database has been used successfully to investigate this relation. The technique can be applied to investigate associations between other drugs and possible side effects

indications for the drugs were not known. Finally, the exposure periods of 45 days or ever exposure may not adequately explore the temporal relation between exposure to topical preparations and gastrointestinal complications. The variables were chosen empirically and different exposure variables may yield different results.

With these limitations in mind we could find no significant independent associations between use of topical non-steroidal anti-inflammatory drugs and admission to hospital for upper gastrointestinal bleeding and perforation.

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Risk of pneumococcal septicaemia in patients with chronic lymphoproliferative malignancies

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Guidelines for the prevention of infection in patients with an absent or dysfunctional spleen have recently been prepared.¹ However, another group of patients (with intact spleens) is also particularly susceptible to such infections. Lymphoproliferative malignancies such as chronic lymphocytic leukaemia, myeloma, and low grade non-Hodgkin's lymphoma are associated with immune paresis.² Such patients are often treated with corticosteroids, and a combination of these two factors renders them vulnerable to infections with encapsulated organisms such as *Streptococcus pneumoniae*. These infections have a high morbidity and mortality. Over a period of 16 months we found that pneumococcal sepsis was a far greater problem in patients with lymphoproliferative disorders than in patients who had had a splenectomy; we decided to investigate further.

Patients, methods, and results

We studied all blood cultures that gave positive results from 1 July 1993 to 31 October 1994 in South Tees Health District (population 300 000). Forty seven cultures grew isolates of *S pneumoniae*. Seven of the samples were from patients with a lymphoproliferative disorder (table).

In South Tees district about 200 patients have a lymphoproliferative disorder, giving an annual incidence of pneumococcal infection of 2.6% during the study. Four of the seven patients were hypogammaglobulinaemic and four were receiving corticosteroids. None of the patients was neutropenic and none had had a splenectomy. Mortality was 43% (table).

In this district about 180 patients have had a splenectomy (30 000 nationwide). None developed pneumococcal septicaemia during the study period. Forty episodes of pneumococcal septicaemia thus occurred in the general population, giving an annual incidence of 0.01%. Of these 40 patients, only one was immunocompromised; this patient had ectodermal dysplasia and IgG₂ deficiency but survived. Mortality was 25% (10 patients died).

Comment

This report highlights the increased risk of pneumococcal septicaemia in chronic lymphoproliferative malignancies (table). These patients tend to be elderly; only one was aged under 65. Mortality in these patients was higher (43%) than that in patients of all ages from South Tees who were not immunosuppressed by disease or drugs (25%).

Measures should be implemented to prevent such infections or at least initiate prompt referral and treatment. Similar measures have been proposed in those at high risk of sepsis after splenectomy and in those at risk of varicella infection while taking corticosteroids.^{1,3} The patient should be educated in the same way as patients who have had a splenectomy or who have a dysfunctional spleen.¹ Patient information may be documented on a card, which the patient should carry at all times. General practitioners should

Details of patients with lymphoproliferative disorder and pneumococcal septicaemia

Case No	Age (years)	Sex	Diagnosis	Delay in admission or treatment (days)	Antibiotic prophylaxis	Corticosteroid treatment	IgG (g/l)*	Treatment before admission	Outcome
1	65	M	Chronic lymphocytic leukaemia	6	Yes	No	2.8	Ciprofloxacin	Survived
2	55	F	Multiple myeloma	1	No	Yes	3.2	None	Survived
3	71	F	Multiple myeloma	1	No	Yes	7.2	None	Died
4	71	M	Non-Hodgkin's lymphoma	7	No	Yes	11.7	None	Died
5	65	M	Non-Hodgkin's lymphoma	3	No	Yes	6.5	None	Survived
6	73	F	Chronic lymphocytic leukaemia	4	No	No	35.1	Ciprofloxacin	Died
7	74	F	Non-Hodgkin's lymphoma	2	No	No	14.6	None	Survived

*Normal range 7.2-17.0 g/l.