

Gruppo Italiano Studi
Epidemiologici in Dermatologia
(GISED)

Cutaneous Reactions to Analgesic-Antipyretics and Nonsteroidal Anti-Inflammatory Drugs

Analysis of Reports to the Spontaneous Reporting System of the Gruppo Italiano Studi Epidemiologici in Dermatologia

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Key Words

Analgesic-antipyretics and
nonsteroidal anti-inflammatory
drugs
Cutaneous adverse reactions
Spontaneous reporting system

Abstract

We analyzed the cutaneous reactions to systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs reported to the spontaneous reporting system of the Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED). The system has been active since 1988, with periodic intensive surveillance exercises, and 202 dermatologists have collaborated. Up to December 1991, 2,137 reactions had been collected, of which 713 were reactions to systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs. A general profile of the reactions was identifiable. It included, in order of frequency, urticaria/angioedema, fixed eruptions, exanthemas, erythema multiforme and Stevens Johnson syndrome. Fixed eruptions and Stevens Johnson syndrome were reported with exceedingly high frequency in association with fenpropion. Our system also revealed previously unreported reactions, including fixed eruption to nimesulide, fixed eruption to piroxicam and fixed eruption to flurbiprofen.

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Introduction

The nonsteroidal anti-inflammatory and nonnarcotic analgesic and antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated, although the majority of them are weakly acidic, which share certain therapeutic effects on inflammation, fever and pain. The inhibition of prostaglandin biosynthesis partly explains the therapeutic effects and, the prototype being aspirin, these compounds are sometimes referred to as aspirin-like drugs.

Even if these drugs may have other mechanisms of action, it is generally accepted that the rank order of potency as inhibitors of prostaglandin synthesis *in vitro* tends to reflect their anti-inflammatory potency *in vivo* [2]. Differences in the therapeutic activities justify a broad distinction between the analgesic-antipyretics, including weak inhibitors of prostaglandin synthesis, e.g. para-aminophenol derivatives like paracetamol and salicylates, and the more potent inhibitors, strictly speaking the nonsteroidal anti-inflammatory drugs, which are mainly used for rheumatologic disorders [3]. Although cutaneous reactions to systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs are considered to be frequent, we have only limited data about the general profile of these reactions. The most recent systematic review, based on data from the Adverse Drug Reaction Reporting System of the American Academy of Dermatology, was conducted in 1984 [4]. In recent years, an increasing number of new analgesic-antipyretics and nonsteroidal anti-inflammatory drugs have been introduced into the market, including, for example, in Europe, nimesulide, and oxicams. Specialist assessment and update of dermatologic reactions to these new drugs are needed to have a balanced and satisfactory profile of the clinical patterns [5-8]. The postmarketing surveillance program of the Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED) was started in 1988 and was conceived as a set of research activities including a spontaneous reporting system [9] and selected epidemiologic studies [10]. The spontaneous reporting system works through periodic intensive monitoring exercises, with the participation of about 200 Italian dermatologists. Up to December 1991, 2,137 cutaneous reactions had been collected, of which 713 were reactions to systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs. We have analyzed the profiles of these reactions, with special emphasis on the recently introduced drugs.

Materials and Methods

The aim, general organization and functioning of the spontaneous reporting system of GISED have been previously reported [9]. Briefly, the program involves thirty-three hospital-based services. In each center a monitor, i.e. a specifically trained dermatologist, coordinates the study locally, asking all dermatologists working in the hospital and in services outside the hospital in his area to participate by reporting all the adverse reactions they observe in their practice during prespecified 2-month periods. Up to December 1991, 202 dermatologists had agreed to participate. Most of them were practicing dermatologists working both in public services and in private offices and about 35% of them worked inside the participating hospitals. The study was based on spontaneous collaboration of dermatologists and we did not attempt to cover a defined population. However, from administrative data provided by the hospitals participating in the study, the population base could be estimated at about 10 million people (for severe conditions leading to hospitalization, this would represent a valid estimate of the surveyed population). Four 2-month monitoring periods, one between June and December 1988, one between May and August 1989 and two between April and December 1991, were agreed upon by the dermatologists in each center. Monitoring periods varied from one center to another, within the broad intervals specified above, according to the choices made by each center. In the periods between the monitoring phases, dermatologists were asked to limit signalling the more serious or unusual reactions. The few reports collected in these periods were not included in this analysis. Adverse drug reactions were noted on a standard form and the forms collected by the monitor were periodically sent to the study's coordinating center. The coordinating center carefully evaluated the records, judging in particular the completeness and internal consistency, and reclassified the reactions according to a standardized vocabulary. The degree of confidence in the association between the drug(s) and the event(s) was reviewed by a panel of clinicians, applying a modified version of the decision table proposed by Karch and Lasagna [11] and was expressed as 'definite', 'probable', 'possible' and 'not related' (reactions in which more than one drug was suspected were usually included in the 'possible' category). Each form was subsequently codified to allow computer input for data management. Drugs were entered by trade name, but it was possible to reclassify them by nonproprietary name and Anatomical Therapeutic Chemical (ATC) code. For the purposes of this study we abstracted reactions to anti-inflammatory and antirheumatic products (ATC code M01) and to analgesics (ATC code N02). Specific slow-acting antirheumatic agents (e.g. gold salts) were excluded from the analysis. Opioid analgesics and antimigraine preparations were also excluded. Sulfamazone, which is a derivative of 4-formyl-fenazone and sulfamethoxypyridazine, classified as both a chemotherapeutic agent (ATC code J03) and an antirheumatic, was kept in the analysis.

Cases of toxic epidermal necrolysis were excluded from our surveillance, since they were the object of the case-control study we are conducting on this disease [10, 12].

Results

During the four intensive monitoring periods we collected 713 reactions to systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs, representing 33% of

Table 1. Distribution of the reactions according to the suspected drug and clinical pattern

	Fixed eruption	Erythema multiforme	Stevens-Johnson s.	Exanthema	Urticaria/angioedema	Purpura	Photo-sensitivity	Anaphylactic shock	Cutaneous necrosis	Lichenoid dermatitis	Total
Feprazone alone	29	8	5	8	8						58
combination ¹	30	10	10	3	6						59
Acetylsalicylic acid	16	7	1	11	40	1					76
Dipyrone	12	2		3	23			2			42
Propyphenazone ²	7	1		3	8					1	20
Naproxen	2			4	10						16
Diclofenac		1		4	7			1			13
Ketoprofen		1		2	6	1					10
Piroxicam	4	1		1	3		1				10
Paracetamol ³	3			4	2						9
Fenazone ⁴	3			2	4						9
Sulfamazone	3			1	3						7
Ibuprofen	1	1	1	1	2						6
Nimesulide	3			1							4
Indomethacin				1	2				1		4
Etodolac				2	1						3
Flurbiprofen	1				2						3
Floctafenine				1							1
Flunoxaprofen				1							1
Tenoxicam				1							1
Tiaprofenic acid				1							1
Benzylamine					1						1
All drugs	114	32	17	55	128	2	1	3	1	1	354

¹ The combination with paracetamol and guaifenesin accounted for 4 reactions and that with paracetamol, chlorphenamine maleate and phenylpropanolamine accounted for 55 reactions.

² Include the following combinations: with allobarbitol (6 reactions), with paracetamol and caffeine (8 reactions), with phenacetin and caffeine (5 reactions).

³ Include the combination with pseudoephedrine and triprolidine (3 reactions).

⁴ All the reactions to the combination product with caffeine and butalbital.

Table 2. Most serious and/or unusual reactions judged to be *possibly* related to use of analgesic-antipyretics and nonsteroidal anti-inflammatory drugs

Reaction	Suspected drug(s)	Reports, n
Vasculitis	flurbiprofen	1
	piroxicam	1
	feprazone	1
	acetylsalicylic acid	3
Stevens-Johnson s.	acetylsalicylic acid; sulfamazone	1
	diclofenac; dypirone	1
	feprazone; paracetamol	1
	dypirone	1
	paracetamol	1
	paracetamol + chlorphenamine maleate + phenylpropanolamine + feprazone	1
	diclofenac	1
Lichenoid dermatitis	feprazone	1
	ketoprofen; diclofenac	1

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total number of 2,137 reactions collected. The reactions judged to be possibly associated in 346 cases (48%), including 204 cases in which more than one drug was suspected, probably in 220 cases (31%) and definitely associated in 134 cases (19%). 13 reactions (2%) were discarded because they were judged not to be associated or because of other major flaws. The distribution of culpability scores for reactions to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs was quite similar to the distribution of reactions to several other major classes of drugs in the data base, suggesting that application of assessment criteria by participating dermatologists was uniform. To give an example, definite/probable reactions represented 50% of all reactions to analgesics and nonsteroidal anti-inflammatory drugs, and 53% of all reactions to antibiotics (ATC class J01). We considered for the main analysis the 354 reactions probably/definitely associated with systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs use. The profile of these reactions is reported in table 1. Urticaria, fixed eruptions and exanthemas accounted for more than 80% of all the reactions reported and these patterns of reaction, even with differences between drugs in their relative frequency, were shared by most of the drugs analyzed. Fixed eruptions represented 50% of all the reactions to feprazone reported, while urticaria was only 12%. The pattern was the reverse for acetylsalicylic acid. Erythema multiforme, and Stevens Johnson syndrome accounted for a great part of the remaining reactions, being reported with especially high frequency in association with feprazone. Sporadically reported reactions included anaphylactic shock, purpuras, photosensitivity, and vasculitis. Table 2 lists those reactions judged as *possibly* related to drug use which were more serious or unusual. 175 (25%) of the 700 patients experiencing reactions judged as related to drug use had histories of previous adverse drug reactions. The suspected drug was stopped for 564 (81%) cases; for 56 (51%) cases no other drug, including any treatment for the adverse reaction, was administered. As a consequence of the adverse reaction, 176 (25%) patients were hospitalized.

Discussion

We analyzed the cutaneous reaction profiles of systemic analgesic-antipyretics and nonsteroidal anti-inflammatory drugs, based on reports to the spontaneous reporting system of GISED. Our aim was to look for signals and previously unreported reactions. Although analgesic-antipyretics and nonsteroidal anti-inflammatory drugs are a

chemically heterogeneous group of compounds, a common general profile of reactions was identifiable from our study, including, in order of frequency, urticaria/angioedema, fixed eruptions, exanthemas, erythema multiforme and Stevens Johnson syndrome. This pattern, which could be defined as the 'expected' reaction profile of the drugs examined, is not peculiar to analgesics and nonsteroidal anti-inflammatory drugs but seems to reflect a more general experience in our surveillance. Figures for probable/definite reactions to all classes of systemic drugs, obtained from our data base, rank urticaria/angioedema first, with about one-third of all the reactions, followed by exanthemas (about 20%), fixed eruptions (15%) and erythema multiforme/Stevens Johnson syndrome (7%). These profiles are different from those obtained from traditional spontaneous reporting systems, which rank several types of 'rash', urticaria and pruritus as the most frequent patterns of reactions [13]. Differences could largely be explained by the setting of surveillance, which in our case is speciality- and mostly hospital-based.

Besides similarities, differences between drugs were observed with reference to the relative frequencies of single reaction patterns, with fixed eruptions and erythema multiforme/Stevens Johnson syndrome being reported with exceedingly high frequency in association with feprazone. This drug alone was responsible for 52% of all cases of fixed eruptions and 67% of all cases of erythema multiforme/Stevens Johnson syndrome attributed to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs. These findings are in agreement with data from surveillance systems in other countries in which regulatory actions have been taken [14]. Another serious reaction reported with unusually high frequency was anaphylactic shock, in association with dipyrone. Anaphylactic shock, as an idiosyncratic phenomenon, is a known reaction to the pyrazolone derivatives aminophenazone and dipyrone [15]. The findings from our study are in general agreement (although comparisons have to be limited to a few drugs) with the experience of the Adverse Drug Reaction Reporting System of the American Academy of Dermatology except for the frequency of photosensitivity and vesicobullous reactions to piroxicam [4]. These reactions are probably rarer than would be inferred from the data reported to the American Academy system, which gave special emphasis to newly discovered adverse reactions. It is also possible that the participating dermatologists underreported photosensitivity and bullous reactions. Photosensitivity has been reported in association with other analgesic-antipyretics and nonsteroidal anti-inflammatory drugs, including naproxen [16], tiaprofenic acid [17], ibuprofen, indometha-

cin and ketoprofen [18, 19], and none of these drugs was associated with photosensitivity in our study. In general, special caution should be taken when interpreting data for relative frequencies of reactions calculated from spontaneous reports [20, 21]. Differences could be explained in terms of differences in the frequencies of exposure and indications for drug use in the populations and of differences in the frequencies of reporting of the reactions by the doctors. We tried in our study to reduce the bias of selective reporting by asking dermatologists to report *all* the adverse events diagnosed in their current clinical practices during intensive monitoring periods and, in this respect, it was reassuring that the culpability scores were uniformly distributed between different drug classes in our survey. On the other hand, finding appropriate denominators (i.e. people exposed to the drug at a given time in the population) is a formidable task not adequately addressed in any study based on spontaneous reporting [21]. Roughly, based on drug utilization surveys recently conducted in selected areas in Italy [22], the most frequently prescribed analgesic-antipyretics and nonsteroidal anti-inflammatory drugs during the study period included, in order of decreasing frequency (with a ratio between the more and the less prescribed drug, greater than 1:10), several pyrazolone derivatives (i.e. feprazone, dipyrone, propyphenazone), acetylsalicylic acid and paracetamol, followed by diclofenac, ketoprofen, piroxicam, nimesulide, naproxen, indomethacin, ibuprofen, tiaprofenic acid, and etodolac. These figures, however, are based on a sample of only 300 prescribers and, for example, do not take into account over the counter drugs and self-prescriptions.

In our survey, to the best of our knowledge, some previously unreported reactions were collected. These included fixed eruption to nimesulide, fixed eruption to piroxicam, and fixed eruption to flurbiprofen. These are not completely unexpected findings, given the overall profile of reactions to analgesic-antipyretics and nonsteroidal anti-inflammatory drugs outlined before. Other interesting signals from our study included lichenoid dermatitis and vasculitis as possible reactions. Lichenoid dermatitis was associated with phenacetin and propyphenazone in a multiple agent drug (1 case), with diclofenac (1 case), with feprazone (1 case) and with ketoprofen and diclofenac taken together (1 case). Vasculitis was reported in association with flurbiprofen (1 case), with piroxicam (1 case) and with feprazone (1 case). Lichenoid dermatitis has been reported before in association with naproxen, aminophenazone and phenylbutazone [19, 23]; vasculitis has been previously reported in association with naproxen, acetylsalicylic acid, aclofenac, ibuprofen, indomethacin, phenylbutazone,

piroxicam, tiaprofenic acid and meclofenamate [4, 19, 24]. Both lichenoid reactions and vasculitis are reactions difficult to investigate by spontaneous reporting systems, because of the several possible etiologic factors involved and, in our opinion, more formal epidemiologic studies are needed [20].

The spontaneous reporting system of GISED is a new mechanism for reporting of adverse reactions by Italian dermatologists. The term 'spontaneous' as applied to our method is probably inaccurate. 'Spontaneous' reports originate in the absence of sustained external stimuli [25]. In our system we asked a network of dermatologists to play an active role by both systematically reporting, during limited periods, all the reactions they observed in their practice and by disseminating the method to other dermatologists. The main advantage of our method, as illustrated by our results, is the accurate clinical definition of cases, producing more specific profiles of adverse skin reactions. The method is probably biased toward identification of more serious and/or unusual and/or difficult-to-diagnose cutaneous manifestations (e.g. fixed eruption, Stevens-Johnson syndrome). Notably, it has been estimated that no more than 10% of severe adverse reactions have been reported to the traditional spontaneous monitoring programs [26]. A pitfall of the method is that milder reactions, e.g. pruritus, are probably underreported or not detected. These could include early manifestations of more serious slowly developing reactions (a striking example are the ocular symptoms induced by practolol). In principle, a speciality-based system could be more susceptible to a 'notoriety' bias, i.e. underreporting of adverse reactions that are not currently of great interest. The low rate of reports excluded by our coordinating center suggests, to some extent, that there was a conservative attitude in signalling, i.e. only clear patterns of adverse reactions were reported, with doubtful cases neglected. More in general, our method, like any other method based on spontaneous reporting, is subject to problems of overascertainment (physicians may attribute an adverse outcome to a drug when in fact it is not one) or underascertainment and suffers from the lack of good estimates of the population at risk, so that it is not possible to calculate rates. Signals could only arise based on level of causality, severity of reaction and the number of similar cases reported [27].

In conclusion, in spite of the above-mentioned limitations, our work provides evidence of the usefulness of a speciality-based surveillance system for spontaneous reporting of adverse reactions to drugs. We were able to collect a large number of reports from collaborating dermatologists, increasing our knowledge of the reaction profiles

some recently marketed drugs. Moreover, based on several hundred contacts with collaborating dermatologists, we believe that our system has increased the dermatologists' awareness of problems connected with identification and reporting of adverse reactions. The view of adverse reactions provided by our surveillance is limited to one organ, i.e. the skin, and it is desirable, in our opinion, that similar surveillance systems be activated for other specialities.

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