From evidence based medicine to mechanism based medicine.
Reviewing the role of pharmacogenetics

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Abstract  Aim of the review  The translation of evidence
based medicine to a specific patient presents a considerable
challenge. We present by means of the examples nortriptyline, tramadol, clopidogrel, coumarins, abacavir
and antipsychotics the discrepancy between available pharma-
cogenetic information and its implementation in daily
clinical practice. Method  Literature review. Results  A
mechanism based approach may be helpful to personalize
medicine for the individual patient to which pharmacoge-
genetics may contribute significantly. The lack of consistency
in what we accept in bioequivalence and in pharmacoge-
genetics of drug metabolising enzymes is discussed and
illustrated with the example of nortriptyline. The impact of
pharmacogenetics on examples like tramadol, clopidogrel,
coumarins and abacavir is described. Also the present
status of the polymorphisms of 5-HT2A and C receptors in
antipsychotic-induced weight gain is presented as a phar-
codynamic example with until now a greater distance to
clinical implementation. Conclusion  The contribution of
pharmacogenetics to tailor-made pharmacotherapy, which
especially might be of value for patients deviating from the
average, has not yet reached the position it seems to
deserve.

Keywords  Drug metabolising enzymes · Mechanism
based medicine · Pharmacodynamics · Pharmacogenetics ·
Pharmacokinetics

Introduction

Evidence based medicine applies guidelines developed on
the basis of consensus from randomized clinical trials
(RCTs). These RCTs are performed in carefully selected
patient-populations studied under strongly regulated con-
ditions. It often is a challenge to translate the results of
the RCTs to a specific patient in the real world [1]. In RCTs
often (young) people having one specific disease are
selected. In daily clinical practice a significant part of the
patients consists of elderly patients often having multiple
morbidities. For the majority of these patients still no
evidenced based medication is available. Therefore in these
situations there seems to be a need for a mechanism based
approach towards medicine personalized for the individual patient. In mechanism based medicine it is already common practice to adjust drug dose to age, liver and renal function. Pharmacogenetics—the study of variations in DNA sequence as related to drug response—is trying to obtain its position among these factors [2]. Nevertheless we experience a lack of enthusiasm in the implementation of pharmacogenetics, especially when compared with for instance adaptation of drug dosing to liver or renal function or bodyweight for children.

**Aim of the review**

To review the evidence for the usefulness of pharmacogenetic information in relation to clinical implementation of this pharmacogenetic information.

**Method**

We summarized the available information in the literature for the pharmacogenetic information for nortriptyline (CYP2D6), tramadol(CYP2D6), clopidogrel(CYP2C19), coumarins(CYP2C9 and VKORC1), abacavir(HLA-B*5701) and the relation between polymorphism of 5-HT2A and C-receptors and antipsychotic induced weight gain as typical examples and compared this with the clinical implementation of these pharmacogenetic parameters. This is put into the perspective of accepted differences in bioequivalence.

**Results/Discussion**

In evidence based medicine the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1/corr) is applied to assess whether generic medicines are bioequivalent with the already marketed reference drugs. In this guideline, bioequivalence is accepted if the 90% confidence interval of the ratio of the Area Under the Curve (AUC) of the generic drug and the AUC of the reference drug lies within 80.00–125.00%. For highly variable drug products we accept extreme values up to 69.84–143.19% if this extent of variation is considered clinically irrelevant as long as the geometric mean ratio lies within 80.00–125.00%. With this in mind it is remarkable that regulatory authorities do not require the application of pharmacogenetics during the process of drug prescribing and dispensing in the numerous examples of drugs for which the AUC appears to deviate much stronger on a pharmacogenetic basis, as accepted in the above mentioned guideline. Here we present such an example, discuss barriers for the clinical implementation of pharmacogenetics and plea for a more mechanism based approach to medicine.

A classic example of pharmacogenetics is the variability in effect of the antidepressant nortriptyline due to different genotypes. The plasma levels of nortriptyline may vary almost tenfold depending on the number of functional CYP2D6 alleles. Still we accept to use the same dose in ultra-rapid metabolisers for CYP2D6 (5–10% of the Caucasian population) and for intermediate and poor metabolisers for CYP2D6 (15–25% of the Caucasian population) as for the so called extensive metabolisers [3, 4]. In other words the same tablet of nortriptyline administered to a poor or intermediate metaboliser is not bioequivalent with the tablet administered to an extensive metaboliser. Therefore, a one size fits all starting dose for nortriptyline can not be considered an example of evidence based medicine.

A second example for which from the perspective of evidence based medicine it is hard to understand that pharmacogenetics are not applied is tramadol, a μ-receptor agonist which also inhibits reuptake of serotonin and noradrenaline [5]. This drug demonstrated efficacy in several neuropathic pain conditions. However tramadol is a 50:50 mixture of (+)R,R- and (−)S,S-enantiomer which are O-demethylated by CYP2D6 to the so called M1 metaboites [6]. (+)- and (−)-Tramadol as well as (+)- and (−)-M1 strongly differ in affinity for the μ-receptor, the noradrenaline- and 5-HT-uptake [7]. This results in a different pharmacological profile of tramadol for the different CYP2D6 phenotypes. In ultrarapid and extensive metabolisers tramadol has much more μ-receptor agonist effect than in poor metabolisers [8]. In the latter a more pronounced noradrenaline- and 5-HT-uptake mediated effect will be observed. The evidence for the successful treatment of neuropathic pain with tramadol is based predominantly on extensive metabolisers, because this is the largest phenotype group. However, in these patients we deal with another active principle for tramadol than in patients with variant genotypes for CYP2D6 where the effect will be more dominated by the μ-receptor agonistic (ultrarapid metabolisers) or the noradrenaline- and 5-HT-uptake inhibiting effect (poor metabolisers). Therefore in the Netherlands it is advised to select an alternative for tramadol in poor, ultrarapid and intermediate metabolisers for CYP2D6 [3].

A third example is the antiplatelet drug clopidogrel. In evidence based medicine one often develops pharmacotherapeutic strategies based on post hoc or subgroup analysis of large randomized clinical trials. However, before applying pharmacogenetic knowledge from post hoc analysis, in daily clinical practice one calls for additional randomized studies. Prasugrel, another antiplatelet drug, was compared to clopidogrel in over 13,000 patients with
an acute coronary syndrome undergoing a percutaneous coronary intervention (PCI) in the TRITON-TIMI 38 study [9]. In a post hoc analysis in approximately 3,500 patients with ST segment elevation myocardial infarction (STEMI), prasugrel appeared to be more effective than clopidogrel in preventing the occurrence of cardiovascular ischemic events without an increased risk of developing bleedings [10]. The NICE appraisal recommends prasugrel as an option when immediate PCI for STEMI is necessary. In another post hoc analysis including clopidogrel treated patients of the TRITON-TIMI 38 study, the influence of genetic variants of CYP2C19 on the occurrence of cardiovascular ischemic events was studied. Clopidogrel is a prodrug which requires biotransformation to the active metabolite by the polymorphic CYP2C19. Carriage of genetic variants encoding for non functional CYP2C19 enzyme was associated with an increased risk of stent thrombosis and the combined endpoint of cardiovascular death, myocardial infarction or stroke [11]. This association was also observed in other studies and recently even resulted in a boxed warning by the FDA about the reduced effectiveness of clopidogrel in homozygous carriers of a CYP2C19 non functional allele. Nevertheless experts do not recommend routine genetic testing yet since there is no or limited information regarding the predictive value of genetic testing and the effect of a genotype guided treatment strategy on clinical outcome based on the results of randomized studies with sufficient power [12].

Besides genetically determined differences in pharmacokinetics, the variability in drug response can also be attributed to genetic variability in factors influencing drug action, for example, the drug receptor level (pharmacodynamics) [13]. As an example, in psychiatric pharmacotherapy at least two subtypes of the serotonin (5-HT) receptor have shown to be important: the 5-HT2A and the 5-HT2C receptor [14–16]. Polymorphisms in the HTR2C gene coding for the 5-HT2C receptor are of interest because of the association between HTR2C polymorphisms and the response of antipsychotic drugs [17] but also because of the association between HTR2C polymorphisms and antipsychotic-induced weight gain [16]. The translation to the corresponding clinical phenotype of pharmacodynamic polymorphisms like HTR2C is more complex than the translation of pharmacokinetic polymorphisms like CYP2D6. The consequences of pharmacokinetic polymorphisms can quite easily be measured with standard pharmacokinetic parameters (surrogate endpoints) like the steady state concentration, elimination half-live and the area under the curve (AUC) of administered drugs. The consequences of pharmacodynamic polymorphisms are more difficult to measure [13]. The pharmacodynamic polymorphisms have to be translated to a clinical phenotype based upon the expected function of the gene where the polymorphism is located. One of the limitations of this approach is that the clinical phenotype as a result of gene expression is not well known for many drug targeting receptors. The gene coding for the 5-HT2c receptor is an example of a drug targeting receptor with a relatively unknown phenotype. One of the suggested clinical phenotypes of the HTR2C gene is a function in regulation of food intake and weight gain but results are conflicting [18–25]. This pharmacodynamic polymorphism is one example of many others. However, the difficulties as described above impede implementation of genotyping of pharmacodynamic in contrast to pharmacokinetic polymorphisms in daily clinical practice at this moment.

Especially pharmacokinetic examples illustrate the discrepancy between the generally accepted limits for bioequivalence applied by the regulatory authorities and their position taken in pharmacogenetics. However, there are examples where the regulatory authorities took a clear standpoint with respect to the application of pharmacogenetics. Because of the increased risk of hypersensitivity reactions, on March 10, 2008 the CBG-MEB has revised the Summary of Product Characteristics of abacavir to include the advise to screen for HLA-B*5701 prior to treatment initiation and that abacavir should not be used in carriers of this polymorphism, unless there is no therapeutic alternative. An overview of drugs with a pharmacogenomic labelling from EMA and FDA for which genotyping is recommended or required can be found for instance in the paper of Becquemont [26]. Also the draft Guideline on the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products from the EMA (EMA/CHMP/37646/2009) reflects a clear role for pharmacogenetics in the evaluation of efficacy and safety of drugs as considered by the regulatory authority.

Where are we standing now? The current use of genotyping is mostly limited to diagnostics with a focus on adverse drug events in individual patients. Prevention of toxicity and treatment optimization through prospective screening is still far from being common practice. However, there are major developments in the field. Multiple relatively rare adverse drug events such as fluvoxacilline-induced liver injury [27], Stevens-Johnson syndrome induced by carbamazepine [28], and the hypersensitivity reaction to abacavir [29] have all been associated with specific HLA-B genotypes. For the latter, a prospective study showed that the hypersensitivity reaction can be prevented by screening patients prior to treatment with abacavir [29].

Furthermore, pharmacogenetic research has progressed from searching for associations between individual SNPs and treatment outcome, through combinations of multiple SNPs affecting pharmacokinetics and pharmacodynamics, to the use of pharmacogenetic models including SNPs as
well as more traditional clinical variables such as age, renal function and bodyweight. The inclusion of these traditional clinical variables is essential since individuals belonging to the same pharmacogenetic class still may vary about 10-fold in metabolic ratio, demonstrating that pharmacogenetics can not explain all interindividual differences, but is only one additional component [30].

For the coumarins much clinical evidence is present (especially from observational research) for the added value of knowledge of the genotype of CYP2C9 and VKORC1 for safe application which is not reflected yet in clinical application (see e.g. [31, 32]). The progress from individual SNPs to pharmacogenetic models is well exemplified by the coumarin warfarin. This drug is metabolised by the polymorphic enzyme CYP2C9. The CYP2C9 genotype alone explained 5–18% of the variation in required warfarin dose [33]. It was already reported that genetic variability in VKORC1, a gene coding for vitamine K epoxide reductase, a key enzyme in the vitamine K cycle, could explain 15–37% of the variation in required warfarin dose [34–37]. Recently models including genetic variants of VKORC1, CYP2C9 and clinical factors such as age, sex, height and bodyweight have been reported to explain up to 50% of variation in required warfarin dose [38].

We know that genotyping can give useful information for the prescription of certain drugs which could lead to a balanced use of genotyping. It should be emphasized that the role of pharmacogenetics may be more compelling if at the start of therapy with a new drug a quick finding of the right dose is of importance or in cases where hypersensitivity reactions are involved. If there is chosen for the approach of starting with an almost universally tolerated dose, which then is gradually increased until the desired effects are achieved or the onset of unacceptable side effects, the advantage of the application of pharmacogenetics may be less pronounced although even then a more appropriate, tailor made starting dose may be selected. Also Therapeutic Drug Monitoring could be improved by

### Table 1: Examples of therapeutic (dose) recommendations

| Drug (Enzyme) | Genotype or phenotype | Gene-drug interaction | Therapeutic (dose) recommendation | References |
|---------------|-----------------------|-----------------------|----------------------------------|------------|
| Tramadol (CYP2D6) | PM | Yes | Select alternative drug (e.g. acetaminophen, NSAID, morphine NOT oxycodone or codeine) or be alert to symptoms of insufficient pain relief | [43–48] |
| | IM | Yes | Select alternative drug (e.g. acetaminophen, NSAID, morphine NOT oxycodone or codeine) or be alert to symptoms of insufficient pain relief | [43, 44, 49] |
| | UM | Yes | Select alternative drug (e.g. acetaminophen, NSAID, morphine NOT oxycodone or codeine) or be alert to ADE (e.g. nausea, vomiting, constipation, respiratory depression, confusion, urinary retention) | [50] |
| Phenytin (CYP2C9) | *1/*2 | Yes | Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7–10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation) | [51–57] |
| | *1/*3 | Yes | Standard loading dose. Reduce maintenance dose by 25%. Evaluate response and serum concentration after 7–10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation) | [51–55, 58–65] |
| | *2/*2 | Yes | Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation) | [51–54, 56, 57] |
| | *2/*3 | Yes | Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation) | [52, 57] |
| | *3/*3 | Yes | Standard loading dose. Reduce maintenance dose by 50%. Evaluate response and serum concentration after 7–10 days. Be alert to ADE (e.g. ataxia, nystagmus, dysarthria, sedation) | [51, 54–56, 60, 66–69] |
| Citalopram/ Escitalopram (CYP2C19) | PM | Yes | No | [70–76] |
| | IM | Yes | No | [72, 73, 75–77] |
| | UM | Yes | Monitor plasma concentration and titrate dose to max. 150% in response to efficacy and ADE or select alternative drug (e.g. fluoxetine, paroxetine) | [73, 78] |

For a complete list of therapeutic (dose) recommendations see ref. [3]
including genetic information. Pharmacogenetics may increase benefit and reduce harm in people whose drug response is not ‘average’ [39]. However, clinical implementation remains limited [40]. Maybe the cause of the slow integration of pharmacogenetic testing in clinical practice to improve dosing and minimize safety risks is the urge for appropriate education of prescribing physicians, ethics committees, and investigators on the use and interpretation of the pharmacogenetic information provided in the drug label [41]. The above mentioned example of the coumarins seems to indicate that clinical evidence does not suffice to implement pharmacogenetics in daily practice, but first mega-trials have to be performed [31]. The availability of the genotype information and the connected turn around time for the lab are also often referred to, but are solvable problems. The pronounced discussion on cost-effectiveness in the field of genotyping contrasts with the implementation of specific requirements for e.g. drug dosing in children or therapeutic drug monitoring. Furthermore it is highly likely that this cost discussion will fade away in the not so distant future since the costs of genotyping are dropping every day [42]. Between 10 and 20 years from now we will probably all have our DNA sequence available in medical records. By then genotyping costs will no longer be important, however it will be even more important to have guidelines on how to clinically make use of all this information.

To support the implementation of pharmacogenetics, the Royal Dutch Association for the Advancement of Pharmacy (KNMP) installed a multidisciplinary working group with the objective to develop pharmacogenetics-based therapeutic (dose) recommendations based upon a systematic review of the literature and to assist prescribers by integrating the recommendations into computerized systems for prescribing and automated medication surveillance [3]. These data are electronically available to all pharmacists in the Netherlands. Examples of these are provided in Table 1. For each genotype/phenotype-drug combination it is clearly stated whether there is an interaction or not with the polymorphism specified and which action is required. It would contribute to medication safety if in those cases were genotyping results in adaptation of pharmacotherapy, genotyping would indeed be performed.

**Conclusion**

In conclusion, evidence based medicine still aims at an average patient from a carefully selected patient population, but does not do justice to the individual characteristics of patients. If one adds knowledge of the mechanisms of pathology, knowledge of mechanism of action of drugs, both pharmacodynamically and pharmacokinetically, as well as the knowledge of the individual patient including his pharmacogenetic characteristics if relevant for the pharmacotherapy considered, the result will be a tailor-made pharmacotherapy. This might be considered a commodity in the current era so strongly characterised by an emphasis on attention for medication safety.

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