Different Risks for NSAID-Induced Anaphylaxis

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BACKGROUND: After drugs are marketed, spontaneous reporting systems can provide valuable information regarding the occurrence of suspected adverse drug reactions. The Netherlands Pharmacovigilance Foundation has received a substantial number of anaphylactic reaction reports related to the use of nonsteroidal antiinflammatory drugs (NSAIDs).

OBJECTIVE: To investigate whether the risk of anaphylactic reactions being reported during the use of various NSAIDs is greater than with other classes of drugs and if differences among NSAIDs exist.

METHODS: In a case/noncase design, reporting odds ratios (RORs) were calculated using logistic regression analysis. Cases were defined as reports in which anaphylactic or anaphylactoid reactions were reported; all other reports were considered as noncases. The index group consisted of reports in which NSAIDs were mentioned as the suspected medication; the reference group consisted of all other reports.

RESULTS: Between January 1985 and November 2000, the Netherlands Pharmacovigilance Foundation Lareb received 76 cases concerning anaphylactic reactions to NSAIDs. These drugs are strongly associated with anaphylactic reactions. The ROR adjusted for age, gender, and source of the reports was 9.4 (95% CI 6.9 to 12.7). Anaphylactic reactions associated with the use of naproxen, ibuprofen, and diclofenac were reported disproportionately with respect to other drugs. The corresponding RORs from logistic regression analysis adjusted for age, gender, and reporting source for diclofenac, naproxen, and ibuprofen were 17.2 (95% CI 12.1 to 24.5), 9.1 (95% CI 5.2 to 15.9), and 5.5 (95% CI 2.5 to 11.9), respectively.

CONCLUSIONS: The results of this study strengthen previous findings concerning the relative high risk of developing an anaphylactic reaction during the use of NSAIDs, particularly diclofenac, ibuprofen, and naproxen.

KEY WORDS: anaphylaxis, nonsteroidal antiinflammatory drugs, pharmacovigilance, quantitative signal detection.

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Nonsteroidal antiinflammatory drugs (NSAIDs) have a prominent place in the treatment of pain and arthritis.[1,2] NSAIDs, however, are also associated with serious and nonserious complications. The most frequently occurring adverse drug reactions (ADRs) related to NSAID use concern the gastrointestinal tract and kidney; blood cell or liver function disorders rarely occur.[3] NSAIDs have also been associated with acute allergic reactions, varying from urticaria and angioedema to anaphylactic reactions. With respect to the occurrence of anaphylactic reactions, limited evidence is available concerning the relative safety of these drugs. van der Klauw et al.[4] have shown that among patients admitted to a hospital because of anaphylactic reactions, NSAIDs were a frequent cause. Also, in spontaneous reporting systems (SRS) for adverse drug reactions, NSAIDs were frequently associated with anaphylactic reactions.[5] Although these potentially serious ADRs are reported with various NSAIDs,[4-20] it is not clear whether there are differences between individual agents.

After new drugs reach the market, SRS can provide valuable information regarding possible new ADRs. Furthermore, data sets of SRS contain information about ADRs that are already known, but were reported because of the seriousness of the reaction involved or concern of the reporting healthcare professional. In this context a substantial number of reports of anaphylactic reactions related to the use of NSAIDs were received by the Netherlands Pharmacovigilance Foundation Lareb. The aim of our study was to investigate whether the risk of anaphylactic

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reactions being reported during the use of various NSAIDs is greater than with other classes of drugs and if differences among NSAIDs exist.

Methods

SETTING

The Netherlands Pharmacovigilance Foundation Lareb maintains the national SRS on behalf of the Dutch Medicines Evaluation Board. ADRs are reported by physicians and pharmacists on a voluntary basis, and reports that are received are subject to review by qualified assessors. Special attention is paid to the description of the ADR. If needed, additional information concerning the clinical details of the report is retrieved. Data concerning the suspected ADR and the drugs involved are coded using the World Health Organization (WHO) ADR terminology and the Anatomical Therapeutic Chemical (ATC) classification system, respectively, and subsequently filed in a database.[21] In the ATC classification system, the drugs are divided into different groups according to the organ or system on which they act and their chemical, pharmacologic, and therapeutic properties.[22]

The primary goal of an SRS is to give an early warning of a possible causal relationship between an ADR and a drug of which the relation was previously unknown or incompletely documented.[23] For signal detection, every new report is reviewed on a regular basis in a discussion meeting in which the reported association between the suspected drug and ADR is assessed. This meeting is attended by assessors with specific experience in the field of spontaneous reporting. In addition to this case-by-case analysis, the extent to which a possible ADR is reported for a given suspected drug can be analyzed statistically.[24-29] We analyzed the association between NSAIDs and anaphylactic reactions using a case/noncase design and expressing the strength of the association as the ADR reporting odds ratio (ROR).[24,29]

DESIGN

The analysis included all reports received by the Lareb from January 1, 1985, through November 1, 2000, in which data concerning age and gender of the patients were available. Patients <10 years of age were excluded, because NSAIDs are rarely used in children in the Netherlands. In a case/noncase design, RORs were calculated by means of logistic regression analysis. The ROR is defined as the ratio of the exposure odds among reported cases to the exposure odds among reported noncases.[24,29] Cases were defined as all reports coded with the WHO preferred term anaphylactic shock or anaphylactoid reaction. These codes encompass the WHO-included terms anaphylactic shock, anaphylactoid reaction, anaphylactic reaction, anaphylaxis, and red-neck syndrome. Both preferred terms are considered to be a manifestation of an anaphylactic reaction, which can be considered as an acute systemic adverse reaction, simultaneously involving several organ systems.[30]

Characteristic symptoms of such a reaction may involve the skin, respiratory system, cardiovascular system, gastrointestinal system, or neuropsychological symptoms.[31] In the event that allergic symptoms concerning two or more organ systems were reported, the ADRs were classified as an anaphylactic reaction. Additionally, if shock-like symptoms were reported and the blood pressure was known to have decreased, reports were classified as anaphylactic shock. If symptoms pertaining to only one system and organ class were reported, like urticaria, bronchospasm, or shock, the ADRs were coded as such, and subsequently were treated as noncases; all other reports were considered as noncases. The index groups consisted of reports on which an NSAID (ATC code beginning with M01A) was mentioned as the suspected medication. The reference group consisted of all reports in which no NSAID was mentioned as the suspected medication.

Since 1985, the Netherlands Pharmacovigilance Foundation Lareb received reports on 23 different ATC codes concerning NSAIDs or combinations of NSAIDs and other drugs. Because of this large volume, results of the analysis of all separate NSAIDs were restricted to those drugs from which more than 100 reports were received.

NSAIDs can be used in combination with other drugs, such as misoprostol. Theoretically, one of the other drugs in the combination could be responsible for the anaphylactic reaction. When combinations of NSAIDs and other drugs were registered in the Netherlands, however, reports on these drugs were regarded as reports on the NSAID included in the combination. In the event where another medication was also a potential cause of the anaphylactic reaction, the reports were included as reactions to the NSAID involved.

RORs adjusted for age and gender of the patients, year of reporting, and source of the reports, either physician or pharmacist, were expressed as point estimates with corresponding 95% confidence intervals. For all statistical analyses, SPSS 10.0 was used.

Results

Between January 1985 and November 2000, a total of 28 003 reports of suspected ADRs were received. Of these, 841 reports were excluded because the patient was younger than 10 years; 252 reports were excluded because gender and/or age of the patients were not reported. Of the remaining 26 910 reports, 76 concerned a possible relationship between an NSAID and an anaphylactic reaction. All cases referred to the oral dosage form, except for one case concerning a diclofenac injection. Table 1 shows the distribution of age, gender, and source of the reports among cases and noncases. Among the cases, the age of patients was significantly higher; these cases were also more frequently reported by physicians as compared with pharmacists. The distribution between cases and noncases for different NSAIDs are shown in Table 2. Among the NSAIDs on which more than 100 reports were received,

Table 1. Distribution of Age, Gender, and Source of the Reports Among Cases and Noncases

Parameter	Cases (n = 190)	Noncases (n = 26 720)	p Value
Age (y), mean (SD)	52.2 (17.6)	47.7 (15.5)	<0.01[a]
Women, n (%)	121 (63.7)	17 294 (64.7)	NS[b]
Reporting physicians, n (%)[c]	149 (78.4)	18 690 (69.9)	<0.05[b]

NS = not significant.
[a]Student's *t*-test.
[b]Pearson χ^2.
[c]In comparison with the number of pharmacists.

Table 2. Distribution of Cases and Noncases Among Various NSAIDs and Other Suspected Drugs

Drug	Cases (n = 190) n (%)	Non cases (n = 26 720) n (%)
NSAIDs	76 (40)	2420 (9.1)
diclofenac	51 (26.8)	866 (3.2)
naproxen	15 (7.9)	448 (1.7)
ibuprofen	7 (3.7)	296 (1.1)
piroxicam	1 (0.5)	180 (0.7)
ketoprofen	0	175 (0.7)
indomethacin	0	105 (0.4)
other	2 (1.1)	350 (1.3)
Other suspected drugs	114 (60.0)	24 300 (90.9)

NSAIDs = nonsteroidal antiinflammatory drugs.

anaphylactic reactions were reported on diclofenac, naproxen, ibuprofen, and piroxicam. On ketoprofen and indomethacin no cases were reported, implying no ROR could be calculated for the latter drugs. Among the NSAIDs on which fewer than 100 reports were received, there were 2 additional cases (sulindac, nabumetone). Table 3 shows the results of the univariate and multivariate analysis. NSAIDs were strongly associated with reports of anaphylactic reactions. The ROR adjusted for age, gender, and source of the reports was 9.4 (95% CI 6.9 to 12.7).

The total number of reported reactions, the RORs with corresponding confidence intervals adjusted for age, gender, and source of the reports and the number of cases for different NSAIDs are shown in Figure 1. Anaphylactic reactions were disproportionally reported more for ibuprofen, naproxen, and diclofenac. For diclofenac, the adjusted ROR was 17.2 (95% CI 12.1 to 24.5), for naproxen 9.1 (95% CI 5.2 to 15.9), and for ibuprofen 5.5 (95% CI 2.5-11.9).

Discussion

The results of our study show that risk of an anaphylactic reaction being reported is increased during the use of NSAIDs, notably with diclofenac, naproxen, and ibuprofen; diclofenac appears to have the highest reporting rate among those agents.

Interpretation of the results originating from SRS should be done with great care. The method applied provides quantitative information about the extent of the associations between reported suspected drugs and ADRs with respect to other reports sent to the SRS. The rationale of the case/noncase design is that the proportion of ADRs is relatively constant over time and, for this reason, the reference group can be considered a measure of the background frequency of the suspected ADRs. This implies that interpretation of the quantitative results based on data sets of SRS requires specific knowledge of the composition of the database. For this reason, SRS are primarily used for signal detection purposes and not for hypothesis testing. An estimation of the actual incidence of the ADR in populations using the suspected drug cannot be made. Prescription data cannot be used to estimate the actual use of the drugs since some NSAIDs, like ibuprofen and naproxen, are also available without prescription in the Netherlands.

A case–cohort study[4] in the Netherlands showed that diclofenac in particular was among the most frequent causes of anaphylactic reactions leading to hospital admission, the relative risk of anaphylaxis relative to all other drugs being 9.5 (95% CI 3.7 to 24.5). The results of our study are in accordance with these findings, and furthermore demonstrate that anaphylactic reactions are also reported disproportionately for naproxen and ibuprofen.

Anaphylaxis is an immediate (type I) hypersensitivity reaction to an allergen, caused by its rapid cross-linking with specific immunoglobulin (Ig) E on tissue mast cells and peripheral blood basophils. It requires previous exposure to the foreign antigen. An anaphylactoid reaction, however, is not an IgE-mediated response but, similarly, involves inflammatory mediators to be released from mast cells and basophils. This activation of immune cells may occur both directly and as the result of disturbances in arachidonic acid metabolism and immune complex–mediated activation of complement.[32] These non-IgE mediated reactions, or anaphylactoid reactions, do not require previous exposure and may also be caused by NSAIDs.[20,32,33] Although pathophysiology differs to a certain extent, anaphylactic reactions and anaphylactoid reactions share the same clinical features and cannot be distinguished on clinical grounds.[32,33] It is unclear whether anaphylactic or anaphylactoid reactions predominate. For this reason, no distinction could be made between these reactions in this study.

An anaphylactic reaction was fatal in one patient during the use of an NSAID. This patient, a 62-year-old woman, used diclofenac. There were four fatal cases among the patients in whom an anaphylactic reaction was reported in association with another drug. Fatal cases associated with an anaphylactic reaction were not statistically significant

Table 3. Results of Univariate and Multivariate Logistic Regression Analysis

	Univariate Analysis		Multivariate Analysis	
	ROR	95% CI	ROR	95% CI
NSAIDs	6.7	5.0 to 9.0	9.4	6.9 to 12.7
diclofenac	12.5	9.0 to 17.6	17.2	12.1 to 24.5
naproxen	7.1	4.1 to 12.3	9.1	5.2 to 15.9
ibuprofen	5.0	2.3 to 10.9	5.5	2.5 to 11.9
piroxicam	1.2	0.2 to 8.5	1.2	0.2 to 11.7
other	1.2	0.3 to 4.9	1.4	0.3 to 5.6

NSAIDs = nonsteroidal antiinflammatory drugs; ROR = reporting odds ratio.

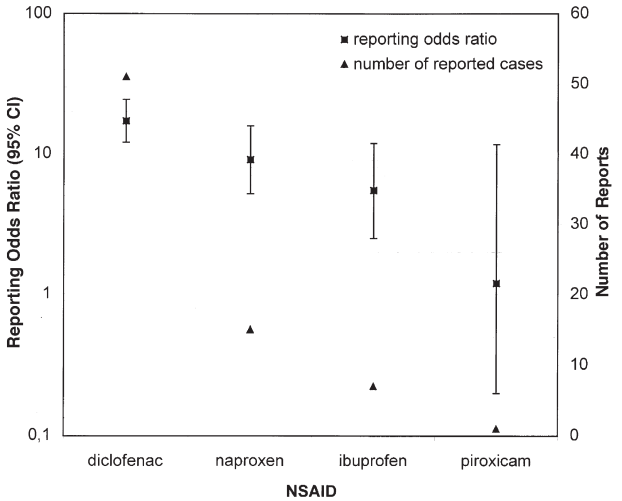

Figure 1. Results of the analysis of anaphylaxis associated with various NSAIDs versus all other reported cases. The total number of reported cases and the reporting odds ratios (semi-logarithmic scale) are shown, adjusted for gender and age of the patient, year of reporting, and source of the reports, with corresponding 95% confidence intervals for diclofenac, ibuprofen, naproxen, and piroxicam. NSAID = nonsteroidal antiinflammatory drug.

between NSAIDs and other drugs (Fisher's exact test $p > 0.05$).

NSAIDs can be subclassified with respect to their chemical structure. Diclofenac, tolmetin, and ketorolac belong to the heteroaryl acetic acids; ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, and oxaprozin belong to the arylpropionic acids.[34] When NSAIDs that have a similar chemical structure are grouped, heteroaryl acetic acids have an adjusted ROR of 19.7 (95% CI 13.8 to 28.1), while the adjusted ROR for the arylpropionic acids was 6.7 (95% CI 4.2 to 10.6). This suggests that the risk for an anaphylactic reaction is higher with the use of heteroaryl acetic acids.

In our study, of the 166 reports on the combination of diclofenac and misoprostol, 2 were characterized as anaphylactic reactions and were labeled as reports on diclofenac. The distribution of cases and noncases among diclofenac and the combination of diclofenac/misoprostol were similar (Fisher's exact test $p > 0.05$), showing that misoprostol was not likely to have an additional effect on the chance of an anaphylactic reaction being reported. In the event that combinations of NSAIDs and other drugs are considered to be noncases, the ROR adjusted for year of reporting, age, gender, and source of the reports for diclofenac referred to all reports on non-NSAIDs was 17.0 (95% CI 11.7 to 24.6).

Another suspected medication has been reported in 95 cases. These reports were not excluded in our study, but were regarded as reports on the NSAID involved. In 2 of these cases, an anaphylactic reaction was reported. The distribution among cases and noncases between the reports in which 2 or more suspected medications were used did not differ from cases where only an NSAID was reported (Fisher's exact test $p > 0.05$). This suggests that the anaphylactic reactions were likely to be caused by the NSAIDs involved. When reports with suspected drugs other than NSAIDs were regarded as noncases, the adjusted ROR for diclofenac was still 20.0 (95% CI 13.7 to 29.2).

Nonselective reporting of either the suspected drug or the suspected ADR has a similar effect on numerator and denominator of the ROR. For this reason, nonselective reporting has no influence on the magnitude of the ROR.[24] Selective reporting on the combination of drug and ADR reflecting the concern of healthcare professionals involved, however, may influence the ROR. We believe that this nondifferential bias, for instance precipitated by specific media attention to anaphylactic reactions occurring with certain drugs, is not likely to have occurred. Another confounding factor can be the intermittent use of some types of NSAIDs that enhance the chance of sensitization.

Elevated concentrations of leukotrienes can be found in tissues or exudates in several diseases, including asthma, diverse allergic states, psoriasis, spondyloarthritis, and gout.[35] It is unclear whether these elevated concentrations also enhance the chance for anaphylaxis; the indication for use subsequently might have been a confounding factor. Unfortunately, it was not possible to take intermittent use or the indication for use into account in this study, since this information is only available for a limited number of reports.

In the context of studying ADRs, the presence of contraindications is rather commonly predictive of the outcome criteria for ADRs, and may act as a confounder.[36] For example, in studying the risk for peptic ulcers among patients using NSAIDs, a previous history of gastric complaints may act as a confounder. Anaphylactic reactions, however, can be considered type B or idiosyncratic effects. These ADRs are characterized by their unpredictable nature, occur rarely, and are not primarily related to the main pharmacologic action of the drug.[23,37] Cross-hypersensitivity among NSAIDs may occur,[3] and a previous history of an anaphylactic reaction to an NSAID may be a reason to refrain from prescribing another NSAID in the future. Presumably, however, this condition is rare and therefore the risk of channeling is low. Channeling refers to the phenomenon that a drug is prescribed preferably for a specific group of patients with certain recognized risk factors.[38]

Finally, in the event of concomitant use of β-blocking drugs, signs of an anaphylactic reaction may become more severe.[39] Theoretically this may lead to a greater reporting rate. In an additional analysis, we looked for the existence of possible risk factors among the users of NSAIDs. Age, gender, and use of β-blocking agents among the users of NSAIDs did not differ significantly from other reports in the database.

Summary

Spontaneous ADR reporting data in the Netherlands show that anaphylactic reactions are more frequently reported in association with NSAIDs than is expected from the background frequency in the database, and that the connection is particularly strong for diclofenac, ibuprofen, and naproxen. Statistical analyses of reporting patterns support the view that diclofenac carries a higher risk for anaphylactic reactions than other NSAIDs. Although an estimation of the actual incidence of the ADR in populations using the suspected drug cannot be made, the results of our study lend support to previous findings concerning the relatively high risk of developing an anaphylactic reaction with NSAIDs. Anaphylaxis is a rare ADR; even if the risk for developing this ADR is increased by NSAID use, the actual risk is still low. More study is needed to determine the actual incidence of NSAID-induced anaphylaxis.

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EXTRACTO

OBJETIVO: El Sistema de Reporte Espontáneo utilizado para monitorear las reacciones adversas a medicamentos una vez son lanzadas al mercado provee información valiosa sobre la incidencia de estas reacciones. La Fundación para la Farmacovigilancia de los Países Bajos recibió un sinnúmero de reportes de reacciones anafilácticas asociadas al uso de los antiinflamatorios no esteroidales. El propósito del estudio era investigar si la incidencia de reacciones anafilácticas con los antiinflamatorios era mayor que con otras clases de fármacos y si existía diferencia entre antiinflamatorios.

MÉTODOS: Se calculó la relación de transformación de las probabilidades (RTP, ¨reporting odds ratio¨) entre los reportes identificados como casos y los que no fueron identificados como tal. El grupo identificado como casos fue constituido por aquellos reportes donde reacciones anafilácticas o de tipo anafiláctica fueron reportados; los demás reportes no fueron identificados como casos. El grupo primario consistió de los reportes donde los antiinflamatorios no esteroidales fueron identificados como los agentes causales; el grupo referencia consistió de todos los demás reportes.

RESULTADOS: La Fundación para la Farmacovigilancia de los Países Bajos recibió 76 casos de reacciones anafilácticas asociadas al uso de los antiinflamatorios no esteroidales entre enero de 1985 y noviembre de 2000. La asociación entre la anafilaxis y estos fármacos es fuerte. La RTP, ajustada por edad, sexo, y fuentes de los reportes, fue 9.4 (95% CI 6.9–12.7). Las reacciones anafilácticas asociadas al uso de naproxen, ibuprofen, y diclofenac fueron reportadas de manera desproporcionada al compararse con otros fármacos. La RTP correspondiente del análisis de regresión, ajustado por la edad, sexo, y fuentes de los reportes para diclofenac, naproxen, e ibuprofen fue 17.2 (95% CI 12.1–24.5), 9.1 (95% CI 5.2–15.9), y 5.5 (95% CI 2.5–11.9), respectivamente.

CONCLUSIONES: Los resultados de este estudio fortalecen los hallazgos previos sobre el riesgo de desarrollar reacciones anafilácticas cuando se usan antiinflamatorios no esteroidales, particularmente diclofenac, ibuprofen, y naproxen.

Mitchell Nazario

RÉSUMÉ

OBJECTIF: Les systèmes de déclaration spontanée d'effets indésirables permettent de recueillir des informations précieuses sur l'incidence d'effets indésirables suivant la mise en marché des médicaments. Le centre Netherlands Pharmacovigilance Foundation a reçu un nombre considérable de rapports de réactions anaphylactiques reliées à l'usage d'anti-inflammatoires non stéroïdiens (AINS). Le but de cette étude était d'évaluer si le risque de rapporter des réactions anaphylactiques suivant la prise d'AINS était supérieur à celui d'autres classes de médicaments et s'il existait des différences entre les divers AINS.

MÉTHODE: Il s'agit d'une étude cas-témoins où des risques relatifs approchés (RRA) ont été calculés en utilisant des analyses de régression logistique. Les cas ont été définis comme les cas rapportés de réactions anaphylactiques ou anaphylactoïdes. Les autres cas rapportés au centre ont constitué le groupe des cas témoins. Le groupe Index constituait les cas reliés possiblement à la prise d'AINS; le groupe de référence comprenait tous les autres cas rapportés.

RÉSULTATS: Entre janvier 1985 et novembre 2000, le centre a reçu 76 cas de réactions anaphylactiques reliées aux AINS. Le RRA de rapporter une réaction anaphylactique reliée aux AINS, ajusté pour l'âge, le sexe, et la source des rapports, était de 9.4 (IC 95% 6.9–12.7). Les réactions anaphylactiques associées à l'utilisation du naproxen, ibuprofène, and diclofénac ont été rapportés de façon disproportionnée par rapport aux autres médicaments; les RRA étaient respectivement de 17.2 (IC 95% 12.1–24.5) pour le diclofénac, de 9.1 (IC 95% 5.2–15.9) pour le naproxen, et de 5.5 (IC 95% 2.5–11.9) pour l'ibuprofène.

CONCLUSIONS: Les résultats de cette étude s'ajoutent aux données existantes indiquant le risque relatif important de développer une réaction anaphylactique suivant l'usage d'AINS, notamment avec le diclofénac, l'ibuprofène, et le naproxen.

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