TOPICAL NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND HOSPITALISATION FOR UPPER GASTRO-INTESTINAL BLEEDING AND PERFORATION: A RECORD-LINKAGE CASE-CONTROL STUDY

J M M Evans BA (Oxon)	**Research Assistant**
A D McMahon BSc	**Statistician**
M M McGilchrist PhD	**Senior Computer Programmer**
G White	**Senior Computer Programmer**
F E Murray MD FRCPI	**Consultant Physician**
D G McDevitt DSc MD FRCP	**Professor of Clinical Pharmacology**
T M MacDonald MD FRCP	**Senior Lecturer and Hon Consultant Physician**

Medicines Monitoring Unit
Department of Clinical Pharmacology
Ninewells Hospital & Medical School
Dundee DD1 9SY
Phone: 01382-660111 Ext 3406
Fax: 01382-667120

Correspondence to Dr T M MacDonald

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Abstract

Objective: **To evaluate the relationship between topically applied non-steroidal anti-inflammatory drugs and upper gastro-intestinal bleeding and perforation.**

Study population: **The population of 319,465 people who were resident in Tayside and were registered with a Tayside GP between January 1989 and October 1994. A record-linkage database containing all hospital event and dispensed drug data between 1989 and 1992 was used for this population.**

Design: **A case-control study with 1,103 cases who were hospitalised for upper gastro-intestinal bleeding or perforation between January 1990 and December 1992. Two different control groups were used, with six community controls and with two hospital controls for each case. Prior exposure to topical NSAIDs, oral NSAIDs and ulcer healing drugs was assessed.**

Main outcome measures: **Unadjusted and adjusted odds ratios of exposure in hospitalised cases compared with controls.**

Results: **Significant unadjusted associations were detected between all three classes of drug and upper gastro-intestinal complications. The significant association detected for topical NSAIDs was no longer evident in analyses which adjusted for the confounding effect of concomitant exposure to oral NSAIDs and ulcer healing drugs (OR = 1.45, 0.84-2.50 using community controls; OR = 1.06, 0.60-1.88 using hospital controls).**

Conclusion: **In this study, topical NSAIDs were not significantly associated with upper gastro-intestinal bleeding and perforation, after adjusting for the confounding effects of concomitant oral NSAIDs and ulcer healing drugs.**

Introduction

It is known that the use of oral non-steroidal anti-inflammatory drugs (NSAIDs) is associated with upper gastro-intestinal complications, particularly perforated and bleeding peptic ulcer[1]. Meta-analyses suggest that the relative risk is approximately three[2]. Recent studies have shown this risk to be dose-related[3,4]. This is one reason why the use of topically applied NSAIDs (topical NSAIDs) is advocated, as plasma concentrations of the NSAIDs remain relatively low after topical application. Despite this, spontaneous reporting data from the "Yellow Card" system of the Medicines Control Agency[5] suggest that the risks of topical NSAIDs may not be negligible. For example, since July 1963, there have been seven reports of adverse events in the gastro-intestinal tract following topical application of diclofenac, four with ibuprofen, one with ketoprofen, 25 with piroxicam and 47 with felbinac (an active metabolite of fenbufen)[6].

Furthermore, in a post marketing study of 23,590 patients exposed to topical Felbinac 3% gel (Traxam©, Lederle Pharmaceuticals), 327 patients experienced 331 adverse events of which 24 were related to the gastrointestinal tract[7]. This study may have been confounded by the use of other drugs as 17 of these patients were taking additional medication. Nevertheless, six were judged to be "definitely" or "probably" related to topical NSAID use.

In order to clarify the risks associated with topically applied NSAIDs, we have carried out a case-control study with multiple control groups using a record-linkage database containing data for a population of 319,465 people, purpose built for carrying out such pharmacoepidemiological research.

Methods

The study was carried out using the Medicines Monitoring Unit's record-linkage database at the University of Dundee. This database contains prospectively gathered information on all dispensed community prescriptions for NSAIDs and ulcer-healing drugs in Tayside from January 1 1989, and diagnostic and demographic data on all hospitalised patients in Tayside from 1980 (Scottish Morbidity Record 1). These data can be linked by a unique ten-digit number, the Community Health Number. The data collection methods for this database have been described in detail elsewhere[8]. In brief, prescriptions encashed at Tayside pharmacies were sent to the Medicines Monitoring Unit following dispensing. The patient's name, address and other prescription details were used to find the unique Community Health Number 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 were entered onto the prescription database with the Community Health Number.

When patients in Tayside are discharged from hospital, codes for their diagnoses (International Classification of Disease version 9) and codes for their operations (Office of Population Censuses and Surveys, fourth revision) are entered onto the Tayside section of the Scottish Morbidity Record database, using 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 dispensed prescription data and hospitalisation data. In addition, since the Medicines Monitoring Unit has lists of

every patient registered with a General Practitioner in Tayside and every person hospitalised in Tayside, both community and hospital controls can be generated.

SAMPLE SIZE CALCULATION

In a preliminary analysis, the extent of topical NSAID prescribing and the preparations most commonly prescribed were investigated for the population of Tayside between 1989 and 1992. Using this information, the minimum odds ratios which could be detected with the sample sizes used in the case-control study were calculated.

STUDY POPULATION

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.

CASES

A case was defined as any individual within the study population who had an International Classification of Disease code for upper gastrointestinal bleeding or perforation in their computerised discharge summary for a hospitalisation episode between January 1 1990 and December 31 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. *(A full list of codes is available from the Journal on request).* The first hospitalization 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 International Classification of Disease codes to identify cases in this study. Hospital episodes containing any gastro-intestinal code were identified for all patients over 50 years of age who had cashed a prescription for an NSAID 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, using predetermined criteria, were judged to be acute bleeds or perforations, or otherwise. It was thus possible to determine how many "true cases" (ie acute bleeds and perforations) would be missed, and how many "non-cases" would be incorrectly selected, if case identification was based on the International Classification of Disease 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 case'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 gastro-intestinal bleeding and perforation within 90 days of the case. The index date of the hospital control was the date of admission.

ANALYSES

Prior exposure to three classes of drugs were investigated - oral NSAIDs (excluding aspirin), ulcer-healing drugs and topical NSAIDs. Odds ratios were calculated for two pre-defined exposure variables for each, and modelled using conditional logistic regression[9,10]. These were:

1. Forty five day exposure: One or more prescriptions dispensed during a 45 day period prior to the index date.

2. Ever exposure: One or more prescriptions dispensed at any time from January 1 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

SAMPLE SIZE CALCULATION

The utilisation of topical NSAID preparations in the study population between 1989 and 1992 is displayed in Table 1. The level of exposure during the time of the study was 7%. Since the study included 1,103 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 = 1,081). With only two controls per case, the minimum odds ratio was 1.5 (n = 958)[11].

CASES AND VALIDATION OF CASES

There were 1,103 patients hospitalised for upper gastro-intestinal bleeding and perforation between January 1 1990 and December 31 1992. 569 (52%) were male and 534 (48%) were female. 78% were over the age of 50 years.

The validation study examined 3,078 admission-discharge events that contained at least one upper gastro-intestinal diagnostic code, of which 542 were acute bleeding events and 75 were perforations. The sensitivity of using 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 6,593 suitable community controls and 2,184 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

Using community controls, oral NSAIDs, topical NSAIDs and ulcer healing drugs were significantly associated with upper gastro-intestinal bleeding and perforation, whether 45 day exposure or ever exposure variables were used (Table 2). With hospital controls, both the exposure variables were statistically significant for ulcer healing drugs but only 45 day exposure was significant for oral NSAIDs. Neither exposure variable was statistically significant for topical NSAIDs (Table 3).

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, are shown in Tables 4 and 5. The few cases which had both bleeding and perforation were excluded. Oral NSAIDs and ulcer healing drugs were significantly associated with an increased risk of gastro-intestinal complications in all cases. There were no significant associations between topical NSAIDs and gastro-intestinal events after adjusting for confounding by oral NSAIDs and ulcer healing drugs.

The effects of confounding were investigated in further conditional regression analyses. With community controls, topical NSAIDs were still associated with upper gastro-intestinal complications after adjusting for oral NSAIDs alone, suggesting that there was

further confounding from ulcer healing drugs. Similarly, there was confounding from ulcer healing drugs after adjusting for oral NSAIDs. However, with hospital controls, 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 NSAIDs among cases compared to hospital controls was among patients exposed to both oral NSAIDs and ulcer healing drugs simultaneously. However, the excess risk with community controls seemed to be more evenly distributed among patients on different combinations of these drugs. *(The analyses and contingency tables for these effects are shown in Appendix 1. They are not intended for publication but we suggest that they be available from the Journal on request).*

To investigate further the validity of the result for topical NSAIDs, the analyses were recalculated using a repeated random control selection technique. Ten further hospital and ten further community control groups were assembled and the analyses repeated for each. The adjusted results for 45 day exposure and ever exposure to topical NSAIDs are shown in Fig 1. *(The individual components and the data for Fig 1 are enclosed to aid publication).*

Discussion

These results show that whilst there were associations between the use of topical NSAIDs and upper gastro-intestinal complications in the unadjusted analyses, these associations were mainly due to confounding by concomitant use of oral NSAIDs and ulcer healing drugs. In analyses which adjusted for the effects of all the three classes of drug simultaneously, there were no significant associations between topical NSAIDs and upper gastro-intestinal complications.

There was some disparity between the results obtained using the different control groups. Assessing the validity of different control groups is often a difficult problem in case-control studies. However, irrespective of the source of controls, the final results were similar, in that topical NSAIDs did not carry an independent significant risk of gastro-intestinal complications.

One possible weakness of this study may relate to statistical power. The original power calculations were based on 7% exposure to topical NSAIDs. However, this was appropriate only for the ever exposure analyses. Based on 45 day exposure to topical NSAIDs, to which 2% of cases and controls were exposed, the minimum odds ratios which could have been detected were nearer 2^{11}. An adjusted odds ratio of 1.45 was found for 45 day exposure to topical NSAIDs using community controls. This was not significant, but this may have been due to lack of power. Indeed, the plot of 45 day exposure using community controls suggests that a very small risk associated with topical NSAID use might be present. This may not represent a true toxic effect but may be evident because patients already at high

risk from upper gastro-intestinal complications are prescribed topical NSAIDs in an effort to avoid the toxicity of oral NSAIDs.

An independent estimated relative risk of 2.6 (2.1 - 3.2) was found for oral NSAIDs using community controls, and 2.0 (1.6 - 2.5) using hospital controls. These figures are consistent with previous research[2]. An independent increased risk associated with ulcer healing drugs was also found in this study. This is unlikely to be a causal association but probably arises because people known to be at high risk from gastro-intestinal bleeding and perforation, or have symptoms already, are prescribed ulcer-healing drugs.

The importance of misclassification and bias must be considered.

MISCLASSIFICATION OF DISEASE STATUS

Concerns have been expressed as to the accuracy of International Classification of Disease 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%[12]. Our case record validation 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.

EXPOSURE MISCLASSIFICATION

Misclassification of exposure is also a possible source of bias. Prescriptions were assigned to individuals by looking up their Community Health Number on computer from name and address details recorded on their prescriptions. A small proportion of Community Health Numbers could not be identified, while 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 between cases and controls which would tend to mask any associations[13]. We do not think a significant exposure bias exists as the well described association between oral NSAIDs and gastro-intestinal bleeding and perforation is evident.

SELECTION BIAS

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 this study was due to a computing technicality which meant that community controls were still alive in September 1992, whereas cases could have died after hospitalisation. This could mean that controls were healthier than cases and therefore less likely to be exposed to drugs. However, this bias would tend to increase the odds ratio, 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 using the different control groups.

One of the strengths of the present 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[14], although we could not control for patients who were non-compliant.

There are some limitations to the study design. No information was available on confounding factors such as smoking and alcohol. Past medical history of gastro-intestinal events was not controlled for. Also, the indications for the drugs were not known. Finally, the exposure periods of 45 days or ever exposure may not adequately explore the temporal relationship between exposure to topical NSAIDs and gastro-intestinal complications. The variables were chosen empirically and different exposure variables may yield different results.

With these limitations in mind, no statistically significant independent associations between topical NSAID use and hospitalisation for upper gastro-intestinal bleeding and perforation have been found.

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LEGENDS TO TABLES

Table 1: Utilisation of topical NSAIDs in study population 1989-1992

Table 2: Crude odds ratios for exposure variables (community controls)

Table 3: Crude odds ratios for exposure variables (hospital controls)

Table 4: Final conditional logistic regression analyses (community controls)

Table 5: Final conditional logistic regression analyses (hospital controls)

Preparation	No of prescriptions	No of patients
Diethylamine salicylate (Algesal©, Duphar)	92	25
Glycol salicylate (Algipan©, Whitehall)	93	73
Ammonium salicylate (Aspellin©, Fisons)	53	30
Methyl salicylate (Balmosa©, Pharmax)	28	17
Benzydamine hydrochloride (Difflam©, 3M)	9,500	4,848
Piroxicam (Feldene©,Pfizer)	16,357	9,925
Ibuprofen (Ibugel©, Dermal)	432	330
Ibuprofen (Ibuleve©, Dendron)	54	41
Salicylamide (Intralgin©, 3M)	138	103
Salicylic acid (Movelat©, Panpharma)	1,869	1,089
Ketoprofen (Oruvail©, Rhone-Poulenc Rorer)	815	677
Ibuprofen (Proflex©, Zyma)	2,486	1,405
Tetrahydrofurfuryl salicylate (Transvasin©, Lederle)	332	200
Felbinac (Traxam©, Lederle)	5,358	3,314
Diclofenac (Voltarol©, Geigy)	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

Table 1

	Cases (n = 1,101)	Controls (n = 6,593)	Unadjusted odds ratio (95% CI)	p value
Oral NSAIDs				
45 day exposure	186 (16.9%)	457 (6.9%)	2.81 (2.33, 3.40)	<0.001
Ever exposure	457 (41.5%)	2131 (32.3%)	1.53 (1.33, 1.75)	<0.001
Topical NSAIDs				
45 day exposure	23 (2.1%)	54 (0.8%)	2.59 (1.58, 4.23)	<0.001
Ever exposure	98 (8.9%)	415 (6.3%)	1.48 (1.17, 1.88)	<0.001
Ulcer-healing drugs				
45 day exposure	243 (22.1%)	393 (6.0%)	4.61 (3.85, 5.52)	<0.001
Ever exposure	421 (38.2%)	849 (12.9%)	4.33 (3.74, 5.01)	<0.001

Table 2

	Cases (n = 1,096)	Controls (n = 2,184)	Unadjusted odds ratio (95% CI)	p value
Oral NSAIDs				
45 day exposure	186 (17.0%)	206 (9.4%)	1.98 (1.60, 2.46)	<0.001
Ever exposure	457 (41.7%)	909 (41.6%)	1.00 (0.86, 1.17)	0.970
Topical NSAIDs				
45 day exposure	23 (2.1%)	29 (1.3%)	1.59 (0.92, 2.74)	0.099
Ever exposure	97 (8.9%)	192 (8.8%)	1.00 (0.78, 1.30)	0.983
Ulcer-healing drugs				
45 day exposure	242 (22.1%)	288 (13.2%)	1.88 (1.55, 2.28)	<0.001
Ever exposure	417 (38.0%)	569 (26.1%)	1.75 (1.50, 2.05)	<0.001

Table 3

Exposure variable	Adjusted odds ratio	p value
All cases		
45 day exposure - oral NSAIDs	2.59 (2.12, 3.16)	<0.001
45 day exposure - topical NSAIDs	1.45 (0.84, 2.50)	0.184
Ever exposure - ulcer healing drugs	4.21 (3.63, 4.88)	<0.001
Bleeding		
45 day exposure - oral NSAIDs	2.18 (1.75, 2.71)	<0.001
Ever exposure - topical NSAIDs	1.43 (0.81, 2.54)	0.221
Ever exposure - ulcer healing drugs	4.30 (3.67, 5.03)	<0.001
Perforation		
45 day exposure - oral NSAIDs	8.75 (4.77, 16.06)	<0.001
Ever exposure - topical NSAIDs	5.50 (0.70, 44.40)	0.106
Ever exposure - ulcer healing drugs	3.51 (2.13, 5.79)	<0.001

Table 4

Exposure variable	Adjusted odds ratio	p value
All cases		
45 day exposure - oral NSAIDs	2.00 (1.60, 2.50)	<0.001
45 day exposure - topical NSAIDs	1.06 (0.60, 1.88)	0.851
Ever exposure - ulcer healing drugs	1.76 (1.51, 2.07)	<0.001
Bleeding		
45 day exposure - oral NSAIDs	1.74 (1.37, 2.22)	<0.001
45 day exposure - topical NSAIDs	1.05 (0.57, 1.92)	0.875
Ever exposure - ulcer healing drugs	1.74 (1.47, 2.05)	<0.001
Perforation		
45 day exposure - oral NSAIDs	4.84 (2.49, 9.39)	<0.001
45 day exposure - topical NSAIDs	0.86 (0.10, 7.28)	0.892
Ever exposure - ulcer healing drugs	1.87 (1.07, 3.27)	0.028

Table 5