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Case-Population Studies in Pharmacoepidemiology

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Abstract

The case-population approach aims at providing a risk estimate by comparing the incidence of the disease of interest among those exposed to the drug under study with the incidence among the non-exposed. For that purpose, the cases with the disease of interest have to be ascertained independently of the exposure status. Their rate and pattern of exposure have to be ascertained by interview with a structured questionnaire. Information on the patterns and the prevalence of drug consumption is needed in order to estimate the rate of exposure, and drug consumption statistics can be used to this end. In this paper, we review the main characteristics of studies using this approach or a similar one, and studies where series of cases exposed to the drug of interest were compared with drug consumption statistics. We looked at selected basic methodological requirements. Most of the studies reviewed suffer from incomplete case ascertainment, inaccurate definition of the disease of interest, incomplete information on exposures and other risk factors, and/or limited control of potential confounding, among other limitations. All the reviewed studies had several limitations regarding the estimation of the population at risk.

The methods used in case-population studies should be clearly described, particularly with respect to the identification of the cases (numerator) and the estimation of the consumption prevalence (denominator). Case-population studies can give approximate risk estimates, but the method should be validated by comparing its results with those of case-control studies.

When a new drug is released for marketing, its safety regarding the risk of rare adverse events is substantially unknown. When a new, previously undescribed adverse drug reaction (ADR) is identified, health authorities may take an array of different actions, such as modifying information on ADRs in the Summary of Product Characteristics, limiting indications, extending contraindications, reducing the recommended dose, or withdrawing the drug from the market. Drug withdrawal is the most worrying of these situations, and can be regarded as the tip of the iceberg in the domain of drug-safety decision making.

In Europe and in the US, 3 to 4% of all newly marketed drugs from 1974 to 1993 had to be withdrawn because of adverse events.[1] Of these, the most frequent were type B reactions – unexpected, non-dose related, not predictable adverse effects[2] – mainly hepatotoxicity, blood dyscrasias and cutaneous reactions.[1,3] The median time between the

date of regulatory approval and the date of discontinuation ranged from 1 to 5 years, depending on the country.[1]

These adverse events have been discovered by means of case reports by clinicians and, in a limited number of cases, from the results of observational studies.[4-6] In this context, spontaneous reporting can be regarded as an extension of publication of single case reports, because it consists of assembling as large as possible a series of cases. It is generally acknowledged that spontaneous reporting is useful for signal generation, but is invalid for risk estimation. On the other hand, regulatory action should be ideally based on quantitative evidence from epidemiological controlled studies. However, these usually take time, and may thus prove useless for regulatory decision taking. In this article we describe the case-population approach, an epidemiological strategy aimed at providing early estimates of the magnitude of the risk of rare ADRs.

1. Limitations of Spontaneous Reporting

Over the years, spontaneous reporting has been useful for the discovery of many previously undescribed ADRs. However, it suffers from several limitations, mainly under-reporting, selective reporting and incomplete drug histories.[7]

1.1 Under-Reporting

Only a small proportion of ADRs is reported.[7] The extent of under-reporting is substantially unknown; in the UK it has been estimated to be about 90%,[8] while in France one study suggested lower reporting rates (around 1/25 000 ADRs).[9]

1.2 Selective Reporting

The probability that an adverse event is diagnosed or recognised as an ADR depends on several aspects, such as latency period, nature and frequency. Immediate adverse events are more likely to be recognised. Anaphylaxis, cutaneous conditions and blood dyscrasias are also more likely to be clinically recognised as ADRs. In general, rare events generate more medical interest than more common conditions: it would have taken longer to recognise that thalidomide is teratogenic had its effect been, for example, a cardiac septal defect. Adverse events that are serious, those that have been previously described, those associated with new drugs, and those to which the professional literature (or even the lay press) recently referred tend to be preferentially reported.[7,10]

1.3 Incomplete Drug Histories

Figure 1a shows a spontaneous report form, called a 'yellow card', where a case of agranulocytosis attributed to cotrimoxazole (trimethoprim-sulfamethoxazole) was reported. After permission was requested from the reporting physician, the patient was approached and consented to be interviewed. Additional information obtained by interviewing the patient with a structured questionnaire is shown in figure 1b.[7] Although complete comprehensiveness cannot be guaranteed, structured questionnaires provide a systematic means to obtain drug histories, with details on the drugs taken, doses and dosage schedules, route of administration, reasons for use, and accurate timing of drug use and the appearance of the symptoms of the disease under study. Information obtained through direct structured interview of patients, including not only an open question on drug use, but also questions on symptoms which frequently lead to drug use, is more complete and reliable, in terms of the number of drugs taken by the patient, and in terms of clinical details.[11,12] In addition, this information enables accurate establishment of the time sequence between drug use and the first symptoms of the adverse event.

Under-reporting precludes estimation of the absolute risk. Selective reporting precludes comparisons between drugs used in the same indications. Incomplete drug and clinical information confounds evaluations based on voluntary reporting. Although this spontaneous reporting is useful for identifying new ADRs, usually it cannot give even an approximate estimate of the absolute risk. Formal epidemiological studies are thus needed.

a

		Sex M	Age 73yr		Weight 54kg
DRUG (S)	**ROUTE**	**DAILY DOSE**	**DATE STARTED**	**ENDED**	**INDICATIONS**
co-trimoxazole	p.o.	2-0-2	18/04	26/04	sore throat
REACTIONS			**STARTED**	**ENDED**	**OUTCOME**
Agranulocytosis			–	07/05	Recovered
ADDITIONAL NOTES					
Agranylocytosis by dipyrones (sic)					

b

		Sex M	Age 73yr		Weight 54kg
DRUG (S)	**ROUTE**	**DAILY DOSE**	**DATE STARTED**	**ENDED**	**INDICATIONS**
co-trimoxazole	p.o.	2-0-2	18/04	26/04	sore throat
penicillin	i.m.	?	29/03	04/04	gingivitis
streptokinase/ streptodornase	p.o.		18mo ago	?	?
cinepazide	p.o.	600mg	18mo ago	22/04	arteriosclerosis
salicylic acid + anthraquinonic glycosides	topical		29/03	04/04	gingivitis
calcium/ dobesilate	p.o.	750mg	18mo ago	5wks	arteriosclerosis
REACTIONS			**STARTED**	**ENDED**	**OUTCOME**
Agranulocytosis			–	07/05	Recovered
ADDITIONAL NOTES					
3 wks before admission (26/04) he presented with gingivitis and sore throat;					
10 days before admission abdominal pain started; 4 days before admission fever					
and general malaise appeared.					
He had been diagnosed of leucopenia 1 year before.					

Fig. 1. (**a**) A spontaneous report received by our centre at the Fundació Institut Català de Farmacologia describing a patient who developed agranulocytosis attributed to cotrimoxazole (trimethoprim-sulfamethoxazole); (**b**) The information on the same case, after interviewing the patient with a structured questionnaire. **i.m.** = intramuscular; **p.o.** = oral.

2. Limitations of Case-Control Studies

In a case-control study, cases with the disease of interest, independently of their previous exposures, are assembled, and their exposure to the risk factor of interest is compared with that of a series of controls (i.e. people without the disease of interest). Conceptually, this epidemiological design is the most adequate for the aetiological study of rare diseases. The size of the study depends on the α error (generally set at 0.05); the β error (generally set at 0.20); the minimum odds ratio that is judged of interest (which depends, among other factors, on the incidence and the severity of the disease under study); the number of controls included for each case; and the prevalence of use of the drug of interest. When this is low, the number of exposed controls will be low, and this will determine statistical instability of the 2×2 table and therefore of the risk estimate. Thus, when the prevalence of use of the exposure of interest is low (which is usually the case with newly marketed drugs), case-control studies have a limited value for risk estimation. On the other hand, the potential of cohort studies is limited, because the outcome of interest (i.e. the adverse event under study) is rare, and this confers limited statistical power.

As an example of the main limitation of case-control studies, assuming a prevalence of use of the drug of interest in the general population of 1%, an α error of 0.05, a β error of 0.20, an odds ratio judged as relevant of 5, and 3 controls per case, around 200 cases and 600 controls would be needed. It is important to underline that this would be the case of a drug with a very high prevalence of use. However, if the prevalence of use is lower, for instance 0.5% of controls exposed, and assuming the same determinants as in the previous example, around 400 cases and 1200 controls would be needed. Again, this would still be the case of drugs with a relatively high prevalence of use. Taking the same assumptions as before, but with a prevalence of use of 1 per 1000, which would correspond to the prevalence of use of a commercially successful new drug, around 2000 cases and 6000 controls would be needed.[7]

The limited power of case-control studies can be illustrated with an example on a major study, the International Agranulocytosis and Aplastic Anaemia Study (IAAAS).[13] The IAAAS was carried out in eight regions between 1980 and 1986, in a population of about 22 million, with a follow-up of approximately 120 million person-years. Table I shows the risk estimates for all the drugs which were found to be associated with a significant risk of agranulocytosis. Except for salicylates, the confidence intervals of the risk estimates of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) were wide. An association of agranulocytosis with cotrimoxazole was also confirmed, but, again, the confidence interval of the risk estimate was wide, because only 0.4% of controls had been exposed to cotrimoxazole during the relevant risk period. An increased risk of agranulocytosis was also found in association with β-lactam antibiotics, macrolides, antithyroid drugs, corticosteroids and other sulfonylureas, but the risk associated with these drugs had to be estimated for the whole group instead of individual drugs, because of the low numbers of exposed controls. For two drugs (sulfasalazine and cinepazide), there were no exposed controls, and for others (cefuroxime, cephalexin, cloxacillin, benzathine benzylpenicillin, phenoxymethylpenicillin, procaine penicillin, erythromycin, betamethasone, cortisone, dexamethasone, aprindine, procainamide) there was only one exposed control.

3. The Case-Population Approach

One of the aims of drug surveillance is the early detection and estimation of the risk of serious ADRs. Although spontaneous reporting may give rise to early signals, under-reporting, selective reporting and incomplete drug histories seriously limit its value for risk estimation.[7] Under-reporting and selective reporting would be overcome if the necessary steps were taken to ensure that all cases of the disease of interest - not only those that have been presumably caused by a particular drug - are assembled, by a process that should be independent of exposure to the suspected cause. Incompleteness of drug and clinical histories would be

limited if all cases of the disease of interest were approached and interviewed with a structured questionnaire, as is done in *ad hoc* case-control studies.[14] To estimate the order of magnitude of the risk, the incidence of the disease among the exposed is compared with the incidence among the non-exposed.

The case-population approach thus has two components: ascertainment of the cases of interest within a clearly defined population and identification of their status of exposure to the drug of interest; and estimation, based on statistics on drug consumption, of the exposed and non-exposed person-time in the source population and of the mean dose of the drug of interest taken daily by patients. The first component thus needs the following: specification of the population and time of the study; proper definition of the diagnostic criteria; systematic ascertainment of all patients with the disease of interest (or of a known fraction of them, irrespective of exposure status and suspected aetiology); and interview of the patients with a structured questionnaire. In order to estimate the second component, i.e. the exposed and non-exposed person-time, reliable information on drug consumption by the population in the defined geographical area during the specified time period is needed. Thus, the incidence of the disease in both the exposed and the non-exposed can be estimated, and a relative risk can be obtained. Estimation of the incidence among those exposed (i.e., the absolute risk) is of particular interest for benefit/harm assessment. Additionally, when different members of a pharmacological group are compared, the method also allows ranking of drugs according to the risk of a particular disease associated with their use.

Table I. Drugs significantly associated with a risk of agranulocytosis in the International Agranulocytosis and Aplastic Anaemia Study[13]

Drug	No. of exposed cases (%) [n = 270]	No. of exposed controls (%) [n = 1870]	OR (95% CI)
Metamizole[a]	28 (10.4)	20 (1.1)	16.0 (6.9-38)
Butylpyrazolidines	11 (4.1)	12 (0.6)	3.9 (1.4-11)
Indomethacin	10 (3.7)	13 (0.7)	6.6 (2.6-17)
Salicylates	56 (20.7)	181 (9.7)	2.0 (1.3-3.2)
Cotrimoxazole (trimethoprim-sulfamethoxazole)	14 (5.2)	8 (0.4)	16.0 (6-43)
β-Lactam antibiotics	28 (10.4)	31 (1.7)	2.8 (1.4-5.7)
Macrolides	10 (3.7)	1 (0.05)	54.0 (17-171)[b]
Antithyroid drugs	43 (15.9)	5 (0.3)	97.0 [36-262]
Carbamazepine	4 (1.5)	4 (0.2)	11.0 (1.9-62)
Corticosteroids	13 (4.8)	20 (1.1)	4.1 (1.8-9.5)
Other sulfonylureas	10 (3.7)	16 (0.9)	4.5 (1.8-11)
Sulfasalazine	6 (2.2)	0 (0)	∞
Aprindine[c]	5 (1.9)	1 (0.05)	49.0 (14-174)
Dipyridamole	8 (3.0)	18 (1.0)	3.8 (1.3-11)
Procainamide	7 (2.6)	1 (0.05)	50.0 (15-165)
Propranolol	22 (8.1)	26 (1.4)	2.5 (1.1-6.1)
Troxerutin	5 (1.9)	9 (0.5)	6.0 (1.7-22)
Digoxin	20 (7.4)	67 (3.6)	2.5 (1.1-5.4)
Acetyldigoxin[d]	14 (5.2)	30 (1.6)	9.9 (2.3-42)
Cinepazide	6 (2.2)	0 (0)	∞

a Only in Germany and in Spain.

b Crude estimate.

c Only in Spain.

d Only in Germany.

CI = confidence interval; **OR** = odds ratio.

The first component of the case-population approach is dealt as in case-control studies. However, instead of controls, drug consumption data are used to estimate the fraction of the exposed population from where cases arise. This avoids the main limitation of case-control studies when the prevalence of use of the drug of interest is low.

4. Review of Studies Where Risk Was Estimated Based on Consumption Data

Although the case-population approach is not mentioned as such in any of the main textbooks on pharmacoepidemiology,[15,16] the concept has been used in several studies, where cases of a particular disease suspected to be an ADR were related to the consumption of the suspected drug by the general population. However, retrieving these studies from the main bibliographic databases is difficult, because the term case-population is not included as a keyword in any of the most widely used thesauri. A Medline search using the term 'case-population' did not identify any study, and searching with the terms 'drug consumption' *and* 'risk' did not identify any study where this or a similar approach was used.

With support from the WHO Programme on Essential Drugs, our Institute (Fundació Institut Català de Farmacologia) manages a database, including more than 50 000 references to articles on pharmacoepidemiology, clinical pharmacology and therapeutics (SIETES, Sistema de Información Esencial sobre Medicamentos y Salud). Particular attention is paid to the methods of the studies. SIETES is aimed mainly at teaching, research and health management in Spanish-speaking countries; summaries are written in Spanish. SIETES does not aim at comprehensiveness, but rather at relevance, and it is based on the systematic manual review of more than 80 journals of pharmacology, clinical pharmacology, pharmacoepidemiology and general medicine. We have used SIETES to identify studies where exposure in cases was compared with aggregate exposure data in a population. Although not all these studies did intend to be case-population studies, their critical evaluation may help to better identify the key methodological elements of the case-population approach. 33 studies were identified (table II).[17-49] We examined their methods and compared them with the proposed case-population approach by looking at selected basic methodological requirements: definition of the disease of interest, sources and methods for ascertainment of cases, drugs of interest, methods for recording information on risk factors and confounding, definition of the risk period, estimation of the population at risk, control of confounding, and estimation of the association.

4.1 Definition of the Disease of Interest

Most studies dealt with type B reactions,[2] mainly blood dyscrasias (aplastic anaemia,[23,24,32-36,41,46,47] agranulocytosis,[24-27,32,33,39,40,43,45,48,49] thrombocytopenia[24,32,33] or a combination[24]). Only a few dealt with type A reactions[2] (lactic acidosis,[19,31] gastrointestinal bleeding,[22,44] extrapyramidal syndromes[17,18] and withdrawal syndrome of selective serotonin reuptake inhibitors[20]).

A basic requirement in any epidemiological study is an accurate definition of the disease of interest and of the eligibility criteria of the cases. This avoids misclassification.[50] Except in analyses based on series of cases assembled in case-control studies,[26,43-49] inclusion criteria were rarely explicitly established. Most studies relied on diagnoses written on spontaneous reporting forms, medical records or other documents. Eligibility criteria were predefined mainly in studies using data from registers of hospital discharge diagnoses[33,37-39] and in some of the studies based on spontaneous reporting.[21,23-27,32,33]

4.2 Sources for Patient Ascertainment

In any epidemiological study, nonselective ascertainment of cases (i.e. regardless of exposure status and suspected aetiology) is crucial. In most of the studies reviewed, cases had been identified through spontaneous reporting schemes.[17,19-33,36] In some of them, the information was completed by reviewing the hospital medical records.[19,22,24,26,31,33,36] In three studies, cases were identified from mortality

Table II. Main characteristics of the 33 studies reviewed

Drug(s) of interest	Disease of interest	Source of patient identification	Information on risk factors and confounding	Source of drug consumption data	Reference
Metoclopramide	Extrapyramidal reactions	SR	SR	IMS	17
Metoclopramide, prochlorperazine	Extrapyramidal reactions	General practitioner[a]	General practitioner[a]	Community pharmacists	18
Phenformin, metformin	All ADRs, with special reference to lactic acidosis	SR	SR + medical records for severe cases	National sales figures + routine nationwide prescription survey	19
Fluoxetine, paroxetine, sertraline	Withdrawal reactions	SR	SR	IMS	20
Zimeldine	Guillain-Barré syndrome certain or highly probable	SR	SR + medical records	National sales figures + routine nationwide prescription survey	21
Piroxicam and 7 other NSAIDs[b]	Upper gastrointestinal bleeding, perforation and ulcer	SR	SR	IMS	22
Acetazolamide	Aplastic anaemia (IAAAS inclusion criteria)	SR	SR + medical records + autopsy data	National sales figures + routine nationwide prescription survey	23
Cotrimoxazole (trimethoprim-sulfamethoxazole)	Leucopenia, agranulocytosis, thrombocytopenia, nonhaemolytic anaemia, combinations, (bicytopenia, tricytopenia) with predefined criteria	SR	SR	National sales figures + routine nationwide prescription survey	24
Sulfasalazine	Agranulocytosis (IAAAS inclusion criteria)	SR	SR	National sales figures + routine nationwide prescription survey	25
Sulphonamide, cotrimoxazole	Agranulocytosis (IAAAS inclusion criteria)	SR + case-control study	SR + medical records + structured questionnaire	National sales figures + routine nationwide prescription survey	26
Dapsone	Agranulocytosis (IAAAS inclusion criteria)	SR	SR	National sales figures + routine nationwide prescription survey	27
Omeprazole, cimetidine, ranitidine	Visual disorders	SR	SR	IMS	28
Erythromycin salts	Hepatotoxicity	SR	SR	National health service prescription data	29
Brodimoprim *vs* amoxicillin, azithromycin, cotrimoxazole, rufloxacin	All ADRs	SR	SR	?	30
Metformin	Lactic acidosis	SR	SR + medical records	National sales figures + routine nationwide prescription survey	31
All drugs	Agranulocytosis, thrombocytopenia, pancytopenia, aplastic anaemia (predefined criteria)	SR	SR	National sales figures + routine nationwide prescription survey	32
All drugs	Aplastic anaemia, agranulocytosis, haemolytic anaemia, thrombocytopenia (predefined criteria)	SR + hospital discharge diagnoses	Medical records	National sales figures + local sample of prescriptions dispensed	33
Chloramphenicol	Fatal aplastic anaemia	Mortality register	Medical records	Registration holder	34
Chloramphenicol	Fatal aplastic anaemia	Mortality register	Medical records	Registration holder	35

Table II. Contd

Drug(s) of interest	Disease of interest	Source of patient identification	Information on risk factors and confounding	Source of drug consumption data	Reference
Phenylbutazone, oxyphenbutazone	Fatal aplastic anaemia	Mortality register + SR	Medical records	National health service prescription data	36
Glafenine *vs* indomethacin, nitrofurantoin, oral penicillins	Anaphylactic reactions (predefined criteria)	Hospital discharge diagnoses	Inquiry to physicians + hospital discharge summaries	Reimbursement figures	37
Glafenine, paracetamol (acetaminophen), amoxicillin, diclofenac, other NSAIDs, penicillins	Anaphylactic reactions (predefined criteria)	Hospital discharge diagnoses	Inquiry to physicians + hospital discharge summaries	Representative sample of pharmacies	38
All drugs	Agranulocytosis (predefined criteria)	Hospital discharge diagnoses	Medical records + inquiry to responsible physicians and pharmacists	Representative sample of pharmacies	39
Dipyrone (metamizole)	Agranulocytosis	Hospital discharge diagnoses	Medical records	IMS	40
Chloramphenicol	Aplastic anaemia	Tertiary referral centre for haematology	Medical records	Registration holders	41
Antiepileptic drugs	Stevens-Johnson syndrome and toxic epidermal necrolysis	Registry	Medical records	?	42
Cinepazide	Agranulocytosis (IAAAS inclusion criteria)	SR + case-control study	SR + structured questionnaire + medical records	National health service prescription data	43
Analgesics and NSAIDs	Upper gastrointestinal haemorrhage	Case-control study	Structured questionnaire + medical records	National health service prescription data + IMS	44
Aprindine	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data	45
Ocular chloramphenicol	Aplastic anaemia (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	Registration holder	46
Nifedipine	Fatal aplastic anaemia (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data	47
Pyrithyldione	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data + IMS	48
Calcium dobesilate	Agranulocytosis (IAAAS inclusion criteria)	Case-control study	Structured questionnaire + medical records	National health service prescription data	49

a Mail survey to prescribers.

b Ibuprofen, naproxen, fenoprofen, tolmetin, sulindac, meclofenamate sodium, diflunisal.

ADR = adverse drug reaction; **IAAAS** = International Agranulocytosis and Aplastic Anaemia Study; **IMS** = Intercontinental Medical Statistics; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **SR** = spontaneous reporting.

registers,[34-36] in six from hospital discharge diagnoses computerised registers,[33,37-41] in one through inquiries to hospitals,[42] and in another through inquiries to prescribers.[18] In eight studies, the cases were those which had been assembled in *ad hoc* case-control studies.[26,43-49]

The limitations of voluntary reporting for case ascertainment have already been described in section 1. Studies based on computerised registers of hospital diagnoses have fewer limitations, but for the majority of diseases they do not guarantee complete and comprehensive identification of cases. Other methodological limitations were that inadequate information (or lack of it) on the procedures and forms for collecting and recoding patients' diagnoses in the hospital discharge data sheet may be a cause of misclassification.

4.3 Information on Risk Factors and Confounding

The quality and completeness of the information on exposures and other risk factors is a crucial aspect in controlled observational studies.[51] The most comprehensive information on exposure to risk factors is obtained through personal interview of the patient with a structured questionnaire.[11,12] However, in the majority of studies reviewed here, this information was mainly collected from spontaneous reports or from medical records. Analyses where information regarding cases from *ad hoc* case-control studies had been used were the exception. Except in these studies, no special efforts were made to complete the drug history exhaustively by interviewing the patient.

4.4 Drugs of Interest

Most studies focused on analgesics/NSAIDs[22,36-38,40,44] and antibiotics.[24,26,29,30,34,35,37,38,41,46] In most studies, the drugs of interest were usually taken in predefined dosage schedules, which facilitates estimation of the number of exposed patients from drug consumption statistics.

4.5 Definition of the Risk Period

Structured questionnaires such as those used in some *ad hoc* case-control studies allow enough information to be obtained to confidently establish the index day, that is, the day when the first symptom of the ADR occurred. The 'aetiological window' (i.e. the period during which present pathophysiological knowledge suggests that aetiological factors may exert their action) or risk period is different for each disease, which is usually arbitrarily determined. When a causal association exists, inappropriate widening of the aetiological window with the aim of increasing statistical power leads to risk underestimation, because relative differences of exposures between cases and controls tend to dilute as the time window considered widens.

In studies using spontaneous reporting data, it is assumed that a causality analysis was performed to determine the potential suspected drugs. This kind of analysis usually takes into account the aetiological window and the index day. Among the other studies, a causality analysis was done in only a few,[36,37] thus assuming a 'worst case' situation, i.e. that all cases, independently of alternative explanations, are in principle attributed to the exposure of interest. The aetiological window was specified in only two studies,[36,39] and the index day in one.[39]

4.6 Estimation of the Population at Risk

A central issue in case-population studies consists in estimating the number of individuals exposed to the drug of interest. To this end, three pieces of information are needed: consumption of medicines by the general population; mean consumed daily dose of each drug; and duration of each treatment course.[52] In the studies examined, consumption figures within national health services,[19,21,23-27,29,31-33,36,37,43-45,47-49] from IMS figures[17,20,22,28,34,35,40,41,46] or from both were used.[44,48] These sources of consumption data have some limitations. National health services' prescription figures do not include consumption of over-the-counter medicines, and they seldom include infor-

mation on the prescribed or consumed dose or on the length of treatment. On the other hand, it is well known that not all prescribed drugs are dispensed and not all dispensed drugs are taken by the patient. In the majority of the studies, the mean consumed daily dose was assumed to be the defined daily dose (DDD) or the prescribed daily dose (PDD).[53] For a number of drugs, the DDD may differ widely from the dose actually consumed.[53]

Ideally, consumption should be expressed as the number of individuals exposed to the drug of interest. This was rarely done in the studies included in this review, probably because information on the dose taken and on the length of treatment in the exposed population from which cases arose was not available. In a few studies, this information was estimated from registers of dispensed drugs.[19,21,23-27,31-33,36] In some instances the results were expressed as person-time exposed without any assumption on the duration of treatment.[23,25-27,31,32,35,36,43,45,48,49] However, in the majority of studies the risk was expressed in terms of number of cases per units sold, prescriptions, DDDs or PDDs.

None of the reviewed studies applied any correction for differential use of the drug of interest according to particular demographic characteristics (e.g. sex and age when dealing with oral contraceptives, or age when dealing with drugs indicated for diseases typical of specific age groups).

4.7 Control of Potential Confounding Factors

With the case-population approach, the main confounding factors regarding risk estimation are the patient's medical history and concomitant drug exposures, which can act either as additive or as independent confounders. In observational studies, multivariate regression models are usually used to adjust for confounding factors. This is not feasible in the case-population approach, where, to prevent confounding, the analysis has to be restricted to the cases without any potentially confounding medical conditions, to those exposed only to the drug of interest, or to both. Alternatively, it has to be stratified according to these factors, as was partially done in one of the reviewed studies.[39] Additionally, information on concomitant exposures and/or other confounding factors in the general population would be needed. In many instances this is a serious limitation, because restriction would not apply when the drug of interest is usually coprescribed with other drugs (e.g. antiepileptic drugs), or when the number of cases available for the analysis is low (which is usually the situation with rare diseases and with drugs with a low prevalence of use).[54] Only in one of the studies reviewed was the analysis restricted to cases exclusively exposed to the drug of interest.[44]

4.8 Estimation of the Association

In the studies reviewed here, the most common measure of association was an absolute risk, where the denominator (i.e. the consumption of the drug of interest) was expressed either in number of units or in number of prescriptions,[17,18,22,30,46] number of DDDs,[19,20,24,28,29,41] number of PDDs,[21] or number of patient-time estimated based on the value of the DDD or the PDD.[23,25-27,31,32,35,36,43,45,49]

In several studies the risk was expressed as a risk ratio.[17,27,37-39,44,47-49] In three studies where a risk ratio was calculated, risk was based on the number of cases identified from national hospital discharge diagnostic databases in the numerator and reimbursement figures of the (prescription) drugs of interest in the denominator.[37-39] In two studies,[37,38] the risk of developing severe anaphylaxis to glafenine was compared with that associated with other drugs (indomethacin, nitrofurantoin and oral penicillins), and it was expressed as a ratio. In a study on drug-induced agranulocytosis, a relative risk was estimated in the same way, but the reference category was no exposure to any of these drugs (the authors called this strategy a population-based case-cohort study).[39] In four other studies using cases from *ad hoc* case-control studies, a relative risk was calculated by comparing the incidence of these diseases among the population exposed to the drug of interest with the incidence among the non-exposed population.[44,47-49]

5. Conclusion

In a case-population study, all the cases of the disease of interest are assembled by a process that is independent of previous exposures or suspected causes. The rate of exposure among the cases is ascertained with a structured questionnaire. The rate of exposure among the general population is estimated from general consumption statistics. With this information, the incidence of the disease among those exposed is compared with the incidence among the non-exposed, and a relative risk can be estimated. Therefore, the method allows calculation of a relative risk (the magnitude of which is related to causation) and an absolute risk (which is important for benefit/harm assessment). The case-population strategy has been used in a limited number of studies,[37-39,43-49] but a number of analyses have been published where non-representative series of cases have been compared with consumption figures, with the aim of estimating an incidence or an absolute risk of particular drug-induced diseases.

We have reviewed 33 studies where this general approach was used to evaluate the risk of various drug-induced diseases. These studies mainly used data from spontaneous reporting (18 studies), hospital diagnoses registers (6) and mortality registers (3), and therefore complete ascertainment of cases was not guaranteed. Additionally, strict diagnostic criteria of the disease under study were not usually prespecified; as a consequence, the index day was only exceptionally determined in a systematic way. The aetiological window was defined in only two studies, and in some of them it was assumed that a causality analysis had been performed for each case. Additionally, data from case-control studies were also used to estimate an absolute risk, particularly when the low prevalence of use of the drug of interest precluded estimation of the odds ratio in the case-control study.

The majority of the ADRs under study were of type B, mainly blood dyscrasias. Different drug groups were evaluated (mainly antibiotics, analgesics and NSAIDs). In all but one study, all patients exposed to the drug of interest were included in the numerator independently of concomitant exposures to other drugs during the risk period. Only one study restricted the analysis to the cases exposed only to the drug of interest.[44] The information on exposures during the aetioloogical window was inaccurate, and it was generally based on the data appearing in the reporting form or in the medical record. Incidence and absolute risk were the most frequently used estimators of the risk. This was generally expressed as the number of cases per volume of prescriptions dispensed or units sold. In some instances, the fraction of the general population exposed to the drug of interest was estimated from IMS data or from other prescription figures, and the risk was expressed as the number of cases per person-years exposed, based on the DDD or the PDD, or as a risk ratio.

In the absence of drug utilisation studies, the lack of information on the pattern of use and on the distribution of consumption in the general population from where cases arise is one of the major limitations of the case-population approach. However, more accessibility to existing drug consumption databases and more accurate information on drug consumption would ease application of the case population approach. Thus, the main limitations of case-population studies regarding risk estimation lie in the source used for case ascertainment, the absence of an accurate definition of the disease of interest when the source of identification is spontaneous reporting, the way information on exposures was obtained, the way the population at risk was estimated, and limited control of potential confounding.

The case-population strategy should thus be validated, by comparing its results with those generated by the gold standard design for the aetiological study of rare diseases, i.e. the case-control study.

This review shows the need to clarify the methods of the case-population approach. Future publications should clearly indicate how the numerator and denominator were estimated in each study. Including the keyword ‘case-population’ in the most-used thesauri would also foster progress with this method.

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