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Pharmacoepidemiology – Assessing the Risks and Benefits of Drugs in the Postmarketing Phase

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Abstract: The Basel Pharmacoepidemiology Unit (BPU) is a research unit affiliated with the Institute of Clinical Pharmacy at the University of Basel, the Division of Clinical Pharmacology and Toxicology at the Basel University Hospital, and the Boston University School of Medicine. The main research activities of the BPU are drug safety studies in the post-marketing phase, but drug utilisation studies as well as clinical epidemiology projects are also part of the research activities of the BPU. Many of the research projects of the BPU are done upon request by and in close collaboration with the pharmaceutical industry. The main research tool the BPU currently uses is the UK-based 'General Practice Research Database' (GPRD), a unique and ongoing data collection of some 5 million outpatient records including demographics, diagnoses and drug prescriptions. The BPU uses various study designs (*e.g.* follow-up, case-control studies) to address the study questions of interest. The BPU conducts epidemiological research projects covering a wide spectrum of exposures and outcomes.

Keywords: Case control studies · Drug safety · Observational studies · Pharmacoepidemiology

Pharmacoepidemiology

Before a new drug can be marketed, the manufacturer has spent several hundred millions of dollars to detect an active lead substance, to develop a drug formulation, and to document in randomised trials that the new drug works, *i.e*. that it actually has some efficacy in treating or preventing a disease of interest. These controlled clinical trials also need to prove that the safety profile of the new drug is acceptable. However, exposure to a drug in a randomised trial is often of short duration, the number of patients taking the new drug is rather small (several hundred to a maximum of a few thousand), and the investigators often only include patients without comorbidities, who do not need to take concomitant medications. Thus, even though the efficacy of a new drug can be shown in such a setting, the information on drug safety is very limited and often restricted to acute and rather frequent adverse effects (AEs). However, AEs which are very rare, which only occur after an exposure of several months or even years, which only occur in subjects who also suffer from additional comorbidities (*e.g*. liver or renal failure), which occur only in special situations that have not been tested in prospective trials (*e.g*. pregnancy, lactation, use in children), or drug interactions will rarely be detected in controlled trials.

Thus, we need additional tools to assess and quantify beneficial or adverse drug effects occurring in the population after a drug has been marketed. Pharmacoepidemiology is a scientific discipline that tries to quantify what people do with drugs and what drugs do to people in large populations. It is a relatively young scientific discipline which has its origin in severe and unexpected drug safety problems observed in the 1960s and 1970s (*e.g.* birth defects caused by thalidomide) when manufacturers and drug authorities started to realise that some sort of postmarketing surveillance is needed to detect and quantify potential harm caused by drugs after large numbers of patients started using them [1].

Drug Safety

A core goal of pharmacoepidemiology as a scientific discipline is to study AEs of drugs in large populations. As mentioned above, rare AEs or those occurring only after extended periods of exposure (*e.g.* cumulative toxicity, carcinogenic effects) cannot be studied in randomised trials of limited size, limited exposure duration, and limited follow-up. These are the main reasons why pharmacoepidemiology plays an important role in quantifying such adverse drug effects. The cornerstone of drug safety in the post-marketing phase are spontaneous reporting systems in countries where health professionals report their observations to drug safety or pharmacovigilance centres (in Switzerland they are located in the five University Hospitals), to manufacturers, and/or to the drug authorities (the Swissmedic in Switzerland). These centres exchange this information, store it in databases and share it with the World Health Organisation (WHO) which runs a large database in Uppsala, Sweden. Even though these spontaneous reports are crucial for the early detection of so-called 'signals' (*i.e.* clusters of effects associated with particular drugs used), they do not allow reliable quantification of potential adverse effects for two main reasons: the numerator (*i.e.*

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the number of reported outcomes believed to be an AE) is too erratic since not all health professionals identify and/or report a drug safety problem, and the denominator (*i.e.* the number of patients exposed to a given drug) is only known very crudely from sales figures and does not allow to quantify properly the absolute risk of a patient of developing an AE.

Pharmacoepidemiologists use various tools (*e.g.* electronic databases, see below) to quantify effects of drugs in large populations. Particularly in the area of drug safety, pharmacoepidemiological approaches are of crucial importance to explore whether a drug of interest is indeed associated with a higher rate of a certain outcome or not (which may have been postulated based on spontaneous reports), as well as what the magnitude of such an association may be, and whether a certain potential drug induced-problem affects all patients or only a particular subgroup (*e.g.* the elderly, females, patients with certain underlying conditions, *etc*.). Most pharmacoepidemiological studies are conducted retrospectively, *i.e.* they analyse existing patient records which have been recorded over time before the data analysis takes place. This is an essential point, since it allows the study of associations between drugs and outcomes that could not be studied prospectively for various reasons: it may be unethical to expose patients just to learn more about the risk of certain adverse effects [2][3], or a prospective trial may take much too long and cost too much to provide results that are urgently needed [2][3]. The BPU has published numerous drug safety studies in recent years focussing on the safety of statins [4], antidepressants [5], antimalarials [6], antihypertensive drugs [7], and antiasthmatics [8].

Protective Effects of Drugs

Pharmacoepidemiological methods can be used not only to study adverse effects of drugs, but also to explore whether the risk of developing a certain outcome of interest is reduced in users of a certain drug. For example, the association between aspirin use and a lower risk of developing myocardial infarction was documented in observational studies before randomised trials confirmed this association [9]. Since the data analysis is retrospective, and since the data have already been collected before, it is possible to study the association between drug use and a reduced risk of an outcome of interest based on a hypothesis only, or based on animal models. Later on, if animal models and pharmacoepidemiological studies indicate that a drug may indeed by associated with a possible 'protective' effect, randomised trials are justified and may (or sometimes may not) confirm the findings from observational research. The BPU has conducted various such studies to explore potential beneficial effects of drugs which are used for different reasons. Statins, for example, are lipid-lowering agents which are taken to lower cholesterol. Animal models provided evidence that they may also affect bone metabolism and increase bone mass. We conducted a large population-based nested case-control analysis to see if we could find a reduced fracture risk in patients taking statins. This we found indeed [10]. We also found significantly fewer fractures in patients taking beta-blockers in a large observation study which we conducted based on animal data and previous small observational studies in humans [11].

Drug Utilisation

Pharmacoepidemiologists also study how doctors and/or patients use drugs, how drug use over time may change, and how specific diseases are treated in specific areas of the world, as well as how new drugs can have an impact on the likelihood of getting a diagnosis of a disease [12]. These figures can be useful for marketing purposes as well as for health authorities who would like to understand better what doctors prescribe to which patients and why.

Data Sources

In the early days of pharmacoepidemiology most studies were hospital-based and exposure information was assessed through patient interviews. In the late 1980s, electronic databases were initiated in various health systems. This represented a milestone in pharmacoepidemiology, since all of a sudden large collections of patient data were available to researchers and could be accessed and analysed much quicker and at relatively little costs. In the US, large health maintenance organisations (HMOs) began to record their activities (patient demographics, diagnoses, drug prescriptions, hospitalisations) on computer. In the United Kingdom, a large database was built which was based on patient records from general practitioners (GPs), and called the 'General Practice Research Database' (GPRD) [13]. The UK is very well-suited for epidemiological research since GPs play a key role in the management of patients. They record all relevant demographic and medical information of their patients on computer and send the anonymised information on a regular basis to a central server. The database encompasses some 5 million residents in the UK who have been registered with selected GPs who have agreed to provide patient data for research purposes. The age and sex distribution of patients in the GPRD is representative of the UK population. The accuracy and completeness of the data have been well documented and validated [14]. Information in the GPRD is recorded electronically by GPs, independent of any future study hypothesis which may arise and which may be studied by researchers later on, and includes patient demographics and characteristics (*e.g.* height, weight, smoking status), symptoms, clinical diagnoses, referrals to consultants, hospitalisations, drug prescriptions and vaccinations. Drug prescriptions are recorded in detail using a specific coding system, and drug prescriptions are generated directly from the computer and recorded in the patients' computerised profile. It is obvious that a database with some 5 million patient records including drug prescriptions and diagnoses in chronological order is of enormous interest for pharmacoepidemiologists, since it allows the study of even rare drug effects as well as AEs which only occur after longer term use of a drug with a long latency period.

The BPU is a sub-licensee of this database at the UK drug authorities (MHRA, Medicines Health Regulatory Agency). Most of our current research activities are based on this unique data collection. The BPU currently also looks into opportunities to work with electronic data from hospitals as well as with data from Swiss health insurances. However, the Swiss health system is not well-suited for epidemiological research for a variety of reasons [15].

Study Designs and Methodology

The most common study designs used in pharmacoepidemiology are the follow-up (or cohort) study and the case-control study [1][16]. In the follow-up study, patients are identified based on an exposure of interest and followed in time to see what happens to them. This allows the risk of developing an outcome of interest in a given exposure group to be quantified, and for the risk to be compared to the incidence rate in a comparison group (*e.g.* non-exposed subjects or patients using another drug). The risks are expressed as incidence rates, *i.e.* the number of newly identified cases of interest over the entire person-time of follow-up in this group of patients (*e.g.* five events/1000 person-years). Person-time is accumulated for each individual in the study who is at risk of developing an outcome of interest. It is the number of days, months or years from start of follow-up (*e.g.* the first exposure to a drug of interest) until a person develops an outcome of interest or until the observation period ends. If two or more incidence rates are compared, one can estimate a relative risk of developing an outcome of interest in comparison to another drug treatment.

The case-control study first identifies patients with the outcome of interest (in the absence of information on drug exposure),

then samples an appropriate control group of subjects who do not have this particular disease of interest, and then compares the exposure of interest between these two groups. The likelihood of having been exposed in the case group (with the disease of interest) and the control group (without the disease) is expressed in terms of an odds ratio (OR). This design is often used in pharmacoepidemiology because it is efficient and allows the direct comparison of the risk of developing an outcome of interest (*e.g.* an adverse effect) in relation to a drug exposure. It does not, however, allow the absolute risk of a patient of developing an AE using a given drug to be quantified. The latter can be achieved with the follow-up design [1][16].

Confounding and Bias

Randomisation in a randomised trial has one major goal: it should make sure that all known and measurable parameters (*e.g.* age, sex, smoking status, body mass index, *etc.*) as well as unknown parameters (*e.g.* genetic influence) are equally distributed by chance across the various exposure groups. Thus, if one patient group gets the study drug X, and the comparison group gets a placebo or a comparison drug, and if treatment was assigned at random, the two groups should only differ by treatment. All other parameters which may potentially distort the results should in theory be equally balanced between the two groups. In epidemiology, this is not so easy. When a pharmacoepidemiologist tries to study the effect of a drug in a population, exposure to this drug did not happen at random, but it was assigned by a doctor for a specific reason. Thus, if we compare the rate of AEs in a group of drug users and compare it for example to a group of non-users, these two groups will *a priori* differ from each other in so far as the drug users have a disease that requires treatment while the comparison group does not. In addition, these two groups may well differ with respect to many other variables, such as age, sex, location, life style habits, diet, physical activity, socio-economic status and much more. All these factors can be associated both with the risk of developing the outcome of interest as well as with the likelihood of taking (or not taking) a certain drug treatment. These parameters which may potentially severely distort the association between drug exposure and an outcome of interest are called confounders. It is a challenge in epidemiological research to handle confounders appropriately in the design phase of a study or later on in the statistical analysis [1][16]. Despite all attempts to quantify confounding and to control for in the statistical analysis, there is always a risk of observing a spurious association between drug use and an outcome of interest in an observational study. Therefore, it is crucial for pharmacoepidemiologists to use valid data and to be well-trained to reduce the risk of reporting spurious associations between drug use and the risk of developing an outcome of interest.

The Basel Pharmacoepidemiology Unit (BPU)

The BPU started its activities in 1998 after the head of the group (Dr. Christoph Meier) returned from a research fellowship in Boston, USA. The unit is currently part of the Division of Clinical Pharmacology and Toxicology at the Department of Internal Medicine at the Basel University Hospital. The staff of the small research unit currently encompasses (besides the head of the group) a postdoc pharmacist (Dr. Raymond Schlienger) and two pharmacy PhD students (Claudia Becker and Yolanda Brauchli). It has been a particular focus of recent research activities to study cardiovascular outcomes [17][18], as well as to quantify the effects of lipid-lowering drugs called 'statins' [4][10]. However, the BPU also conducts studies for the pharmaceutical industry on a regular basis. Aside from drug safety projects, drug companies are increasingly interested in studying various aspects of diseases for which they already have launched or intend to launch a new treatment [19]. We tend to get an increasing number of requests from drug companies to conduct epidemiological studies on a disease of interest in a large population, focusing on incidence rates, clinical risk factors, drug treatment patterns as well as risks of developing subsequent health problems during follow-up. The company is then in a position to be prepared for the post-marketing phase, in which all kinds of spontaneous reports associated with their newly launched drug will be reported and published. Thus, this pro-active approach helps drug companies and the medical community to learn more about background rates of certain outcomes (*e.g.* liver enzyme elevations, bleedings, ulcers, serious infections, cancer, *etc.*) in a given population before the new treatment option is being launched, and this helps to put the nature and the number of future spontaneous reports about potential AE in perspective.

In addition, the BPU also gets involved in projects focusing on drug–drug interactions [20] as well as clinical epidemiology, *i.e.* to explore the association between diseases without focusing strictly on drug effects. Recent examples are studies on the association between rheumatoid arthritis and the risk of developing myocardial infarction [21], or on obesity and the risk of developing liver disorders [22].

In summary, the BPU is a small research unit affiliated with the Institute of Clinical Pharmacy of the Department of Pharmaceutical Sciences, located at the Division of Pharmacology and Toxicology at the Basel University Hospital. The BPU is specialised in conducting (pharmaco-)epidemiological research projects. It mainly conducts projects using the large UK-based GPRD, a unique database which allows powerful analyses in the field of drug safety, drug utilisation as well as disease epidemiology. Despite the fact that the Swiss health system is not well-suited for epidemiological research, future activities of the BPU may also aim at analysing health insurance data from Switzerland.

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