Adverse Drug Reactions and Their Measurement in the Rheumatic Diseases

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ABSTRACT. Drugs administered as therapy for rheumatological disorders are a relatively common cause of adverse events. Important data regarding the effects of drugs on patients with rheumatological conditions is being lost or rendered inaccessible because of deficiencies in classification, measurement, and collection methods for adverse drug reactions. A significant number of adverse reactions to drugs will not be known before marketing, and hence vigilance on the part of clinicians and patients in observing and documenting these reactions is paramount in building our knowledge and modifying our practice accordingly. A variety of systems and methods for detecting adverse drug reactions are described, critically evaluated, and compared for cost, potential bias, ethical concerns, and subject recruitment required for necessary statistical power. Systems need to be developed to give access to the wealth of clinical experiential data available in the individual practices of a broad spectrum of clinicians. To facilitate this, representative organizations need to make adverse drug reactions a high priority as well as contributing expertise and finance to database formulation and accessibility. (*J Rheumatol 1995;22:983–8*)

Key Indexing Terms:
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Drugs used in rheumatological conditions have been prominent in causing serious adverse drug reactions (Table 1). The substantial number of nonsteroidal antiinflammatory drugs (NSAID) in this list is worthy of note because of the widespread use of these agents in the community. As an increasing number of new therapies are used in clinical trials and registered for the treatment of rheumatic diseases, it is timely to consider clinicians' ability to identify, understand, and assess the risk of adverse reactions to antirheumatic drugs. It is important to consider these adverse reactions in the overall cost-benefit analysis of prescribing for rheumatic diseases.

EPIDEMIOLOGY

Adverse drug reactions account for 1–3% of all hospital admissions. Once in hospital, 10–20% of patients have an adverse drug reaction, and 0.2–3% of inpatient deaths are reported to be due to adverse drug reactions[1-3]. NSAID induced serious upper gastrointestinal (GI) tract bleeding contribute significantly to these figures[4]. Adverse drug reactions are more likely in patients who have a history of allergy, are elderly, and take multiple drugs and the risk generally increases with increasing duration of drug therapy[5]. One exception to the generalization regarding duration of therapy relates to the incidence of upper GI tract bleeding due to NSAID, which has been shown to diminish in patients after continuous therapy with 4 successive prescriptions[6].

Identification of adverse drug effects is not always easy and depends upon the incidence of the adverse effect in the population exposed to the drug, whether the effect is part of the expected pharmacology of the drug, and whether the effect produced is common or rarely seen.

Table 1. *Serious adverse effects leading to withdrawal or restricted availability of some drugs used in rheumatology*

Drug	Adverse Effect
Alclofenac	Hypersensitivity: skin reactions
Benoxaprofen	Hepatotoxicity, renal failure, photosensitivity
Clobuzarit	Skin reactions, including Stevens-Johnson syndrome
Fenclofenac	Toxic epidermal necrolysis
Ibufenac	Hepatotoxicity
Indoprofen	Small intestinal ulceration
Isoxicam	Skin reaction, toxic epidermal necrolysis
Osmosin (slow release indomethacin)	Small intestinal ulceration and bleeding
Phenacetin	Analgesic nephropathy, renal failure
Phenylbutazone	Aplastic anemia
Suprofen	Flank pain
Tienelic acid	Hepatotoxicity
Zomepirac	Hypersensitivity and bronchospasm

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CLASSIFICATION

Not all adverse drug reactions can be neatly classified. One widely used classification scheme identifies 4 broad categories of adverse reaction[7-9] (Table 2) that can be applied in a rheumatological context.

Type A (augmented) adverse drug reactions are dose related in nature and part of the known pharmacological spectrum of effects of the drug. The adverse effect could be due to an excessive primary effect, such as severe lymphopenia due to cyclophosphamide, or due to an unwanted side effect, such as diarrhea due to colchicine. Type A adverse effects will be more likely the closer the therapeutic dose is to the toxic dose, that is, when the therapeutic ratio is low. Methotrexate has a low therapeutic ratio with predictable bone marrow suppression resulting from a moderate increment in weekly dose in some patients.

Pharmacokinetic variability is a common reason for type A adverse effects, and variation in rates of drug elimination is most commonly responsible. The presence of hepatic disease, the effect of smoking and alcohol intake, metabolic drug interactions, and genetic polymorphism in drug metabolizing enzymes are factors leading to variation in rates of hepatic drug metabolism. For example, cyclosporine A metabolism is inhibited by ketoconazole, which can result in serious cyclosporine A toxicity. This interaction has been used to reduce the dose of cyclosporine required for therapeutic effect[10]. Decreased glomerular filtration rate in elderly patients can lead to reduced drug clearance, higher drug concentrations, and an increased risk of adverse drug effects. Thus, methotrexate marrow toxicity is more likely in people with renal impairment if dosage is not reduced[11,12].

Type A adverse effects may occur secondary to pharmacodynamic mechanisms, particularly when compensatory mechanisms are impaired by age or disease. Thus, an individual with cirrhosis of the liver with reduced hepatic synthetic capability will have a greater risk of serious bleeding due to insufficient concentrations of clotting factors, and the risk is compounded by taking NSAID, with their inherent risk of GI ulceration and propensity to inhibit platelet function. Patients with renal hypoperfusion due to cardiac failure, hypovolemia, or bilateral renal artery stenosis, or with intrinsic renal disease are dependent upon renal prostaglandin synthesis to counterbalance the vasoconstrictive actions of catecholamines and angiotensin II[13]. NSAID will inhibit prostaglandin synthesis and glomerular filtration will decline accordingly, potentially leading to acute renal failure.

Type B or bizarre adverse drug reactions are usually not dose related and often not predictable. Immunological and allergic reactions fit this category. A history of allergic disease or hereditary angioedema increases the risk for this type of reaction[14]. Thus, aspirin or NSAID induced hypersensitivity manifest as acute asthma is more likely in patients with nasal polyposis and sinusitis. Inheritance of certain HLA types is associated with immunological adverse effects. Procainamide or hydrallazine induced systemic lupus erythematosus are more likely in women who have the slow acetylator phenotype and are positive for HLA-DR4. Proteinuria due to penicillamine induced glomerular injury is more likely in patients who are HLA-DR3 and HLA-B8 positive[15,16].

A number of recognized immunological mechanisms lead to type B reactions. However, it is unlikely that immunological mechanisms alone account for these reactions, as overlap with other mechanisms is common. These immunological mechanisms include type II or cytotoxic reactions (phenylbutazone induced immune neutropenia) and type III or immune complex reactions, where serum sickness occurs, as is seen with sulfasalazine[17]. Cutaneous vasculitis is just one of the many varieties of immunological reaction to drugs. Interestingly, allopurinol associated cutaneous vasculitis is more likely in patients with renal impairment when the concentrations of its active metabolite oxipurinol are greater[18]. Although dose related, this appears to be a hypersensitivity reaction. Similarly, gold salts can cause exfoliative dermatitis, but again this is more likely with higher doses, and as

Table 2. *A classification of adverse drug effects (after Rawlins & Thompson[7]; Grahame-Smith & Aronson[8])*

Type	Characteristics	Examples
A	Dose dependent; predictably results from the primary and secondary pharmacology of the drug and is reduced by lowering the dose	Methotrexate induced hematological toxicity
B	Idiosyncratic; nondose dependent and may not be predictable from a knowledge of the drug's pharmacology. Accounts for many drug induced deaths	Aplastic anemia after exposure to aspirin or NSAID
C	Conditions associated with longterm therapy, which can be anticipated on the basis of chronicity of dosing and overall exposure to a drug	Hypothalamic-pituitary-adrenal axis suppression with longterm corticosteroid therapy
D	Delayed effects occur in a proportion of patients treated with the drug, and continue despite its cessation in some cases	Secondary malignancies following cytotoxic or immunosuppressive therapies

with allopurinol, desensitization is possible. Allopurinol, gold salts, and sulfasalazine are known causes of toxic epidermal necrolysis.

Type C reactions are those due to effects of longterm drug exposure, with dose also being influential. In the rheumatological field, this is exemplified by the adverse effects of sudden withdrawal of chronic glucocorticoid therapy and acute adrenal insufficiency that follows. Other examples include cyclosporine A induced hypertension, the prevalence of which increases as a function of dose and duration of therapy.

Type D adverse effects are delayed effects and include effects of cytotoxic drugs on reproductive function. Drug induced or promoted carcinogenesis is another example of this type of adverse effect. Exposure to chlorambucil in low dose in patients with rheumatoid arthritis (RA), and the consequent increase in skin and hemopoietic malignancy, is an example[19]. Bladder tumors following cyclophosphamide therapy also fit this category. Effects on fertility, such as the reversible suppression of spermatogenesis by sulfasalazine and azathioprine, are examples of type D adverse effects. Teratogenesis is a potential type D adverse effect if cytotoxic drugs are taken in the first trimester of pregnancy.

IDENTIFICATION

Type A adverse effects are usually well known at the time of drug registration from animal and early controlled clinical studies. At registration, only 2000–3000 patients have been studied and usually for relatively short periods. Types B, C, and D reactions of low to moderate incidence relative to drug usage will usually only be discovered postmarketing. It is sobering to consider that to have a 95% chance of identifying 3 cases of a serious adverse effect that has an incidence of 1 in 10,000 individuals exposed to the drug would require observation of 65,000 patients[8]. In the rheumatic disorders, which are generally chronic and therefore commonly involve chronic drug therapy, the identification of types B, C, and D adverse drug reactions is increasingly important, particularly with the more aggressive approach now being pursued in RA and the imminent availability of a wide range of novel biological molecules, including cytokines and enzyme inhibitors. The general methodologies available and their broad characteristics for detecting adverse drug effects in these categories are indicated in Table 3. An interesting option is to involve patients in identifying adverse events. This approach may be a sensitive method of detecting symptomatic adverse effects of a new drug[20].

FREQUENCY

The frequency with which an adverse drug reaction occurs can be expressed in a number of ways. The relative risk (RR) and absolute risks for an adverse drug reaction are necessary to make an informed decision, the clinical and practical significance of a particular RR decreasing as the absolute risk declines. Thus, a statistically significant relative risk of 3 is more important if the absolute risk is described by an incidence of 10 per 1000 patient years of therapy compared to 1 per 1000 patient years of therapy. "Incidence" describes new cases of adverse drug reactions as a function of population exposed and a stated duration of exposure, whereas "prevalence" describes the proportion of the exposed population affected, and therefore includes individuals with preexisting cases, either drug induced or spontaneous. As the duration of exposure to a drug is variable and may be decreased by the occurrence of an adverse reaction, and the risk of an adverse reaction is not constant over the time of exposure, life tables may be a preferable method of description[21,22]. Waller notes the lack of precision in the use of the terms incidence and prevalence to describe absolute risk and prefers the use of "frequency" of adverse drug reaction such as a percentage with definition with regard to the time period[22].

Table 3. *Methods of identifying adverse drug effects and some characteristics of these methods*

Randomized, double blind, placebo controlled trials: Optimal but expensive; difficult to achieve power needed; ethical concerns; issue of generalizability
Cohort studies: Not randomized, therefore subject to bias; expensive; large numbers required
Case control studies: Economical; small numbers; focus on adverse effect of interest; bias possible in control selection and ascertainment of exposure to drug
Record linkage: Valuable resource for performing cohort studies (retrospective or prospective), controlled cohort studies, and case control studies (retrospective or prospective); reliance on data quality
Intensive monitoring schemes: Expensive; lack focus; need large numbers; ascertainment of exposure
Spontaneous reporting, including "letters to the editor": Useful; gross underreporting; unusual adverse effects less likely to be reported than "identified" adverse effects; no way to calculate incidence or prevalence; important to promote as raises awareness of adverse reactions as well as acting as a signal
Postmarketing surveillance: Often more a promotional exercise than a research study; data quality and population size often inadequate

MEASURING (Table 3)

Spontaneous reporting of possible adverse drug reactions is considered an imperfect alerting system. Spontaneous reporting is facilitated by the blue and yellow reporting cards used in Australia and UK, respectively, and equivalent systems in other countries, all of which supply data to the World Health Organization database on adverse drug reactions[23]. It is recognized that only a small proportion of events that could be caused by drugs are reported by physicians. Reporting is highest in the first 2 years postmarketing and this is promoted in the UK by marking the product information of new drugs with a black triangle identifier. Regulatory anxiety and publicity about a possible adverse drug reaction lead to marked increases in reports of that particular reaction, while similar reactions to another member of the same drug class may be overlooked[24]. Detection of unexpected adverse drug

reactions by these spontaneous reporting systems cannot be assumed. Adverse reaction rates cannot be measured by these systems as the drug usage denominator is not accurately known. Various proxy measures of drug usage can be used to give crude indicators of risk, such as expression of the number of defined daily doses used by the population, calculated from drug sales data or prescription numbers.

Despite these difficulties, spontaneous reports by physicians remain the most important method of identifying rare and serious drug reactions. Physicians' reports were the impetus to undertake 13 of 18 investigations of serious adverse reactions in the UK[25]. Physician reporting rates were improved dramatically by an education program undertaken in Rhode Island, and these reports include a substantial proportion of severe reactions[26]. It was the spontaneous reporting system operated by the US Food and Drug Administration that led to the identification of flank pain syndrome with the NSAID suprofen[27]. However, recent work continues to emphasize that there is much room for improvement in knowledge about and attitudes to spontaneous reporting schemes[28].

Intensive monitoring schemes for detecting adverse drug reactions include programs such as the hospital based Boston Collaborative Drug Surveillance program and the British Prescription Event Monitoring (PEM) scheme. These schemes collect data on drug exposure and clinical events in large numbers of individuals, with the PEM scheme focussing on specific drugs and depending on prescribers reporting clinical events[29]. Although PEM was designed to overcome underreporting of suspicious adverse events, this was not apparent with the cough induced by the ACE inhibitor, enalapril[30-32]. Intensive monitoring schemes suffer from biases due to lack of randomized allocation of the drug in question or an appropriate control, and the related difficulty of uncertainty about the background frequency of a particular adverse event[30].

Cohort studies performed to measure the risk of drug related adverse events involve identifying a cohort of individuals who have taken (retrospective) or will take (prospective) the drug, and recording adverse events or an event of interest. This sort of cohort study requires a control cohort (either with or without the clinical outcome of interest) whose members are not exposed to the drug in order to produce a RR value. Uncontrolled cohort studies performed over a defined period measure incidence and absolute risk of an adverse event occurring. Cohort studies, especially studies of large cohorts, are theoretically attractive but, because of the large numbers involved, are expensive and slow unless record linkage can be employed. A good example of cohort studies in the rheumatological field is the study by Carson, *et al*[6] of NSAID induced upper GI hemorrhage in a very large cohort of individuals exposed to NSAID over 6 months in 1980, with a control cohort matched except for NSAID exposure.

Record linkage studies link drug exposure data, usually from prescription records, to definable clinical outcomes such as hospital admissions, such information being collected for administrative and billing purposes by organizations such as Medicaid and Kaiser Permanente in the US, the Saskatchewan Drug Plan in Canada, and the VAMP program in the UK. There are problems with data quality and verification, assurance the criteria for particular diagnoses have been met, inadequate statistical power, and increasing concerns regarding privacy. Despite these concerns and many others[33-35] the technique is a fast and relatively inexpensive method of undertaking controlled cohort studies and case controlled studies. A good example is the Strom and Carson study relating NSAID to admission for upper GI hemorrhage using the Medicaid billing system database in the US[35]. Apart from providing data on the risks of adverse drug reactions, record linkage programs can provide information for drug utilization review (DUR) programs, which can be used to identify individuals at high risk for adverse reactions and thereby modify prescribing. A pilot study of a DUR database using the Medicaid system reduced inappropriate prescriptions by 61% and hospitalizations by 27%[36]. Many believe that improving and extending record linkage systems is the most practical approach to identifying and establishing the frequencies and risks of adverse drug reactions[22,24].

Randomized controlled clinical trials, although the optimal method of establishing an association between a drug and an adverse effect, are usually undertaken in the early phases of drug development. They are too small to identify adverse reactions of even moderate frequency, are too short to detect drug effects related to longterm therapy, and the populations studied are usually not representative of the population that will ultimately be exposed to the drug[26]. However, rigorous definition and collection of adverse events in the course of extensive clinical trial programs, with centralized storage and evaluation using sophisticated databases, has been advocated as very effective in informing prescribers of the expected adverse reaction profile of a drug[37].

Case controlled studies are useful for testing hypotheses that a drug causes a particular adverse reaction. The frequency of use of the drug in individuals suffering the adverse outcome is compared to controls not afflicted, giving an odds ratio for drug use that approximates the RR for the adverse outcome. This technique has been used extensively to measure the RR for serious upper GI tract bleeding due to NSAID[38]. The technique is relatively expensive (but not as expensive as randomized, double blind, placebo controlled trials or cohort studies), slow to characterize the risk for a particular drug and side effect, and subject to a number of potential biases[39]. Absolute frequency for an adverse reaction can only be estimated by calculating the "attributable fraction" of the adverse event in the population due to the drug and multiplying this by the frequency of the adverse outcome (includes "spontaneous occurrence") in the population, if this is known.

Postmarketing surveillance studies sponsored by the pharmaceutical industry have not been useful in identifying unusual adverse reactions or determining absolute and RR rates for adverse reactions. Problems include lack of random allocation to drug and control groups, unrepresentative study populations, and inadequate patient numbers and study duration[40].

ESTABLISHING WHETHER AN ADVERSE EVENT IS AN ADVERSE DRUG REACTION

Cohort studies, spontaneous reporting, and intensive monitoring systems that are uncontrolled are unable to distinguish spontaneous or background from drug induced events. Various methods have been suggested to separate drug induced adverse events from background occurrence. These consist of a number of subjective criteria, such as determining whether "there is a temporal relationship between drug exposure and the adverse event"[41–44].

PROBLEMS IN IDENTIFYING AND EVALUATING THE SIGNIFICANCE OF ADVERSE DRUG REACTIONS IN THE RHEUMATIC DISORDERS

Rheumatic disorders are among the most common ailments with a prevalence that increases with age, and these disorders have a heavy dependence on pharmacotherapy. It is not surprising that adverse reactions from drugs used in these disorders make up a significant proportion of all adverse reactions reported and also include a considerable proportion of serious adverse reactions. Adverse reactions are a major determinant of prescribing practice in the rheumatic disorders, especially in the selection of disease modifying agents for RA.

Too little research into the mechanisms and identification of risk factors for adverse reactions in general and in the treatment of rheumatic disease in particular is undertaken, given the significance to the practice of rheumatology. The identification of adverse reactions to drugs used in the rheumatic diseases needs to be given higher priority by rheumatologists. A wealth of patient data and experience is being lost due to the inability to use methods for capturing it. Our representative organizations need to make adverse drug reactions a high priority for attention. Methods for accessing clinical experiential data from practising primary care doctors and rheumatologists need to be developed so that practice is assisted and improved at the same time that data become available. The pioneering work of Fries and colleagues using the American Rheumatism Association Medical Information System database system[45,46] and the additional work of, among others, Pincus and Callahan[47] and Wolfe and colleagues[48] in collating comprehensive diagnostic and therapeutic and outcome data in rheumatic patients needs to be built upon with the aim of incorporating an increasing proportion of practitioners as data providers.

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