

DUR Experience in Europe

Ulf Bergman

Karolinska Institutet, Huddinge University Hospital, SE-141 86 Stockholm, Sweden

Drug utilization was defined as “the marketing, distribution, prescription and use of drugs in a society, with special emphasis on the resulting medical, social and economic consequences”. Epidemiology was defined as the study of the distribution and determinants of health-related states and events in populations, and “the application of this study to control of health problems”. While drug utilization studies employ various sources of information focusing on drugs, e.g. wholesale and prescription registers, the term “epidemiology” implies that pharmacoepidemiological studies are population based, and link health events to drug exposure.

During the past decades, the public, regulatory agencies and industry have raised a number of drug safety issues. Parallel with these increasing concerns about drug safety, the importance of drug surveillance and the application of epidemiologic techniques have grown rapidly. With this came the recognition of a new discipline, pharmacoepidemiology. Since 1985 an international conference on pharmacoepidemiology has been held each year. This is now organized by the international Society for pharmacoepidemiology and the 16th conference was held in Barcelona in 2000. Furthermore, the third editions of introductory and advanced textbooks in pharmacoepidemiology have now been published.

To a large extent, progress in pharmacoepidemiology stems from the increasing use of computerized health care data. Much of the time and money in these investigations was earlier spent on assembling cohorts of exposed subjects or collecting cases for case-control studies. By the use of computerized pharmacy or billing records, drug exposure is now linked to files, which include diagnoses. Linkage is done via a unique personal identifier number (PIN). To ensure patient confidentiality, analyses are done by use of “scrambled” numbers. Access to patient charts for validation of exposure and diagnoses is also obtained via these scrambled numbers. All personal-identifying information is removed before copies of the charts are made available. Thus, these record-linkage system provide “objective” drug histories (prospectively recorded and thus unbiased by the outcome) for pharmacoepidemiological cohort and case-control studies. Linking these administrative databases provides large “clinical” databases as powerful tools for drug evaluation. Studies applying these new techniques are now increasingly utilized in North America and Europe (see also separate contributions from Denmark in this issue).

Since the 1980s the area of pharmacoepidemiology has shifted from being focused on adverse drug

reactions, to also include rational use and health economic aspects of drug utilization. A modern definition of pharmacoepidemiology is: *The study of the use of and the effects of drugs in large numbers of people with the purpose of supporting a rational and thereby cost effective use of safe and effective drugs in the population.*

Population Vased Drug Databases in Sweden

Pioneering pharmacoepidemiology surveys of prescriptions purchased from defined populations in Czechoslovakia and Sweden were initiated in the late 1960s. In Sweden, two such population-based drug databases for research are still in use in the County of Jmtland and in the Community of Tierp.

1. The County of Jämtland Project

In the county of Jmtland 1-in-7 of the population has been included in this longitudinal patient-specific database. All prescriptions dispensed to these 17,000 individuals have been continuously monitored since 1970. The recorded information includes the patient's identity number (PIN), name, dosage, quantity and price of the drug, data of dispensing and pharmacy, and prescribing physician category.

In the annual publication "Swedish Drug Statistics" key epidemiological data such as *incidence* and *prevalence* of drug use by age and sex is presented from the County of Jmtland Project. In 1999, 54% of all men and 75% of all women purchased prescription drugs in Jmtland. Five and six percent of men and women, respectively, obtained 30 or more prescriptions, and among those 60years and older it was 10% to 17% that obtained 30+ prescriptions (one year's supply corresponds to four prescriptions). Thus, use of prescription drugs in the population is rather a rule than an exception and as with health care utilization in general, drug use is also skewed in the population and this is particularly prominent among the elderly.

This basic information on drug use in the population can only be obtained if there is a personal identifier on the prescription. In Sweden today such drug use data can only be found in the county of Jmtland. The importance of a population-based approach in drug evaluation is illustrated by the retrospective survey of drugs purchased by people who committed suicide in Jmtland. Most patients who committed suicide are depressed. However, at the time of the suicide only 15% of 80 patients who committed suicide in the Jmtland Project during a 15-year period had received antidepressant treatment during their last three months. Similarly in a national forensic toxicological screening among suicides in 1990-91 (and in a corresponding survey 1992~94) we found that only about 15% had antidepressants in their blood(19, 20). It was therefore concluded that undertreatment of depressed patients was a significant clinical problem in Sweden in the early 1990s. Since then there has been a fourfold increase in the use of antidepressants, mainly SSRIs (selective serotonin reuptake inhibitors). Parallel with this there has also been a 25% decrease in the suicide rate in Sweden. According to Swedish guidelines, treatment of depression should be for at least a six-month period. In agreement with this and the decreased suicide rate, we found six months antidepressant treatment to be three times as common in 1996 as in 1991 in the county of Jmtland. Whether there is a causal

association between the increased use of antidepressants and the decrease in suicide rate cannot be conclusively established but available data indicates that this is the case. The same correlation is also seen in Denmark, Finland and Norway and was recently also reported from Hungary.

2. The Community of Tierp Study Database

In the community of Tierp prescriptions and morbidity data have routinely been recorded for all 22,000 residents since 1972. Drug data are kept on an aggregate pharmacological/therapeutic level and with few exceptions (psychotropics being one) it is difficult to study individual drugs. Thus, conducting analytical pharmacoepidemiological studies requires, in this as well as in other databases, that both exposure (drugs) and outcome (diagnosis) should be validated. This has unfortunately not always been the case.

Examples from Tierp, on longitudinal patient-specific studies are long term use of benzodiazepines and evaluating the implementation of guidelines in the treatment of diabetes over a 20-year period.

In both Jmtland and Tierp many pharmacoepidemiological studies have been done illustrating the advantage of working with a *local database* and the longitudinal patient-specific studies, but these studies have also illustrated the limitations with the small sizes of the populations covered.

Researchers from many other countries have taken advantage of the experiences from the County of Jmtland Project and the community of Tierp Study Database and in these countries the issue of patient confidentiality has been dealt with in a satisfactory way. In Denmark, where the county councils (amts with 4~500,000 inhabitants) have access to corresponding data on drug use by individuals, many important studies (e.g. quality of care, polypharmacy, drug interactions, drug abuse, physicians' prescribing habits) have been done (30~34). Unfortunately, because of sensitivity to the issue of data confidentiality in Sweden, the correspondingly recorded data on prescriptions (since 1997) relative to individual patients in other parts of Sweden is not available for use in health care audits or research.

DU 90% as a Tool in Improving Drug Prescribing

With these limitations in access to patient specific data on drug use, focus is now instead on improving the quality of drug prescribing by using available drug statistics produced by the National Corporation of Swedish Pharmacies. The Swedish Medical Quality Council proposed to focus on the number of drugs that account for 90% of the use (DDD/ATC methodology) - the Drug Utilization 90% segment -DU90%- and adherence to guidelines in this segment, as indicators for assessing the quality of drug prescribing. These indicators are now being tested in primary health care and at hospital clinics in several places and in different specialities in Sweden. Bar-coded prescriptions purchased at pharmacies were compared with the guidelines issued by the regional drug committees. In Stockholm this guideline is based on the principles of evidence-based medicine and contains about 200 mainly first-line drugs for common diseases. Experiences from a primary health care (PHC) center with 5 GPs serving 8,000 inhabitants in Stockholm have now been published. Prescriptions purchased at pharmacies during the last quarter of 1998 and 1999, respectively, were

compared within the DU90% segment with the guideline (index of adherence). The 1998 data were presented at the PHC centre in 1999. In agreement with an increased drug market in Sweden as an adaptation to the EU regulations, the number of different drugs purchased at the pharmacies had increased from 417 to 443. However, those accounting for 90% (DU90%) were essentially the same: 138 in 1998 and 136 in 1999. The adherence to the guideline within this segment was 74% and 78%, respectively. In 1998, the number of DU90% drugs per physician ranged from 82 to 110 and the index of adherence from 62% to 78%.

The DU90% segment has also been applied to look at to what extent the evidence of relative gastrointestinal toxicity with non-steroidal anti-inflammatory drugs (NSAID) was implemented in clinical practice in three areas of Europe in 1996. The proportion of "high risk" NSAIDs (azapropazone, ketoprofen, piroxicam) was highest in Bologna, Italy. The best profile (with 63% "low risk" ibuprofen, diclofenac) was found in Funen, Denmark. Stockholm, Sweden was in between. Factors other than evidence-based medicine seemed to have a dominating impact on the use of prescription NSAIDs in 1996. In conclusion, although the DU90% method neither examines the appropriateness of use nor provides outcome data, it was shown to be an inexpensive, flexible and simple method for assessing the general quality of drug prescribing.