EFFECTIVENESS OF A REGIONAL REPORTING PROGRAM IN IMPROVING QUALITY OF ADVERSE DRUG REACTION CASE REPORTS

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ABSTRACT

The Canadian voluntary adverse drug reaction (ADR) reporting program is an established surveillance method for monitoring drug safety, using case report data for signaling the occurrence of new or unexpected adverse drug reactions in a timely manner. In 1990, as part of improvements to the Canadian system of post-marketing drug surveillance, a pilot regional ADR reporting program (SaskADR) was developed in the province of Saskatchewan to investigate whether ADR reporting could be enhanced through decentralization of the national program.

During the first two years of SaskADR operation, there was a four-fold increase in the annual number of reports submitted by Saskatchewan practitioners to SaskADR as compared to the national program. The purpose of this research was to evaluate whether implementation of the SaskADR program not only improved the quantity of ADR reports, but also improved the quality of information documented on the ADR case reports.

Comparisons of ADR case report quality were made between 566 case reports submitted by Saskatchewan health professionals to the SaskADR program during the first two years of operation and 281 case reports submitted by Saskatchewan health professionals to the national ADR reporting program in the four years prior to implementation of SaskADR. The methodology for this research involved the development of indicators and criteria for the measurement of case report quality, which reflected the purpose and function of voluntary ADR reporting programs.

Implementation of the SaskADR reporting program was associated with an improvement in the quality of ADR case report data in comparison to case reports submitted to the national program. The SaskADR program demonstrated an increased reporting of "important reactions" or reactions which are serious or unexpected, or occur with a newly marketed drug. Information useful for characterization of the reaction and assessment of drug causality were better documented in the SaskADR reports. In addition, information considered essential for the submission of a valid ADR case report was more complete on the SaskADR reports.

Improvement in the quality of ADR information enhances the utility of the case report submissions in meeting the goals and objectives of the voluntary ADR reporting program. Demonstration of an *improved quality* of case reports, in combination with an increased rate of reporting, supports the development of regional ADR reporting centres as a mechanism of improving the Canadian voluntary ADR reporting program.

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LIST OF ABBREVIATIONS

ADR	Adverse drug reaction
ADRs	Adverse drug reactions
CIOMS	Council on International Organization of Medical Sciences
COSTART	Coded Symbols for Thesaurus of Adverse Reaction Terms
CPS	Compendium of Pharmaceuticals and Specialties
FDA	Food and Drug Administration
HPB	Health Protection Branch
ICD	International Classification of Diseases
PEM	Prescription Event Monitoring
PMS	Post-marketing surveillance
WHO	World Health Organization
WHOART	World Health Organization Adverse Reaction Terminology

Chapter 1

1. Introduction

The thalidomide tragedy of the early 1960s dramatically revealed deficiencies of the clinical trial process in identifying the unusual and less common adverse drug effects which could occur in the general population. Very quickly, the need for development of methods to monitor drug safety after marketing was recognized. In many countries, this single event spawned the introduction of *voluntary* or *spontaneous adverse drug reaction (ADR) reporting programs* which encouraged health professionals and the pharmaceutical industry to submit case reports of suspected adverse drug reactions seen in everyday clinical practice. From case reports submitted to these programs, both within the country and through international databases later set up, ADR reporting programs monitored for "signals" of new or unexpected drug problems.

In the years following thalidomide, the detection, evaluation and measurement of post-marketing adverse drug effects received considerable interest and attention. Although voluntary ADR reporting programs continued to exist, they frequently received less attention than newer initiatives developed for identifying drug-induced disease. Many hospitals established surveillance programs to evaluate and quantify adverse drug reactions (ADRs) in hospitalized patients and those which led to hospital admissions. The medical literature offered scores of papers detailing personal opinions of drug safety risks, methods for ADR detection and algorithms for "causality assessment" or how to best judge whether an adverse effect was drug-related. Refinements to observational studies commonly used in epidemiology, such as case-control and cohort studies, specific for the evaluation of drug-induced disease enhanced the "science" of the study of adverse

drug effects. The development of methods using large, computerized administrative health databases added another powerful technique for the identification of drug-induced illness in the population. The discipline of "pharmacoepidemiology" emerged in the 1980s providing expertise in the utilization of these advanced scientific designs and technologies to study drug effects in the general population.

Despite advances and refinements in methods of post-marketing drug surveillance, countries around the world have not abandoned voluntary ADR reporting programs and they remain an integral part of the drug safety monitoring process. It is recognized that these programs can offer a practical, cost-effective method of drug surveillance encompassing the entire population and realm of marketed products. They provide drug surveillance from the moment a drug is approved for marketing, an important advantage over other methods that need to wait for accumulation of data. However, under-reporting and inadequate resources for evaluation and assessment of ADR case reports remain as major problems limiting the effectiveness of voluntary ADR reporting programs to generate early warning signals of drug safety problems.

The Canadian voluntary ADR reporting program, the ADR Reporting Unit, Continuing Assessment Division, Bureau of Drug Surveillance, (originally the Drug Adverse Reaction Reporting Program), was developed in 1965 at the Health Protection Branch (HPB) in Ottawa. Expansion and enhancement of the system for monitoring adverse drug reactions in Canada was begun in 1990 as part of other initiatives designed to strengthen the Canadian post-marketing drug surveillance program. Development of regional reporting centres was proposed as a method for improving awareness and reporting of ADRs by health care practitioners, two of the major factors limiting the effectiveness of voluntary ADR reporting programs.

The first centre for regional ADR reporting, called *SaskADR*, began in Saskatchewan as a pilot project with the College of Pharmacy and Nutrition, University of Saskatchewan, and the HPB. The major objectives for the pilot project were to investigate whether a regional centre would increase awareness of ADR reporting within the province and increase the quantity and quality of ADR case reports submitted by Saskatchewan health care professionals to the national ADR reporting program.

Initially, SaskADR staff conducted a variety of educational and promotional activities throughout the province to inform physicians, pharmacists and the hospital community of the importance of post-marketing drug surveillance and of sharing clinical experiences thought to be adverse drug effects with the ADR reporting program through submission of an ADR case report. Improvement in the ADR reporting rate from Saskatchewan health practitioners was readily apparent. In the first year of operation, SaskADR received 333 ADR case reports compared to an annual average of 70 ADR case reports submitted by Saskatchewan health practitioners in the four years prior to regional centre development (SaskADR, 1991; personal communication HPB ADR reporting program). However, effectiveness of a voluntary ADR reporting program is based not only on the quantity, but also on the quality of the information submitted on the ADR case report form. Regulatory agencies at the national level must make decisions on whether or not drug safety is a concern based on the individual case reports received. Preliminary judgements of drug causality and characterization of the nature of the adverse event which might be occurring is dependent on the quality of information provided on the case report forms.

1.1 Research Problem

The HPB in Canada operates a voluntary ADR reporting program for the purpose of identifying drug safety concerns. Regionalization of the ADR reporting program as a pilot project in the province of Saskatchewan was shown to increase the *number of case reports* submitted by health care practitioners in the province. An equally important aspect, yet to be evaluated, is the *quality of case report data* submitted to the ADR reporting program. Improvement in the quality of ADR information would presumably enhance the utility of the case report submissions in meeting the goals and objectives of the voluntary ADR reporting program.

It is unknown whether development of a regional ADR reporting centre contributes to an increased quality of ADR information documented on the case report form. In-depth examination of case report data received by voluntary ADR reporting

programs with respect to quality of documented information has not been done. Moreover, quality indicators and criteria on which to base judgements of case report quality are not available.

1.2 Purpose of the Research

The purpose of this research is to evaluate and compare the quality of ADR case reports received by the HPB from Saskatchewan health care practitioners before and after implementation of the SaskADR regional reporting program, with the hypothesis that development of the regional ADR reporting program improved the quality of ADR case report information.

Evaluation of case report quality requires the development of criteria for quality which reflect the function of ADR reporting programs. Measures of quality to be examined for this research include: reports identifying serious, unexpected and new drug reactions which are of most value to an ADR reporting program (*important reports*); reports documenting information useful for characterization of the reaction and judgement of possible drug causality (*useful reports*); reports completing information judged to be essential and desirable for database entry and case report validity; and, the timeliness of reporting to the ADR program.

1.3 Research Objectives

Using case reports submitted by Saskatchewan health care practitioners directly to the HPB ADR reporting program before implementation of the SaskADR regional reporting program (*HPB Reports*) and case reports submitted to the SaskADR regional reporting program (*SaskADR Reports*), the objectives for this research are as follows:

1. To develop criteria for judgement of case report quality.

2. To identify and compare "important reports"; i.e., those reports which document

serious, unexpected and new drug reactions.

3. To identify and compare "useful reports"; i.e., those reports which provide information necessary for characterization of the adverse event and drug causality association.

4. To identify and compare the completion of "essential and desirable" data on the case report form; i.e., information important for database entry and case report validity.

5. To compare the timeliness of reporting to the HPB and SaskADR by evaluating the time period between onset of the adverse event and the date the case report was received by the HPB or SaskADR programs.

6. To examine factors which may relate to improved quality of ADR information.

Chapter 2

2. Literature Review and Background

The current research project involved an evaluation of the quality of case report information provided to a voluntary ADR reporting program. Very little research on the functioning of these programs has been done, yet they are used in many countries around the world to monitor for drug safety. As background information for this research, the important events in the history of adverse drug reactions, how they are defined and how they are perceived by the public are briefly discussed. Voluntary ADR reporting programs and many aspects of current drug legislation have been initiated in response to high profile drug misadventures. Discussion of the different methods of monitoring for adverse drug reactions includes the role of voluntary ADR reporting programs as one method of post-marketing surveillance.

Judgement of whether a drug caused an adverse event is a difficult problem, encountered by all who monitor for drug safety, including clinicians at the bedside, manufacturers conducting clinical trials, regulators reviewing drug safety data and researchers conducting sophisticated pharmacoepidemiologic studies. Collection of the appropriate information is a vital prerequisite for decisions regarding drug causality. Voluntary ADR reporting programs which provide drug safety information must aim for collection of this relevant information.

The purpose and structure of voluntary ADR reporting programs, including their strengths and limitations, are reviewed. Recent initiatives for improving the Canadian ADR reporting program led to the development of the first regional ADR reporting program in the province of Saskatchewan. The goals and objectives of the SaskADR regional program provide the basis for the current investigation of whether this program

was effective in improving the quality of case report data.

2.1 Historical Perspective

The idea that medicinal products could cause harm dates as far back as the history of medicine (Davies, 1991). Some of the early writings of medical scholars warned of the dangers of popular remedies used to treat ailments and questioned their purity. In 1785, observations that large doses of foxglove (digitalis) produced certain undesirable symptoms led to the first definitive description of an adverse drug reaction (Withering, 1785). Formal enquiries into suspected adverse drug reactions were launched in 1880, investigating the sudden deaths associated with chloroform anaesthesia and again, in 1922, reviewing cases of jaundice following arsenical treatment of syphilis. Despite these few examples, most of the natural remedies used prior to 1930 had little toxicity, but also, had little, if any, positive effect on a patient's disease or symptoms. This situation began to change in the 1930s, with the development of new, potent pharmaceutical agents which showed great promise in the mitigation of diseases and symptoms, but were also recognized for their potential to cause serious adverse reactions.

In 1929, coinciding with the publication of the first compendium of drug remedies in the United States, Leake pointed out his concerns regarding the testing of new drugs, stating that "there is no short cut from the chemical laboratory to the clinic except one that passes too close to the morgue" (Leake, 1929). Unfortunately, his words came true in 1937 when 107 deaths occurred from ingestion of sulfanilamide elixir containing the toxic solvent, diethylene glycol. The manufacturer had not thought to enquire whether the solvent would be safe for human use, a tragedy which could have been avoided since toxicity to diethylene glycol and related compounds had already been documented. This incident was the instigating force behind the development of new legislation in the United States that forbade the marketing of new drugs until they were deemed safe by the Food and Drug Administration (FDA). In the years that followed, concern about adverse drug reactions was minimal and transient, as the continued, explosive development of new

pharmaceutical products revolutionized the practice of medicine.

Concerns regarding drug safety began to surface again with publication of the first textbook devoted solely to adverse drug reactions in 1952 by Leo Meyler, himself a victim of an adverse drug reaction (Meyler, 1952). The American Medical Association set up a registry, also in 1952, for reports of drug-induced blood dyscrasias in response to increasing awareness of chloramphenicol-induced aplastic anemia. However, nothing in the history of adverse drug reactions rivaled the disaster of 1961, when the increased incidence of babies born with limb deformities was linked to use of thalidomide in pregnant women. The full realization of the harm a single drug could do was brought into the public arena, prompting an outcry for better methods of ADR detection (Davies 1991; Dukes and Swartz, 1988).

In the years that followed the thalidomide crisis, major revisions in drug regulations were adopted, new systems to monitor drug safety post-marketing were established and epidemiologic research methodologies were applied to studies evaluating drug risk. Although these developments contributed a great deal to improving drug safety, serious, unexpected adverse reactions continued to occur (Bakke *et al.*, 1984; Bakke *et al.*, 1995). Since thalidomide, examples of serious reactions prompting withdrawal of drugs from the market in various countries have included: subacute myelo-optic-neuropathy (SMON) from clioquinol in 1970; oculomucocutaneous syndrome from practolol in 1976; lactic acidosis from phenformin in 1977; liver damage from ticrynafen in 1980; liver damage and serious skin reactions from benoxaprofen in 1982; neuropathies, convulsions and liver damage from zimeldine in 1983; anaphylactic shock and renal failure from zomepirac in 1983; acute flank pain and renal failure from suprofen in 1986; and amnesia and psychiatric reactions from triazolam in 1991. History has taught us that prevention of untoward events from drugs cannot be guaranteed and the risk assessment process must continue throughout the entire marketing life of drug products.

2.2 Definition of Adverse Drug Reactions

Many different definitions and classifications of adverse drug reactions have been used in monitoring programs and research studies designed to detect and quantify adverse drug reactions (Manasse, 1989). Use of different criteria for identifying and classifying ADRs has led to major differences in the reported incidence of ADRs, making comparisons between studies difficult (Karch and Lasagna, 1975). Results from studies of adverse drug reactions in hospital patients conducted in the early 1970s had reported incidences varying anywhere between 1.5 and 35 percent. A review of published studies between the years of 1966 to 1989 identified a range of 0.2 to 21.7 percent of hospital admissions have resulted from drug-induced illness (Einarson, 1993). One of the major reasons cited for the variability in reported incidences and rates of hospitalizations has been the difference in definition and criteria used for evaluation of adverse effects from drugs. Presented with such wide estimates of the frequencies of adverse drug reactions, published opinions on drug risk have varied from remarkably non-toxic (Jick, 1974) to concerns of epidemic proportions (Talley and Laventurier, 1974) with the truth probably somewhere in between.

Voluntary ADR reporting programs capture data on adverse drug reactions and, as such, require an operational definition for users of the system. Most programs, including the Canadian ADR reporting program, utilize the definition agreed to by the World Health Organization (WHO), which defines an adverse drug reaction as:

> "a noxious and unintended response to a drug, which occurs at doses normally used or tested for the diagnosis, treatment or prevention of a disease or the modification of an organic function."
>
> (Canada Gazette, 1995)

Of the several ADR classifications, one of the simplest and most practical to use is the division of ADRs into two categories (Rawlins and Thompson, 1977). Type A reactions occur as a result of the drug's pharmacologic effect in persons unusually susceptible to the pharmacologic actions or in whom higher doses are used. These reactions are relatively common, predictable and dose-dependent. A reduction in dose

usually improves the symptoms, which are seldom severe and seldom cause death. Type B reactions are unexpected, or sometimes termed "idiosyncratic" and cannot be explained by the drug's pharmacology, for example, drug-induced aplastic anemia or Stevens-Johnson syndrome. In contrast to Type A reactions, they are generally uncommon, unpredictable and may occur at any dose. Type B reactions tend to be more severe, necessitating drug withdrawal for symptoms to improve and are more often fatal. Type A reactions are usually identified during the clinical trial process and risks can be adequately defined (Inman, 1986). This is not true for Type B reactions which, depending on their nature and incidence, often cannot be delineated from pre-marketing data. Although all reactions cannot be neatly placed into these two categories, this classification has been widely used for describing how adverse reactions are detected during drug development and clinical use.

2.3 Public Perception of Drug Risk

Public perception is that marketed drug products should be completely safe and effective (Heilmann, 1988). It is true that drugs are administered for the purpose of providing positive outcomes in the prevention and treatment of disease; however, there will always be a certain amount of risk that an untoward event will happen whenever a drug is taken. It has been said that a truly safe drug would most likely be ineffective (Dunlop, 1991).

In general, the risks from drugs are minimal in comparison to the benefits gained. Modern drug therapy has been a major contributing factor in the increased life expectancy seen during this century. However, media influence and an over-concentration on the adverse effects of drugs has produced a public extremely fearful and intolerant of even rare drug-related risks. This can be contrasted to the complacency with which the public perceives common, everyday risks which pose a far greater danger to health and safety than adverse effects from drugs (e.g., surgery, alcoholism, cigarette smoking, traffic accidents). Perceived risks do not necessarily equal to real risks.

Appropriate risk-benefit decisions should be made for each patient whenever

drugs are prescribed, so that the treatment chosen will achieve the desired therapeutic results with the least amount of associated drug toxicity. The amount of risk the patient should be willing to assume depends a great deal on the nature and severity of the illness for which the drug is prescribed. To make these risk-benefit decisions, health care providers and patients need access to valid information concerning what and how much risk is involved with drug therapy. However, the magnitude of drug risk depends upon many factors, only one of which is the inherent toxicity of the drug (Manasse, 1989). Other contributing factors which modify drug risk are the manner in which it is prescribed, administered (frequency, dosage, dosage form) and the conditions under which it is consumed (e.g., with alcohol, other drugs, foods or diseases). Consequently, the evaluation of drug risk can be a very difficult task.

2.4 Monitoring for Adverse Drug Reactions

2.4.1 The Clinical Trial Process

When a drug is first marketed, the information which is available to make appropriate risk-benefit decisions on whether the drug should be prescribed for a particular patient and what adverse effects to monitor for while taking the drug, comes from clinical trial data. Since the thalidomide tragedy, the documentation of adverse experiences during clinical trials and scrutiny by drug regulatory agencies has been greatly enhanced. Experimental, randomized clinical trials are the cornerstone of the drug approval process and it is expected that pre-marketing data provide invaluable information about the more common adverse effects which may occur.

Limitations in the clinical trial process preclude the determination of the complete adverse effect profile a of new drug at the time of marketing (Johnson and Tanner (a), 1993; Spilker, 1991). Clinical trials enroll relatively small numbers of study patients, usually less than three thousand (3,000). Therefore, it is unlikely that all adverse drug effects can be detected and the true picture of some observed adverse effects evaluated. Many *adverse events* documented during clinical trials cannot be identified as *adverse*