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Methods and Systems to Detect Adverse Drug Reactions in Hospitals

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Abstract

Detection of adverse drug reactions (ADRs) in hospitals offers the chance to detect serious ADRs resulting in hospitalisation and ADRs occurring in hospitalised patients, i.e. patients with high comorbidity and receiving drugs that are administered only in hospitals. The most commonly applied methods involve stimulated spontaneous reporting of doctors and nurses, comprehensive collection by trained specialists and, more recently, computer-assisted approaches using routine data from hospital information systems. The different methods of ADR detection used result in different rates and types of ADRs and, consequently, in different drug classes being responsible for these ADRs. Another factor influencing the results of surveys is the interpretation of the term ADR, where some authors adhere to the strict definition of the World Health Organization and many others include intended and unintended poisoning as well as errors in prescribing and dispensing, thus referring to adverse drug events. Depending on the method used for screening of patients, a high number of possible ADRs and only few definite ADRs are found, or vice versa. These variations have to be taken into account when comparing the results of further analyses performed with these data. ADR rates and incidences in relation to the number of drugs prescribed or patients exposed have been calculated in only a few surveys and projects, and this interesting pharmacoepidemiological approach deserves further study. In addition, the pharmacoeconomic impact of ADRs, either resulting in hospitalisation or prolonging hospital stay, has been estimated using different approaches. However, a common standardised procedure for such calculations has not yet been defined. Although detection of ADRs in hospitals offers the opportunity to detect severe ADRs of newly approved drugs, these ADRs are still discovered by spontaneous reporting systems. The prospects offered by electronic hospital information systems as well as implementation of pharmacoepidemiological approaches increases the possibilities and the value of ADR detection in hospitals.

In the 1960s the first reports about adverse drug reactions (ADRs) as a cause of hospital admission[1] and ADRs observed during hospitalisation were published.[2] In 1998 a meta-analysis of trials on ADRs in hospitals[3] aroused public concern, as fatal ADRs were calculated to range between the fourth and sixth leading causes of death in the US. However, these data warrant careful interpretation, because of the heterogeneity between studies and the fact that these studies were not designed and powered to allow for estimation of fatalities.[4] Surprisingly, only few methodological changes have occurred during the last 40 years with regard to the methods of detection of ADRs – with the exception of computer assistance to ease and standardise case-finding.[5]

This review discusses the methods used for ADR detection in hospitals on the basis of exemplary studies with regard to the different aims pursued. It is not within the scope of this article to review all studies on ADR detection in hospitals.[3,4,6]

1. Usefulness of Adverse Drug Reaction (ADR) Detection in Hospitals

ADRs can be the reason for hospital admission or they can occur during hospital stay. Both 'types' of ADR can be assessed with different goals. Since only moderate to severe ADRs lead to hospital admission, these ADRs can be used to generate signals for serious risks, especially of newly approved drugs. A comprehensive collection of all ADR-related hospitalisations to one hospital or department enables the ADR-associated morbidity as well as the economic impact of ADRs to be calculated.[6,7] Using prescription data of the region (record linkage), incidences of serious ADRs for frequently administered drugs can be estimated and compared.[8-11] Moreover, when analysing the preventability of certain ADRs (e.g. disregard of decreased renal function in patients receiving digoxin or contraindications on prescriptions), an indicator for the safety and quality of ambulatory prescribing can be obtained.[12,13] Collecting ADRs in the hospital setting provides, particularly, data on safety of drug use in special patient populations (e.g. patients with haemodynamic instability) and data on safety of drugs used exclusively in hospitals, such as most of the intravenous antibacterials, cytokines and anaesthetics. Again, consequences (e.g. prolongation of hospital stay) and associated cost can be calculated.[14,15]

2. Methods Applied for Detection of ADRs in Hospitals

The shortcomings of spontaneous reporting systems in hospitals, even after special training of doctors and nurses, are similar to the problem of under-reporting known for the ambulatory sector. Stimulated reporting or intensified collection of ADRs, as a result of increased awareness of physicians, nurses and pharmacists, may yield higher reporting rates, but is not yet sufficient for calculation of prevalence and incidence of ADRs. Whereas comprehensive collection of ADRs is time consuming and can be performed only in the framework of well defined projects,[8,9,12,16-19] ADR collection under predefined conditions (e.g. only ADRs occurring on an intensive care unit[20] or detected by means of computer signals, such as pathological laboratory values[5,21-24]) may be implemented into the daily routine of hospitals as a means of quality control.

3. Comprehensive Collection of ADRs in Hospitals

Comprehensive collection of ADRs can be used to detect ADRs occurring during hospitalisation and ADRs leading to hospital admission. This method can be applied either retrospectively or prospectively. Retrospective analyses[24-26] rely on chart review. However, according to Lau and coworkers,[27] 25% of prescription drugs used were not recorded in the medical charts, but their use was indicated in the hospital pharmacy record. 61% of patients in general internal medicine wards took at least one drug that was not documented in the charts. Prospective collection of ADRs (and adverse drug events; ADEs) is performed by frequent, usually daily, visits by a trained health professional (e.g. clinical pharmacologist, pharmacist

or nurse) on selected wards or departments over a restricted time period to record all patients and all events.[8,9,16,18-20,28,29] In contrast to retrospective data collection, additional investigations, interviews or tests can be performed to assure the causality of an ADR. Because of the completeness of the data collection, estimates of type and incidence of ADRs and ADEs occurring in such a defined patient population can be calculated, whereas numbers calculated from data of retrospective chart review may be less reliable. Moreover, risk factors for ADRs such as age and sex, underlying disease and comedication can be analysed. Almost all studies revealed age and the number of drugs taken concomitantly as the most important factors increasing the risk for an ADR. Therefore, a number of studies have been carried out focusing on elderly patients, in whom a much higher incidence of ADRs – both the reason for admission and occurring during hospital stay – has been reported.[17,30,31] Interestingly, female sex has been identified as an important risk factor as well.[8,15,18,32] However, it remains unclear whether this results from the fact that women in some studies were older than male patients and received more drugs[18] or whether the neglect of physiological sex differences accounts for the higher rate of ADRs observed in women.[33]

3.1 ADRs Occurring during Hospitalisation

During daily ward rounds, Leape and colleagues[29] identified 33 ADEs (including prescribing errors) per 1000 patient-days on an intensive care unit. According to Moore and colleagues,[18] 6.6% of patients in medical departments experienced an ADR. In a study by the French network of regional pharmacovigilance centres, the prevalence of ADRs in hospitalised patients (all specialities) was calculated to be 10.3% (of which 33% were serious) with an incidence rate of 1.8%.[34] These investigations were performed prospectively by comprehensive monitoring. A meta-analysis pooled data from publications with different methodological approaches and estimated an average rate of 10.9% of patients experiencing an ADR during their hospital stay (serious 2.1%, fatal 0.19%).[3] Because of economic pressures, duration of hospitalisation decreases steadily in most hospitals. Thus, it may be more helpful in future to calculate incidence of ADRs per patient-day rather than per patient to compare data between hospitals and over time. In addition, it would be interesting to know whether shorter duration of hospitalisation results in more or fewer ADRs.

3.2 ADRs Leading to Hospital Admission

Probably under the assumption that most patients with an ADR are admitted to departments of internal medicine, most investigators focused on ADRs in this speciality. In the aforementioned study by Moore and colleagues[18] in medical departments, 3% of admissions were caused by ADRs. Hallas et al.[8] reported that 8.4% of hospital admissions to medical wards were caused by ADRs and a further 3.0% by therapeutic failures. In a French cross-sectional study, comprehensive surveillance of all patients admitted to 62 departments of internal medicine at 33 hospitals during an observation period of 14 days was conducted.[35] From a total of 3137 admissions, 3.19% were due to an ADR. All these studies used the comprehensive surveillance approach as defined above. Slightly lower incidence rates of ADR-related admissions were reported from Australian studies (2.4 to 3.6%)[30] and US studies (4.7%).[3] Interestingly, Muehlberger and colleagues[6] reported a frequency of ADR-related admissions of 1.6% for studies using spontaneous or intensified ADR reporting, whereas the ADR frequency in studies with comprehensive collection came to 5.7%, emphasising the influence of the type of data collection on the estimated incidence rates of ADRs.

4. Detection of ADRs Using Computer-Assisted Approaches

Computerised hospital information systems represent an elegant tool to detect ADRs. The HELP system of the LDS Hospital in Salt Lake City, USA, has been described in several papers.[5,15,21] The HELP system contains an integrated patient database including data from the laboratory, micro-

biological department, radiology service, pharmacy and other sources.[36] Predetermined parameters from this system can be used as 'trigger signals' for potential ADRs, e.g. decrease in drug dosage, ordering of an antidote or pathological laboratory values. This method offers the advantage of a standardised and automated approach, although some types of ADR may not be detected, e.g. movement or psychiatric disorders following antiparkinsonian or antiepileptic drugs.[37] However, even in the case of a 'signal', the physician of that patient has to be contacted to verify the ADR.

A similar procedure has been reported from Switzerland for two medical departments in two different hospitals.[32] All available routine data, such as demographic data and laboratory values, in addition to drug prescriptions and predefined 'clinical events', were entered into a relational database. Causality assessment was performed after patients' discharge, and in 11% of all hospitalised patients at least one clinically relevant ADR was recorded. Since most hospitals cannot yet provide for such elaborate information systems, some researchers used pathological laboratory values as a source for signals suggestive for potential ADRs. In a pilot study[24] retrospectively analysing 153 admissions to a gastroenterological ward, 40 ADRs were detected by chart review. 65% of these ADRs could have been identified by abnormal laboratory values. Similar results were obtained by Tegeder and co-workers,[26] also using retrospective chart review. A comparison with stimulated reporting was published by Dormann et al.;[23] 34 ADRs were detected by the automated system and only 17 reported by physicians. Even when compared with retrospective chart review, monitoring of abnormal values reveals slightly more than half of all ADRs occurring on medical wards. In addition, depending on the speciality of the department/ward, different sensitivities and specificities for pathological parameters are calculated because of the prevailing underlying diseases. For example, in one ward pathological liver enzymes have a high predictive value for an ADR (e.g. cardiology), whereas on a gastroenterological ward most abnormal liver enzymes are due to the underlying disease. This discrepancy becomes even larger when comparing different departments such as internal medicine, neurology and paediatrics.[37] It has been suggested that pathological laboratory signals could be used as early markers for incipient ADRs and may therefore prevent development of serious ADRs. The use of this method for pharmacoepidemiology and pharmacovigilance, however, remains to be proven, especially with more hospitals having electronic patient charts.

5. Factors Contributing to Differences in Results

5.1 Definition of ADRs and Causality Assessment

When comparing the studies reported above with respect to spontaneous, comprehensive and computerised monitoring, it should be noted that different definitions of ADRs were applied. An ADR according to the World Health Organization criteria is an unintended noxious reaction after administration of a certain drug taken in the appropriate dose.[38] More recently, a broader definition has been suggested.[39] In some studies, intended and unintended poisoning, prescribing and dispensing errors,[14,15,22,40] therapeutic failures[8] and noncompliance[41] are included as ADEs or drug-related problems.[16] Whereas the stricter definition is suitable to detect risks attributable to a certain drug, the wider approach allows for estimation of a drug's risk in the therapeutic context, i.e. including noncompliance due to poor tolerability, the possibility of poisoning and difficulties in appropriate prescribing and dispensing. In some studies, ADRs were classified according to Rawlins[42] as type A and type B reactions. Irrespective of the type of survey, about one-third of ADRs were type B (bizarre, idiosyncratic) reactions,[18,28] whereas the majority of ADRs could be explained by the drug's pharmacological action. More recently, additional types of ADRs were suggested by Edwards and Aronson,[39] regarding chronic and delayed effects as well as withdrawal syndromes and therapeutic failures. With respect to

the type B reactions, some of them can now be explained by genetic differences, e.g. in drug metabolism or in the immune system; however, the latter, especially, are still poorly understood.[43]

A major source of discrepancies between studies lies in the distribution of ADRs with respect to their causality assessment, reflecting the different detection systems, different algorithms applied or the way algorithms were handled. Whereas in some studies[23,28] about 50% or more of ADRs detected were described as possible and less than 10% as definite, Classen et al.[21] described 62% of ADRs detected as definite or very likely and fewer than 1% as only possible ADRs. In all these studies the same algorithm of Naranjo et al.[44] was applied, and all of them used computer-assisted systems including pathological laboratory parameters with or without additional sources of information such as change in prescription or antidote ordering. When calculating the incidence of ADRs and ADEs, there is no general rule to include or exclude possible reactions or events, to calculate separately for mild, moderate or severe reactions. The variability in handling the probability of ADRs and their severity makes a relevant contribution to the differences reported in their frequency.

5.2 Types of ADRs and Causative Agents

Some aspects of ADR assessment in general and in the context of a hospital setting should be taken into consideration. It is obvious that differences will be observed in the type and frequency of ADRs when collected on a surgical ward or in a department of geriatric patients, in a hospital in a rural area or in a large city, or in a third world country or an industrialised country. The type of drug class, their rank order for inducing ADRs and consequently the types of ADRs vary extremely between studies. Drugs causing an ADR leading to hospital admission reflect the 'typical' risk of ambulatory prescription behaviour. Therefore, in studies including or solely documenting ADR-related hospitalisations, nonsteroidal anti-inflammatory drugs causing gastrointestinal bleeding play a major role, followed by cardiovascular drugs and drugs acting at the CNS.[1,8,18,35] In contrast, antibacterials/anti-infectives very often cause ADRs in hospitalised patients (especially allergic reactions), as do opioids, cardiovascular drugs and anticoagulants.[2,15,18,28,34] However, even when comparing investigations in hospitalised patients, the types of ADRs detected differ astonishingly. Classen et al.,[15] using the computerised surveillance system mentioned above, described allergic reactions, nausea and vomiting, and CNS effects as the most common ADRs (induced mainly by opioids, digoxin and antibacterials), whereas others observed predominantly cardiovascular, metabolic and renal ADRs.[18,28,34] It should be noted that different wards and/or hospitals using different types of drugs were involved in the surveys, and most of the studies pooled ADRs causing admission with ADRs occurring in inpatients.[8,15,34] However, certain methods appear to detect predominantly certain types of ADRs, whereas others seem to focus on different ADRs and/or drug classes. The screening of patients may follow different 'trigger signals', e.g. looking closely at elderly patients or using abnormal laboratory values as the trigger, and thus result in different types of ADR detected.

6. Linkage between ADRs and Drug Prescriptions

To identify drugs with a high risk for ADRs, the incidence of ADRs caused by a certain drug has to be related to the number of exposures. Prescription data can be obtained from the pharmacy records. As early as 1969, Hurwitz and Wade[2] described eight ADRs occurring in 103 patients exposed to ampicillin, in comparison to no ADRs following administration of other penicillins in 167 patients. Similar drug comparisons were provided by Bowman,[28] suggesting either that 'dangerous' drugs should be avoided or that more attention should be paid when using these drugs. The database of ambulatory prescriptions resulting in ADRs and subsequent hospital admission is more difficult to obtain and validate. Hallas and co-workers[8] used regional drug sales data to calculate ADR-related admissions following prescriptions of certain drug

classes by means of the defined daily dose approach. Schneeweiss and colleagues[9] evaluated the ADR risk of certain drugs by means of pharmacy sales data and the number of patients exposed. Some methodological aspects have to be considered: pharmacy sales data are often given according to postal code areas or specified regions; however, not all patients from that region visit the same hospital. The options provided by information technology and record-linkage were recently discussed.[11] The world's largest database of general practice patients,[45] the UK General Practice Research Database, includes data on hospital admissions as does the Medicines Monitoring Unit (MEMO) in Dundee, Scotland.[10] In the MEMO system, prescription data can be linked with hospital admissions for studies on prespecified risks, e.g. gastrointestinal bleeding following the use of different nonsteroidal anti-inflammatory drugs or severe hypoglycaemia in patients with diabetes mellitus receiving ACE inhibitor treatment.[10] Other large databases from public or private health insurance companies can be found in the US [Computerized On-Line Medical Pharmaceutical Analysis and Surveillance System (COMPASS), Group Health Cooperative of Puget Sound (GHC) and Canada (Saskatchewan).[11] However, most of these routine healthcare databases were not designed for scientific or pharmacovigilance purposes and have several drawbacks.

7. Economic Considerations

Projects to detect ADRs and especially ADEs were used to calculate attributable excess length of stay, cost of hospitalisations due to ADRs and additional use of healthcare resources. From a meta-analysis on studies detecting ADR-related hospital admissions, the cost of admissions to medical departments has been calculated.[7] These ADR-related admissions resulted in an average length of hospital stay (LOS) of 8.7 days, allowing for country-specific calculations of the impact on the healthcare system. The situation becomes more complex when the prolongation of LOS due to ADRs occurring during hospitalisation is calculated. By just comparing the crude LOS data of patients with and without ADR, Moore et al.[18] estimated an increase of the LOS of about 8.5 days. However, when adjusting for the above-mentioned risk factors age, sex and number of drug classes, the difference decreased to 7 days. Interestingly, according to the judgement of the responsible physician, the ADRs prolonged LOS only by 3 days. When the LOS is even further corrected for admission diagnoses, the ADR-attributable additional LOS comes to 3.5 days.[23] Implementation of a comorbidity index and a severity of disease scale into the estimations further reduces the excess LOS caused by ADRs to 2.2 days.[14] These examples emphasise the relevance of adjustment for underlying diagnoses and ADR risk factors to provide for meaningful economic calculations. In addition, sensitivity analyses may be required to correct for possible, probable and definite ADRs.

None of the mentioned publications accounted for the alternative: what would have happened if the suspected drug had not been given? In all instances, where the ADR was not preventable or where there were no treatment alternatives, the risk and cost of nontreatment has to be taken into consideration. In addition, most studies took LOS as an indicator for economic impact of ADRs, this may not be suitable for the perspective of the hospital, depending on the national health system and reimbursement scheme. Although health insurance in some countries may pay per hospital day, the additional cost of ADRs may not be covered adequately in the Diagnoses-Related Group (DRG) system. At present, no standards for the estimation of ADR-related cost for hospitals and the healthcare systems have been established. It has often been claimed that prevention of ADRs could result in cost savings.[7] Prerequisites are preventability of ADRs (roughly 30%[7,21]) and implementation of prevention programmes.[29,46] The preventability of ADRs and ADEs has so far been judged only retrospectively, i.e. after occurrence of the ADR or ADE. It has not yet been demonstrated if indeed 30% of ADRs/ADEs can be prevented. Certain projects, e.g. additional computer programs[47] or regular visits of a clinical pharmacist,[29] implemented into clinical routine

were able to prove significant reductions in the rate of ADRs. Intervention programmes including evening symposia for general practitioners and leaflets on ADRs showed a reduction of preventable ADR-related hospital admissions by 83%.[46] Unfortunately, only very few of the studies published on ADR detection in hospitals were followed by intervention programmes, demonstrating the potential economic impact of ADR prevention.

8. Conclusions

Different systems are applied to detect ADRs leading to hospital admissions and those occurring during the hospital stay. Whereas comprehensive monitoring seems to give the most reliable figures on incidence and even further allows for pharmacoepidemiological analyses, it requires a large amount of personal resources, and cost-effectiveness in terms of ADR prevention has been proven for only a few projects.[14] However, it should be noted that comprehensive ADR monitoring in hospitals guarantees a high level of quality of ADR reports to the drug approval authorities. Despite the intensity of ADR monitoring in the studies quoted, there is a lack of information about whether new (not yet claimed) ADRs were detected.[18] Computer-assisted methods and record linkage with ambulatory healthcare data represent a feasible way for the future, and widespread use may be implemented especially as a means of quality management.[10,11,48] However, these automated approaches, in addition to networking of many hospital databases, could also be useful to supervise newly introduced drugs for rare ADRs, e.g. idiopathic thrombocytopenic purpura following administration of clopidogrel.[49,50] Considering the progress in drug development, the attributable risk[3] and recent developments regarding health economics, the value of ADR detection in hospitals cannot be denied.[48,49] However, the methods and systems used have to be further evaluated, and more standardisation (e.g. with regard to definition of ADR terms, causality assessment and pharmacoeconomic analyses) is required.[39,51]

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