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PHARMACOGENOMICS OF ADVERSE DRUG REACTIONS: A REVIEW

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ABSTRACT

Pharmacogenomics aims to investigate the genetic basis of inter-individual differences in drug responses, such as efficacy, dose requirements and adverse events. Research in pharmacogenomics has grown over the past decade, evolving from a candidate-gene approach to genome-wide association studies (GWASs). Genetic variants in genes coding for drug metabolism, drug transport and more recently human-leukocyte antigens (HLAs) have been linked to inter-individual differences in the risk of adverse drug reactions (ADRs). The tight association of specific HLA alleles with Stevens–Johnson syndrome, toxic epidermal necrolysis, drug hypersensitivity syndrome and drug-induced liver injury underscore the importance of HLA in the pathogenesis of these idiosyncratic drug hypersensitivity reactions. However, as with the search for the genetic basis for common diseases, pharmacogenomic research, including GWAS, has so far been a disappointment in discovering major gene variants responsible for the efficacy of drugs used to treat common diseases. This review focuses on the pharmacogenomics of ADRs, the underlying mechanisms and the potential use of genomic biomarkers in clinical practice for dose adjustment and the avoidance of drug toxicity. We also discuss obstacles to the implementation of pharmacogenomics and the direction of future translational research.

KEYWORDS: Pharmacogenomics, efficacy, adverse drug reactions, hypersensitivity, drug toxicity.

INTRODUCTION

Classification of Adverse Drug Reactions

There are many different classifications for adverse drug reactions. For the purpose of this chapter, we will use the original classification proposed by Rawlins and Thompson (1991), which divided adverse drugs reactions into two types: type A (pharmacological) and type B (idiosyncratic). The type A reactions represent an augmentation of the known pharmacological actions of a drug, are dose dependent, and, perhaps more importantly from the viewpoint of safety, are readily reversible on drug withdrawal, or even simply after dose reduction. In contrast, the type B, or idiosyncratic, adverse reactions are bizarre, cannot be predicted from the known pharmacological actions of the drug, do not show simple dose dependency, and cannot be reproduced in animal models. The type A reactions are more common than the type B reactions (Einarson, 1993) accounting for over 80% of all reactions. Although they cause a great deal of morbidity, in general, type A reactions are proportionately less severe and less likely to result in fatalities than type B reactions.[1,2,3,4]

Type A Adverse Drug Reactions

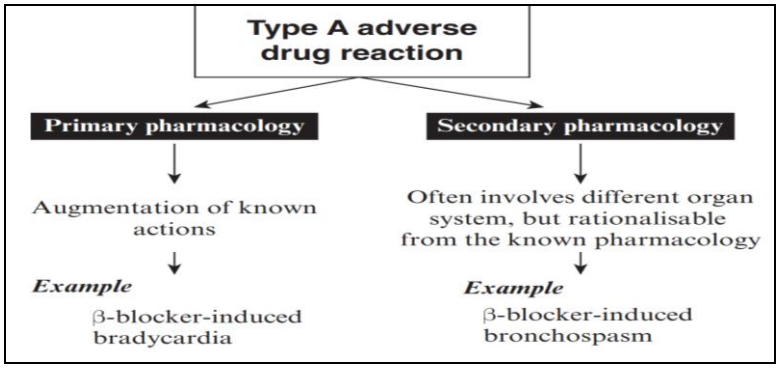

Fig: Type A Adverse Drug Reactions.

Pharmacological (type A) adverse drug reactions are the most common forms of drug toxicity (Pirmohamed et al., 1998). They can be due to the primary and secondary pharmacological characteristics of the drug More emphasis is now placed on the secondary pharmacology of new drugs during preclinical evaluation, in order to anticipate, and thus avoid, problems that might arise once the drug is introduced into humans.[5]

Type B or Idiosyncratic Adverse Drug Reactions

Idiosyncratic adverse reactions are less common than the pharmacological adverse reactions, but are as important, if not more so, because they are often more serious and account for many drug-induced deaths. The possible mechanisms of idiosyncratic adverse effects. The toxic reactions may affect many organ systems either in isolation or in combination. Type B ADRs.

Characteristic	Type A	Type B
Dose dependency	Usually shows a good relationship	No simple relationship
Predictable from known pharmacology	Yes	Not usually
Host factors	Genetic factors may be important	Dependent on (usually uncharacterized) host factors
Frequency	Common	Uncommon
Severity	Variable, but usually mild	Variable, proportionately more severe than type A
Morbidity	High	High
Mortality	Low	High
Overall proportion of adverse drug reactions	80%	20%
First detection	Phases I–III	Usually phase IV, occasionally phase III
Mechanism	Usually due to parent drug or stable metabolite	May be due to parent drug or stable metabolite, but CRMs also implicated
Animal models	Usually reproducible in animals	No known animal models

Fig: Characteristics Of Type A And Type B Adverse Drug Reactions.[9]

Have been characterized as being dose independent or rather there is no simple relationship between dose and the occurrence of toxicity (Park et al., 1998). Certainly, evaluation of patients with and without hypersensitivity to a particular compound shows very little difference in doses received; indeed, in the patients with hypersensitivity, the doses may have been lower since the drug had to be withdrawn. Furthermore, even within the hypersensitive group, there is little relationship to the occurrence and severity of toxicity and the dose administered. However, intuitively, there must some kind of dose–response relationship since if the patient had not received the drug they would not have developed the hypersensitivity reaction.[6,7,8]

Genetics Related Adverse Drug Reactions

Pharmacogenetics is an area of research that addresses the genetically determined variation in how individuals respond to specific drugs, in terms of differences in dose requirement, efficacy and the risk of adverse drug reactions (ADRs). Since the completion of the Human Genome Project, pharmacogenomics has been touted as the field with greatest clinical potential to radically improve patient care through the implementation of personalized medicine. The terms personalized medicine and pharmacogenomics are often used together, as both aims to maximize therapeutic benefit and avoid ADRs. In addition to improving patient care, pharmacogenetics-based personalized approaches have the potential to save money by improving the cost-effectiveness of health care delivery. There are many commonly prescribed drugs that fail to work for some patients. For example, many patients with high cholesterol fail to respond to statins, and many hypertensive patients do not respond to beta-blockers Adverse drug reactions are a major cause of death and illness in patients and an important cause of drug attrition in the pharmaceutical industry both during drug development and after licensing. These reactions are normally classed as idiosyncratic reactions that are not related directly to drug concentration but instead may be due to an unusual patient phenotype. Most serious adverse drug reactions can be classified as either type A, which is dose dependent, or type B (idiosyncratic), where the reaction is not predictable from normal drug pharmacology and is generally independent of dose. Idiosyncratic reactions are rarer in comparison to type A.[10]

Recent pharmacogenomics studies that have evolved from a candidate-gene approach to the Genome-Wide Association Study (GWAS) have greatly advanced the discovery of genes associated with inter-individual differences in drug response, especially genes that predispose individuals to ADRS and, to a lesser extent, genes responsible for drug efficacy. These studies also have advanced our understanding of the underlying mechanisms of ADRs and drug efficacy. Based on these discoveries, the Food and Drug Administration (FDA) has relabelled over 100 approved drugs to include genetic information. A list of valid genomic biomarkers for clinical guidance can be found on the FDA website

Table of Pharmacogenomic Biomarkers in Drug labels'.[11,12]

Approaches for identification of causative genes

Pharmacogenomic studies to identify genes that contribute to susceptibility to adverse drug reactions have up to the present involved case-control association studies using either a candidate gene approach or genome-wide association (GWA) analysis. Though the development of GWA studies has led to considerable progress in the area of complex disease genomics and this would be generally considered the more appropriate approach to use currently to identify genes involved in adverse drug reactions, there are a several examples where candidate gene studies have been valuable in identifying causative genes. most genetic risk factors identified have large effect sizes and are generally in biologically obvious genes. However, GWA studies have the advantage of their open approach where all genes and common variation are examined and there are now a few examples of entirely novel associations that would have been unlikely to have been predicted by candidate gene approaches. Using GWA is particularly valuable in detecting small effects, but a limitation with most studies on adverse drug reactions is that the number of cases available for study is small, which limits power to detect significant effects.[13,14]

Drug Metabolizing Enzymes

When the Genome wide technology were not available early pharmacogenomic studies relied on candidate-gene approaches; thus, genes affecting drug metabolism and detoxification were obvious candidates. As a result, numerous metabolic biomarkers have been identified. As of July 2012, 67 drugs with valid metabolic biomarkers for dosage adjustment have been listed. 87% of these have genetic tests approved or cleared by the FDA. However, for most there are no guidelines to direct the clinical use of this genetic information. Among these drugs, about 25% are metabolized by cytochrome P450, family 2, subfamily D, polypeptide 6 (CYP2D6) and their rates of metabolism can vary >100-fold depending on allelic variability in different ethnic groups. Seven percent of Western Europeans are CYP2D6 poor metabolizers who require lower prescribing doses, whereas an estimated 20 million individuals are ultra-rapid metabolizers who experience no response to standard treatment. For example, one meta-analysis demonstrated a reduction in about 50% in the average dose for most tricyclic antidepressants in patients who are CYP2D6 poor metabolizers (CYP2D6*3/*3). In the case of codeine, which requires CYP2D6 cometabolites experience little therapeutic effect, whereas morphine conversion is increased in ultra-rapid metabolizers (CYP2D6*1/*1 and *1/2), which results in severe or life-threatening toxic side effects following standard doses. bioactivation and conversion to morphine, poor metabolizers experience little therapeutic effect, whereas morphine conversion is increased in ultra-rapid metabolizers (CYP2D6*1/*1 and *1/2), which results in severe or life-threatening toxic side effects following standard doses.[15]

Another important drug-metabolizing enzyme is thiopurine S-methyltransferase (TPMT), which metabolizes 6-merceptopurine and azathioprine. TPMT-deficient patients carrying the non-functional alleles TPMT 2, TPMT 3Ahematologic toxicity, and homozygous-TPMT-deficient patients require substantial dose and TPMT 3C are at high risk of severer hematologic toxicity, and homozygous-TPMT-deficient patients require substantial dose reductions.[16]

In addition to the metabolizing enzymes that affect drug pharmacokinetics, there are genetic variants that influence drug pharmacodynamics. One successful example of a drug for which both pharmacokinetic and pharmacodynamic biomarkers are used for individualized dose prediction is warfarin. Warfarin is the most commonly prescribed anticoagulant. Despite its clinical effectiveness, warfarin has a narrow therapeutic index and shows large inter-individual variability. Warfarin overdose is often associated with major bleeding complications. Both candidate-gene and GWA studies have confirmed that dose requirement of warfarin is primarily determined by CYP2C9, coding for the enzyme that metabolizes the potent S-isomer of warfarin, and vitamin K epoxide reductase enzyme complex subunit 1 (VKORCI), encoding the warfarin target protein. The percentage of drugs with genetic information on responding metabolic enzymes in their drug labels related to dosage adjustment or risk for adverse events is shown. (From: Pharmacogenomics of adverse drug reactions: implementing personalized medicine).[17]

Enzymes in inborn error of metabolism

Enzymes affecting drug metabolism can also be found in two classical inborn errors of metabolism, dihydropyridine dehydrogenase (DPD) deficiency and glucose-6-phosphate dehydrogenase (G6PD) deficiency. DPD is the rate-limiting enzyme involved in the catabolism of thymidine and uracil. It is also the main enzyme involved in the degradation of structurally related compounds like 5-fluorouracil (5-FU) or its prodrug capecitabine, two widely used anticancer drugs. A decrease in DPD activity can result in toxicity to 5-FU and capecitabine; therefore, these drugs should not be used in DPD-deficient patients. G6PD deficiency is characterized by abnormally low levels of G6PD, a metabolic enzyme involved in the pentose phosphate pathway. The most notable symptom of G6PD deficiency is haemolytic anaemia caused by ingestion of drugs, food and other trigger substances that cause oxidative stress.[18,19]

Drug Transporters

Drug transporters represent another class of genes affecting drug pharmacokinetics. These are mainly classified into two major super families: the efflux transporter ATP-binding cassette (ABC) and the influx

transporter solute carrier (SLC) transporters. For instance, genetic variants of ABCB1, encoding p-glycoprotein (Pgp) associated with multiple drug resistance, may account for a difference of 25% in the renal clearance of cyclosporine. In fact, the functional polymorphism ABCB1 34355TT is strongly associated with cyclosporine induced nephrotoxicity. Similar subjects with Q141K variant of ABCG2, which codes for breast cancer resistance protein, are at risk of gefitinib-induced diarrhoea.[20] Statins, or HMG-CoA reductase inhibitors, are one of the most commonly prescribed classes of drug for reducing cholesterol levels and preventing cardiovascular events. However, patients treated with a statin are at risk for muscle complications, including myopathy or fatal rhabdomyolysis. A recent GWAS study identified a strong association between simvastatin-induced myopathy and the SLC organic anion transporter family member 181 (SLCO1B1), which encodes the organic anion-transporting polypeptide (OATP1B1).[21]

Human Leucocyte Antigen (HLA)

The HLA system has been a major focus for Type B ADRs, i.e. those associated with drug hypersensitivity reactions, including Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), hypersensitivity syndrome (HSS) and drug-induced liver injury. Evidence supports the view that drug hypersensitivity is mediated by adaptive immunity, which involves MHC-restricted drug presentation, activation and clonal expansion of T cells. The specific MHC molecules involved have been identified, for example, HLA-B*5701 in abacavir induced drug hypersensitivity and HLA-B*1502 in carbamazepine (CBZ)-induced SJS.

Examples of Adverse drug reaction with HLA- Abacavir, Allopurinol, Aminopenicillin, Amoxicillin-clavulanate etc.[22,23,24]

Future Prospects

It is well recognized that genetics affect clinical outcomes of drug therapy. The greatest obstacle to the clinical implementation of genetic biomarker tests is that, with some exception, few of them have sufficient sensitivity, specificity and predictive value to be clinically useful as screening tools to predict drug efficacy and prevent ADRs. This is especially true for the genes responsible for drug efficacy, as thus far pharmacogenomic studies on the efficacy of drugs used to treat common diseases have been disappointing. There are several reasons for the slow progress of the pharmacogenomic study of drug efficacy for common diseases. First, the causes of common diseases are multifactorial, involving both genetic and environmental factors, and in most cases genetic determinants underlying the disease pathogenesis are unknown. Thus, drugs used to treat these common diseases, such as statins, may target only one of the factors/pathways. If the cause of elevated blood lipid levels for an individual is not targeted by a statin, a statin would be ineffective. To better understand the mechanisms of drug efficacy and identify clinically useful biomarkers requires a better understanding of the diseases. Secondly, the effects of many drugs are influenced by drug-drug or drug-diet interactions. Drug efficacy may be modulated by concomitant drugs or diet, making it difficult to control pharmacogenomic studies.[25,26]

Paediatrics

About 80% of listed medication labels disclaimed usage or lacked dosing information for children. Only 20-30 % of drugs approved by the FDA were labelled for paediatric use. Only 38% of new drugs potentially useful in paediatrics were labelled for children when initially approved.

ICH Expert Working Group finalized guidance for industry in 2000 E11

Clinical Investigation of Medicinal Products in the Paediatric Population. General Principles Guiding Paediatric Product Development as stated in ICH E-11 is

1. Paediatric patients should be given medicines that have been properly evaluated for their use in the intended population.
2. Product development programmes should include paediatric studies when paediatric use is anticipated. Development of product information in paediatric patients should be timely and, often requires the development of paediatric formulations.
3. The rights of paediatric participants should be protected and they should be shielded from undue risk.
4. Shared responsibility among companies, regulatory authorities, health professionals and society as a whole.[27,28]

Paediatric Product Development General Principles Regarding Process

- In general, new products are developed for use in adult and paediatric patients. Paediatric product development should be integrated into the adult development programme and not be an add-on or afterthought.
- Tools for this integration include those provided by the paediatric legislation: BPCA and PREA.
- Paediatric product development must be conducted with the same scientific and ethical rigor as for adults with additional ethical protocol. .
- FDA regulatory requirements must be met for marketing approval.

On the 26th of January 2007, the "Paediatric Regulation" entered into force (Regulation EC No 1901/2006 of the European Parliament and of the Council, amending regulation EEC No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation EC No 726/2004). The Regulation aims to "facilitate the development and accessibility of medicinal products for use in the paediatric population, to ensure that medicinal products used to treat the paediatric population are subject to

research of high quality and are appropriately authorized for use in the paediatric population, and to improve the information available on the use of medicinal products in the various paediatric population".[29]

Scope

The principles of this guideline should be considered during the pharmaceutical development of all paediatric medicines as proposed in marketing-authorization applications (MAAs) or applications to extend or vary marketing authorizations to the paediatric population (MAVs). Depending on the phase of the development, the principles of this guideline should also be considered for the purpose of the paediatric investigation plan (PIP) applications. While taking into account that the regulation of medicinal products must be fundamentally aimed at safeguarding public health, it is important to realize that this aim must be achieved by means that do not impede the free movement of safe medicinal products within the Union.

General Considerations

Any medicine should be designed to meet patient needs and to consistently deliver the intended product performance. A systematic approach to the pharmaceutical development in accordance with ICH Q8 could be followed in order to meet these objectives. When applied, the quality target product profile (QTPP) should be established taking into consideration the specific needs of the paediatric population. Based on the QTPP the critical Product Quality Attributes (CQAs) should then be identified as well as the formulation and process parameters that may affect them.

In deciding on the appropriateness of the pharmaceutical design of a paediatric medicine the following should also be considered

- The minimum age, the relevant developmental physiology and the age characteristics of children in the target age group(s);
- The condition to be treated and the condition-related characteristics of the child (e.g. Children with physical or mental disabilities, under fluid restriction, with a high degree of co-medication, unable to swallow due to critical illnesses);
- The criticality of the dose (i.e., steep dose/pharmacodynamic response curve, narrow therapeutic window) and the dosing regimen (i.e., dose calculation, dose titration, flexibility of dosing)
- The age associated activities of children in the target age group(s) (e.g., school, nursery);
- The maximum duration of the therapy and the dosing frequency:
- The environment setting where the product is likely to be used (e.g., hospital or community);
- The child and caregiver's characteristics and their behaviour.

Characteristics of The Active Substance

The physic-chemical characteristics of a particular active substance may be desirably modified by the choice in which the active moiety is manufactured into a paediatric medicine as the active substance. For example, in some cases the manufacture of a liquid medicinal product may require a substance with improved solubility e.g. a different salt, or a salt instead of the base. Also, child acceptability may be Guideline on pharmaceutical development of medicines for paediatric use EMA/CHMP/QWP/805880/2012 Rev.2 Page 5/24 favoured by the selection of a less soluble form of the active substance to overcome taste issues, e.g. the base instead of the salt. At an early pharmaceutical development phase, it is recommended that the selection of the form of the active substance (acid/base, salt, polymorph, solvate, etc.) takes into consideration the properties affecting development of paediatric medicinal products.

Route of Administration and Dosage Form

Oral Administration

Oral administration can be achieved via several types of dosage forms. In general, the main choice in oral administration is between liquids and solid dosage forms. The advantages and disadvantages of a given oral dosage form in relation to children in the target age group(s) should be considered when selecting a particular dosage form. Oral solid single-unit dosage forms may provide a stable and easy dosing approach. However, where individually adapted dosing is necessary, the number of strengths needed to treat patients in the target age group(s) will increase. For tablets, alternatives which may provide dosing flexibility include addition of break marks enabling administration of a fraction of a full tablet dose or (small) tablets containing only a fraction of the required dose which may be taken simultaneously to deliver the required dose.[30,31]

Oral Solid Preparations

1) Powders and granules

Powders and granules may be given to children from birth provided they can be administered as a liquid preparation. In their solid form, they are usually given with semi solid food. If given with semi-solid food, they can be considered acceptable from the moment the infant is able to accept the semi-solid food, which is usually around six months of age. The risk of aspiration, choking and where relevant chewing, of powders/granules should be discussed in relation to the target age group(s), size, shape and quantity (volume) of powders/granules and any specific characteristics of the preparation. Administration of powders and granules requires a measuring device unless they are packed in single dose containers such as sachets.[30,31]

2) Tablets

The size and shape of a tablet are fundamental to the ability of a child to swallow it. Therefore, the acceptability of the size and shape of tablets by the target age group(s) should be justified, and where relevant

supported by appropriate studies or clinical evidence. It should be noted that limited data are available in the literature regarding the influence of size, shape and the number of tablets on acceptability in different paediatric age groups. For chronic diseases, the acceptability of tablets with a particular size and shape in children may be improved by adequate training. Tablet size and shape acceptability may also be improved by adequate instructions for co-administration with semi-solid food.[30,31]

3) Capsules

Capsules are usually intended to be taken intact. Where appropriately justified, hard capsules may also be opened and their contents taken as such, provided that the feasibility of opening the capsule and removing the contents from the capsule has been demonstrated. If a hard capsule is to be opened prior to use, its content should meet the same requirements as normally applied for the type of the content e.g., granules. The suitability of taking capsules intact or opened should be discussed and justified for all the indicated target age group.[30,31]

4) Modification of oral solid preparations to facilitate administration

When oral solid preparations are to be given to children, it is likely that some children may not be able or willing to take the dosage form as intended, even when the dosage form is generally considered as age appropriate. In the absence of alternative age-appropriate dosage forms, other strategies for administering the oral solid preparations should be considered by applicants and discussed (e.g. dispersing or crushing tablets, opening of capsules, mixing with food or drinks). In addition to the agreed age-appropriate preparation, applicants are encouraged to propose alternative strategies for administration of the preparation.[30,31]

Bioavailability or bioequivalence studies may not always be required. Existing information from the (adult) development programme, established practices, literature data and/or in vitro studies provide sufficient justification. Additional information supporting the proposed modification may be provided from clinical trials where the target patient groups have been administered the product according to the alternative strategy and the organoleptic and administration attributes were found acceptable**.**

5) Oral Liquid Preparations

Oral liquid dosage forms are normally considered acceptable for children from full term birth and for pre-term neonates who are able to swallow and accept enteral feeding. Aqueous liquid dosage forms in multiple-dose containers will normally need to be preserved, whereas oral solid dosage forms will normally not. This would favour the use of oral solid dosage forms over the use of oral liquid dosage forms in children. However, the use of preservatives should not be the only aspect in deciding on the choice between oral liquid versus oral solid dosage forms.[30,31]

6) Administration through feeding tubes

Oral medicinal products are likely to be administered via a feeding tube to patients who are tube fed due to their condition or age related limitations e.g. pre-term neonates, unable to swallow but able to receive enteral feeds. Where administration through feeding tubes is used, either as a main route or as a very likely option, the feasibility of administration through the feeding tube needs to be addressed. The particle size, viscosity, dosing and rinse volume(s), chemical compatibility of the oral medicinal product with the tube material and the risk of physical blockage of the tube should be considered during pharmaceutical development. Dose recovery after extrusion needs to be demonstrated using feeding tubes and rinse volumes relevant to the target age group(s). In addition, and if relevant depending on the location of the tube, the risks associated with the accidental aspiration of the medicinal product and the possible effect on the bioavailability should be discussed.[30,31]

7) Nasal preparations

Nasal preparations will normally be considered suitable for children of all ages. The suitability of the nasal route of administration for local and systemic treatment with a particular paediatric medicinal product should be discussed and justified in terms of the likelihood that the active substance (and excipients) will cause pain or irritation. The use of any preservative should be justified as outlined in section 9. The patient acceptability should also be discussed in relation to the palatability and sensation of the medicinal product on administration.[30,31]

8) Preparations for inhalation

The patient acceptability and age-appropriateness of orally inhaled paediatric medicines (including solutions for nebulization) need to be justified. Pressurized metered dose inhalers may be applied to children from birth if in combination with a specific spacer system and face mask. Older children may use the inhaler with or without a spacer. Companies should justify the suitability of the proposed equipment for use in the target age group(s).[30,31]

9) Rectal preparations

The size (length and diameter) of the suppository should take into account the age and size of the child. Due to the high risk of dosing errors related to inhomogeneous distribution of the active substance and difficulties in reproducible cutting, suppositories should not be cut to provide a smaller dose unless they have been specially designed for this purpose.[30,31]

10) Eye and ear preparations

Preparations for the eye and ear are mostly developed for a single patient group, including children, adults and the

elderly. Preparations for the eye and ear may be poorly accepted by some children. However, in the absence of better alternatives, they should be considered acceptable dosage forms for children of all ages.[30,31]

11) Parenteral administration

Parenteral administration is the most commonly used route of administration for active substances for children who are seriously ill and for clinically unstable term and preterm neonates. The choice of an intravenous, subcutaneous or intramuscular injection is to be justified in terms of the intended clinical effect, relevant characteristics of the active substance and child acceptance (pain). The route of intravenous administration (central or peripheral), site of injection, the injection volumes, the rate of administration, the viscosity, pH, buffering, osmolarity and, if relevant, the needle thickness and needle length should be described and justified. The age and weight of the child, the maximum number of injections per day and the duration per treatment should also be discussed. Where appropriate, the use of micro-needles or needle free injectors could be considered, especially for medicines requiring frequent or long treatment period.[30,31]

12) Fixed dose combinations

Fixed dose combinations are often developed as an alternative substitution therapy for patients already treated with the individual components, especially for chronic diseases such as HIV or tuberculosis. They may be of value for patients to simplify therapy and improve adherence.[30,31]

Dosing Frequency

The choice of the dosing frequency should be justified in terms of the characteristics of the active substance, the pharmacokinetic profile, the indication, the convenience and therapeutic adherence of the child or caregiver. Taking these criteria into consideration, a maximum of twice daily dosing is preferred for out-patient use.[32]

Excipients in the Formulation

The choice of suitable excipients in a paediatric medicinal product is one of the key elements of its pharmaceutical development. Although the basic considerations regarding the use of a specific excipient are similar for adult and paediatric preparations, the inclusion of any excipient in paediatric preparations, even those which are normally accepted for use in medicines for adults or those which are present in authorized paediatric medicines, requires special safety considerations.

Overall, the following aspects are to be considered when selecting an appropriate excipient for inclusion in a paediatric medicinal product:

- The function of the excipient in the formulation and potential alternatives;
- The safety profile of the excipient for children in the target age group(s) on the basis of single and daily exposure (and not the concentration or strength of the preparation);
- The expected duration of the treatment i.e. short term (single dose/few days) versus long term (weeks, months, chronic);
- The severity of the condition to be treated (e.g. life-threatening disease) and the therapeutic alternatives;
- The patient acceptability including palatability (e.g. local pain, taste);
- Allergies and sensitization.[33]

Colouring Agents

The use of any specific colouring agent in a paediatric preparation should be discussed and justified in terms of allergenic potential, minimal toxicological implications in the target age group(s), patient acceptability and the need to avoid accidental dosing errors. Where there is a need to differentiate between similar preparations to avoid accidental dosing errors, the use of other strategies e.g. shape, size and embossing should be considered prior to the use of colouring agents. The justification should address both the necessity to colour the preparation and the selection of a particular colouring agent.[34]

Flavours

Adequate palatability plays an important role in patient acceptability, especially in oral liquid formulations, and flavours may be necessary to achieve this goal. The rationale for the use of a particular flavour in a paediatric preparation should be clearly described and justified. The qualitative and quantitative composition of any components of the flavouring agent that are known to have a recognized action or effect should be provided. Safety concerns should be discussed, including the risk of allergies and sensitization.[35]

Preservatives

The use of preservatives is normally considered acceptable in multidose preparations. However, for many preservatives there is still limited data regarding the levels of safe exposure in children of different ages. The need to preserve a paediatric preparation and the choice of the preservative system at the lowest concentration feasible should be justified in terms of benefit-risk balance.[36]

Sugars and Sweeteners

Adequate patient acceptability of oral paediatric preparations is paramount and sweetness plays an important role in this. The choice and concentration of sweetening agents depends on the properties of the active substance and the use of flavours. The rationale for the use of a particular sweetening agent in a paediatric preparation should be clearly described and justified. Safety concerns should be discussed, including conditions that would restrict the use of a particular sugar or sweetener (e.g. diabetes, severe renal insufficiency).[37]

Patient Acceptability

Patient acceptability is likely to have a significant impact on patient adherence and consequently, on the safety and efficacy of a medicinal product. Acceptability is determined by the characteristics of the product and the user. The product aspects relate to pharmaceutical characteristics such as:

Palatability, swallowability (e.g. size, shape, texture)

- Appearance (e.g. colour, shape, embossing);
- Complexity of the modification to be conducted by the child or its caregivers prior to administration;
- The required dose (e.g. the dosing volume, number of tablets, etc.);
- The required dosing frequency and duration of treatment;
- The selected administration device;
- The primary and secondary container closure system;
- The actual mode of administration to the child and any related pain or discomfort.
- User information (summary of product characteristics and package leaflet).

Applicants should provide clear user instructions that favour the correct and full administration of a paediatric medicine. These instructions should take account of the different administration scenarios to children from birth into adulthood. Where relevant, instructions that are both suitable for the caregiver as well as the child are strongly recommended. User instructions should be sufficiently robust towards unwilling children, especially where full adherence is critical for therapeutic outcomes.[38]

Pregnancy and Lactation

The clinical trial programme of a medicinal product under development rarely includes pregnant women, (unless the product is intended specifically for use during pregnancy), however, some pharmacological treatments cannot be discontinued during pregnancy. In most clinical trials in which women of childbearing age are included, effective contraception must be used. For this reason, the only data available to evaluate reproductive risk when a new medicinal product is approved for marketing is virtually from non-clinical studies, and although these non-clinical studies can be useful to predict human risk, the extent of prediction needs to be taken with caution. Consequently, many medicinal products are subject to contraindications or special warnings because they have not been sufficiently studied during pregnancy or studies in animals have revealed adverse effects on the foetus (teratogenic, fetotoxic or other). Once a product is marketed, the major objective of pharmacovigilance with regard to the exposure of pregnant women is to collect information on safety in pregnancy so that better information can be provided to health care practitioners and patients. Information on drug exposure in pregnancy is necessary to identify agents harmful to the developing foetus. Conversely, data on pregnancy exposure can also establish that the foetal toxicity of a product is limited.[39]

Scope of the Guideline

This guideline aims at providing criteria to select medicinal products for which active surveillance for collecting post-authorization data in pregnancy is necessary. It provides guidance on how to monitor accidental or intended exposure to medicinal products during pregnancy and specific requirements for reporting data and adverse outcomes of pregnancy exposure. The guideline also includes detailed recommendations regarding presentation of data collected on exposure in pregnant women. The guideline relates in particular to new products, for which a summary of the potential risks of exposure in pregnancy and of the potential need for the product during pregnancy should be included in the Pharmacovigilance Specification provided by the Marketing Authorization Holder (MAH) at the time of the MA application. The aim of these specifications is that the MAH proposes a Pharmacovigilance Plan in order to evaluate the potential risk of a product and/or to provide missing information on the safety of the product in pregnancy.[39]

LEGAL BASIS

This guideline should be read in conjunction with the Council Regulation (EEC) 2309/93 (Title II, Chapter 3), European Parliament and Council Directive 2001/83/EC, as amended (Title IX), Commission Regulation (EC) 540/95, Council Regulation (EEC) No 2309/93 and with other EU and ICH Guidance documents, especially

- Volume 9 of the Rules Governing Medicinal Products in the European Union. (Pharmacovigilance Medicinal Products for Human Use).
- **ICH topic E2C:** Note for Guidance on Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs (CPMP/ICH/288/95, adopted in December 1996)
- Addendum to ICH topic E2C (CPMP/ICH/4679/02, adopted in February 2003)
- **ICH topic E1A:** The Extent of Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions (CPMP/ICH/375/95, adopted in November 1994)
- **ICH topic E2B(M):** Note for Guidance on Clinical Safety Data Management: Data Elements for Transmission of Individual Case Safety Reports (CPMP/ICH/287/95, adopted in November 2000)
- **ICH topic E2B(M):** Questions and answers to CPMP/ICH/287/95. (CPMP/ICH/3943/03, adopted in November 2003).
- **ICH topic E2A:** Note for Guidance on Clinical Safety Data Management: Definitions and Standards for expedited reporting (CPMP/ICH/377/95, adopted in November 1994)
- Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (ENTR//F2/BL D (2003)-adopted in April 2003,

Eudra vigilance-CT Module) ICH E2E: Note for Guidance for Pharmacovigilance Planning (CPMP/ICH/5716/03 released for 6 months' consultation in November 2003)

- **ICH E2D: Note for Guidance on Post-Approval Safety Data Management:** Definitions and Standards for expedited reporting (CPMP/ ICH/3945/03, adopted in November 2003)
- All applicable ICH guidelines and standards for electronic reporting of Individual Case Safety Reports (i.e., M1, M2).
- The 'Note for Guidance on the Electronic Data Interchange (EDI) of Individual Case Safety Reports (ICSRs) and Medicinal Product Reports (MPRS) in pharmacovigilance. during the pre and post-authorization phase in the European Economic Area (EEA)', Doc. Ref. EMEA/115735/2004 (adopted at Community level in September 2004).
- The EMEA guidance Technical Documentation – Eudra Vigilance Human Version 7.0 Processing of Safety Messages and ICSRs' (Doc. Ref. EMEA/H/20665/04) (adopted at Community level in July 2004).
- 'Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudra Vigilance Clinical Trial Module), (Doc. Ref. ENTR/CT4, Revision 1, adopted at Community level in April 2004).
- Guideline on Risk Management Systems for Medicinal Products for human use (EMEA/CHMP/96268/2005).[40]

Geriatrics

The geriatric assessment is a multidimensional, multidisciplinary diagnostic instrument designed to collect data on the medical, psychosocial and functional capabilities and limitations of elderly patients. Various geriatric practitioners use the information generated to develop treatment and long-term follow-up plans, arrange for primary care and rehabilitative services, organize and facilitate the intricate process of case management, determine long-term care requirements and optimal placement, and make the best use of health care resources. The geriatric assessment differs from a standard medical evaluation in three general ways:

(1) It focuses on elderly individuals with complex problems,
(2) It emphasizes functional status and quality of life, and
(3) It frequently takes advantage of an interdisciplinary team of providers.

Whereas the standard medical evaluation works reasonably well in most other populations, it tends to miss some of the most prevalent problems faced by the elder patient.

These challenges, often referred to as the "Five I's of Geriatrics", include intellectual impairment, immobility, instability, incontinence and iatrogenic disorders. The geriatric assessment effectively addresses these and many other areas of geriatric care that are crucial to the successful treatment and prevention of disease and disability in older people.

Performing a comprehensive assessment is an ambitious undertaking. Below is a list of the areas geriatric providers may choose to assess:

- Current symptoms and illnesses and their functional impact.
- Current medications, their indications and effects.
- Relevant past illnesses.
- Recent and impending life changes.
- Objective measure of overall personal and social functionality.
- Current and future living environment and its appropriateness to function and prognosis.
- Family situation and availability.
- Current caregiver network including its deficiencies and potential.
- Objective measure of cognitive status.
- Objective assessment of mobility and balance.
- Rehabilitative status and prognosis if ill or disabled.
- Current emotional health and substance abuse.
- Nutritional status and needs.
- Disease risk factors, screening status, and health promotion activities.
- Services required and received.[41]

Guidelines for Drug Safety in Geriatrics

Labeling (including patient package inserts and Medication Guides)

FDA-approved drug product labeling is the primary source of information about a drug's safety and effectiveness, and it summarizes the essential scientific information needed for the safe and effective use of the drug. Compliance with the recently issued physician labeling rule 9 for prescription drugs is expected to further enhance the usefulness of product labeling and further facilitate the safe and optimal use of prescription drugs. Labeling for prescription drug products is directed to healthcare professionals, but may include sections that are intended for patients and that also must be FDA-approved. For some prescription drugs, such as oral contraceptives and estrogens, FDA long ago determined that the safe and effective use of the drug required additional labeling in non-technical language to be distributed directly to patients by their healthcare provider or pharmacist (21 CFR 310.501 and 310.515). These patient package inserts also may be provided voluntarily by manufacturers for other drugs and are regulated by FDA as product labeling.[42]

Public Health Advisories

FDA issues Public Health Advisories (PHAS) to provide information regarding important public health issues to the general public, including patients and healthcare professionals. For example, PHAS may: Highlight important safety information about a drug.

- Inform the public about the status of FDA's evaluation of an emerging drug safety issue.
- Announce the implementation of a Risk MAP for a drug.
- Advise the public regarding a manufacturer's suspension of marketing of a drug due to safety concerns.
- Provide other important public health information.[43]

Patient Information Sheets

Patient Information Sheets encourage patients to talk with their healthcare providers for further information. Patient Information Sheets also provide telephone and e-mail contact. information for FDA's Drug Information line to address specific questions. FDA continues to collect input on the usefulness of these consumer communications through feedback mechanisms, such as focus groups, surveys, and public meetings, and anticipates that these. consumer communications will continue to evolve.[44]

Healthcare Professional Sheets

Healthcare Professional Sheets provide a summary of important, and often emerging. drug safety information for a particular drug or drug class and also can be found on the FDA's Index to Drug Specific Information. Healthcare Professional Sheets begin with al summary Alert paragraph (see section below on Alerts) followed by more detailed sections explaining the Alert, including clinical considerations or recommendations for the healthcare professional, a summary of the data, and, when applicable, implications of the Alert.[45]

Alerts on Patient Information and Healthcare Professional Sheets

When FDA becomes aware of emerging information on a potentially important drug safety issue and we determine patients and healthcare professionals should know about the information while we continue our evaluation, we currently provide this information in Patient Information Sheets and Healthcare Professional Sheets as an Alert. Alerts also may be used to highlight important new information in product labelling or an important change in a risk management programme. For example, an Alert may describe:

- Newly observed, serious adverse events that may be associated with use of a drug.
- Information about how such serious adverse events might be prevented by appropriate patient selection, monitoring of patients, or use or avoidance of the therapy.
- Information regarding a serious adverse event that FDA believes may be associated with use of a drug in populations in whom the drug was not previously studied.[45]

CONCLUSIONS

The emergence of pharmacogenomics may herald a new era of individualized therapy. Hence, nonpreventable ADRs may become at least in part preventable, as a first step in optimizing drug therapy with genetic information. This study provides empirical evidence that the use of pharmacogenomics could potentially reduce ADRs, a problem of major significance. Our study illustrates the adage, "the sum can be greater than its parts": how 2 bodies of literature can produce additional insights when combined, and our study provides a foundation for future research. In the future, we may all carry a "gene chip assay report" that contains our unique genetic profile that would be consulted before drugs are prescribed. However, the application of pharmacogenomics information faces significant challenges, and further basic science, clinical, and policy research is needed to determine in what areas pharmacogenomics can have the greatest impact, how it can be incorporated into practice, and what are its societal implications.

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ABBREVIATIONS

GWASs -	Genome-wide association studies
HLAs -	Human-leukocyte antigens
ADRs -	Adverse drug reactions
FDA -	Food and drug administration
CYP2D6 -	Cytochrome P450, family 2, subfamily D, polypeptide 6
TPMT -	Thiopurine S-methyltransferase
VKORCI -	Vitamin K epoxide reductase enzyme complex subunit
DPD -	Dihydropyridine dehydrogenase
G6PD -	Glucose-6-phosphate dehydrogenase
ABC -	ATP-binding cassette
OATP -	Organic anion-transporting polypeptide
HLA -	Human Leucocyte Antigen
SJS -	Stevens-Johnson syndrome
TEN -	Toxic epidermal necrolysis
HSS -	Hypersensitivity syndrome

ICH - International Council for Harmonisation
BPCA - Best Pharmaceuticals for Children Act
PREA - Paediatric Research Equity Act
MAAs - Marketing-authorization applications
PIP - Paediatric investigation plan
QTPP - Quality target product profile
CPQA - Critical Product Quality Attributes
MAH - Marketing Authorization Holder
ICSRs - Individual Case Safety Reports
EDI - Electronic Data Interchange
MPRs - Medicinal Product Reports

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