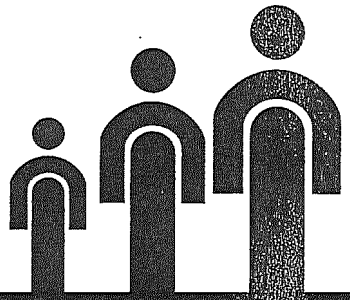
	津谷喜一郎(訳)	第10章　薬理遺伝学に関連する薬剤経済学的考慮	津谷喜一郎(監訳)	ファーマコジェネティクス－薬物治療の改善を目指して－	テクノミック	東京	2005	139-59
	高田容子(訳)	第11章　コミュニケーションと教育	津谷喜一郎(監訳)	ファーマコジェネティクス－薬物治療の改善を目指して－	テクノミック	東京	2005	161-73
	玉起美恵子(訳)	第12章　未解決の問題と発展への障害	津谷喜一郎(監訳)	ファーマコジェネティクス－薬物治療の改善を目指して－	テクノミック	東京	2005	175-86
	具嶋弘(訳)	Annex 7　日本における薬理遺伝学とゲノム薬理学	津谷喜一郎(監訳)	ファーマコジェネティクス－薬物治療の改善を目指して－	テクノミック	東京	2005	214-8
			杉山雄一 津谷喜一郎(編)	臨床薬理に基づく医薬品開発戦略	廣川書店	東京	2006	
3-1	津谷喜一郎	11　ファーマコジェネティクス臨床試験の問題と解決法－CIOMS レポートを中心に－	杉山雄一 津谷喜一郎(編)	臨床薬理に基づく医薬品開発戦略	廣川書店	東京	2006	181-99
3-2	玉起美枝子，具嶋弘	13　ファーマコゲノミクスと倫理	杉山雄一 津谷喜一郎(編)	臨床薬理に基づく医薬品開発戦略	廣川書店	東京	2006	215-26
3-3	内田英二	15　医薬品開発における International Harmonization(ICH)	杉山雄一 津谷喜一郎(編)	臨床薬理に基づく医薬品開発戦略	廣川書店	東京	2006	239-47

雑誌（Journal）

	発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
1	額賀淑郎, 津谷喜一郎	「遺伝子例外主義」問題の動向	日本医師会雑誌	134(12)	2385-90	2006
2	Fukuda T, Maune H, Ikenaga Y, Naohara M, Fukuda K, Azuma J	Novel structure of the CYP2D6 gene that confuses genotyping for the CYP2D6 5 allele	*Drug Metab Pharmacokinet*	20(5)	345-50	2005
3	Kubota T, Nakajima-Taniguchi C, Fukuda T, Funamoto M, Maeda M, Tango E, Ueki R, Kawashima K, Hara H, Fujio Y, Azuma J	CYP2A6 polymorphisms are associated with nicotine dependence and influence withdrawal symptoms in smoking cessation	*The Pharmacogenomics Journal*	6	115-9	2006
4	Nonen S, Okamoto H, Akino M, Matsui Y, Fujio Y, Yoshiyama M, Takemoto Y, Yoshikawa J, Azuma J, Kitabatake A	No positive association between adrenergic receptor variants of α2cDel322-325, β1Ser49, β1Arg389 and the risk for heart failure in the Japanese population	*Br J Clin Pharmacol*	60(4)	414-7	2005
5	Ikenaga Y, Fukuda T, Fukuda K, Nishida Y, Naohara M, Maune H, Azuma J	The frequency of candidate alleles for CYP2D6 genotyping in the janapese population with an additional respect to the -1584C to G substitution	*Drug Metab Pharmacokinet*	20(2)	113-6	2005
6	Kubo M, Koue T, Inaba A, Takeda H, Maune H, Fukuda T, Azuma J	Influence of itraconazole co-administration and CYP2D6 genotype on the Pharmacokinetics of the new antipsychotic ARIPIPRAZOLE	*Drug Metab Pharmacokinet*	20(1)	55-64	2005
7	Inaba M, Otani Y, Nishimura K, Takaha N, Okuyama A, Koga M, Azuma J, Kawase I, Kasayama S	Marked hyperglycemia after androgen-deprivation therapy for prostate cancer and usefulness of pioglitazone for its treatment	*Metabolism Clinical and Experimental*	54	55-9	2005

8	Ohmoto M, Uejima E, Takahasi K, Abe K, Sakoda S, Kurokawa N, Azuma J	Pharmacokinetic evaluation of anticonvulsants in a patient with porhyria	*Jpn J Clin pharamacol Ther*	35(6)	291-6	2004
9	Niwa T, Hiroi T, Tsuzuki D, Yamamoto S, Narimatsu S, Fukuda T, Azuma J, Funae Y	Effect of genetic polymorphism on the metabolism of endogenous neuroactive substances, progesterone and *p*-tyramine, catalyzed by CYP2D6	*Molecular Brain Research*	129	117-23	2004
10	内田英二	治験におけるファーマコゲノミクス研究の進展のために－医療現場の状況と方向性－	臨床薬理	36(6)	326-8	2005
11	増井徹，高田容子	英国バイオバンクプロジェクト	実験医学	23(4)	522-9	2005
12	増井徹	Pharmacogenetics test の利用を支えるコアコンピタンス	臨床薬理	36	57S-58S	2005
13	増井徹	私たちはどのような世界に住みたいのか？	国際 BIOETHICSNETWORK	39	55	2005
14	増井徹	個人と集団	社会薬学	24	11-3	2005
15	増井徹	Pharmacogenomics test の利用を支えるコアコンピタンス	臨床医薬	21	694-700	2005
16	増井徹	くすりと医療を支える社会基盤	平成 17 年度大阪大学大学院薬学研究科公開講座「くすりと医療」		59-71	2005

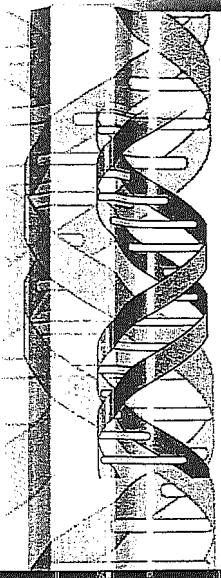


CIOMS publications may be obtained directly from CIOMS, c/o World Health Organization, Avenue Appia, 1211 Geneva 27, Switzerland or by e-mail to cioms@who.int

Both CIOMS and WHO publications are distributed by the World Health Organization, Marketing and Dissemination, Avenue Appia, 1211 Geneva 27, Switzerland and are available from booksellers through the network of WHO sales agents. A list of these agents may be obtained from WHO by writing to the above address.

Price: CHF 25.—

Towards improving treatment with medicines — CIOMS



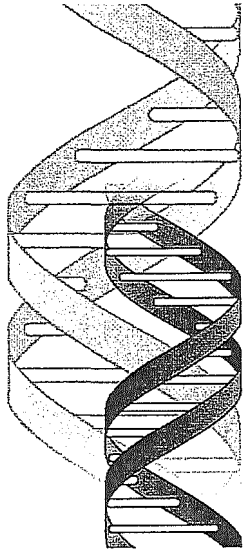
Pharmacogenetics

Towards improving treatment with medicines

CIOMS

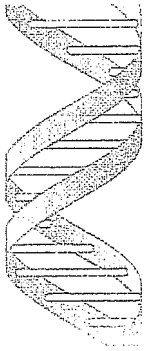
Geneva
2005

B-1



Pharmacogenetics

Towards improving treatment with medicines



CIOMS

Geneva 2005

ISBN 92 9036 078X
Printed in Switzerland

Acknowledgements

The Council for International Organizations of Medical Sciences (CIOMS) gratefully acknowledges the contributions of the members of the CIOMS Working Group on Pharmacogenetics as well as the drug regulatory authorities, pharmaceutical companies and other organizations and institutions which supported the work that resulted in this publication. Drafting and redrafting of chapters, their review and a number of debates in the Working Group required patience, motivation, active collaboration and extra working hours from all members.

CIOMS acknowledges especially all those members who chaired the meetings of the Working Group. The Editorial group, comprised of Drs Celia Brazell, Larry Lesko, Rashmi Shah, Brian Spear and Elora Weringer, merits special mention and thanks.

CIOMS also wishes to express special appreciation to Rashmi Shah, who as Chief Editor of the final report, assured the scientific and technical quality of the publication.

Geneva, 12 January 2005

Juhana E. Idänpään-Heikkilä, MD, PhD
Secretary-General, CIOMS

Preface

The notion that genetic factors can be responsible for altered drug response in some patients evolved in the late 1950s. The term 'pharmacogenetics' was coined in 1959 to describe a new scientific discipline that dealt with inherited differences in the response to drugs. It has been suggested that selection of drug therapy based on the genetic make-up of a patient may result in not only an improved therapeutic response but also a clinically important reduction in adverse drug reactions.

Increasingly, sponsors of new drugs are integrating pharmacogenetics in their drug development programmes. The outcome of this integration will present challenges to the traditional paradigms for drug development, regulatory evaluation of safety and efficacy and clinical use of drugs. Ethical, legal and pharmacoeconomic issues are also integral to the debate.

Pharmacogenetics is still an evolving discipline and a very active area of research. It promises to revolutionise therapeutics by 'personalising medicine'. The term 'personalised medicine' is potentially misleading and may be interpreted to mean that drugs are *developed* for individual patients. A term that we prefer to use is 'individually targeted therapy'. In principle, genotype-based individually targeted prescribing ought to be more effective at improving response rates and decreasing the burdens of adverse drug reactions.

The extent to which this promise of pharmacogenetics is fulfilled remains to be seen. The experience to date is mixed with a few successes but many frustrations. Discovering highly predictive genotype-phenotype associations during drug development and demonstrating their clinical validity and utility in well-designed prospective clinical trials will no doubt better define the role of pharmacogenetics in future clinical practice. In the meantime, pharmacogenetic research deserves support from all concerned but without unrealistic expectations.

This Report, an outcome of inspiring discussions among a number of senior scientists from drug regulatory authorities, pharmaceutical companies and academia, addresses many of these issues in detail. It reflects their views and visions today and expectations for the future. The reader will find that there is duplication of information in various chapters. This is deliberate. The CIOMS Working Group on Pharmacogenetics considered that each chapter should be self-standing with its own references.

CIOMS and its Working Group on Pharmacogenetics hope that readers will enjoy this contribution to the ongoing discussions and debate.

Contents

Disclaimer 6

Chapter

1. Introduction and Problem Statement 7
2. Abnormal Drug Response (I): Clinical, Social and Economic Burden 13
3. Abnormal Drug Response (II): Opportunities for Risk Reduction Through Pharmacogenetics 27
4. Exploring Pharmacogenetics in Drug Discovery and Development 45
5. Impact of Pharmacogenetics on Drug Discovery and Development 71
6. Improvements in Existing Therapies 89
7. Regulatory Perspectives in Pharmacogenetics 103
8. Genetic Testing, Genetic Data and Genetic Information 113
9. Ethical Issues 127
10. Pharmacoeconomic Considerations in Pharmacogenetics 145
11. Communication and Education 167
12. Unresolved Issues and Barriers to Progress 179

Annex

1. Process and Membership of CIOMS Working Group on Pharmacogenetics 191
2. Pharmacogenetics and Pharmacogenomics in Australia 193
3. Pharmacogenetics and Pharmacogenomics in Canada 195
4. Pharmacogenetics and Pharmacogenomics in China 197
5. Pharmacogenetics and Pharmacogenomics in Chinese Taipei . . . 200
6. Pharmacogenetics and Pharmacogenomics in the European Union 204
7. Pharmacogenetics and Pharmacogenomics in Japan 214
8. Pharmacogenetics and Pharmacogenomics in the Republic of Korea 218
9. Pharmacogenetics and Pharmacogenomics in Singapore 221

Disclaimer

Although most chapters enjoyed an undivided support, there were others where unanimity was not possible. Therefore, the views expressed in this Report should be considered majority-based consensus views and not necessarily the unanimous views of all the members of the CIOMS Working Group on Pharmacogenetics (*see Annex 1*) or of the affiliations served by these members.

Chapter 1

Introduction and Problem Statement

1. Introduction

The latter half of the last century has witnessed the development of most of the drugs that are used today. The introduction of these drugs has led to dramatic changes in the practice of medicine since it has allowed for the first time the effective treatment of many common diseases such as hypertension, angina pectoris, depression, schizophrenia, lymphomas and leukaemias to name only a few.

Right from the beginning of modern drug therapy it was observed that there was substantial variability among patients both in therapeutic efficacy and the occurrence of side effects. Moreover, for all major classes of drugs (angiotensin converting enzyme inhibitors, ß-adrenoreceptor antagonists, selective serotonin reuptake inhibitors, tricyclic antidepressants, statins and ß-agonists) a significant proportion of patients will not respond, or respond only partially, when standard doses of the particular drug are administered. The realisation that dose was a poor predictor of therapeutic response stimulated efforts in elucidating the mechanisms responsible.

From these studies it became apparent that the rate at which drugs are eliminated from the body showed substantial interindividual differences. In particular, drug metabolising enzymes were identified to play a pivotal role in the elimination process of most drugs. Since individual optimisation of dosage with such drugs in clinical practise is difficult, there follows sub-optimal treatment, prolonged periods of trial and error and non-compliance with a consequential increase in morbidity, mortality and costs. Therefore, considerable efforts have been expended to identify the mechanisms underlying the marked variability of drug response. As possible mechanisms, heterogeneity of the disease and such clinical variables as age, gender, diet, co-administration of drugs, renal and hepatic function were identified. In addition to these factors it was recognised that genetic factors involved in drug disposition (absorption, distribution, metabolism and elimination) or drug action (receptors and signalling pathways) can modify drug response or are risk factors for adverse drug reactions.

2. Birth of pharmacogenetics

Genetic factors have been suggested, depending on the drug, to account for 20 to 95% of the variability in drug disposition and effects [1, 2]. The concept that genetic factors which alter the pharmacokinetics and pharmacodynamics of drugs can be responsible for altered drug response in some patients evolved in the late 1950s. At that time it was demonstrated that an inherited deficiency of glucose-6-phosphate dehydrogenase was responsible for the severe haemolysis observed in some patients when exposed to the antimalarial primaquine. This discovery also provided an explanation for why primaquine-induced haemolysis mainly affected the African Americans – this deficiency occurred with a much higher frequency in this ethnic group and was rarely observed in Caucasians of Northern, Western and Eastern European descent. [3]

In 1959, Vogel coined the term 'pharmacogenetics' to describe a new scientific discipline that dealt with inherited differences in the response to drugs [4]. In recent years, the term pharmacogenomics has been introduced to describe the progressive transition from genetics to genomics realising that the genome is more than the sum of its genes. It introduces an additional element of a genome-wide approach to identify genes that contribute to a specific disease. *Pharmacogenetics* is defined as the study of interindividual variations in DNA sequence related to drug disposition (pharmacokinetics) or drug action (pharmacodynamics) that can influence clinical response. In contrast, *pharmacogenomics* is defined more broadly as the application of genomic technologies to elucidate disease susceptibility, drug discovery, pharmacological function, drug disposition and therapeutic response. This approach will lead to a new classification(s) of diseases at the molecular level. Moreover, identification of new disease genes will provide new drug targets. Of the 30,000 diseases presently known, there is either no drug treatment or improved drug treatment is needed for more than a 100 to 150 major common diseases. The drugs used today are targeted at approximately 500 pharmacologically active biological targets and there is a great hope that there are at least 3,000 to 10,000 'drugable' targets [5].

3. Pharmacogenetics and therapeutics

Severe adverse drug reactions (ADRs) such as hepatotoxicity or drug-induced arrhythmias continue to be a significant problem both during the development and in the postmarketing phase of new drugs. ADRs increase morbidity and mortality and are associated with considerable cost

to the healthcare system. The timeliness of this problem is emphasised by a recent survey indicating that adverse drug reactions may be responsible for over 100,000 deaths annually in the US and account for about 5% of all hospital admissions [6]. Recent studies indicate that genetic factors play a role in the pathogenesis of both predictable and unpredictable ADRs. It has been suggested that drug therapy based on the individual genetic make-up of a patient may not only result in an improved response but also in a clinically important reduction in ADRs. For example, Philips and co-workers identified in their systematic review 27 drugs frequently cited in ADR studies [7]. Among these drugs, 59% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 20% of randomly selected drugs were metabolised by enzymes that are known to be expressed polymorphically. This analysis suggests that genetic variability in drug metabolising enzymes is a contributor to the incidence of ADRs.

4. Pharmacogenetics and drug development

Worldwide, new drug applications are declining although the number of new chemical entities (NCEs) screened has increased with the use of modern high throughput technology. Ninety percent of new candidates selected from the preclinical phase fail during the clinical development. In 80% of those drugs entering the clinical trials, poor response or side effects are the reasons for terminating development. Thus, there is an urgent need to increase the success rate. One way of improving the success rate is to identify potential responders and non-responders to the drug under investigation on the basis of genetic testing before inclusion into a clinical trial. It is hoped that this approach will not only increase the success rate but also lead to a reduction in the number of patients required to demonstrate efficacy of the drug. As a consequence, the time for the clinical phase of development could be shortened and the costs reduced. However, there are safety-related limitations to this approach. At least one to two drugs are withdrawn every year from the market because of severe ADRs. Recent examples include troglitazone, mibefradil, some newer fluoroquinolones and cerivastatin. Since only a very small number of patients experienced these severe ADRs, it is quite likely that genetic factors predispose these patients to toxicity. Withdrawal of a drug is associated with enormous financial costs to the pharmaceutical industry since it costs about 500 to 700 million Euros to develop a drug and take it through its various preclinical and clinical phases. The industry, and indeed the society, cannot afford such withdrawals, as recent data indicate that the fall in the num-

ber of new drugs approved in the US is reaching a crisis point and that new drug applications are down worldwide. Identification of genetic factors associated with severe ADRs could save some of these drugs [8-10].

5. Pharmacogenetics and targeted prescribing

With the complete sequence of the human genome now available, it is hoped that better targeted medicine will soon become a reality. The expectations are that with the use of genomic information, we will be able to better predict an individual's likely response to a drug and select the appropriate dose of the drug. This would allow achieving the optimal therapeutic response, avoiding therapeutic failure and minimising side effects and toxicity. Although many genes responsible for inherited differences in the metabolism, transport and action of drugs have been identified, this new knowledge has not been translated into clinical practice. With the exception of a few examples of drug metabolising enzymes, the contribution of genetic polymorphisms to individual differences in drug effects and toxicity are not well understood. Moreover, most of these studies have focused on the consequences of a single gene polymorphism for an altered drug response. This approach, however, neglects the fact that drug response phenotype like most disease phenotypes is a complex polygeneic trait with non-genetic factors contributing to the manifestation of the phenotype [11].

6. Limitations of pharmacogenetics

The extent to which genetic factors contribute to drug response/toxicity phenotype will depend on whether the candidate gene is a gene of major, moderate or minor effect. There are also misconceptions with respect to the information provided by a pharmacogenetic test. Even in the case of a gene with maximum effect, the presence or absence of a mutation will not provide a straight forward 'yes' or 'no' answer but rather the likelihood that in a subject with a given mutation, an event will or will not occur. The highest positive predictive value of a genetic test will be observed for genes with major effect. In the case of drug metabolising enzymes, mutations leading to a loss of function will result in higher drug concentrations. If these higher drug concentrations are associated with toxicity, the likelihood that a patient who has this genotype will develop toxicity is increased provided the patient is prescribed the same dose as the remainder of the patients who carry the wild type of the gene. However, the negative predictive value (likelihood that a patient without the mutation will not have toxicity) can be rather poor if non-genetic factors that lead to high drug concentrations (which are associated with drug toxicity) are neglected. If a patient who carries a wild type gene is concomitantly treated with a drug that inhibits the enzyme, the patient will develop the phenotype of high concentration that is usually associated with the presence of two mutant alleles, a phenomenon known as 'phenocopying'. Neglecting the impact of non-genetic factors on the manifestation of a drug response phenotype has led to claims that genotyping for the deficient alleles of thiopurine S-methyltransferase (TPMT) has a poor predictive value for the development of severe myelosuppression, which is seen with the use of 6-mecaptourine or azathioprine. It is vital therefore that pharmacogenetic information is used to improve prescribing decisions and considered alongside other key information in a holistic manner.

One of the major limitations, which has prevented the use of pharmacogenetic testing in the clinical setting, is the lack of prospective clinical trials demonstrating that pharmacogenetic testing can assist in the selection of the appropriate drug and dose for the individual patient in order to achieve the optimal therapeutic response, avoid therapeutic failure and minimise side effects and toxicity. The current pharmacogenetic research being undertaken by both the private and the public sectors will need to address this deficit.

With the rapid progress being made in molecular genetics, more and more genes that can alter drug response will be identified. Since drug response involves several genes, the positive and negative predictive values of pharmacogenetic testing will be improved by combining information from each of the contributing genes. Thus with the advances made in technology, the cost of genotyping will become affordable and it should be possible to establish pharmacogenetics for optimising drug development and drug therapy.

REFERENCES

[1] Evans WE, McLeod HL.
Pharmacogenomics – drug disposition, drug targets and side effects.
N Eng J Med. 2003; 348: 538-549

[2] Weinshilboum R.
Inheritance and drug response.
N Engl J Med. 2003; 348: 529-537

[3] Beutler E.
Drug induced haemolytic anaemia.
Pharmac Rev. 1969; 21: 73-103

[4] Vogel F.
Moderne Probleme der Humangenetik.
Ergeb Inn Med Kinderheilkd. 1959; 12: 52-125
[5] Drews J.
Genomic sciences and the medicine of tomorrow.
Nat Biotechnol. 1996; 11: 1516-1518
[6] Lazarou J, Pomeranz BH, Corey PN.
Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.
JAMA. 1998, 279, 1200-1205
[7] Phillips KA, Veenstra DL, Oren E, Lee JK, Sadee W.
Potential role of pharmacogenomics in reducing adverse drug reactions: a systematic review.
JAMA. 2001; 286: 2270-2279
[8] Anon.
Guiding drug discovery through 2003.
Nat Rev Drug Discov. 2003; 2: 3
[9] Knowles J, Gromo G.
A guide to drug discovery: Target selection in drug discovery.
Nat Rev Drug Discov. 2003; 2: 63-69
[10] Marshall E.
Preventing toxicity with a gene test.
Science. 2003; 302: 588-590
[11] Evans WE, Relling MV.
Moving towards individualized medicine with pharmacogenomics.
Nature. 2004; 429: 464-468

Chapter 2

Abnormal Drug Response (I): Clinical, Social and Economic Burden

1. Introduction

From the very beginning of monitoring drugs for their safety, attention has been paid to the economic consequences of adverse drug reactions (ADRs) [1-3]. ADRs have long been recognised as a significant cause of morbidity and mortality but the true extent of the problem has remained a matter of discussion and informed speculation. Almost a quarter of a century ago, Mach and Venulet [3] considered methodological issues for estimating the economic aspects of ADRs, and calculated direct and indirect costs using several case scenarios.

Prescribing the most effective drug in individual patients is more often than not a process of trial and error. Therefore, in addition to ADRs, failure of efficacy of a drug also imposes significant burdens. However, data quantifying the healthcare and economic impacts of patients failing to respond to the medicines prescribed first time are sparse.

The most common ADRs are dose- or concentration-related (type A) pharmacological reactions that account for about 75-80% of all ADRs. These include reactions related to prescription of inappropriate drug or inappropriate doses of a drug as well as drug interactions. Usually, clinically relevant drug interactions result in an increase in plasma concentration of one of the interacting drugs to toxic levels. Other common types of ADRs are immunologically-mediated (type B for bizarre, idiosyncratic or hypersensitivity reactions). Classification of ADRs has also included those termed type C (following continuous or chronic use), type D (that are delayed such as carcinogenic or teratogenic effects) and type E (end-of-use ADRs that result from withdrawal of a drug; "rebound phenomenon"). Recently, ADRs of type F have been added to this increasingly complex classification and these result from unexpected failure of therapy.

As early as 1972, it was estimated that 6.9 to 22% of all ADRs are in fact due to drug interactions [4]. Although the majority of drug interactions result in pharmacokinetic changes with no clinical consequences, about 1 in 7 drug interaction studies, submitted to the US Food and Drug Administration (FDA) during the period 1992-1997, led to changes in

labelling, the majority of which involved dose adjustments [5]. One review of the available studies suggests that up to 30% of hospital patients and 70% of ambulatory patients could be receiving potentially interacting drugs [6]. Drug interactions are increasing and are now recognised as a frequent cause of hospital admissions [7-10]. The number of drugs withdrawn recently because of their interaction potential and clinical consequences testifies to this increasing problem, resulting from (generally unintentional) polypharmacy.

There are a large number of international studies that estimate the scale of the clinical burden due to ADRs. Others have attempted to quantify the social and economic consequences of ADRs in terms of healthcare availability, resource implications and gross national productivity. All those involved in the development and use of medicines, whether they be payers, pharmaceutical companies, patients, physicians, or regulators agree that ADRs are associated with suffering and costs.

This chapter reviews a sample of representative studies on the overall impact of ADRs and failure of efficacy.

2. ADR-related morbidity and mortality

2.1 ADRs in community medicine

In one of the earliest studies assessing the impact of ADRs, Mulroy reported that 1 in 48 consultations in general practice in the UK was due to an ADR [11]. A study by Lumley et al estimated that 0.8% of all general practitioner consultations are directly due to ADRs [12]. Following a survey of 817 patients and using a much broader definition of ADR, Martys reported that 41% of the patients in general practice have had a reaction to the drug prescribed [13].

More recent studies from France have estimated an incidence of about 2 adverse effects per general practitioner per day [14] and 2.6 cases of serious ADRs per general practitioner per year [15]. Despite the enormous progress in therapeutics since the late 1970s, the incidence of ADRs has not changed [16-20].

2.2 Drug-related hospital admissions

Using data compiled prior to 1977, Venulet reported the incidence of ADRs in already hospitalised patients as ranging from 2 to 18% [21]. A review in 1993, based on 36 English-language studies of ADRs leading to hospital admissions, reported that on average, 5.5% of all hospital admissions are due to ADRs [22]. The incidence varied from 0.2% to 21.7% depending on the population under investigation.

In an Italian hospital, 235 of 5,497 patients who visited the emergency department over a 1-year period (October 1994 to September 1995) did so because of an ADR. Of these, 45 were hospitalised. Dose-related therapeutic failures (55.6%) were the main cause of drug-related admissions whereas ADRs (63.8%) caused the most frequent drug-related visits. Although drug interactions accounted for only 3.8% of the visits, their consequences were more severe, and most of these patients had to be hospitalised [23].

The percentage of hospital admissions due to drug-related causes, including ADRs and therapeutic failures, has been variously estimated to be 11.4% in Denmark (study period was March 1988 to May 1989) [24], 13.8% in Sweden (September 1997–October 1998) [25] and 5.7% in Australia (November 1994–December 1994) [26]. In one study of 452 admissions to a university hospital in the USA, 16.2% of the admissions were considered drug-related which included 8.8% due to drug therapy failure (July 1993–August 1993) [27].

The percentage of hospital admissions specifically due to ADRs has been estimated at 8.4% in Denmark [24], 7.5% in the UK [28], 3.3-7% in Switzerland (from 1996 onwards) [29, 30], 3.2-7.2% in France (March–April 1998 in one of the studies) [31, 32], 2.7% in Australia [26] and 2.4% in Germany (October 1997–March 2000) [33]. The most recent study (November 2001 to April 2002) reported a 6.5% prevalence of ADR-related hospital admissions in two major hospitals in the UK [34].

In the US, the overall incidence of serious ADRs was computed to be 6.7% on the basis of a meta-analysis of 39 prospective studies from hospitals [19]. Of these, 2.1% had occurred in patients while in hospital and 4.7% were present in patients requiring admission as a result of ADRs. Seventy-six per cent of ADRs were Type A dose-dependent. Another meta-analysis of studies confirmed the heterogeneity of the published data. However, these studies do consistently emphasise the considerable proportions of all hospital admissions that are related to ADRs. Larger studies have shown lower percentages although the elderly were reported to be at a 4-fold greater risk. Beijer and de Blaey reported

that 88% of the ADR-related admissions in the elderly and 24% in the non-elderly were preventable [35].

2.3 Drug-related mortality

The data on drug-related or ADR-related mortality are complicated by the heterogeneous nature of the studies but they do provide an estimate of the problem.

Shapiro et al reported as long ago as 1971 that as many as 160,000 deaths resulted from ADRs each year in US hospitals [36]. The overall evidence from a number of recent studies suggests that 0.3-0.5% of deaths are related to ADRs.

In England and Wales, the number of deaths related to ADRs has risen steadily over the last 10 years. One UK study of 3,277 Coroner's Inquests during 1986 to 1991 identified 10 deaths due to prescribing errors and another 36 deaths caused by ADRs [37]. These 46 deaths accounted for approximately 1 in 2,000 of all the deaths during the study period. A prospective 6-month study from Norway reported 1% drug-related mortality among 3,082 hospitalised patients [38]. Only 2 of these were recognised as drug-related by the attending clinicians. This gross under-recognition of ADR-related mortality is supported by another study from US that compared the number of deaths attributed to ADRs on death certificates with data in the spontaneous post-marketing surveillance system of the FDA (MedWatch) during 1995. During this period, 206 deaths were certified as being due to ADRs, whereas the MedWatch tabulated 6,894 fatalities [39]. It is recognised that the fatal outcomes recorded in MedWatch are not necessarily causally drug-related. However, this 34-fold variation must be a matter of concern.

ADR-related mortality was reported to be 1% in the UK [28] and among 4,331 hospital admissions, 0.18% in Switzerland [29]. ADRs were estimated to be between the fourth and sixth leading cause of death in the USA; the fatality rate as a result of ADRs amongst the hospitalised patients was 0.32 % [19]. Pirmohamed et al reported an overall mortality rate of 0.15% due to ADRs [34].

3. Healthcare burden

In terms of time spent in the hospital, it is not surprising that a patient with an ADR spends longer time in a hospital and consequently, imposes greater economic burdens on the healthcare systems.

3.1 Duration of hospitalisation

Mean duration of hospital stay was 15.1 days for each of the 10 patients with an ADR and 10.7 days for those without an ADR in one study from France (conducted during May 1993–October 1993). In the same study, the mean stay was 19.2 days for the 21 patients in whom the ADR occurred in the hospital [40]. Other studies have estimated the duration of hospital stay at 13 ± 10.6 days in Germany (October 1997–March 2000) [33] and 10.6 days for patients with ADRs and 6.8 days for matched controls in the USA (August 1998-December 1998) [41]. ADR-related excess stay in hospital was computed at 7.6% of all hospital days in France [40] and 5.9% of all emergency beds in Australia [26]. For the 1,225 ADR-related hospital admissions in the UK, the median duration of hospital stay was 8 days [34].

3.2 Drug-related hospitalisation costs

Estimates on costs of ADRs leading to hospitalisation are complicated by geographical differences in healthcare costs and a lack of common units of measurement and methodologies.

The cost of ADRs leading to hospitalisation was estimated at Euro 11,357 per hospital bed per year in France [32] while a study from Switzerland estimated a mean cost per case at Swiss Francs 3,586 or a total of Swiss Francs 821,204 over the 6-months study period [30]. In the US, the cost of hospitalisation was US$ 22,775 per case for patients with an ADR and US$ 17,292 per case without an ADR [41]. In Australia, the annual cost for all drug-related admissions was estimated at just under A$ 3.5 million (comprised of A$ 1.63 million for unavoidable, A$ 1.67 million for avoidable and A$ 0.2 million for definitely avoidable admissions) [26]. The cumulative direct costs for hospitalisation over the 30-month study period in Germany were estimated to be Euro 4 million in the two urban study areas and the annual direct cost for the whole country was estimated to be Euro 400 million [33]. In the French study above, about 5-9% of hospital costs were related to ADRs [40]. When Pirmohamed et al extrapolated their findings to the entire National Health Service in the UK, the projected annual cost of ADR-related admissions was estimated to be £466 million [34]. Others had previously estimated these costs in the UK to be in the range of £1.5-2.6 billion [42].

Lazarou et al [19] estimated the direct hospital costs due to ADRs in the US to be US$ 1.6-4 billion. Ernst and Grizzle [43] updated their previous 1995

estimate of US$ 76.6 billion for the annual cost of drug-related morbidity and mortality resulting from drug-related problems in the ambulatory setting in the United States to reflect treatment patterns and costs in 2000. They estimated that in 2000, the mean cost for a treatment failure was US$ 977 per patient. For a new medical problem, the mean cost was US$ 1,105, and the cost of a combined treatment failure and resulting new medical problem was US$ 1,488. Overall, the cost of drug-related morbidity and mortality in the US exceeded US$ 177.4 billion in 2000. Hospital admissions accounted for nearly 70% (US$ 121.5 billion) of total costs, followed by long-term care admissions, which accounted for 18% (US$ 32.8 billion).

4. ADRs and pharmacovigilance

4.1 Costs of pharmacovigilance

Pharmacovigilance, or activity and programmes to detect and monitor ADRs, and efforts to reduce and prevent ADRs each incurs significant costs. These costs include administration of national and global monitoring systems (e.g. the Yellow Card Scheme in the UK or the MedWatch Scheme in the US), changes in prescribing information, dissemination of this information and in extreme cases, withdrawal of drugs.

An indirect estimate of costs of ADRs may be obtained by examination of the benefits of Bar Code Regulations issued by the FDA in February 2004 [44]. The preliminary estimate of the cost for implementing this bar coding is thought to be between US$ 0.5 billion and 1.4 billion over a 10-year period. The purpose of bar coding is to ensure accurate identification of medications, and thereby reduce medication prescribing errors, and ultimately, mortality and morbidity. As stated above, one study estimated these at more than US$ 177 billion including US$ 121.5 billion in hospital costs and US$ 32.8 billion in long-term care expenses [43].

4.2 ADRs and drug withdrawals

Drug withdrawals are costly for the companies. Worldwide there were 121 safety-related drug withdrawals between 1960 and 1999. Market life was known for 87 of these. About 31% of these products were withdrawn within the first two years and up to approximately 50% were withdrawn within the first five years [45].

In the UK, a total of 583 new active substances (NAS) were approved between the years 1972 and 1994 and of these, 59 were later withdrawn.

This represents a withdrawal rate of 2.57 NAS per year over this period [46]. Thirty-four drugs have been withdrawn from various markets for safety reasons over the 15-year period from 1990 to 2004 and have included a number of high profile drugs as shown in Table 1.

Table 1
Drugs withdrawn from various markets (1990 to 2004) for safety reason

Drug	Year of withdrawal	Reason(s) for withdrawal from market
Dilevalol	1990	Hepatotoxicity
Triazolam	1991	Neuropsychiatric reactions
Terodiline	1991	QT interval prolongation and TdP (TdP = torsade de pointes)
Encainide	1991	Proarrhythmias
Fipexide	1991	Hepatotoxicity
Temafloxacin	1992	Hypoglycaemia, haemolytic anaemia and renal failure
Benzarone	1992	Hepatotoxicity
Remoxipride	1993	Aplastic anaemia
Alpidem	1993	Hepatotoxicity
Flosequinan	1993	Excess mortality possibly due to proarrhythmias
Bendazac	1993	Hepatotoxicity
Soruvidine	1993	Myelotoxicity following drug interaction
Chlormezanone	1996	Hepatotoxicity and severe skin reactions
Tolrestat	1996	Hepatotoxicity
Minaprine	1996	Convulsions
Pemoline	1997	Hepatotoxicity
Dexfenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Fenfluramine	1998	Cardiac valvulopathy and pulmonary hypertension
Terfenadine	1998	Drug interactions, QT interval prolongation and TdP
Bromfenac	1998	Hepatotoxicity following prolonged administration
Ebrotidine	1998	Hepatotoxicity
Sertindole	1998	QT interval prolongation and potential for TdP
Mibefradil	1998	Statin-induced rhabdomyolysis following drug interaction and concerns on other potential drug interactions, including the risk of TdP
Tolcapone	1998	Hepatotoxicity
Astemizole	1999	Drug interactions, QT interval prolongation and TdP
Trovafloxacin	1999	Hepatotoxicity
Grepafloxacin	1999	QT interval prolongation and TdP
Troglitazone	2000	Hepatotoxicity
Alosetron	2000	Ischaemic colitis
Cisapride	2000	Drug interactions, QT interval prolongation and TdP
Droperidol	2001	QT interval prolongation and TdP
Levacetylmethadol	2001	Drug interactions, QT interval prolongation and TdP
Cerivastatin	2001	Rhabdomyolysis following drug interactions
Rofecoxib	2004	Myocardial infarction and strokes

(Tdp = torsade de pointes)

The withdrawals of perhexiline (an antianginal drug) and phenformin (an oral hypoglycaemic agent) in late 1980s are almost certainly related to genetically mediated toxicity. Both these drugs are metabolised almost exclusively by CYP2D6 and their clinical uses were associated with serious neuropathy and hepatotoxicity (perhexiline) and lactic acidosis (phenformin). Available evidence strongly incriminates CYP2D6 as a risk factor for both. For a number of other older drugs now removed from the market, there is a body of evidence which, when viewed collectively, also supports the notion that genetic factors may have contributed substantially to their withdrawal from the market. These drugs include encainide (CYP2D6), terodiline and prenylamine (CYP2D6 and potassium channel mutations) and terfenadine, cisapride and levacetylmethadol (potassium channel mutations). Although the costs of developing new drugs are difficult to estimate precisely, overall costs have been estimated at approximately US$ 400 million in 1998 and US$ 800 million in 2001 [47, 48]. Although these are overall costs and include the costs of failures during early development, they do indicate the substantial loss of investment due to ADRs.

Drug withdrawals deprive patients who did not suffer from ADRs of the benefits of the medicine. For example, following the withdrawal of terodiline in the UK (one of the three major markets of this drug), the regulatory authority in the UK received representations from a number of patients and physicians to make this drug available, albeit on a named patient basis. Similar demand had followed the withdrawal of perhexiline, an antianginal drug that was highly effective in patients who did not respond to other drugs and were not suitable for coronary artery bypass surgery.

5. ADRs and litigation

ADRs inflict additional burdens on healthcare resources through litigations. One study by Kelly [49] identified 1,520 significant adverse drug events published in ClinAlert during the period 1976 to 1997. Of these, 56% (n = 846) were life-threatening, 29% (n = 447) resulted in death and 15% (n = 227) resulted in permanent disability. Litigation was reported in 14% of fatal cases of ADRs and the settlement averaged US$ 1.1 million. Other data from this study [50-52] relevant to this report are summarised in the Table 2.

Table 2
Analysis of adverse drug events published in ClinAlert during the period 1976 to 1997 – adapted from Kelly WN [49]

	All serious	Life-threatening	Fatal	Permanent disability
Adverse drug **events** cases identified	1,520 (100%)	846 (55.7%)	447 (29.4%)	227 (14.9%)
Adverse drug **reactions**	52%	50%	58%	43%
Type A reactions	19%	7%	34%	9%
Type B reactions	61%	93%	66%	91%
Setting where drug started:				
- Hospital	67%	89%	56%	57%
- Out-patient	29%	5%	41%	38%
Usual recommended dose in	73%	82%	64%	43%
Common drug classes				
- CNS	24%	26%	24%	16%
- CVS	10%	11%	12%	5%
- Oncology	11%	7%	17%	15%
Litigation				
- Reported in	13%	1%	14%	56%
- Mean settlement	US$ 3.1 m	US$ 1.1 m	US$ 1.1 m	US$ 4.3 m

Claims and litigation are an additional burden on healthcare. In the UK National Health Service, these amounted to £400 million in paid litigation in 1998/99 with an expected potential liability of £2.4 billion. In countries such as India, the inclusion of the medical profession under Consumer Protection Act has resulted in ever increasing litigation and malpractice suits [53].

Private litigations against pharmaceutical companies have also increased, as seen in class actions related to dexfenfluramine ("fen-phen" leading to primary pulmonary hypertension and cardiac valvulopathy) and cerivastatin (leading to rhabdomyolysis). The potential liability from such class actions usually runs into billions of dollars. In the US, the sponsor of dexfenfluramine had taken charges related to "fen-phen" related litigation of US$ 13.2 billion, an amount estimated to be sufficient to cover the overall funding requirements [54]. With regard to cerivastatin, the lawyers had stated that the compensation could total around US$ 800 million, related to just the fatal cases alone. Given that the total number of all potential claimants is thought to be more than 4,000, it has been estimated that settlement could reach US$ 5 billion [55].

6. ADRs and indirect costs

Indirect costs are those sustained by the community as a result of ADRs. They arise from the loss of individual contribution to the gross national product (GNP). This loss in GNP is related to (a) the excess time spent in the hospital, (b) the time taken by the individual to fully recover from an ADR (usually a serious one) to the point when (s)he can return to previous work, (c) the time taken by the individual's family member(s) to care for him or her and (d) social benefits paid to the individual while off work.

These indirect costs may vary enormously and can amount to hundreds of thousands of dollars, particularly in cases in which the ADR results in permanent disability [3]. There is a great need to review and further develop methodology for assessing these indirect costs.

7. Conclusions

ADRs and other drug-related problems result in considerable clinical morbidity and mortality. They account for a significant proportion of hospital admissions and such patients generally spend longer time in the hospital. Consequently, the direct implications for healthcare and economic resources are considerable. Indirect economic costs and social burdens are difficult to compute but estimates suggest that these may be comparable if not even greater.

A number of valuable drugs have had to be withdrawn from the market as a result of the clinical risks they posed. Withdrawal of these drugs also has consequences for those patients in whom they are effective.

Since the majority of ADRs are dose- or concentration-related, they may be preventable, or at least reduced, by paying careful attention to factors that may increase plasma concentrations. Non-genetic factors such as inappropriate doses or drug interactions may possibly be controlled in the majority of cases. Increasingly, however, many ADRs appear to have a genetic substrate. It seems likely that genetic influences resulting in pharmacodynamic variability may be even more important than those resulting in pharmacokinetic variability [56].

The present agenda for "value for money" in healthcare provides the impetus to better quantify the problem and develop measures that minimise human and healthcare costs. These measures include reduction in the frequency or prevention of ADRs.

Given the advances in pharmacogenetic technology, there is a pressing need to study systematically whether pharmacogenetics can help minimise further the burdens of drug-related problems. This requires at least 'preliminary' evidence indicating that many drug-related problems may in fact have a pharmacogenetic basis.

Acknowledgement:

We like to express our appreciation to Dr June Raine, Medicines and Healthcare products Regulatory Agency, UK for outlining the aspects of adverse drug reactions that should be considered for inclusion in this chapter.

REFERENCES

[1] Hurwitz N.
Admissions to hospital due to drugs.
Br Med J. 1969; 1: 139

[2] United States Department of Health, Education and Welfare.
Task Force on Prescription Drugs: Final Report.
Washington DC, Government Printing Office, 1969

[3] Mach P, Venulet J.
The economics of adverse reactions to drugs.
WHO Chronicle. 1975; 29: 79-84

[4] Boston Collaborative Drug Surveillance Program.
Adverse drug interactions.
JAMA. 1972; 220: 1238-1239

[5] Marroum PJ, Uppoor RS, Parmelee T, et al.
In vivo drug-drug interaction studies - A survey of all new molecular entities approved from 1987 to 1997.
Clin Pharmacol Ther. 2000; 68; 280-285

[6] Jankel CA, Speedie SM.
Detecting drug interactions: a review of the literature.
DICP Ann Pharmacother. 1990; 24: 982-989

[7] Dallenbach MF, Desmeules J, Bovier P, Dayer P.
Drug interaction detection using Epocrates in a walk-in clinic.
Clin Pharmacol Ther. 2003; 73: P11 (abstract PI-39)

[8] McDonnell PJ, Jacobs MR.
Hospital admissions resulting from preventable adverse drug reactions.
Ann Pharmacother. 2002; 36: 1331-1336

[9] Doucet J, Chassagne P, Trivalle C, et al.
Drug-drug interactions related to hospital admissions in older adults: a prospective study of 1000 patients.
J Am Geriatr Soc. 1996; 44: 944-948

[10] Curtis LH, Ostbye T, Sendersky V, et al.
Prescription of QT-prolonging drugs in a cohort of about 5 million outpatients.
Am J Med. 2003; 114: 135-141

[11] Mulroy R.
Iatrogenic disease in general practice. Its incidence and effects.
Br Med J. 1973; 2: 407-410

[12] Lumley CE, Walker SR, Hall GC, et al.
The under-reporting of adverse drug reactions seen in general practice.
Pharma Med. 1986; 1: 205-212
[13] Martys CR.
Adverse reactions to drugs in general practice.
Br Med J. 1979; 2: 1194-1197
[14] Haramburu F, Pouyanne P, Imbs JL, Blayac JP, Begaud B.
Incidence and prevalence of adverse drug reactions [Article in French].
Presse Med. 2000; 29: 111-114
[15] Lacoste-Roussillon C, Pouyanne P, Haramburu F, Miremont G, Begaud B.
Incidence of serious adverse drug reactions in general practice: a prospective study.
Clin Pharmacol Ther. 2001; 69: 458-462
[16] Gharaibeh M, Zmeili S, Abu-Rajab A, Daoud Z.
Drug-induced admissions to medical wards at Jordan University Hospital.
Int J Clin Pharmacol Ther. 1998; 36; 478-482
[17] Goettlr M, Schneeweiss S, Hasford J.
Adverse drug reaction monitoring - cost and benefit considerations. Part II: cost and preventability of adverse drug reactions leading to hospital admission.
Pharmacoepidemiol Drug Safety. 1997; 6 (Suppl 3): 79-90
[18] Gonzalez-Martin G, Caroca CM, Paris E.
Adverse drug reactions (ADRs) in hospitalized padiatric patients. A Prospective study.
Int J Clin Pharmacol Ther. 1998; 36; 530-533
[19] Lazarou J, Pomeranz BH, Corey PN.
Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies.
JAMA. 1998, 279, 1200-1205
[20] Muehlberger N, Schneeweiss S, Hasford J.
Adverse drug reaction monitoring - Cost and benefit considerations Part I: Frequency of adverse drug reactions causing hospital admissions.
Pharmacoepidemiol Drug Safety. 1997, 6, S71-S77
[21] Venulet J.
Methods of monitoring adverse reactions to drugs.
In Progress in Drug Research ed. E. Jucker, vol. 21, pp. 233-292, Birkhäuser Verlag, Basel, 1977
[22] Einarson TR.
Drug-related hospital admissions.
Ann Pharmacother. 1993; 27: 832-840
[23] Raschetti R, Morgutti M, Menniti-Ippolito F, et al.
Suspected adverse drug events requiring emergency department visits or hospital admissions.
Eur J Clin Pharmacol. 1999; 54: 959-963
[24] Hallas J, Gram LF, Grodum E, et al.
Drug-relate admissions to medical wards: a population based survey.
Br J Clin Pharmacol. 1992; 33: 61-68
[25] Mjörndal T, Danell Boman M, Hägg S, et al.
Adverse drug reactions as a cause for admissions to a department of internal medicine.
Pharmacoepidemiol Drug Safety. 2002; 11: 65-72
[26] Dartnell JG, Anderson RP, Chohan V, et al.
Hospitalisation for adverse events related to drug therapy: incidence, avoidability and costs.
Med J Aust. 1996; 164: 659-662

[27] Nelson KM, Talbert RL.
Drug-related hospital admissions.
Pharmacotherapy. 1996; 16: 701-707
[28] Green CF, Mottram DR, Rowe PH, Pirmohamed M.
Adverse drug reactions as a cause of admission to an acute medical assessment unit: a pilot study.
J Clin Pharm Ther. 2000; 25: 355-361
[29] Fattinger K, Roos M, Vergeres P, et al.
Epidemiology of drug exposure and adverse drug reactions in two Swiss departments of internal medicine.
Br J Clin Pharmacol. 2000; 49: 158-167
[30] Wasserfallen J, Livio F, Buclin T, Tillet L, Yersin B, Biollaz J.
Rate, type and cost of adverse drug reactions in emergency department admissions.
Eur J Intern Med. 2001; 12: 442-447
[31] Pouyanne P, Haramburu F, Imbs JL, Begaud B.
Admissions to hospital caused by adverse drug reactions: cross sectional incidence study, French Pharmacovigilance Centres.
Br Med J. 2000; 320: 1036
[32] Lagnaoui R, Moore N, Fach J, Longy-Boursier M, Begaud B.
Adverse drug reactions in a department of systemic diseases orientated internal medicine: prevalence, incidence, direct costs and avoidability.
Eur J Clin Pharmacol. 2000; 56: 181-186
[33] Schneeweiss S, Hasford J, Gotzler M, Hoffmann A, Riethling AK, Avorn J.
Admissions caused by adverse drug events to internal medicine and emergency departments in hospitals: a longitudinal population-based study.
Eur J Clin Pharmacol. 2002; 58: 285-291
[34] Pirmohamed M, James S, Meakin S, et al.
Adverse drug reactions as cause of admissions to hospitals: prospective analysis of 18,820 patients.
Br Med J. 2004; 329:15-19
[35] Beijer HJ, de Blaey CJ.
Hospitalisations caused by adverse drug reactions (ADR): a meta-analysis of observational studies.
Pharm World Sci. 2002; 24: 46-54
[36] Shapiro S, Slone D, Lewis GP, Jick H.
Fatal drug reactions among medical inpatients.
JAMA. 1971; 216: 467-472
[37] Ferner RE, Whittington RM.
Coroner's cases of death due to errors in prescribing or giving medicines or adverse drug reactions: Birmingham 1986-1991.
J R Soc Med. 1994; 87: 145-148
[38] Ebbesen J, Buajordet I, Erikssen J, Svaar H, Brors O, Hilberg T.
Drugs as a cause of death. A prospective quality assurance project in a department of medicine [Article in Norwegian].
Tidsskr Nor Laegeforen. 1995; 115: 2369-2372
[39] Chyka PA.
How many deaths occur annually from adverse drug reactions in the United States?
Am J Med. 2000; 109: 122-130
[40] Moore N, Lecointre D, Noblet C, Mabille M.
Frequency and cost of serious adverse drug reactions in a department of general medicine.
Br J Clin Pharmacol. 1998; 45: 301-308

[41] Suh DC, Woodall BS, Shin SK, Hermes-De-Santis ER.
Clinical and economic impact of adverse drug reactions in hospitalised patients.
Ann Pharmacother. 2000; 34: 1373-1379
[42] Anon.
The cost of adverse drug reactions.
Adverse Drug React Toxicol Rev. 1997; 16: 75-78
[43] Ernst FR, Grizzle AJ.
Drug-related morbidity and mortality: updating the cost-of-illness model.
J Am Pharm Assoc (Wash). 2001; 41: 192-199
[44] Anon.
Bar code label requirements for human drug products and biological products:
Final Rule
http://www.fda.gov/cber/rules/barcodelabel.htm
[Accessed on 20 November 2004]
[45] Fung M, Thornton A, Mybeck K, Hsiao-hui Wu J, Hornbuckle K, Muniz E.
Evaluation of the characteristics of safety withdrawals of prescription drugs from worldwide pharmaceutical markets – 1960 to 1999.
Drug Inform J. 2001; 35: 293-317
[46] Jefferies DB, Leakey D, Lewis JA, Payne S, Rawlins MD.
New Active Substances authorised in the United Kingdom between 1972 and 1994.
Br J Clin Pharmacol. 1998; 45: 151-156
[47] Anon.
Clinical time for NCEs approved in 1996-97 dropped 20%, Tuft data show.
The FDC Reports "The Pink Sheet". 1999, 61: 25
[48] DiMasi JA, Hansen RW, Grabowski HG.
The price of innovation: new estimates of drug development costs
J Health Econ. 2003; 22: 151-185
[49] Kelly WN.
Potential risks and prevention, Part 4: Reports of significant adverse drug events.
Am J Health Syst Pharm. 2001; 58: 1406-1412
[50] Kelly WN.
Potential risks and prevention, Part 1: Fatal adverse drug events.
Am J Health Syst Pharm. 2001; 58: 1317-1324
[51] Kelly WN.
Potential risks and prevention, Part 2: Drug-induced permanent disabilities.
Am J Health Syst Pharm. 2001; 58: 1325-1329
[52] Marcellino K, Kelly WN.
Potential risks and prevention, Part 3: Drug-induced threats to life.
Am J Health Syst Pharm. 2001; 58: 1399-1405
[53] Bhatt AD.
Drug-related problems and adverse drug events: negligence, litigation and prevention.
J Assoc Physicians India. 1999; 47: 715-720
[54] Anon.
AHP's fen-phen settlement finalised.
Scrip. 2002; 2713: 17
[55] Anon.
Baycol international class action sought.
Scrip. 2002; 2713: 9
[56] Murphy GM, Kremer C, Rodrigues HE, Schatzberg AF.
Pharmacogenetics of antidepressant medication intolerance.
Am J Psychiatr. 2003; 160: 1830-1835

Chapter 3

Abnormal Drug Response (II): Opportunities for Risk Reduction Through Pharmacogenetics

1. Introduction

An adverse drug reaction (ADR) can result from a variety of risk factors including variability in pharmacokinetics and pharmacodynamics of a drug due to the genetic make-up of an individual. Other important influences are external factors such as co-medications and co-morbidities, which give rise to drug-drug or drug-disease interactions. The net effect of these interactions is that the prescribed dose of a drug is an inappropriate one. Usually, clinically relevant drug interactions result when the plasma concentration of one of the interacting drugs increases to toxic levels.

With careful attention to prescribing information regarding dose, age-related adjustments and populations at risk for drug-drug and drug-disease interactions, the impact of ADRs can be greatly minimised. However, it is unlikely that any single approach will completely eliminate all ADRs. With available data suggesting that some ADRs might have a monogeneic or polygeneic basis, the application of pharmacogenetics provides an opportunity for further reductions in both the incidence and severity of ADRs.

This chapter reviews some of the data on abnormal drug response related to polymorphisms in drug metabolising enzymes, pharmacological targets and drug transporters. It illustrates how, at least in some areas, pharmacogenetics may offer the prospects of minimising the risks of drug toxicity and therapeutic failures.

2. Pharmacogenetics and drug metabolising enzymes

A number of drug metabolising enzymes displays genetic polymorphisms. Candidate gene association studies, investigating the role of these polymorphic drug metabolising enzymes such as CYP2D6, CYP2C9, CYP2C19, N-acetyltransferase (NAT2), thiopurine S-methyltransferase (TPMT), UDP-glucuronosyltransferases (UGTs) and dihydropyrimidine dehydrogenase (DPD), have already shown that there is a genetic predisposition to a number of ADRs.

It is now generally assumed that because of this genetic predisposition, there may be a great potential for preventing ADRs and improving the

safe and effective use of medicines through the increasing knowledge of genetic factors that determine drug response. Polymorphic genes and products of gene expression have been considered as markers for optimisation of drug therapy, most especially in the field of oncology.

2.1 Polymorphic variation in CYP2D6

Studies over the last two decades have shown that any given population may be divided into two phenotypes – extensive metabolisers (EMs) or poor metabolisers (PMs) – depending on their ability to mediate CYP2D6-dependent hydroxylation of the antihypertensive drug debrisoquine. Among the EM phenotype, there are two subgroups of particular interest at either extreme of the EM population distribution. One subgroup, termed the ultrarapid metabolisers (UMs), is comprised of individuals possessing multiple copies of the gene for normal metabolic capacity and the other group, termed the intermediate metabolisers (IMs), is comprised of a heterozygous genotype ("gene-dose effect"). UMs metabolise drugs so avidly that they attain very low concentrations of the parent drug and high concentrations of rapidly accumulating metabolites while IMs display a modest impairment in drug metabolising capacity.

CYP2D6 is responsible for the metabolism of well over 60 drugs that include antiarrhythmics, ß-adrenoreceptor antagonists, antihypertensives, antianginals, neuroleptics, antidepressants, analgesics as well as a number of other miscellaneous drugs. Candidate gene association studies have shown that a number of ADRs to CYP2D6 substrates are related to CYP2D6 genotype (Table 1).

One of the first reports on the clinical significance of CYP2D6 polymorphism and its association with serious toxicity was perhexiline-induced neuropathy in patients with impaired CYP2D6 metabolism. Although the recommended dose of perhexiline was 100mg three times daily, a recent study of 23 patients has shown that to maintain the plasma concentrations of perhexiline within the therapeutic and non-toxic range, PMs required a dose of 10-25 mg/day while EM and ultrarapid EM required 100-250 and 300-500 mg/day respectively [1]. Other clinical consequences for individuals with the PM or ultrarapid phenotypes of CYP2D6 are also shown in Table 1.

Application of pharmacogenetic principles may also improve efficacy. There are several examples where subjects carrying certain alleles suffer from a lack of drug efficacy because of ultrarapid metabolism caused by multiple genes or by induction of gene expression. As with perhexiline, some patients who are ultrarapid metabolisers fail to respond to conventional doses of nortriptyline and require 'megadoses' of this antidepressant. Similarly, poor metabolisers fail to respond to therapeutic effects mediated by metabolites. This is illustrated by the relative loss in PMs of analgesic effects following administration of codeine or tramadol or the loss of antiarrhythmic effects of encainide.

2.2 Polymorphic variation in CYP2C9

Retrospective case studies have shown that the presence of mutant CYP2C9 allele (especially CYP2C9*3 allele) confers a significantly increased risk of bleeding following treatment with warfarin. Available

Table 1
Clinical consequences for PM and ultrarapid EM phenotypes of CYP2D6

Clinical Consequences for the Poor Metaboliser	
	Increased risk of toxicity
Debrisoquine	Postural hypotension and physical collapse
Sparteine	Oxytocic effects
Perphenazine	Extrapyramidal symptoms
Flecainide	? Ventricular tachyarrhythmias
Perhexiline	Neuropathy and hepatotoxicity
Phenformin	Lactic acidosis
Propafenone	CNS toxicity and bronchoconstriction
Metoprolol	Loss of cardioselectivity
Nortriptyline	Hypotension and confusion
Terikalant	Excessive prolongation in QT interval
Dexfenfluramine	Nausea, vomiting and headache
L-tryptophan	Eosinophilia-myalgia syndrome
Indoramin	Sedation
Thioridazine	Excessive prolongation in QT interval
	Failure to respond
Codeine	Poor analgesic efficacy
Tramadol	Poor analgesic efficacy
Opiates	Protection from oral opiate dependence
Clinical Consequences for the Ultrarapid Metaboliser	
	Increased risk of toxicity
Encainide	? Proarrhythmias
Codeine	Morphine toxicity
	Failure to respond
Nortriptyline	Poor efficacy at normal doses
Propafenone	Poor efficacy at normal doses
Tropisetron	Poor efficacy at normal doses
Ondansetron	Poor efficacy at normal doses

data, however, indicate that although the CYP2C9*3/CYP2C9*3 genotype is associated with dramatic over anticoagulation soon after the introduction of oral anticoagulants, overdose during the maintenance period is mostly related to environmental factors [2, 3]. It is also recognised that interindividual variability in warfarin sensitivity also originates from environmental factors. In one study, age and CYP2C9 genotype accounted for 12% and 10% of the variation in warfarin dose requirements, respectively [4]. Clearly, other pharmacodynamic (such as to an abnormality in the target enzyme vitamin K epoxide reductase) and dietary factors also play an important role. In a retrospective cohort study of patients on long-term warfarin, it was found that the mean maintenance dose varied significantly among the six genotypes of CYP2C9. Compared to patients with the wild type genotype, patients with at least one variant allele required longer time to achieve stable dosing and had a significantly increased risk of a serious or life-threatening bleeding event, although patient numbers were small for some genotypes in this study [5].

Similarly, to achieve a therapeutic serum concentration of phenytoin, patients carrying at least one mutant CYP2C9 allele required a mean phenytoin dose that was about 37% lower than that in patients with wild type genotype (199 mg/day versus 314 mg/day) [6]. Since phenytoin has a narrow therapeutic index and genotyping may be carried out rapidly and at a relatively low cost, dosage adjustment based on CYP2C9 genotype, especially at the induction of therapy, would be of value in order to lower the risk of concentration-dependent phenytoin toxicity in the carriers of mutant alleles.

2.3 Polymorphic variation in CYP2C19

CYP2C19 mediates the major pathway responsible for metabolic elimination of proton pump inhibitors. Since therapeutic activity correlates with exposure to the parent compound, it is not surprising that a number of studies have shown that PMs of CYP2C19 respond better to *H. pylori* eradication therapy. These preliminary findings need to be confirmed in large prospective studies [7]. EMs of CYP2C19 require higher doses of these drugs.

2.4 Polymorphic variation in thiopurine S-methyltransferase

Azathioprine and 6-mercaptopurine are metabolised by thiopurine S-methyltransferase (TPMT). The activity of TPMT is inversely related to the risk of developing acute leucopenia associated with the use of these drugs. A number of studies have shown that the risk of azathioprine-induced acute leucopenia can be greatly reduced by basing the initial azathioprine dose on TPMT genotype or phenotype [8, 9]. Of course, not all

azathioprine-induced toxicities have a genetic basis. In one study of 93 patients, it was noted that azathioprine-related gastrointestinal side effects are independent of TPMT polymorphism [10]. The value of genotyping for TPMT is illustrated by a report from Murphy and Atherton [11] that by initiating therapy at dose levels of 2.5-3.5 mg/kg in atopic eczema patients with a normal TPMT level, they felt confident in reducing the frequency with which tests of bone marrow and liver function had to be undertaken.

2.5 Polymorphic variation in UDP-glucuronosyltransferases

Conjugation reactions such as glucuronidation mediated by UDP-glucuronosyltransferases (UGTs) are now also attracting increasing attention, especially in the field of oncology. Glucuronidation is by far the most important conjugation pathway in man. A multigene family encodes the UGTs and a relatively small number of human UGT enzymes catalyse the glucuronidation of a wide range of structurally diverse endogenous (bilirubin, steroid hormones and biliary acids) and exogenous chemicals. Genetic variations and single nucleotide polymorphisms (SNPs) within the UGT genes are remarkably common, and lead to genetic polymorphisms [12, 13]. Some polymorphic UGTs have demonstrated a significant pharmacological impact in addition to being relevant to drug-induced ADRs. Two major isoforms of UDP-glucuronosyltransferase, UGT1A1 and UGT1A9, have been shown to display genetically determined wide interindividual variability in their activities. Studies investigating the role of UGT1A isoforms in the metabolism of drugs such as irinotecan [14, 15], flavopiridol [16, 17], tranilast [18] and atazanavir [19] have been most valuable in explaining the safety issues (myelosuppression, diarrhoea or hyperbilirubinaemia) associated with the use of these drugs.

A meta-analysis by Phillips et al [20] identified 131 specific drugs, 55 drug classes, and 19 therapeutic drug categories as being associated with ADRs. All except three of these drugs were included among the top 200 selling drugs in the United States. The therapeutic categories associated with the most common ADRs were cardiovascular, analgesics, psychoactive drugs and antibiotics. This meta-analysis included 18 of 333 ADR studies and 22 of 61 variant allele review articles. It identified 27 drugs frequently cited in ADR studies. Among these drugs, 59% were metabolised by at least one enzyme with a variant allele known to cause poor metabolism. In contrast, only 7% to 22% of randomly selected drugs were metabolised by enzymes displaying genetic polymorphism ($p = 0.006 - < 0.001$). These data suggest that drug therapy based on the genotype of individual patients may result in a clinically important reduction in adverse outcomes.