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Review Article

Illustrative and historic cases of phenoconversion

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Abstract: Intersubject variability in drug response, whether related to efficacy or toxicity, is well recognized clinically. Over the years, drug selection from our pharmacologic armamentarium has moved from providers' preferred choices to more personalized treatments as clinicians' decisions are guided by data from clinical trials. Since the advent of more accessible and affordable pharmacogenomic (PGx) testing, the promise of precise pharmacotherapy has been made. Results have accumulated in the literature with numerous examples demonstrating the value of PGx to improve drug response or prevent drug toxicity. Unfortunately, limited availability of reimbursement policies has dampened the enthusiasm of providers and organizations. The clinical application of PGx knowledge remains difficult for most clinicians under real-world conditions in patients with numerous chronic conditions and polypharmacy. This may be due to phenoconversion, a condition where there is a discrepancy between the genotype-predicted phenotype and the observed phenotype. This condition complicates the interpretation of PGx results and may lead to inappropriate recommendations and clinical decision making. For this reason, regulatory agencies have limited the transfer of information from PGx laboratories directly to consumers, especially recommendations about the use of certain drugs. This mini-review presents cases (mexiletine, propafenone, clopidogrel, warfarin, codeine, procainamide) from historical observations where drug response was modified by phenoconversion. The cases illustrate, from decades ago, that we are still in great need of advanced clinical decision systems that cope with conditions associated with phenoconversion, especially in patients with polypharmacy.

Keywords: Phenoconversion, genotype, phenotype, pharmacogenomics

Introduction

Phenoconversion is a phenomenon by which there is a mismatch between an individual's genotype-based predicted phenotype and the observed phenotype [1]. Phenoconversion can be caused by extrinsic factors such as environment, food, drugs, or patient- or disease-related factors [1-3]. A simple example is the genotype associated with an individual predicting hair color and the actual hair color observed on that person. Like phenoconversion, this mismatch between the observed phenotype and the genotype-predicted phenotype can be due to extrinsic factors, such as the use of hair coloring agents, or due to patient-specific conditions, such as aging.

There are numerous conditions associated with phenoconversion when predicting drug response (efficacy and toxicity), especially in patients with polypharmacy. This phenomenon is not new and we purposely use older examples - several initiated from our research activities - to demonstrate how our knowledge has evolved and to show how difficult it has been to translate pharmacogenetic results into applied clinical interventions. This topic has recently gained interest with more laboratories interested in promoting pharmacogenomic (PGx) testing, as molecular biology technologies are now more readily accessible and affordable. This review presents examples of increased or decreased drug efficacy or toxicity due to phenoconversion (see **Table 1** for a summary of examples discussed).

Increased efficacy

In 1991, Duff *et al.* reviewed data supporting the use of selected drug combinations to enhance antiarrhythmic activity, specifically the mexiletine-quinidine combination [4]. They had previously found that the co-administration of

Table 1. Examples of conditions and drugs susceptible to phenoconversion

Condition	Victim drug subjected to phenoconversion	Enzyme involved	Perpetrator drug causing phenoconversion	Mechanism	Refs
Increased efficacy	Mexiletine	CYP2D6	Quinidine or other potent CYP2D6 inhibitors such as paroxetine	Quinidine is a potent CYP2D6 inhibitor leading to increased plasma concentrations of mexiletine when the two drugs are co-administered. Improved efficacy at smaller doses of mexiletine and decreased side-effects (gastric irritation).	[4-11]
Increased efficacy	Propafenone	CYP2D6	Quinidine or other potent CYP2D6 inhibitors such as paroxetine	Quinidine is a potent CYP2D6 inhibitor leading to increased plasma concentrations of propafenone but decreased concentrations of its active 5-hydroxymetabolite. Due to different electrophysiological effects, this condition improves overall propafenone efficacy for the maintenance of sinus rhythm in patients with atrial fibrillation.	[12-15]
Decreased efficacy	Codeine	CYP2D6	Quinidine or other potent CYP2D6 inhibitors such as paroxetine	Codeine is a prodrug that needs to be activated into morphine to produce analgesic effects. Inhibition of CYP2D6 decreases morphine formation and codeine analgesic effects.	[16-22]
Decreased efficacy	Clopidogrel	CYP2C19	Omeprazole	Clopidogrel is a prodrug that needs to be activated mostly by CYP2C19 to inhibit platelet aggregation. Inhibition of CYP2C19 decreases clopidogrel efficacy.	[23-31]
Increased toxicity	Warfarin	CYP2C9/CYP3As	CYP2C9 and/or CYP3A4 inhibitors such as amiodarone, macrolide antibiotics, antifungals	Decreases CYP2C9 and/or CYP3A4 activities increases plasma levels of S-warfarin and/or R-warfarin, respectively. These inhibitions lead to greater inhibition of the Vitamin K epoxide reductase complex and increased risk of bleeding.	[38-52]
Decreased toxicity	Procainamide	NAT2/CYP2D6	Quinidine	Inhibition of CYP2D6 by potent inhibitors such as quinidine prevents the formation of N-oxidized, reactive toxic metabolites of procainamide.	[53-56]

CYP2D6, cytochrome P450 2D6; CYP2C19, cytochrome P450 2C19; CYP2C9, cytochrome P450 2C9; CYP3A, cytochrome P450 3A; NAT2, polymorphic *N*-acetyltransferase 2.

these two class I antiarrhythmic agents was more effective at suppressing spontaneous ventricular tachycardia with fewer side effects than high-dose monotherapy [5]. Duff *et al.* also conducted several electrophysiologic studies suggesting the potentiation of drug effects by various parameters, such as the prolongation of the refractory periods of extra stimuli and the prolongation of conduction into the dyskinetic zone of the ventricle [6].

In the 1980s, Turgeon and collaborators conducted several studies on the metabolism, disposition, and electrophysiologic effects of mexiletine [7-10]. Later, in 1991, they reported on the involvement of debrisoquine hydroxylase (CYP2D6) on the disposition of mexiletine and demonstrated different pharmacokinetic profiles between poor metabolizers (PMs) and extensive (EMs) metabolizers [11]. They also used quinidine to inhibit CYP2D6 and convert EMs into PMs, demonstrating that inhibition of CYP2D6 could be associated with a 4-fold increase in mexiletine plasma levels under steady state conditions, as this CYP450 isoform contributes to 75% of the partial metabolic clearance of the drug. Hence, phenoconversion of EMs into PMs by the co-administration of quinidine could explain, at least in part, the potentiation of drug effects observed with the mexiletine-quinidine combination as reported by Duff *et al.* in the same year [4].

The involvement of debrisoquine 4-hydroxylase (CYP2D6) in the metabolism and disposition of propafenone was also well characterized in the 1980s [12]. Funck-Brentano *et al.* demonstrated how low-dose quinidine was able to convert CYP2D6 EMs into PMs when interacting with propafenone [13]. Propafenone is metabolized into an active 5-hydroxymetabolite; the electrophysiologic effects of propafenone include the

blocking of sodium, calcium, and potassium channels, while the 5-hydroxymetabolite mostly exhibits electrophysiological effects through potent inhibition of sodium channels [12, 14]. Taking advantage of the more comprehensive and favorable electrophysiological effects of propafenone over its 5-hydroxymetabolite, O'Hara *et al.* demonstrated the superior efficacy of propafenone when combined with quinidine in patients with atrial fibrillation (CAQ-PAF study) [15]. Recurrence of atrial fibrillation was observed in 22 patients (n=23) with low propafenone levels (<1,000 ng/mL; mostly due to extensive and unblocked CYP2D6 metabolism), while 80% of patients with propafenone levels >1,500 ng/mL (associated with a genetically-determined or quinidine-induced PM phenotype) were in sinus rhythm at one year. In fact, phenoconversion induced by quinidine persisted for the entire study period (one year).

Decreased efficacy

In 1988, Dayer *et al.* demonstrated that codeine was bioactivated into morphine by the debrisoquine 4-hydroxylase (CYP2D6) [16]. In a double-blind randomized cross-over study, Dayer *et al.* also demonstrated that virtually no morphine was observed in PMs or after administration of quinidine to EMs [17]. In EMs, codeine significantly increased subjective (VAS) and objective (R-III reflex) pain thresholds in response to selective transcutaneous nerve stimulation, whereas no significant analgesia was detected after quinidine pretreatment in PMs. The Clinical Pharmacogenetics Implementation Consortium guidelines for selected opioid therapy clearly recommend choosing alternative treatments to codeine for analgesia in patients with a CYP2D6 PM genotype or phenotype (due to phenoconversion and inhibition of CYP2D6) [18]. We have reviewed and reported clinical cases of poor response in phenotypic PMs due to phenoconversion while being treated with codeine [19-21]. Further, in a study performed with data from more than 50,000 adults, we demonstrated the economic burden associated with opioid treatment in patients with polypharmacy causing inhibition of CYP-2D6 [22].

Clopidogrel is another example of decreased efficacy due to phenoconversion. Clopidogrel is a prodrug that undergoes sequential oxidations - mediated mostly by CYP2C19 and CYP-3As - leading to the formation of 2-oxo-clopidogrel and its active metabolite (5-thiol clopidogrel) to produce antiplatelet effects [23]. In the IGNITE study, carrying a variant allele of *CYP2C19* was associated with worse clinical outcomes in patients [24]. A meta-analysis conducted by Mega *et al.* demonstrated that the concomitant administration of clopidogrel and a proton pump inhibitor - especially the CYP2C19 mechanism-based inhibitor omeprazole - was associated with poor clinical outcomes [25]. We have shown that a chronic inflammatory status associated with type 2 diabetes causes a significant (two-fold) decrease in CYP2C19 activity, triggering a phenoconversion like phenomenon [3, 26]. Decreased plasma levels of the 5-thiolactive metabolite, as well as poor clinical response to clopidogrel, has been observed in patients with type 2 diabetes. However, these patients appear to respond well to other antiplatelet agents, such as prasugrel or ticagrelor, that do not require bioactivation by CYP2C19 [27-31].

Increased toxicity

Warfarin has a narrow therapeutic index and therefore the dose required to achieve therapeutic anticoagulation is marginally different to the dose that leads to over-anticoagulation. Additionally, the maintenance dose varies between different individuals and ranges from 0.5 mg/day to more than 10 mg/day [32]. Warfarin is a racemic mixture of two enantiomers: *S*-warfarin and *R*-warfarin. Most pharmacological activity resides at the level of *S*-warfarin, which is two- to five- times more potent than the *R*-isomer [33, 34]. Under steady-state conditions, *R*-warfarin predominates in the plasma of patients at concentrations approximately double those of *S*-warfarin [34, 35]. However, the pharmacokinetics and pharmacodynamics of warfarin are modulated by numerous factors, including age, sex, genetic variants, illnesses, and drug interactions [36, 37].

CYP2C9 is principally responsible for the metabolism of *S*-warfarin, while CYP3A4/5, CYP1A2, and CYP2C19 are responsible for the metabolism of *R*-warfarin. Two of the variant alleles identified for *CYP2C9* (**3* and **6*) are associated with a loss of activity, whereas **2*, **4*, **5*, and **11* are associated with weaker

enzyme activities [38-42]. Scordo *et al.* have demonstrated that the free clearance of *S*-warfarin showed large variability in subjects with *CYP2C9*1/*1*, **1/*2* or **1/*3* genotypes, such that it becomes impossible to predict the dose requirement in these subjects [43]. Only in a fraction of their subjects (8.6%), *i.e.* those with a **2/*2*, **2/*3* or **3/*3,* could a precise warfarin dose requirement be derived.

The contribution of other genetic polymorphisms in the Vitamin K epoxide reductase complex (*VKORC1*) or in *CYP4F2* (rs2108622) involved in the metabolism of Vitamin K1 are associated with warfarin maintenance dose requirements [44, 45]. However, several extrinsic factors including food, such as green vegetables with high Vitamin K content, or concomitant administration of drugs metabolized by or inhibiting CYP2C9, have been associated with phenoconversion and modulation of warfarin dose requirements. We conducted a study to determine the value of genotype-derived (*CYP2C9*, *VKORC1*) or phenotype-derived (using losartan as a CYP2C9 probe drug) determination of warfarin dose requirement in patients with polypharmacy (receiving 11±4 drugs daily). In multivariate analyses, the dose-adjusted international normalized ratio (INR) at day four explained 31% of variability observed in warfarin doses at day 14, whereas genotypic measures (*CYP2C9-VKORC1*) contributed only 6.5%. Some, but not all, studies have shown an association between bleeding and genetic factors, such as *CYP2C9* polymorphisms. They clearly identify the role of extrinsic factors and phenoconversion on the risk of warfarin toxicity [46-52].

Decreased toxicity

Most pharmacogenomics textbooks have demonstrated the value of pharmacogenomics using a positive association with the production of antinuclear antibodies as indicators of procainamide-induced systemic lupus erythematosus. In a study conducted by Woosley *et al.*, it was demonstrated that the rate at which procainamide induces antinuclear antibodies - and therefore lupus erythematosus - was dependent on the acetylator (*NAT2*) genotype; slow acetylators required on average 12±5 months to develop lupus *vs.* 48±22 months in rapid acetylators [53]. Uetrecht *et al.* demonstrated that a rapid acetylator phenotype and extensive formation of N-acetyl-procainamide was associated with a lower incidence of procainamide-induced lupus while the N-oxidation of procainamide lead to the formation of a reactive metabolite, causing revertants in the Ames test [54]. However, the N-acetylation status was not protective of procainamide-induced toxicity, but was predictive of the exposure time associated with toxicity. Hence, the real question remains unanswered: which enzymatic system is responsible for the formation of the toxic N-oxidized reactive metabolites and can their formation be prevented?

We then undertook drug metabolism studies to characterize enzymes involved in the N-oxidation of procainamide. We demonstrated that this metabolic pathway was mediated by CYP2D6 and conducted pharmacokinetic studies in subjects receiving procainamide either alone or following the concomitant administration of quinidine [55, 56]. No N-oxidized metabolites could be measured in the urine of CYP2D6 PM subjects; however, they were present in the urine of EMs. Coadministration of quinidine with procainamide caused a phenoconversion of EMs to PMs, modulated procainamide pharmacokinetics, and prevented the formation of the N-oxidized metabolites. Therefore, we postulated that patients who did not present with lupus upon exposure to procainamide in the studies conducted by Woosley *et al.* were PMs of CYP2D6 - as those were observed in both rapid and slow acetylator groups - and that the concomitant administration of low-dose quinidine with procainamide could prevent the formation of the toxic metabolite due to the phenoconversion of patients into a PM phenotype.

Conclusion

Pharmacogenomic testing has evolved significantly in the last 20 years, with most laboratories using next-generation sequencing techniques. Pharmacogenomic results are now highly reliable and deemed appropriate to predict an expected phenotype. Additionally, testing costs have been reduced significantly, making pharmacogenomics more affordable and attractive for precise pharmacotherapy. In the past decade, polypharmacy has reached epidemic proportions with >40% of older adults taking

five or more prescription drugs a day and nearly 20% take more than 10 drugs a day [57]. Under these conditions, clinicians must have access to advanced clinical decision support systems that allow consideration of phenoconversion to make appropriate medication choices within a drug regimen. Recent studies have demonstrated the value of endogenous markers, such as 4β-hydroxycholesterol (CYP3As) or metabolomic products (CYP2D6), to determine a patient's actual phenotype [58, 59]. This strategy may represent a way forward to clinically understand patients overall drug metabolism capacities, response, and phenoconversion.

Disclosure of conflict of interest

None.

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