PAPERS AND SHORT REPORTS

Ulcerogenicity of piroxicam: an analysis of spontaneously reported data

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Abstract

Previous reports have suggested that piroxicam may be more ulcerogenic than other non-steroidal anti-inflammatory drugs (NSAIDs) in use. Critics have attributed this putative relation to flawed comparisons of spontaneously reported data.

In this study cases of upper gastrointestinal bleeding, perforation, and ulcer reported to the Food and Drug Administration's spontaneous reporting system over 12 years were examined. Reporting rates for eight NSAIDs were compared over identical periods of their marketing life cycles. After adjustments were made for the heterogeneity in the underlying reporting rates the difference in rates between piroxicam and the other drugs was considerably reduced but piroxicam retained its top ranking among the drugs; however, large and clinically important differences in the frequency of cases of upper gastrointestinal bleeding, perforation, and ulcer between piroxicam and the rest of the NSAIDs compared probably do not exist.

Introduction

Altogether 21% of all adverse drug reactions reported to the spontaneous reporting system of the United States Food and Drug Administration are due to non-steroidal anti-inflammatory drugs (NSAIDs). Though many of the adverse drug reactions reported represent fairly trivial and well known consequences of treatment with NSAIDs, two NSAIDs were recently voluntarily withdrawn from use because of such reports: benoxaprofen because of serious and sometimes fatal liver toxicity and zomepirac because of a suspected, greater than acceptable risk of anaphylactic reactions.

Early in 1985 several authors suggested that piroxicam might be associated with an increased risk of upper gastrointestinal bleeding,

perforation, and ulcer when compared with other NSAIDs.^{1,2} The suggestion was based on similar data: clinically observed cases arising from a hospital setting¹ or cases spontaneously reported to a national registry.^{2,3} Subsequently, other reports were published based on data other than spontaneously generated case reports. Of these, one implicated piroxicam⁴; the others either were unable to single out one NSAID as being more strongly associated with an increased risk of upper gastrointestinal bleeding, perforation, and ulcer than the others⁵ or failed to find any difference in risk between the NSAIDs they examined.⁶

As early as 1984 the Food and Drug Administration was aware of an apparent excess of cases of upper gastrointestinal bleeding, perforation, and ulcer associated with piroxicam among reports it had received through its spontaneous reporting system. These data were presented to the administration's arthritis drugs advisory committee in October 1984. This presentation provoked several comments and opinions about how spontaneously reported data should be compared, analysed, interpreted, and used for scientific and regulatory decision making. This study was intended to respond to several important scientific and methodological issues raised by the advisory committee as well as to examine the Food and Drug Administration's spontaneous reporting database specifically for evidence that piroxicam might be associated with a greater risk of upper gastrointestinal bleeding, perforation, and ulcer than other NSAIDs. For greater clarity the primary focus of this report is confined to an examination of the ulcerogenic potential of piroxicam when compared with that of selected NSAIDs approved in or after 1974 and in current use in the United States.

Methods

A general description of the Food and Drug Administration's spontaneous reporting system has been published.⁷ Although the system contains reports received since 1969, this study was confined to eight NSAIDs approved in or after 1974 because reporting of adverse drug reactions from the first year of marketing was not available for NSAIDs approved before 1974. Several NSAIDs approved after 1974 were excluded because of either brief and atypical marketing histories (benoxaprofen, zomepirac) or paucity of reports (mefenamic acid). Also excluded were known duplicate reports, foreign cases, reports arising out of special postmarketing studies, and published cases.

The reports of upper gastrointestinal bleeding, perforation, and ulcer studied were limited to those of 20 specific adverse reactions listed in the

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Food and Drug Administration's COSTART dictionary, which is used to standardise all entries of adverse drug reactions into its computer based spontaneous reporting system.⁸ Briefly, these terms include: duodenal, oesophageal, peptic, and stomach ulcers with and without mention of perforation or haemorrhage, or both; gastrointestinal and oesophageal haemorrhage (including haematemesis reported alone); haemorrhagic gastritis; and the peptic ulcer syndrome.

Data on drug use for the period 1974-84 were obtained from IMS America's national prescription audit⁹ and reported as the number of prescriptions dispensed in the United States. Although the audit is not a true random sample of all pharmacies, IMS assures its subscribers that the panel from which the data arise is representative of pharmacies in the United States in terms of geographical region, type of ownership, and size.

The basis of the three year comparisons of adverse drug reactions and use of the drugs was the calendar year of marketing. There were two exceptions in which the first calendar year of marketing was not the same as the first calendar year after approval of the drug. The Food and Drug Administration approved sulindac and meclofenamate sodium in the latter half of 1978 and 1980, respectively, resulting in some use but no reported adverse drug reactions in these years. Therefore, reports of adverse drug reactions and drug use during 1978 and 1979 (for sulindac) and during 1980 and 1981 (for meclofenamate sodium) were combined and classified as those occurring during the first calendar year of marketing for these two drugs. (The same adjustment was considered for ibuprofen, but we concluded that sufficient use had occurred and adequate time for reporting had elapsed.)

Weber showed that the rate of reporting for new drugs was not the same as that for older drugs.¹⁰ For the NSAIDs he investigated the reporting rate usually increased towards the second calendar year of marketing and thereafter declined. It was thus important that in our series all NSAIDs be compared at identical periods of their marketing life cycle. As only three

fully complete years of data were available for the most recently approved NSAIDs in our series (diflunisal and piroxicam) the first three calendar years of marketing were compared for all the drugs.

Although the reporting rates of bleeding, perforation, and ulcer were clearly higher for the newer NSAIDs, particularly piroxicam, whose first three years of marketing were 1982-4, the overall reporting rates for all adverse drug reactions in the Food and Drug Administration's system rose substantially during this period as well. Table I shows the rate of reporting of adverse drug reactions during 1974-85: rates were reasonably stable for eight years (1974-81), at about 6-9 reports/10⁶ prescriptions, but then jumped to about 15-24 reports/10⁶ prescriptions in the four years beginning in 1982. There was little question that in controlling for the marketing life cycle in the comparisons we would have to make another important adjustment before attempting to interpret these data. This correction for the heterogeneity in the underlying rate of reporting to the spontaneous reporting system was called the secular reporting trend adjustment factor. Its use was especially critical for comparisons between NSAIDs whose first three years of marketing fell entirely within 1974-81 and those whose first three years of marketing began in 1982.

In its simplest estimation the adjustment factor for secular reporting trends was calculated as the ratio of the lowest yearly reporting rate during 1974-84 (6.09 reports/10⁶ prescriptions) to each of the other yearly reporting rates. Table I shows the adjustment factors calculated in this manner for each of the years from 1974 to 1985. The application of these adjustment factors to reporting rates to produce an adjusted reporting rate was accomplished in the following manner. Factors calculated in table I for the first three years of marketing of each NSAID were summed and averaged to become the three year secular reporting trend adjustment factor. Dividing the unadjusted reporting rate by this factor resulted in an adjusted three year reporting rate that was comparable for all NSAIDs regardless of the specific three year period of the comparison. For example, the adjustment factors during the first three years of marketing of piroxicam were 2.43 in 1982, 3.35 in 1983, and 3.44 in 1984, giving a total of 9.22. The three year adjustment factor was therefore 9.22/3 = 3.07. The unadjusted three year reporting rate for piroxicam was 20.02 reports/10⁶ prescriptions; this gave an adjusted three year reporting rate for piroxicam of 6.52 reports/10⁶ prescriptions (20.02/3.07).

TABLE I—Rates of reporting of all adverse drug reactions notified to Food and Drug Administration's spontaneous reporting system, 1974-85

Year	No of reports received	No of prescriptions dispensed (×10 ³)*	Reporting rate/10 ⁶ prescriptions	Adjustment factor (secular reporting trends)*
1974	9 251	1 518 093	6.09	1.00
1975	10 612	1 503 265	7.06	1.16
1976	10 819	1 473 893	7.43	1.22
1977	13 748	1 424 547	9.65	1.58
1978	10 548	1 409 176	7.49	1.23
1979	10 800	1 378 403	7.84	1.29
1980	11 762	1 406 260	8.36	1.37
1981	12 956	1 418 959	9.13	1.50
1982	22 127	1 495 046	14.80	2.43
1983	30 780	1 508 144	20.41	3.35
1984	32 140	1 533 620	20.96	3.44
1985	38 205	1 548 400	24.67	4.05

* Based on data on all retail prescriptions dispensed during 1974-85.⁹

TABLE II—Distribution of reports of upper gastrointestinal bleeding, perforation, and ulcer associated with eight NSAIDs approved after January 1974 and in Food and Drug Administration's spontaneous reporting system during 1974-85

	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	Total
Ibuprofen	0	26	26	16	7	2	2	14	11	18	19	22	163
Naproxen			13	15	5	1	15	20	23	44	39	41	216
Fenoprofen			10	9	4	2	9	5	9	9	11	6	74
Tolmetin			15	18	4	1	9	7	14	13	2	6	89
Sulindac					0	23	65	52	15	18	12	19	204
Meclofenamate sodium							0	3	6	8	2	3	22
Piroxicam									81	151	170	19	421
Diflunisal									3	33	14	8	58

TABLE III—Distribution of use during 1974-85 of the eight NSAIDs under study (expressed as thousands of retail prescriptions dispensed)*

	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	Total
Ibuprofen	1104	10 844	13 650	12 119	11 238	10 686	15 942	17 784	18 932	19 782	20 890	21 729	174 700
Naproxen			1 540	2 703	3 674	4 475	5 734	8 663	9 931	11 461	12 521	11 656	72 358
Fenoprofen			822	2 029	2 845	2 973	3 486	3 924	3 721	3 279	3 187	2 838	29 104
Tolmetin			756	1 800	2 109	2 016	2 799	2 548	2 711	2 449	2 583	2 561	22 332
Sulindac					1 297	10 848	8 918	8 024	7 205	5 790	5 309	5 278	52 669
Meclofenamate sodium							426	2 129	1 983	1 846	1 976	2 153	10 513
Piroxicam									4 407	7 583	8 091	8 788	28 869
Diflunisal									886	2 305	2 671	2 951	8 813

* Based on data on all retail prescriptions dispensed during 1974-85.⁹

Results

Table II shows the number and distribution by year of all reports of upper gastrointestinal bleeding, perforation, and ulcer received by the spontaneous reporting system for eight NSAIDs approved during or after 1974 over the period 1974-85. Table III tabulates by year the number of prescriptions dispensed for each of the eight NSAIDs.

Table IV provides the number of reports of adverse drug reactions, drug use, reporting rates, and ranking of the eight NSAIDs for the first three years of their marketing. It also presents the reporting rates for the first three calendar years of marketing adjusted for secular reporting trends. This adjustment had the effect of reducing the three year reporting rate of each NSAID but affected the more recently introduced NSAIDs most profoundly. Diflunisal's ranking fell from two to six among all eight NSAIDs, but piroxicam retained its top ranking.

Discussion

The purpose of this study was twofold: firstly, to improve existing methods for comparing, analysing, and interpreting spontaneously reported data and, secondly, to investigate whether piroxicam is more ulcerogenic than other NSAIDs in current use. In carrying out these tasks we elected not to proceed on two separate paths to these ends but to integrate these paths. During the study we identified

TABLE IV—Ranking of reporting rates of upper gastrointestinal bleeding, perforation, and ulcer per million retail prescriptions for the first three calendar years of marketing of the eight NSAIDs before and after adjustment for secular reporting trends

	Before adjustment				After adjustment		
	No of reports	No of prescriptions dispensed (10 ³)	Reporting rate/10 ⁶ prescriptions	Ranking	Adjustment factor*	Adjusted reporting rate/10 ⁶ prescriptions	Ranking
Piroxicam	402	20 081	20.02	1	3.07	6.52	1
Tolmetin	37	4 665	7.93	3	1.34	5.92	2
Sulindac	140	29 087	4.81	4	1.35	3.56	3
Naproxen	33	7 917	4.17	5	1.34	3.11	4
Fenoprofen	23	5 696	4.04	6	1.34	3.01	5
Diffunisal	50	5 862	8.53	2	3.07	2.78	6
Ibuprofen	52	25 598	2.03	7	1.13	1.79	7
Meclofenamate sodium	17	6 384	2.66	8	2.16	1.23	8

* Average of the individual adjustment for each drug over the first three calendar years of marketing.

several characteristics of spontaneous reporting in general and of the Food and Drug Administration's system in particular, and their influence on the crude findings of our investigation of piroxicam were factored into the subsequent analysis. We discuss these factors below.

Marketing life cycle—It was clear early on in our study that if the number of cases of upper gastrointestinal bleeding, perforation, and ulcer were simply tabulated and compared for each NSAID at a single time point or over a recent three year period not only would the registry findings of Beermann² and Meyer and Thijs³ be replicated but a major deficiency of their investigations would be repeated as well. This strategy would result in the comparison of drugs well into their marketing life cycles (ibuprofen, fenoprofen, etc) with drugs in their first years of marketing (piroxicam, diffunisal). It is well established, and has been confirmed by Weber,¹⁰ that the first two or three years of marketing produce many more reports of adverse drug reactions than later years, regardless of the actual incidence of such reactions. By itself this "new drug reporting effect" is sufficient reason to confine comparisons of spontaneously reported data to identical periods of the marketing life cycle of each drug, as we did in this study.

Differences in population exposure, drug dose, and duration of treatment—Because some older NSAIDs like ibuprofen and naproxen were heavily promoted in the United States after their approval for use as short term analgesics their patterns of use changed considerably with respect to dose, duration of use, and age of recipients compared with before this approval; in addition, their patterns of use were different from those of other NSAIDs in this series used only as anti-inflammatory agents. Given the acknowledged importance of each of these variables to the development of gastrointestinal disease, it was critical to make adjustments for the differences in use of the drugs. Unfortunately, none of these differences were accounted for in the previously cited registry studies.^{2,3} As spontaneous reports of adverse drug reactions in the United States often fail to provide these data several otherwise useful reports of bleeding, perforation, and ulcer in the Food and Drug Administration's system would have had to be excluded from our analysis if we had elected to compare NSAIDs for 1984 or over a recent three year period such as 1982-4. Confining the comparison of NSAIDs to the first three years of marketing corrected for the differences in use without loss of data as use was found to be reasonably similar for most NSAIDs during their first three years of marketing.

Secular trends of reporting—The spontaneous reporting system received a substantially increased number of reports over the past several years (table II); the increase, which began in 1982, was not confined just to the newer NSAIDs. When overall reporting of adverse drug reactions to the system was considered without regard to a specific drug class, a similar pattern of increased reporting for all drugs was seen, beginning in 1982 (table I). If comparisons were to be confined to the first three years of marketing of each drug an adjustment for differences in the secular reporting to the system for these specific years was necessary. This adjustment was particularly important for comparisons between drugs whose first three years of marketing fell within the period 1974-81, when reporting rates for

all drugs were lower, and drugs that were approved in 1982 or later, when reporting rates for all drugs were considerably higher (as was the case for comparisons with piroxicam).

When the above adjustments were made they profoundly affected many of the relations seen in the unadjusted data. The most important of these changes affected the newest of the NSAIDs, diffunisal and piroxicam. Diffunisal's strong relation to reports of bleeding, perforation, and ulcer virtually disappeared so that it was indistinguishable from most of the other NSAIDs (table IV). Given diffunisal's predominant use among younger patients and its relatively greater analgesic (short term) use compared with other NSAIDs, together with what was learnt about its potential for gastrointestinal toxicity from clinical trials, this ranking among the other NSAIDs is more compatible with postmarketing expectations than was its unadjusted ranking. Although piroxicam retained its top ranking even after adjustments the differential between the reporting rates for piroxicam and the next ranked drug dropped substantially from more than a twofold difference to just over a 10% difference (table IV).

The most obvious explanation for the remaining differences seen in table IV is that the adjustments we made were too crude and incomplete to account fully for the influence of the unadjusted factors on the reported rates. In addition to those factors for which we made adjustments there were others that might have had an effect. These included: (1) the effect of publicity associated with the voluntary withdrawals of benoxaprofen and zomepirac in 1982, which could have affected reporting of adverse drug reactions linked to the newer NSAIDs more than those linked to the older and more trusted NSAIDs; (2) the differences in promotion between the various NSAIDs, which could have resulted in higher reporting rates for the more intensively promoted drugs; (3) the use of certain of the older NSAIDs (for example, ibuprofen and naproxen) at lower doses during their earlier marketing years, which could have not only resulted in lower reporting rates but also increased the disparity in the rates seen between the older and the newer NSAIDs, particularly piroxicam; and (4) the preferential use of piroxicam in patients who were more ill and so had a greater propensity to develop gastrointestinal bleeding regardless of exposure to NSAIDs; this selection bias may have been influenced by piroxicam's once daily dosing regimen.

Any of the above could account for the differences noted in this study if they could be accurately measured. None the less, we cannot rule out the possibility that piroxicam may be more ulcerogenic than the other NSAIDs in our series. If it is, differences of the magnitude suggested are probably outside the ability of spontaneous reporting systems to investigate further and measure with any reasonable degree of scientific certainty.

On a more positive note it is reassuring to observe that reports of bleeding, perforation, and ulcer associated with piroxicam declined dramatically in its fourth year of marketing (table II), as might be predicted from the "new drug reporting effect." The reporting rate for piroxicam in 1985 (2.2 reports per million prescriptions) was well within the limits seen for the other NSAIDs in this series, which ranged from 1.0 to 3.6 reports per million prescriptions. Furthermore, after this study was completed two additional investigations

of the relation between use of NSAIDs and gastrointestinal adverse reactions were reported. The first examined data based on "yellow card" reporting in the United Kingdom for the first five years of marketing of several NSAIDs,¹¹ many of which were identical with those compared in our study. The Committee on Safety of Medicines concluded that piroxicam fell into a group of 12 NSAIDs for which differences in safety "... cannot be clearly distinguished from each other based on yellow card reports." The second study compared five NSAIDs, only one of which (piroxicam) was included in this study, in an innovative postmarketing surveillance scheme, prescription event monitoring.¹² That study examined a wider range of adverse events than either our study or that of the Committee on Safety of Medicines, but the findings relating to the events affecting the gastrointestinal system were interpreted as reflecting no noteworthy differences between the drugs examined. Thus it seems reasonable to conclude that large and clinically important differences in rates of upper gastrointestinal bleeding, perforation, and ulcer between piroxicam and the rest of the NSAIDs probably do not exist.

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Low serum selenium concentration and glutathione peroxidase activity in intrahepatic cholestasis of pregnancy

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Abstract

Serum selenium concentrations were found to be significantly lower in women with intrahepatic cholestasis of pregnancy than in women with normal pregnancies during the last trimester of pregnancy and post partum. The activity of the selenoenzyme glutathione peroxidase had a significant positive correlation with selenium concentration and it was also significantly lower in women with the disease.

These findings suggest that selenium deficiency and reduced glutathione peroxidase activity are associated with the aetio-pathogenesis of intrahepatic cholestasis of pregnancy.

Introduction

The aetiology of intrahepatic cholestasis of pregnancy is unknown. Patients with this condition are abnormally sensitive to oestrogens.^{1,2} Intrahepatic cholestasis of pregnancy is most common in Scandinavia and Chile,¹ regions whose inhabitants have a low dietary intake of selenium.³ Because deficiency of selenium may lead to liver disturbances in animals^{4,5} and in man⁶ we investigated the importance of selenium in intrahepatic cholestasis of pregnancy by measuring the

serum concentration of selenium and the serum activity of the selenoenzyme glutathione peroxidase in pregnant women with and without this disease.

Subjects and methods

Twelve consecutive patients with intrahepatic cholestasis of pregnancy from the antenatal ward and 12 healthy pregnant women from the outpatient maternity centre were studied (table I). Those with the condition suffered from itching and had increased serum bile acid concentrations and serum aspartate aminotransferase and alanine aminotransferase activities. The patients and controls were matched for age (within three years) and parity. Because the serum concentration of selenium correlates strongly with nutritional selenium availability,⁷ which varies in Finland according to the time of year, the patients and controls were studied at the same time and were from the same region. Four of the patients but none of the controls had a twin pregnancy. Venous blood samples were taken weekly from the patients with intrahepatic cholestasis of pregnancy from the 31st to the 37th weeks and from the controls from the 30th to the 35th weeks of gestation until the third to fifth days post partum.

Serum selenium concentrations were determined by hydride generation atomic absorption spectrophotometry and the activity of glutathione peroxidase by a spectrometric method using t-butyl-hydroperoxide as the substrate.

In the statistical analyses of the results the changes within the groups were

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TABLE I—Clinical characteristics of patients with intrahepatic cholestasis of pregnancy and controls studied

	Mean (SD) age (years)	Range/No of primiparas	Mean (SD) gestational age at delivery (weeks)	No of pairs of twins
Patients with intrahepatic cholestasis of pregnancy (n=12)	28.7 (5.4)	0-3/7	37.9 (2.1)	4
Controls (n=12)	26.3 (2.6)	0-3/7	40.8 (1.1)	0