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Detecting and reporting adverse drug reactions to improve patient out comes

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ABSTRACT

Every occasion when a patient is exposed to a medical product, is a unique situation and we can never be certain about what might happen.An adverse drug reaction (ADR) has recently been defined as ''An appreciably harmful or un- pleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product [2]''. Pharmacogenomics may be one of the most immediate clinical applications of the Human Genome Project8 and may become part of standard practice for "quite a number of disordersand drugs by year 2020."[6]Recent developments in technology and bioinformaticspermit the rapid assay and interpretationof 25 000+gene transcripts on smallsolid-state 'chips'This approach has the advantage of sensitivity, in that very low levels of transcripts can bemeasured, but has some significant limitations.Proteins can be measured reliablyin a broader range of biological tissues (e.g.blood, CSF, synovial fluid) than mRNA transcriptsand are the 'business molecules'. On thenegative side, it is more difficult to detect proteinsexpressed in low abundance. Moreover, for theinvestigation to enter clinical practice, a rapidassay of protein markers is required. However,once the biomarkers that characterise a drug responsehave been identified, these proteins couldbe screened by standard immunoassay.Adverse drug reactions (ADRs) have been monitored in many countries since the beginning of the1960s in a so-called 'early warning' function to collect knowledge about ADR profiles in order to acquire information on serious, rare and unknown ADRs at an early stage.Periodic evaluation of ADRs reported in a hospital helps in characterizing the pattern of ADRs and thereby help in designing steps to improve the safety of drug use in the working set up.It is only through the use of efficient, timely, cost-effective use of computerized clinical databases based on the EMR, that we have been able to detect errors in the delivery of medications in patient care. The use of computer-based decision support tools based on EMR in the management of ADE and other clinical situations have been shown to improve day to day patient care, improve the quality of care and outcomes as well as reduce health care costs [26].

Keywords: Adverse drug reactions (ADRs), adverse drug events (ADE) Pharmacogenomics, Proteomics, ADRs monitoring system.

INTRODUCTION

Every occasion when a patient is exposed to a medical product, is a unique situation and we can never be certain about what might happen. A good example for this is thalidomide tragedy in late 1950s and 1960s.Thalidomide prescribed as a safe hypnotic to many thousands of pregnant women caused severe form of limb abnormality known as phocomelia in many of the babies born to those women [1].

An adverse drug reaction (ADR) has recently been defined as ‘‘An appreciably harmful or un-pleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product.” [2]

Accurate data on their incidence is limited butthere is general agreement that they are common and costly. A meta-analysis of 39 studies in the USA from 1966 to 1996 reported that the incidenceof severe ADRs in hospital in-patients was6.7% (Lazarou et al., 1998). ADRs may accountfor 15% of all hospital admissions and significantlyincrease the length of hospital stay [3].˙ADRs can be broadly dividedinto type A (Augmented) and type B (bizarre). Type A reactionsare the more common and may be predicted fromthe known properties of the drug. Arguably themore dangerous are Type B reactions [4].

The diagnosis of ADRs is currently more of aclinical skill than a scientific exercise. It requires alow threshold of suspicion and benefits from clinicalexperience, and where possible, pattern recognition, supported by standard haematological, biochemical and histological services [5].

Potential role of pharmacogenomics in reducing adverse drug reactions:
Onepossible cause ofADRsis genetic variation in how individuals metabolize drugs. The Human Genome Project heralds new opportunities for using genetic information to individualize drug therapy, called *pharmacogenomics*. In fact, pharmacogenomics may be one of the most immediate clinical applications of the Human Genome Project8 and may become part of standard practice for “quite a number of disordersand drugs by year 2020.”[6]

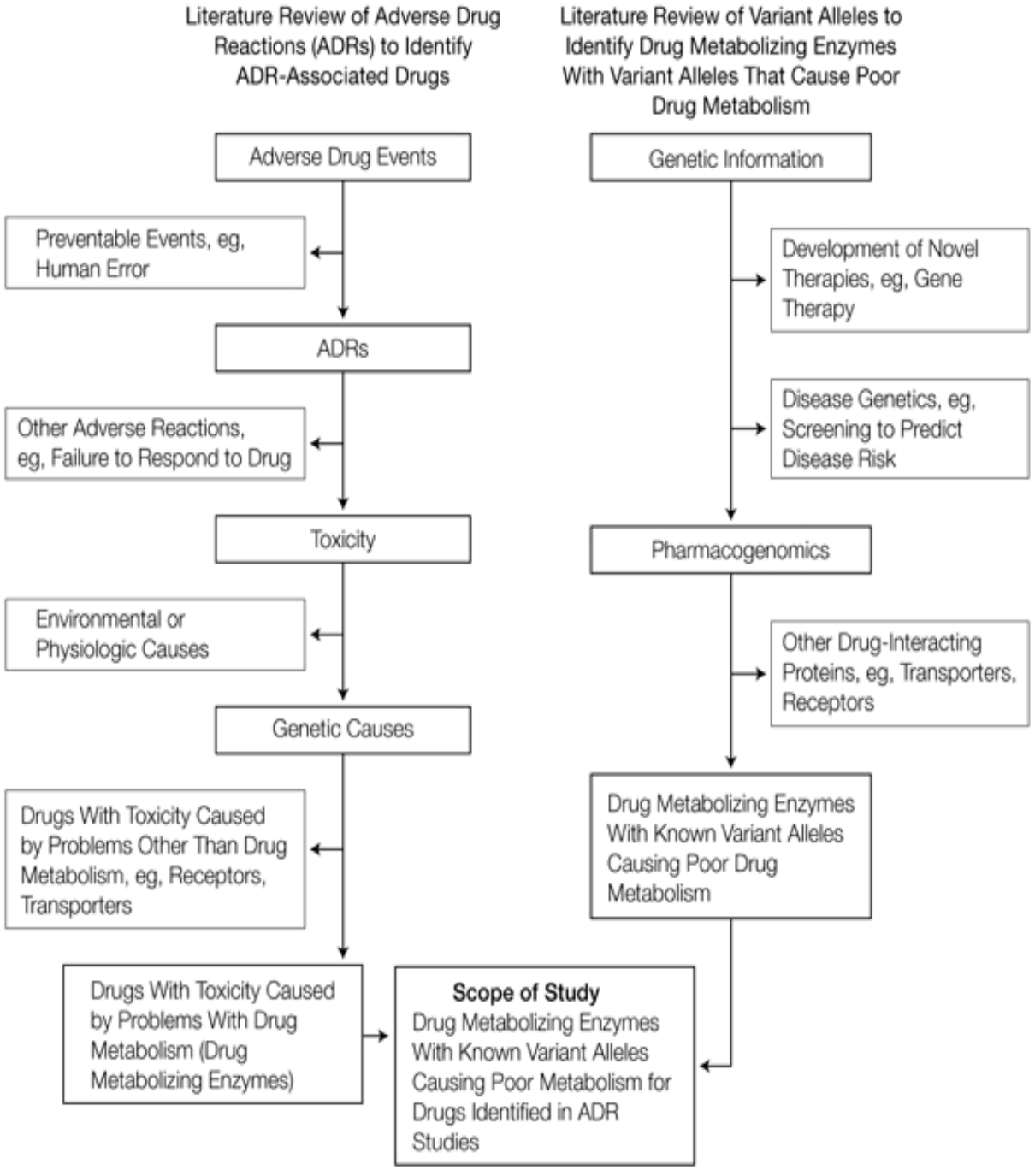
Much of the literature isconcerned with the clinical relevance of geneticpolymorphisms in drug metabolising enzymesbut data are accumulating on the contributionof variations in receptors, ion channels, enzymesand immune response to variation in drug response.To date these studies have examined theassociation with candidate genes but there isgrowing interest and speculation about the applicationof single nucleotide polymorphism
(SNP) profiles (Roses, 2000) [7].

Gene expression profiling:
Recent developments in technology and bioinformaticspermit the rapid assay and interpretationof 25 000+gene transcripts on smallsolid-state ‘chips’. This technique has been employedto study gene expression in a variety oftissues in response to different perturbations, such as hypoxia, gene knockout and drugs. Inprinciple, this technique could be used to detectand define the characteristic change in expressionof several genes following exposure to adrug—that is, detect a gene signature associatedwith toxicity to a drug and thus be of value indiagnosis.This approach has the advantage of sensitivity, in that very low levels of transcripts can bemeasured, but has some significant limitations.While it could be applied to solid tissue samples,such as skin, liver and renal biopsies, it isnot easy to isolate good quality mRNA frombiological fluids. This limits the use of gene expressionprofiling in more accessible samples, such as blood, urine

and synovial fluid. In addition, posttranslational modification ofproteins and concerns over the correlation betweenmRNA and protein abundance meanthat reliance on the measurement of transcriptlevels will not provide the full story andfurther information could be gained fromprotein profiling [8] [9].

PHARMACOGENOMICS IN REDUCING ADRS

Figure. Scope of Study



The role of proteomics

Proteomics is the large scale study of geneexpression at the protein level. The measurementof changes in protein levels are already in diagnosticuse. Liver function tests are not so much ameasure of the function of the liver but of theextent of protein leakage into the circulation as aresult of hepatic damage. In our jaundiced patient, changes in the circulating levels of aspartatetransaminase and alkaline phosphatase were veryuseful in distinguishing between an obstructivecause, for example due to gall stones, and thatdue to hepatocellular damage [10]. Similarly, the measurementof plasma levels of 'cardiac enzymes',troponins and the myocardial isoform of creatinekinase, can be used to identify and follow the timecourse of myocardial infarction, natriuretic peptidelevels and catecholamines are used to monitortreatment in cardiac failure and circulating 'antinuclearantibodies' are used to diagnose connectivetissue diseases[11]. The use of 2-D gels and massspectrometry to measure simultaneously a numberof proteins in a sample extends the application ofthis approach and offers the possibility of identifyingprotein signatures of drug activity.There is considerable interest in the use ofproteomics to identify biomarkers of drug activitythat may be used to monitor both therapeutic andtoxicological responses (Steiner and Witzmann,2000) [9]. Examples are few at present but somesuccess has been recorded. Distinct protein patterns have been associated with exposure toPPAR agonists and non-steroidal anti-inflammatorydrugs that can be used to screen new chemicalentities for activity. Proteomics identified therelationship between changes in the expression ofa calcium-binding protein, calbindin-D 28 kDa, and nephrotoxicity from ciclosporin A in renal biopsies [12]. Similar studies inrats have identified a novel protein in serum thatmay be a marker of renal toxicity from gentamycin(Kennedy, 2001). Proteins can be measured reliablyin a broader range of biological tissues (e.g.blood, CSF, synovial fluid) than mRNA transcriptsand are the 'business molecules'. On thenegative side, it is more difficult to detect proteinsexpressed in low abundance. Moreover, for theinvestigation to enter clinical practice, a rapidassay of protein markers is required. However, once the biomarkers that characterise a drug response have been identified, these proteins could be screened by standard immunoassay. The possibilityof measuring several such proteins simultaneouslyusing antibodies immobilised on 'chips' (antibody arrays) is very attractive [12].

Adverse drug reaction monitoring system:

Adverse drug reactions (ADRs) have been monitored in many countries since the beginning of the1960s in a so-called 'early warning' function to collect knowledge about ADR profiles in order to acquire information on serious, rare and unknown ADRs at an early stage.Periodic evaluation of ADRs reported in a hospital helps in characterizing the pattern of ADRs and thereby help in designing steps to improve the safety of drug use in the working set up. Better health care practice could be ensured by applying this knowledge to individual patients. Data generated from a hospital set up further contributes to the national and international databases on ADRs which will ultimately contribute in drug safety decisions and may serve as a basis for product-labelling revision and design patient education strategies [13].

Adverse drug reaction (ADR) monitoring involves following steps [14]:

I. Identifying adverse drug reaction (ADR)
II. Assessing causality between drug and suspected reaction
III. Documentation of ADR in patient's medical records
IV. Reporting serious ADRs to pharmacovigilance centres /ADR regulating authorities.

I. Identifying adverse drug reaction (ADR)[15]

ADRs are mainly identified in the pre-marketing studies and in the post-marketing surveillance studies. Disadvantages of the pre-marketing studies are that they lack sufficient knowledge to

extrapolate information collected from animal studies directly into risks in humans and very few number of subjects (not more than 4000) are exposed to the new drug prior to the general release of product into market. Another major disadvantage is that clinical trials cannot be done in rare group of subjects like children, elderly and pregnantwomen. For cost reasons clinical trials often have short duration which means they cannot generate information about long term adverse effects.

Post marketing surveillance can be done by different methods:

1. **Anecdotal reporting:**

The majority of the first reports of ADR come through anecdotal reports from individual doctors when a patient has suffered some peculiar effect. Such anecdotal reports need to be verified by further studies and these sometimes fail to confirm problem.

2. **Intensive monitoring studies**:

These studies provide systematic and detailed collection of data from well defined groups of inpatients .The surveillance was done by specially trained health care professionals who devote their full time efforts towards recording all the drugs administered and all the events, which might conceivably be drug induced. Subsequently, statistical screening for drug-event association may lead to special studies.

3. **Spontaneous reporting system:**

It is the principal method used for monitoring the safety of marketed drugs. In UK, USA, India and Australia, the ADR monitoring programs in use are based on spontaneous reporting systems. In this system, clinicians are encouraged to report any or all reactions that believe may be associated with drug use. Usually, attention is focused on new drugs and serious ADRs. The rationale for SRS is to generate signals of potential drug problems, to identify rare ADRs and theoretically to monitor continuously all drug used in a variety of real conditions from the time they are first marketed.

4. **Cohort studies (Prospective studies)**

In these studies, patients taking a particular drug are identified and events are then recorded. The weakness of this method is relatively small number patients likely to be studied, and the lack of suitable control group to assess the background incidence of any adverse events. Such studies are expensive and it would be difficult to justify and organize such a study for every newly marketed drug

5. **Case control studies (retrospective studies)**:

In these studies, patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The prevalence of drug taking in this group is then compared with the prevalence in a reference population who do not have the symptoms or illness. The case control study is thus suitable for determining whether the drug causes a given adverse event once there is some initial indication that it might. However, it is not a method for detecting completely new adverse reactions.

6.**Case cohort studies**: The case cohort study is a hybrid of prospective cohort study and retrospective case control study, Patients who present with symptoms or an illness that could be due to an adverse drug reaction are screened to see if they have taken the drug. The results are then compared with the incidence of the symptoms or illness in a prospective cohort of patients who are taking the drug.

7. **Record linkage:** The idea here is to bring together a variety of patient records like general practice records of illness events and general records of prescriptions. In this way it may be possible to match illness events with drugs prescribed. A specific example of the use of record linkage is the so called prescription event monitoring scheme in which all the prescriptions issued by selected parishioners for a particular drug are obtained from the prescription pricing authority. The prescribers are then asked to inform those running scheme of any events in the patients taking the drugs. This scheme is less expensive and time consuming than other surveillance methods

8. **Meta analysis**:
Meta analysis is a quantitative analysis of 2 or more independent studies for the purpose of determining an overall effect and of describing reasons for variation in study results, is another potential tool for identifying ADRs and assessing drug safety.

9. **Use of population statistics:**
Birth defect registers and cancer registers can be used If drug induced event is highly remarkable or very frequent. If suspicions are aroused then case control and observational cohort studies will be initiated.

II. Assessing causality between drug and suspected reaction [16]:
Causality assessment is the method by which the extent of relationship between a drug and a suspected reaction is established. There are three approaches to asses causality.

These include
a) Opinion of an individual expert
b) Opinion of a panel of experts
c) Formal algorithms

Some of the important algorithms used are Naranjo, WHO, European ABO system, Kramer, Bayesian, Karch and lasanga and French imputation method. There is no gold standard for causality assessment. The categorisation of causal relationship between a drug and suspected adverse reactions varies with the scale adopted. WHO scale categorises the causality relationship into certain, probable, possible, unassessible/unclassifiable, unlikely, conditional /unclassifiable. The Naranjo's scale categorises the reaction as definite, probable, possible or unlikely.

In general the following four different basic points can be considered in attributing a clinical adverse event to the drug.

1. Temporal time relationship between suspected reaction and drug.
2. Dechallenge (cessation of drug)
3. Rechallenge (re introducing drugs)

Detecting adverse drug reactions by electronic medical records:
The detection of adverse drug reactions (ADRs) has become increasingly significant because of introduction of a large number of potent toxic chemicals as drugs in the last two or three decades. WHO has intervened seriously in this matter and established an international adverse drug reactions monitoring centre at Uppsala, Sweden, which is collaborating with national monitoring centres in around 70 countries [17].

In an era of established data and informationoverload medication administration anddrug utilization are significant factors in costescalation, adverse outcomes, and reduced quality in health care delivery. The availabilityand use of large computerized clinical databases linked to electronic medical records(EMR) now provide facilities for the detectionof adverse drug events (ADE) and alsothe decision support tools for clinicians toreact appropriately to their detection[18][19][20].

Decision support tools

In 1993, Prior and Clayton defined core primary clinical decision support tools essential for EMR. It is only through the use of efficient, timely, cost-effective use of computerized clinical databases based on the EMR, that we have been able to detect errors in the delivery of medications in patient care. In a recent study into negligence in medical care Brennan and others concluded that, ‘‘Lawyers generally believe that investigation of substandard care only begins with the medical record and that in many circumstances the medical record even conceals substandard care and that substandard care in not reflected in, or ‘discoverable’ in the medical record. Pooled data in electronic formats provides evidence that ADE originate from a wide range of interactive processes. These include errors in drug prescribing and administration, patient compliance, and errors stemming from pharmacological and physiological factors [23][24].

Current computerized clinical decision support tools that are based on the integrated, longitudinal EMR can be shown to provide. Benefits to health care through the detection of ADE and in the appropriate timing of pre-operative antibiotics in major surgery. Show in table

	1985	1986	1991
% prophylaxis given at optimum time	48%	58%	96%
% infection	1.85%	0.9%	0.4%
Estimated decrease in infection relative to 1985	-	33%	51%
Estimated saving at $1400/case in (thousand $)	-	$462K	$712K
National standard 2-4 infection rate			

Effect of EMR alerts on deep post-operative wound infections at LDS Hospital, Utah

Using the same decision support tools linked to laboratory results leads to more appropriate patient care, reduced length ofstay and time spent in life-threatening situations Benefits to patient care outcomes and costs and quality form the use of EMR functions have been demonstrated across a wide range of clinical activities[26].

CONCLUSION

Proteomics has the potential identify biomarkers of drug activity willmeet many of those requirements for a diagnosticinvestigation. Many new drugs are being introduced every year and so every health care professional must have knowledge about importance of ADR monitoring and pharmacovigilance. The use of computer-based decision supporttools based on EMR in the management of ADE and other clinical situations have been shown to improve day to day patient care, improve the quality of care and outcomes as well as reduce health care costs.

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