Methodological Concepts: What Could We Know and What Should We Know in Drug Epidemiology?

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Epidemiologists and clinical pharmacologists do not always have the same view of things. During the years Professor Kewitz and I have learned to respect the sound scientific principles of both. I am glad to join you in this meeting and to contribute some simple thoughts.

The consumption of drugs in modern societies is widespread and increasing (Anonymous 1985). Drug risks are usually lower than risks from other sources, especially if one takes into account the benefits (Überla 1982b, c). However, our knowledge about such risks is insufficient. We have had sound methodological concepts for more than ten years, (Feinstein 1974; Finney 1965, 1971, 1974; Jick et al. 1970; Lawson et al. 1972; Remington 1978; Royal and Venulet 1972; Slone et al. 1966; Anonymous 1975, 1977) but they are not implemented in an appropriate way. The rare resources in our field are not always properly used due to lack of interest, lack of money, and partly also to the vested interests of various groups.

To be more specific: we do not know the incidence of serious adverse reactions for widely used drugs. Whether such an incidence is smaller than 1:1000, 1:10000, or 1:100000 is not known (Überla 1982b, c). Even the order of magnitude often remains a matter of guesswork and of preconceptions modified in either direction by some more or less scattered and biased data. Of course, we could know the order of magnitude of incidence up to 1:10000, but we don't. This unsatisfactory situation is the same worldwide. It is tempting, and misleads drug companies, authorities, consumer groups, and the public, to determine drug risks by arguments other than scientific ones. If scientists do not succeed in gaining better knowledge, drug risks for man cannot and will not be reduced.

I will first try to give a bird's eye view of the identification of adverse drug reactions (ADRs), of some basic dimensions for the assessment of drug risks, and of the available concepts and instruments. After a short glance at the number of cases and detectable differences I will come to the question of what we could know and what we should know about ADRs in man, mentioning some general principles and commenting on steps toward better knowledge.

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Identification of ADRs and Some Basic Dimensions for Assessment of Drug Risks

When performing studies in drug epidemiology one first has to identify ADRs. If there are no specific events, this is not an easy task. It can be approached in two radically different ways:

1. By applying in an individual case a strict rule based on solid scientific principles, to define whether an event is or is not an ADR. Such algorithms (Kramer et al. 1979) have been used widely and are sufficiently reliable and valid (Hutchinson et al. 1979; Leventhal et al. 1979). They are based on a reasonable temporal sequence following the administration of a drug, on well-known response patterns, on dechallenge and rechallenge, on other forms of treatment, and on the characteristics of the disease which might explain the event. Such algorithms qualify an event as definite, probable, possible, or doubtful. Careful and detailed validation of individual reports and the use of such algorithms allows the identification of individual ADRs, provided one knows what to look for.
2. If this knowledge is not available, the identification of ADRs must follow the second route: any event following drug intake, regardless of whether one expects a causal relation or not, is counted and a statistical relation established.

Both methods are vaild. By using algorithms, we benefit from previous knowledge and can decide on individual cases; by using the events as they are, we avoid any preconceptions about the real world.

One has to consider some *basic dimensions for the assessment of risks*. Such dimensions allow a classification of ADRs:

1. The *quality of ADRs*. There are about 40–80 different ADRs in various organ systems which can be classified according to incidence, proportion of fatalities, and the time relation with respect to exposure. If one uses three broad classes for each of these dimensions, the result is 27 possible combinations describing broadly the quality of ADRs. More serious and more frequent ADRs require more attention. Long-term effects are not so easy to determine. The quality of an ADR for a patient is broadly classified by those three dimensions.
2. The *risks of illness* for which the drug is administered vary widely, and the proportion of fatalities can be used to classify this risk. Since we have to compare the risk posed by the drug with that posed by the disease, this is a necessary dimension.
3. The *frequency of drug use and the manner of access to the drug* is another decisive dimension. Frequency of use is not independent from manner of access to a drug, whether it is sold over the counter, obtainable by prescription only, used mainly in hospitals or intensive care units, or a narcotic.

Available Concepts and Instruments

Principle sources of information on ADRs are controlled clinical trials, cohort studies comprising a variety of specific approaches, case-control studies, voluntary reporting systems, and anecdotal information. These sources can be used independently or in combination. I will briefly comment on these instruments.

1. *Controlled clinical trials* using randomization are the best method of obtaining unbiased information on the efficacy of a drug and on its ADRs (Überla 1981b). Since the number of patients in such studies is restricted to a few hundred or a few thousand per drug, only frequent ADRs of an incidence ranging from 1:100 to 1:1000 can be detected in such studies.
2. *Cohort studies* can be set up in a variety of ways:
   a) *Registered release* is a type of cohort study using the first 10000–50000 patients taking a drug. These patients are registered and the events following drug intake can be observed. This allows as precise an estimation of incidence as one is prepared to make by increasing the number of patients. It is possible to use such registers as starting points for case-control studies, even after decades. Experience with registered release shows some weaknesses; for instance, the control group is missing. However, properly planned registered release seems to be a valuable approach.
   b) *Prescription-event monitoring* (Inman 1981a, b) is another type of cohort study, starting with the identification of patients via prescription through pharmacies. The prescribing physician is also identified and asked to give a short report on each patient containing information on ADRs. Prescription-event monitoring can be designed in a variety of ways. It can give comparative information within drug groups, and it seems to be a reasonable instrument for unbiased incidence estimation up to 1:10000.
   c) *Intensive drug monitoring* (Jick et al. 1970; Lawson 1980; Lawson et al. 1972; Moir 1980; Slone et al. 1966), a third type of cohort study, uses a population of patients in hospitals and observes their ADRs. It can also be used in outpatients. The Boston Drug Surveillance Group has published extensively on this approach. It can be used for hypothesis generation and for hypothesis testing, and partly also for incidence estimation.
   d) *Drug utilization studies:* methods of collecting information on drug use in the population or in subgroups are well-known. A representative sample of people can be selected (Anonymous 1975, 1980) or one can use a carefully selected sample of physicians (Überla 1983). Prescription statistics from public health insurance institutions give valuable information on drug usage. Drug utilization studies are usually cross-sectional. Using the same technique every year one can obtain trends.
   e) *Cancer registers* are established in several countries. Other registries cover patients undergoing special therapeutic or diagnostic techniques or with special events - for instance, malformation registries. Registers usually do not contain the information necessary for evaluating ADRs. They must be connected to other information and they have some drawbacks (Hasford and Selbmann

1983). They can, however, be used as starting points for case-control studies.

f) *Medical record linkage* uses stored information about the same patient from several registries. There are promising studies from Finland (Skegg 1980) and from the United States (Jones et al. 1984), including data from health insurance. The approach is critical with respect to data protection, the size of the data banks, and possible bias. It is relatively cheap, since the data are available. In small countries it is a powerful instrument for ADR monitoring. One can expect that this approach will be further developed in other countries too, even when there are methodological problems.

3. *Case-control studies* (Schlesselman 1982) start with a group of cases having in common the event, the suspected ADR. Retrospectively collected information on exposure is compared between cases and controls. There are methodological problems with such studies, mainly regarding possible bias, and one has to be careful in interpreting an odds ratio because of this bias. Such studies do not allow the estimation of incidence, but do permit the comparison of very rare risks. If several studies with various control groups and varying data collection techniques show similar results, they can establish a causal connection with a reasonable degree of certainty.
4. *Voluntary or spontaneous reporting systems* (Hasford 1983; Inman 1980; Jones 1983; Mandel et al. 1976; Moussa 1978; Royal and Venulet 1972; Überla 1983; Venning 1982, 1983; Anonymous 1975, 1980) are established in several countries. Medical doctors send observations on ADRs to a central collecting and evaluating agency. Such systems do not allow the estimation of incidence. They are subject to bias, but serve as valuable warning systems.
5. *Anecdotal information* on individual cases is published in letters to the editor or in case reports. Case reports are the mother of medicine, as has already been said. Their appearance depends on the scientific attitude and the attention of the individual physician. Like spontaneous reporting systems, anecdotal information is very valuable in hypothesis generation.

All these methods and approaches have been tested, and their advantages and limitations are well-known. No single method can solve all evaluation problems. However, the sensible combination of these methods can tell us nearly everything, we need to know about a specific drug, provided we are willing to expend some intellectual effort and to pay the necessary price and the necessary attention.

Number of Cases and Detectable Differences

It is a well-known fact that if the risk is small, the number of cases required to detect a risk increase is large. It is obvious that with an incidence of 1:10000, one would need to observe on average 30000–50000 people to find 3–5 cases. This does not take into account the expected risk increase and the possible errors. Techniques for estimating the necessary numbers are well-developed (Finkle 1980; Neiß et al. 1982; Überla 1982a). To give an example: we are relatively sure – with an α of 0.05,

a β of 0.20, and the same number of persons in two groups - to detect a twofold risk increase from 1:1000 to 2:1000 with approximately 18000 patients in each group. This seems to be the upper limit of patient numbers which can be reasonably observed in prospective studies. Such numbers limit the detection of increased risks in prospective studies to incidences smaller than 1:1000 or 1:500. Very low incidences cannot be estimated in such studies, but they can be compared in case-control studies. In the case-control studies, large odds ratios can be observed with much smaller numbers.

To summarize: we can estimate risks and their relevant changes in prospective studies up to an order of magnitude of 1:500 or 1:1000. It is not possible to quantify smaller incidences precisely. However, such smaller incidences can be compared in case-control studies using odds ratios, which are subject to bias.

What Could We Know and What Should We Know About ADRs in Man?

I propose to differentiate according to the order of magnitude of incidence and whether the drug is on the market or not.

Before granting a license one should have quantitative estimates on the incidence of ADRs up to an incidence of 1:100 to 1:500. This information can be obtained from controlled clinical trials or cohort studies. One should know the risks of the disease which is being treated, the proportion of fatalities, and the proportion of patients seriously impaired by the disease. One should also know the relative benefit of the respective drug treatment, observing relevant variables and estimating the drug-attributable benefit, that is the amount of risk reduction by the drug. If possible, one should compare these parameters with those of other drugs.

After admission to the market:

1. One should have drug consumption information if possible on a yearly basis. Defined daily doses should be known for the population of patients. The relative frequencies of use in hospitals, prescription by physicians, or sale over the counter should be known for a specific drug, as should the proportionate use for major specific indications or diseases and for sex and age groups. Without such information the risks for the population cannot be properly assessed.
2. One should have information on the proper use of the drug as specified in the labeling. A large proportion of drug risks can be attributed to the prescribing physician and to the patient and not to the drug. In what percentage is the drug used for other indications, and in what percentage is this due to inadequate prescription by physicians. Such information can be gained by special studies every 5 years.
3. For ADRs or events with an incidence of 1:100-1:1000, one should get an exact empirical estimate of this incidence with confidence intervals. This means that risks with an incidence of 1:1000 should be safely detected and the incidences should be known fairly precisely. Controlled clinical trials, cohort studies, prescription-event monitoring, intensive drug monitoring, or recorded release

studies can give these incidences. This information can be correlated to the drug-attributable benefit, and to the information on drug consumption and correct drug use.

4. For ADRs with an incidence lower than 1:1000 we cannot estimate incidence nearly as precisely as is required. We should then have several case-control studies or some comparative information from recorded release, prescription-event monitoring, or other approaches. No estimation of incidence and no calculation of the number of potentially affected patients should be made when the data for the numerator and denominator are not reliable. Decisions cannot be based on incidence figures in such instances, but only on individual cases. These cases must strictly qualify and be identified as ADRs, using an algorithm or expert judgement classifying the cases as definite.
5. When the incidence is smaller than 1:100000, there is generally no sound empirical information available on the incidence of such events. In such a situation one can only try to perform rather crude calculations to compare the benefit with the risk. For instance, if the fatality risk of the disease is 1:1000 and with drug treatment it is 1:2000, an ADR fatality risk lower than 1:100000 is still 100 times lower than the benefit gained from the drug. Such a drug-attributable risk/benefit factor of 100 would make it fairly safe to leave a drug on the market. When the possible incidence is around or lower than 1:100000, one can use only such crude safety factors and the evaluation of individual cases with positive evidence.
6. There remains a broad band in which there is no clear-cut empirical evidence, but only random noise. Below a certain risk level the roulette of random decisions starts. Fortunately, such small risks are not a major hazard for the population. One must specify that we do not know, and that we are in the area where roulette is played. Within this broad band of random and background noise there are only four possible rational decisions: (a) to make no decision; (b) to decide to improve our knowledge; (c) to throw a dice; and (d) to leave the decision to nonscientific arguments and bodies. It is very important to delineate such situations and to specify what we do not know.
7. The essentials about our knowledge of ADRs should be passed to the physicians: the number of patients treated so far, the drug-attributable benefit, the incidence of ADRs as far as we know, drug consumption information, and how sure and unsure we are in the assessment of risks and benefits.

Some General Principles

In trying to gain more precise knowledge of ADRs one would be wise to observe some general principles:

1. There should be *equal depth of information* on all drugs. The range of information on individual drugs differs widely at present. The corresponding safety factors for different drugs vary between 10, 100, and 1000. We need some basic steps to establish approximately equal depth of information and equal safety factors for drugs of comparable groups.

2. Estimating *the incidence of ADRs* should be one of our main goals, using the available techniques to render the numerator and the denominator unbiased. Shapiro has stressed this before. We should specify the order of magnitude to which incidences are known.
3. *Our knowledge should increase with increasing exposition.* This can be done using different sampling rates or spacing the soope or the time length of studies. At present our knowledge is not increasing with increased drug use.
4. *Comparing risks is essential.* Using control groups with competitive drugs or other therapeutic strategies allows calculation of relative risks and relative benefits between drugs or therapies. Risk comparisons can also be made with other fields outside medicine.
5. We should prefer *systematic approaches* to less systematic ones. Planning experiments and observations is better in the long run than waiting for a disaster.
6. *Generating hypotheses* should be differentiated from *verifying hypotheses*. Establishing a causal relationship in man is not one step but a series of steps sometimes taking decades. The period of suspicion should be separated from the period of proven scientific knowledge. It is often impossible to prefer one proposition to the opposite one on empirical and scientific grounds.
7. *Data quality monitoring is required.* There should be no decision without independent verification of some depth. The basic numbers obtainable are not always well-monitored, and the resulting variation in incidence is very large.
8. We need instruments to *test our suspicions* after withdrawing a drug from the market and to *evaluate regulatory decisions*. The temporal and spatial distribution of ADRs and sales can give some indications.

Steps Toward Better Knowledge

The scientific instruments are better than the organizational facilities. The implementation of sound scientific principles in research on ADRs is not in conflict with the law but is also not enforced by it in any very specific ways. The following steps could improve the risk assessment of drugs considerably:

1. Steps to Improve Data Acquisition and Data Bases. This is the chief problem area and there are several possible remedies; for instance:

Introducing Prescription-Event Monitoring. There could be prescription-event monitoring in three to four regions of our country each comparing three to eight drugs per year. Within five years this could give sound and neutral prospective information on the ADRs of 50–100 or more drugs.

Introducing Registered Release. For up to 50 carefully selected older drugs and for up to 50 new substances, information on 10000–50000 consecutive patients could be collected in drug registers. This would take some years and provide another solid base of knowledge in case of emergency situations.

Improving Intensive Drug Monitoring. Quite a number of studies in internal medicine, intensive care units, surgery, or psychiatric patients could be started. They could also cover special problem areas like drug interactions or older people.

Using and Improving Drug Utilization Information. The information contained in the PMS system could be joined and compared with the information of the *Arzneimittelindex* ("Drug Index"). Both data bases could be extended fairly easily. Drug utilization statistics are a backbone of risk assessment. Some questions might warrant new data acquisition; for instance, studies on the proper prescription of drugs, on prescription for other indications, or on underprescription.

Starting Studies in Medical Record Linkage. There could be studies using information from public health insurance and linking it with information from other sources - for instance, hospital records or death certificates. There is the problem of data protection and we would need informed consent, which could be obtained from a large percentage of the population.

Case-Control Studies. There could be more than 50 *case-control studies* to answer some of the open questions with low incidences, which cannot be covered by other approaches.

Improving the Voluntary Reporting System. This system can be improved for instance by better filtering of new ADRs, by comparing ADR profiles, by stimulating the interest of the physicians in certain problem areas, etc.

Starting Studies with Samples from Physicians. With such studies one could ask timely questions every 2 or 3 months.

Starting Studies with Questionnaires from Patients. Such studies could give information on the ADRs in the over-the-counter market and on attitudes of patients to ADRs.

Starting Studies with Pharmacies. Pharmacists do a lot of drug counseling. Studies could give information on this counseling process and on the ADRs following such drug usage, or on the ADRs reported to pharmacists, for instance, when the medication is changed.

2. Some Steps Improving Theory and Methodology. Such steps could be:

- Integrating the available instruments to form a theory of drug epidemiology and developing optimal combinations of instruments with respect to defined knowledge situations and defined goals
- Describing typical situations with respect to the available information and preparing corresponding decision guidelines
- Proposing standards of risk/benefit in specific fields and comparing these with risk/benefit statistics from other fields
- Improving the theory and rationale of risk/benefit assessment in drug epidemiology

There are many other possible steps, and I admit that those mentioned here present my personal point of view.

3. Specific Problem Areas. There are also many open questions and specific problems. I mention only the problems of interaction (Musch and Gugler 1981), of older patients, of long-term effects, of the assessment of weak associations, of inferences regarding the absence of reactions, and of the development of expert systems.

4. Establishing the Proper Organizational Framework for Efficient Drug Epidemiology. In the present situation drug epidemiology is mainly a question of the proper organizational framework. There could be new organizational forms for drug safety studies and for data collection. The individual drug company is not in a position to do the job, and neither are doctors or regulatory agencies alone. There could be new organizational forms for drug evaluation and ADR monitoring. There could be independent drug epidemiology units funded by industry, by government, or from other sources. They should be scientifically oriented and really neutral and independent - neither company-, doctor-, state-, or consumer-related. In such drug epidemiology units, experts who could be called drug managers would each be responsible for between three and ten drugs. They could collect all published material and knowledge on these few drugs and they could organize and implement some of the above-mentioned studies.

New organizational forms of cooperation will develop in any case. They should be carefully planned and structured in order to minimize costs and maximize scientific independence.

A New Quality and a New Quantity in Drug Epidemiology

We can achieve a higher standard and a greater comprehensiveness in the assessment of ADRs and in drug epidemiology. We do have the necessary methodological instruments, and we know what to do if we want to obtain better empirical knowledge. There will be an economy of scale if we take truly decisive steps. There will be spin-offs to other fields, such as chemicals.

Society should no longer need to use irrational methods for lack of empirical evidence. Why should we be content with scattered and biased information, if we can have sound, empirically based, unbiased evidence? Why should we be content with less safety, if we can have more? We should try to reduce the random noise about ten times in comparison to present levels. This is a goal which can be achieved, and it is not a matter of cost alone. It is a matter of the intelligent use of our knowledge and of the commitment of scientists. We do have a complete set of instruments and we can construct a network which is systematic and unbiased, in order to know what we should know in drug epidemiology.

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