Eur J Clin Pharmacol (2000) 56: 733–738
DOI 10.1007/s002280000215

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

**Eugène P. van Puijenbroek · Antoine C. G. Egberts
Eibert R. Heerdink · Hubert G. M. Leufkens**

Detecting drug–drug interactions using a database for spontaneous adverse drug reactions: an example with diuretics and non-steroidal anti-inflammatory drugs

Received: 27 April 2000 / Accepted in revised form: 7 September 2000 / Published online: 7 November 2000

Abstract *Objective*: Drug–drug interactions are relatively rarely reported to spontaneous reporting systems (SRSs) for adverse drug reactions. For this reason, the traditional approach for analysing SRS has major limitations for the detection of drug–drug interactions. We developed a method that may enable signalling of these possible interactions, which are often not explicitly reported, utilising reports of adverse drug reactions in data sets of SRS. As an example, the influence of concomitant use of diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) on symptoms indicating a decreased efficacy of diuretics was examined using reports received by the Netherlands Pharmacovigilance Foundation Lareb.
Methods: Reports received between 1 January 1990 and 1 January 1999 of patients older than 50 years were included in the study. Cases were defined as reports with symptoms indicating a decreased efficacy of diuretics, non-cases as all other reports. Exposure categories were the use of NSAIDs or diuretics versus the use of neither of these drugs. The influence of the combined use of both drugs was examined using logistic regression analysis. *Results:* The odds ratio of the statistical interaction term of the combined use of both drugs was increased [adjusted odds ratio 2.0, 95% confidence interval (CI) 1.1–3.7], which may indicate an enhanced effect of concomitant drug use.
Conclusion: The findings illustrate that spontaneous reporting systems have a potential for signal detection and the analysis of possible drug–drug interactions. The method described may enable a more active approach in the detection of drug–drug interactions after marketing.

Key words Drug–drug interaction · Pharmacovigilance · Spontaneous reporting system

E. P. van Puijenbroek (✉)
Netherlands Pharmacovigilance Foundation Lareb,
Goudsbloemvallei 7, 5237 MH's-Hertogenbosch,
the Netherlands
Tel.: +31-73-6469707; Fax: +31-73-6426136
e-mail: e.vanpuijenbroek@lareb.nl

A. C. G. Egberts[1] · E. R. Heerdink · H. G. M. Leufkens
Department of Pharmacoepidemiology and Pharmacotherapy,
Utrecht Institute for Pharmaceutical Sciences, Utrecht,
the Netherlands

Present address:
[1]Hospital Pharmacy Midden-Brabant,
TweeSteden Hospital and St. Elisabeth Hospital,
Tilburg, the Netherlands

Introduction

Since the early 1960s, spontaneous reporting systems (SRSs) have been used to detect adverse drug reactions (ADRs) after marketing of drugs. Nowadays, these reporting systems play a major role in pharmacovigilance [1]. Since the size of data sets is increasing, automated signal generation may be a promising tool for selecting possible combinations of ADRs and drugs that might be worthwhile analysing in more detail [2, 3, 4]. For signal detection concerning possible unexpected ADRs, various measures of disproportionality can be used, including reporting odds ratios (RORs) [5, 6].

The basic principle of looking for disproportionality can be extended to the detection of drug–drug interactions, which are generally more difficult to detect. Usually a drug–drug interaction might be suspected in the event that similar substances have proven to cause a similar interaction. If this is not the case, detection becomes more complicated. In the event a drug–drug interaction is unexpected given the previous knowledge, it is rarely reported to a SRS. Furthermore, in individual patients, it is usually not clear whether ADRs arise directly from the use of a certain drug or that the ADR concerned is in fact the result of an underlying pharmacodynamic or pharmacokinetic drug–drug interaction. In particular in the elderly, additional factors such

as co-morbidity and multiple drug use may be present, enhancing the number of possible explanations of a certain unexpected clinical event. In pre-marketing trials, patients with multiple drug use are usually excluded, which makes the detection of drug–drug interactions in the post-marketing period even more important.

In the event of a drug–drug interaction, one drug influences the effect of another drug. This may subsequently cause an increase or decrease in the number of reported ADRs of the latter drug. By analysing individual reports, it is usually difficult to recall whether specific concomitant medication was also used in similar reports. An automated statistical approach may be helpful in analysing large numbers of these reports and in revealing the existence of these complex relationships. The influence of the combined use of drugs can be studied by introducing a statistical interaction term in a logistic model for the calculation of RORs, as was shown in a previous study by our group [7].

As an example of the approach described, in reports received by the Netherlands Pharmacovigilance Foundation Lareb, the concomitant use of both diuretics and non-steroidal anti-inflammatory drugs (NSAIDs) was associated with the occurrence of symptoms that may point towards a reduction of the therapeutic effects of diuretics. This drug–drug interaction has been described in several case reports and studies [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21].

Methods

Setting and design

The Netherlands Pharmacovigilance Foundation Lareb is the national centre for submitting spontaneous reports of suspected ADRs originating from health care professionals in the Netherlands [22]. These reports are considered to be a reflection of the ADRs that occur in daily practice, taking into account the various degrees of underreporting that are an inherent attribute of spontaneous reporting [23, 24, 25, 26]. The analysis of drug–drug interactions is based on the assumption that specific ADRs may occur more frequently when both drugs are used concomitantly in comparison with separate use [7, 27]. This specific increase in reports is assumed to be reflected in the number of reports to Lareb.

All reports submitted to Lareb between 1 January 1990 and 1 January 1999 of patients older than 50 years were included in the analysis. Data concerning ages and genders of the patients had to be available.

Selection of cases and non-cases

A decrease in the efficacy of diuretics may express itself as the occurrence of oedema or signs indicating the onset or worsening of congestive heart failure (CHF). After being received by Lareb, the reported possible ADR is coded by a qualified assessor using the World Health Organization (WHO) Adverse Drug Reaction Terminology [28]. The presence of one or more of the following WHO preferred terms on the reports was therefore considered as an indication for this situation: 'oedema', 'oedema dependent', 'oedema generalised', 'oedema peripheral', 'cardiac failure', 'cardiac failure left', 'cardiac failure right', 'pulmonary oedema' and 'oedema legs'. Reports that mentioned one of the aforementioned ADRs were defined as cases. Non-cases were defined as all other reports.

Exposure categories

Information about concomitant drug use is requested on the reporting forms. For the vast majority of the reports Lareb has the patients' drug dispensing history from community pharmacies. All drugs in use at the moment the ADR occurred were considered possible causes of the ADR. If a drug was used to treat the ADR it is not listed as concomitant medication. The reporting health professionals give an indication which drug is considered the suspected drug. Usually, however, only one drug is indicated. Since we were looking for drug–drug interactions, we therefore made no distinction between suspected and non-suspected medication. All medication that the patient was using according the medication history on the calendar date of the event was considered.

Exposure categories were the use of NSAIDs [WHO Anatomical Therapeutic Chemical (ATC) classification code M01A], or diuretics (ATC code C03) versus the use of neither of these drugs. Covariates used in the analysis were: type of health professional that reported the ADR (either pharmacist or physician), year of reporting, age and gender of the patient involved, the use of antidiabetic drugs (ATC code A10), cardiac glycosides (ATC code C01), antihypertensive drugs (ATC code C02), peripheral vasodilatating drugs (ATC code C04), β-blocking agents (ATC code C07), calcium channel blocking agents (ATC code C08) and drugs acting on the renin angiotensin aldosterone system (RAAS, ATC code C09).

Statistical analysis

For the analysis, the following logistic model was used:

$$\log(\text{odds}) = \beta_0 + \beta_1 N + \beta_2 D + \beta_3 N^{*} D + \beta_{n-x} C_{n-x}$$

where N = NSAIDs, D = diuretics, C_{n-x} = different covariates, i.e. age, source and reporting year.

A statistically significant value of the interaction term β_3 indicates an additional effect of concomitant use of diuretics and NSAIDs. Probability (P) values of 0.05 or less were considered statistically significant. For all analyses the statistical package SPSS 8.0 was used.

Results

From January 1990 until January 1999, Lareb received 9907 reports of patients aged over 50 years. Eighty-five reports were excluded because the age or gender of the patient was not known. A total of 9822 reports, which were separated into 305 cases and 9517 non-cases, were included in the analysis.

Characteristics of cases and non-cases concerning age, gender, source of the reports and the use of several cardiac drugs are provided in Table 1. Among the cases, the number of females and the age of the patients ($P < 0.01$, t-test) is significantly higher. Also the use of diuretics, NSAIDs, antihypertensive drugs and calcium channel blocking agents was more frequent among the cases. There were no differences concerning the use of insulin and oral antidiabetic drugs, cardiac glycoside drugs, peripheral vasodilatating drugs, beta-blocking agents, and drugs acting on the RAAS in the medication history.

Among the cases, the following suspected ADRs were mentioned on the reporting forms: oedema ($n = 68$),

Table 1 Characteristics of cases and non-cases. *NSAIDs* non-steriodal anti-inflammatory drugs; *95%CI* 95% confidence interval; *RAAS* renin angiotensin aldosterone system

	Cases, n (%), $n = 305$	Non-cases, n (%), $n = 9517$	Odds ratio (95% CI)
Mean age (years)	67.4	65.9	
Females	224 (73.4)	5848 (61.4)	1.73 (1.34–2.24)
Reports by physicians	210 (68.9)	6220 (65.5)	1.17 (0.92–1.50)
NSAIDs	67 (22.0)	1546 (16.2)	1.45 (1.11–1.91)
Diuretics	78 (25.6)	1697 (17.8)	1.58 (1.22–2.06)
Insulin and oral antidiabetic drugs	17 (5.6)	656 (6.9)	0.79 (0.49–1.31)
Cardiac glycosides	43 (14.1)	1185 (12.5)	1.15 (0.83–1.60)
Antihypertensive drugs	14 (4.6)	209 (2.2)	2.14 (1.23–3.73)
Peripheral vasodilatating drugs	3 (1.0)	79 (0.8)	1.19 (1.37–3.78)
Beta-blocking agents	66 (21.6)	1727 (18.1)	1.25 (0.94–1.64)
Calcium antagonists	127 (41.6)	1246 (13.1)	4.74 (3.74–6.00)
Drug acting on the RAAS system	49 (16.4)	1717 (18.0)	0.87 (0.64–1.19)

Table 2 Distribution of drugs present in cases and non-cases, stratified for the use of non-steroidal anti-inflammatory drugs (NSAIDs) and diuretics. *95%CI* 95% confidence interval; *OR* odds ratio

		Cases	Non-cases	Total	OR (95% CI)
NSAID not present	Diuretic not present	185	6527	6712	
	Diuretic present	53	1444	1497	1.29 (0.95–1.77)
	Total	238	7971	8209	
NSAID present	Diuretic not present	42	1293	1335	
	Diuretic present	25	253	278	3.03 (1.82–5.08)
	Total	67	1546	1613	

oedema dependent ($n = 90$), oedema generalised ($n = 14$), oedema peripheral ($n = 45$), cardiac failure ($n = 14$), cardiac failure left ($n = 6$), oedema pulmonary ($n = 3$) and oedema legs ($n = 66$). The WHO term 'cardiac failure right' was not noted on the report forms. Since more than one ADR can be attributed to one report, the total number of suspected ADRs exceeds the number of cases.

The distribution of drugs present in cases and non-cases, stratified for the use of NSAIDs and diuretics, is shown in Table 2. The corresponding odds ratios with 95% confidence intervals are also shown. If no NSAID was used, the crude odds ratio for the use of diuretics was 1.29 (0.95–1.77). If an NSAID was used by the patient, the crude odds ratio was 3.03 (1.82–5.08).

Crude and adjusted odds ratios and 95% confidence intervals are shown in Table 3. The use of diuretics or NSAIDs alone is not statistically significant as an increased risk for onset or worsening of symptoms of CHF or oedema. However, the odds ratio of the statistical interaction term NSAIDs × diuretics is statistically significant (adjusted odds ratio 2.0, 95%CI 1.1–3.7). This is an indication for an enhanced chance of cases being reported, associated with the combined use of both drugs.

Table 3 Association between non-steroidal anti-inflammatory drugs (NSAIDs), diuretics and covariates on the occurrence of symptoms of congestive heart failure (CHF) during the use of NSAIDs and diuretics. Odds ratio adjusted for age, gender, source, year of reporting and the use of antidiabetic drugs, cardiac glycosides, antihypertensive drugs, peripheral vasodilatating drugs, β-blocking agents, calciumantagonists, and drugs acting on the renin angiotensin aldosterone system (RAAS). *95% CI* 95% confidence interval; *ATC* anatomical therapeutic chemical

Covariates	Adjusted odds ratio (95% CI)	Unadjusted odds ratio (95% CI)
NSAIDs (ATC code M01A)	1.22 (0.86–1.73)	1.15 (0.82–1.61)
Diuretics (ATC code C03)	1.05 (0.75–1.46)	1.29 (0.95–1.77)
Interaction term NSAIDs diuretics	2.00 (1.08–3.69)	2.35 (1.29–4.28)
Age (years)	1.01 (1.00–1.02)	
Gender female	1.80 (1.38–2.34)	
Source (physician)	0.93 (0.71–1.22)	
Year of reporting	0.93 (0.88–0.98)	
Antidiabetic drugs (A10)	0.75 (0.45–1.25)	
Cardiac glycosides (C01)	0.68 (0.48–0.98)	
Antihypertensives (C02)	1.94 (1.09–3.45)	
Peripheral vasodilatating drugs (C04)	0.85 (0.25–2.86)	
β-blocking agents (C07)	1.06 (0.79–1.41)	
Calcium antagonists (C08)	5.25 (4.09–6.75)	
Drugs acting on the RAAS system (C09)	0.83 (0.60–1.15)	

Discussion

Methodology

In the event drug–drug interactions had not been previously observed clinically or experimentally, the detection in the post-marketing phase is troublesome. We developed a method by which drug–drug interactions, which were not reported explicitly, can be detected using a spontaneous reporting system. Although this method was developed to detect unknown drug–drug interactions, in this case the well known interaction between diuretics and NSAIDs was used to illustrate this new approach.

In contrast to the exposure categories diuretics or NSAIDs, the odds ratio of the statistical interaction

term of the combined use of both drugs was increased, which may indicate an enhanced effect of concomitant drug use. As shown in Table 2, the ROR expressing the magnitude of the association between diuretics and signs of oedema or CHF increased when NSAIDs were used among the concomitant medications. This odds ratio can also be calculated as the product of the ROR of diuretics (1.29) and the ROR of the interaction term (2.35).

The analysis rests upon the assumption that the data set of the SRS is a close representative of the event rate occurring in the population of drug users. In this way, the calculated odds ratios approximate the incidence rate of the ADRs in the population of drug users. The observation of a disproportionate association relative to the whole database, even if different adjustments are made, does not imply a causal relationship but suggests an association and serves as a starting point for further analysis. The methodology is to be used for signalling interactions and not for signal testing. Interpretation of the data should be done with great trepidation due to the spontaneous character of the reports giving rise to all possible sources of bias. If there is a specific interest in an interaction for instance, a reporting bias might occur. None of the original reporting forms, however, mentioned a suspicion of a possible drug–drug interaction. Increased reporting due to a recent introduction of a drug or attention for an ADR in the media does not necessarily influence the reporting odds ratio since non-selective reporting bias has a similar effect on both numerator and denominator [5]. Another point of attention is confounding bias. For instance, a third drug may act as a confounder when it is associated with one of the drugs or the concomitant use of both suspected drugs. The interaction term NSAIDs × diuretics also might have been increased due to confounding if a statistical interaction existed between the use of NSAIDs and a pre-existing CHF, for which diuretics were used to treat this condition. Therefore, in a separate analysis, the interaction terms NSAIDs × cardiac glycosides and NSAIDs × ACE-inhibitors were added to the logistic model. The adjusted odds ratios for the latter interaction terms were not significantly increased, whereas the adjusted odds ratio for the interaction term NSAIDs × diuretics was 2.0 (95% CI 1.0–3.7). These findings are supportive for an actual interaction between diuretics and NSAIDs and not for confounding due to an interaction between the use of NSAIDs and a pre-existing cardiac failure.

Different covariates were used in the analysis. Since pre-existing impairment of kidney function, enhancing the risk of using NSAIDs, for instance in case of diabetes mellitus and hypertension, cannot be excluded [29], both antidiabetic drugs and antihypertensive agents were used as covariates. The use of NSAIDs alone (in the absence of the use of diuretics) is also associated with signs of CHF [20, 30, 31] and oedema is a common ADR of these drugs [32]. The use of calcium antagonists is also associated with leg oedema [33]. In our study, the influence of calcium antagonists on the occurrence of symptoms of CHF, mainly oedema, was evident. If an additional analysis is done after exclusion of all reports that mention the presence of one of the calcium antagonists in the medication history, the adjusted odds ratio of the interaction term NSAIDs × diuretics was still 2.6 (95% CI 1.2–5.3).

The source of the reports was also used as a covariate, since physicians might report signs of CHF more often than pharmacists; however, pharmacists might be more familiar with the drug–drug interaction under investigation. In the logistic model we corrected for age of the patient, since the change on CHF increases in elderly patients. In this age group the use of NSAIDs also might increase, i.e. because of rheumatological disorders. Because of the various degrees of underreporting that are inherent to SRS, it is difficult to estimate the true incidence of a possible interaction.

NSAIDs and diuretics

Several reports in the literature suggest that concomitant use of diuretics and NSAIDs might lead to a decrease in the effect of the diuretic drug [8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21]. This applies to sulphonamides as well as thiazide diuretics. Because of the small number of reports with combined use of NSAIDs and diuretics, we did not make a distinction between different classes of NSAIDs and diuretics. In larger databases that also offer the possibility of the use of concomitant medication, studying the different classes of NSAIDs would be possible.

In this study we used a limited number of ADR codes that might indicate a decrease in the effect of diuretics. Since the starting point in the analysis was a reduction in the effect of diuretics, the analysis was not restricted to oedema only. Nevertheless, the number of cases that were coded as cardiac failure was rather low (6.5%). This might be partially related to the original descriptions of the reporting health professional, which sometimes hampers assigning an appropriate diagnosis. In such cases only the symptoms can be coded. Since it was not always clear when codes for dyspnoea and related pulmonary problems should have been attributed to respiratory or cardiological problems, they cannot be used for automated signal detection. In our database, the majority of cases of dyspnoea is used for shortness of breath resulting from a pulmonary cause. Using the code dyspnoea in the analysis will therefore result in a dilution of the effect.

Practical considerations of detecting drug–drug interactions

Detecting drug–drug interactions in data sets of SRS implies a meticulous process. In theory a large number of drug–drug interactions is possible. For various combinations, either selected at random, or selected based

on a related drug–drug interaction, the interaction term of the covariates involved can be derived. For this reason, analysis of drug–drug interactions should be developed as an automated process. The first selection is based on the presence of a disproportionate increase in the number of reports of a certain ADR in association with a combined drug use (unadjusted odds ratio). This step might be executed automatically by a computer programme. A second step is the refinement of the signal using a dedicated correction for possible confounders present in the database (adjusted odds ratio). In general, a sufficient number of cases where both drugs are used concomitantly is a prerequisite for detecting interactions in a database for ADRs. Furthermore, the drug–drug interaction should lead to an increase in the number of reports, which implies a rather strong clinical effect. If the association is monitored for in pharmacist or physician information systems, there is a chance that it will be reported less frequently since it might be considered as a well-known interaction.

The aim of the present study was to illustrate the possible use of an SRS as a tool for signalling drug–drug interactions. Our results were indeed supportive for this drug–drug interaction. Given the fact that this interaction was present in a relatively small database, the use of larger databases may be promising. Although in our example we strengthened a signal that was already known in literature, SRS may also be used for the actual detection of drug–drug interactions, provided high quality reports are available and concomitant drug use is filed in the database. Due to an increase in the size and quality of the SRS databases, detection and analysis of drug–drug interactions clearly offer a major challenge for pharmacovigilance in the near future. In contrast to the present way of detecting drug–drug interactions, the method described provides an active approach in the post-marketing phase of drugs.

Acknowledgements We acknowledge the Netherlands Organisation for Applied Scientific Research (TNO), Prevention and Health subdivision, for partly funding this study (project ZON 28-2632). There was no conflict of interest.

References

1. Meyboom RH, Egberts AC, Edwards IR, Hekster YA, de Koning FH, Gribnau FW (1997) Principles of signal detection in pharmacovigilance. Drug Saf 16: 355–365
2. Bate A, Lindquist M, Edwards IR, Olsson S, Orre R, Lansner A, De Freitas RM (1998) A Bayesian neural network method for adverse drug reaction signal generation. Eur J Clin Pharmacol 54: 315–321
3. Lindquist M, Edwards IR, Bate A, Fucik H, Nunes AM, Stahl M (1999) From association to alert – a revised approach to international signal analysis. Pharmacoepidemiol Drug Saf 8: S15–S25
4. Meyboom RH, Egberts AC, Gribnau FW, Hekster YA (1999) Pharmacovigilance in perspective. Drug Saf 21: 429–447
5. Stricker BHC, Tijssen JGP (1992) Serum sickness-like reactions to cefaclor. J Clin Epidemiol 45: 1177–1184
6. Egberts ACG, Meyboom RHB, de Koning GHP, Bakker A, Leufkens HGM (1997) Non-puerperal lactation associated with antidepressant drug use. Br J Clin Pharmacol 44: 277–281
7. Van Puijenbroek EP, Egberts ACG, Meyboom RHB, Leufkens HGM (1999) Signaling possible drug–drug interactions in a spontaneous reporting system: delay of withdrawal bleeding during concomitant use of oral contraceptives and itraconazol. Br J Clin Pharmacol 47: 689–693
8. Patak RV, Mookerjee BK, Bentzel CJ, Hysert PE, Babej M, Lee JB (1975) Antagonism of the effects of furosemide by indomethacin in normal and hypertensive man. Prostaglandins 10: 649–659
9. Rawles JM (1982) Antagonism between non-steroidal anti-inflammatory drugs and diuretics. Scott Med J 27: 37–40
10. Symmons DP, Kendall MJ, Rees JA, Hind ID (1983) The effect of flurbiprofen on the responses to frusemide in healthy volunteers. Int J Clin Pharmacol Ther Toxicol 21: 350–354
11. Daskalopoulos G, Kronborg I, Katkov W, Gonzalez M, Laffi G, Zipser RD (1985) Sulindac and indomethacin suppress the diuretic action of furosemide in patients with cirrhosis and ascites: evidence that sulindac affects renal prostaglandins. Am J Kidney Dis 6: 217–221
12. Brater C, Chennavasin P (1980) Indomethacin and the response to bumetanide. Clin Pharmacol Ther 27: 421–425
13. Ahmad S (1984) Indomethacin–bumetanide interaction: an alert (letter). Am J Cardiol 54: 246–247
14. Favre L, Glasson P, Riondel A, Vallotton MB (1983) Interaction of diuretics and non-steroidal anti-inflammatory drugs in man. Clin Sci 64: 407–415
15. Baker DE (1988) Piroxicam–furosemide drug interaction (letter). Drug Intell Clin Pharm 22: 505–506
16. Hartmann D, Kleinbloesem CH, Lucker PW, Vetter G (1987) Study on the possible interaction between tenoxicam and furosemide. Arzneimittelforschung 37: 1072–1076
17. Wa TC, Lawson M, Jackson SH, Hitoglou-Makedou A, Turner P (1991) Interaction of ketoprofen and frusemide in man. Postgrad Med J 67: 655–658
18. Herchuelz A, Derenne F, Deger F, Juvent M, Van Ganse E, Staroukine M, Verniory A, Boeynaems JM, Douchamps J (1989) Interaction between nonsteroidal anti-inflammatory drugs and loop diuretics: modulation by sodium balance. J Pharmacol Exp Ther 248: 1175–1181
19. Kaufman J, Hamburger R, Matheson J, Flamenbaum W (1981) Bumetanide-induced diuresis and natriuresis: effect of prostaglandin synthetase inhibition. J Clin Pharmacol 21: 663–667
20. Feenstra J, Grobbee DE, Mosterd A, Stricker BH (1997) Adverse cardiovascular effects of NSAIDs in patients with congestive heart failure. Drug Saf 17: 166–180
21. Heerdink ER, Leufkens HG, Herings RM, Ottervanger JP, Stricker BH, Bakker A (1998) NSAIDs associated with increased risk of congestive heart failure in elderly patients taking diuretics. Arch Intern Med 158: 1108–1112
22. Broekmans AW, Lekkerkerker JFF, De Koning GHP, Vree PH (1996) Current regulations for reporting of side effects in The Netherlands after 1995. Ned Tijdschr Geneeskd 140: 1166–1167
23. Tubert-Bitter P, Bégaud B (1993) Comparing safety of drugs. Post Marketing Surveillance 7: 119–137
24. Martin RM, Kapoor KV, Wilton LV, Mann RD (1998) Underreporting of suspected adverse drug reactions to newly marketed (“black triangle”) drugs in general practice: observational study. BMJ 317: 119–120
25. Pierfitte C, Begaud B, Lagnaoui R, Moore ND (1999) Is reporting rate a good predictor of risks associated with drugs? Br J Clin Pharmacol 47: 329–331
26. Lumley CE, Walker SR, Hall GC (1986) The under-reporting of adverse drug reactions seen in general practice. Pharm Med 1: 205–212

27. Amery W (1993) Analysis of the information in a central ADE database. Int J Risk Saf Med 5: 123
28. Anonymous. WHO Adverse Drug Reaction Dictionary. 1995 WHO collaborating Centra for International Drug Monitoring, Uppsala Sweden
29. Blackshear JL, Davidman M, Stillman MT (1983) Identification of risk for renal insufficiency from nonsteroidal anti-inflammatory drugs. Arch Intern Med 143: 1130–1134
30. Nevins M, Berque S, Corwin N, Lyon L (1969) Phenylbutazone and pulmonary oedema. Lancet 2: 1358
31. Tashima CK, Rose M (1974) Pulmonary edema and salicylates (letter). Ann Intern Med 81: 274–275
32. Coles LS, Fries JF, Kraines RG, Roth SH (1983) From experiment to experience: side effects of nonsteroidal anti-inflammatory drugs. Am J Med 74: 820–828
33. Lim PO, MacDonald RM (1996) Antianginal and β-adrenoreceptor blocking drugs. In: Lim PO, MacDonald M, Dukes MNG (eds) Meyler's side effects of drugs, 13th edn. Elsevier, Amsterdam, pp 488–535