Published in final edited form as:

J Clin Gastroenterol. 2012 July ; 46(6): 437–439. doi:10.1097/MCG.0b013e3182549528.

Lessons from Pharmacogenetics and Metoclopramide: Towards the Right Dose of the Right Drug for the Right Patient

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In this issue of the journal, Parkman et al. reviewed the efficacy and adverse effects in a cohort of 100 patients with gastroparesis (32% with normal gastric emptying) treated with metoclopramide.(1)

The prokinetic effect of metoclopramide is mediated through the blockade of enteric (neuronal and muscular) inhibitory dopamine D₂ receptors, and metoclopramide has the ability to stimulate 5-HT₃ and 5-HT₄ receptors (2). Metoclopramide also exerts inhibitory effects on D₂ receptors centrally (located outside the blood-brain barrier), and these contribute to its antiemetic effect. Metoclopramide binds to α₁D adrenergic receptors, and there is a functional interaction between dopamine and adrenergic receptors; however, the precise mechanism resulting in prokinetic action is unclear.

A novel aspect of the study is the investigation of the association of variation in candidate genes on efficacy and adverse effects. Overall effects of medications result from metabolism, disposition, and effects of the agent. The enzymatic metabolism of drugs involves modifications of functional groups (phase I reactions such as oxidation, dehydrogenation, esterification) or conjugation with endogenous substituents [phase II reactions (3)]. A third class of pharmacological variation may result from genetically induced differences in the target (e.g. receptors) of the medication.

The study by Parkman et al. included 20 single nucleotide polymorphisms (SNPs) that were genotyped in 8 candidate genes (*ABCB1*, *ADRA1D*, *CYP1A2*, *CYP2D6*, *DRD2*, *DRD3*, *HTR4*, *KCNH2*), and the study appraised the functions of transport across cell membranes through P glycoprotein (*ABCB1*), phase I metabolism through cytochrome P450 enzymes, and modified targets: dopaminergic, adrenergic and serotonergic receptors, and voltage-gated inwardly rectifying potassium channel, commonly known as HERG.

The definition of efficacy was based on a 7-point, symmetrical, adjectival scale of overall assessment; however, this does not provide sufficient information about individual symptoms or groups of symptoms that cluster together on factor analysis, such as nausea, fullness and early satiety. The authors summarized the adverse neurological, cardiovascular, musculoskeletal and endocrine effects by simply summation, without specifying information about side effects of significant interest such as cardiac arrhythmia or tardive dyskinesia.

In summary, Parkman et al. report efficacy was associated with polymorphisms in *KCNH2* (rs1805123, p=0.020) and *ADRA1D* (rs2236554, p=0.035) genes, and side effects, which occurred in 64 patients, were associated with polymorphisms in *CYP2D6* (rs1080985,

p=0.045; rs16947, p=0.008; rs3892097, p=0.049), *KCNH2* (rs3815459, p=0.015), and serotonin (5- hydroxytryptamine) 5-HT₄ receptor *HTR4* gene (rs9325104, p=0.026).

The authors are careful to characterize their findings as hypothesis-generating. They studied 100 patients, evaluated 8 genes and 20 genotypes, had no control treatment groups, and assessed efficacy and safety as single factors using univariate associations. Given that the FDA's black box warning regarding the prescription of metoclopramide pertains to the risk of tardive dyskinesia, the study did not specifically address this risk and was underpowered to appraise the potential of genotyping to identify patients at risk. This is, at least in part, because the incidence of tardive dyskinesia is probably much lower than 1% (reviewed in ref. 4), and is certainly lower than the almost 15% proposed in society guidelines (5,6).

The associations reported are all based on univariate analysis. The customary caution is necessary: associations need to be replicated, larger sample sizes are required, and corrections need to be made for false detection rates. In addition, the study does not allow matching of any genetic associations with specific adverse effects. These are significant pitfalls in interpretation of this study.

Nevertheless, there are several interesting observations that illustrate the importance of pharmacogenetics in determining the efficacy and adverse effects to medications.

First, efficacy of metoclopramide was decreased (odds ratio 0.383, lower confidence level [CL] 0.171, upper CL 0.859) by variation (rs 1805123 SNP) in the gene *KCNH2* for the delayed rectifier potassium channel, HERG. This might be expected, since HERG potassium channels are also present in esophageal and gastrointestinal smooth muscle cells and are hypothesized to play a role in the contractile control of GI smooth muscle (7,8). However, it was the rs3815459 SNP in *KCNH2* that was reported to be associated with efficacy in gastroparesis patients treated with domperidone (9). The association of the rs2236554 SNP in *ADRA1D* with reduced efficacy (odds ratio 0.542, lower CL 0.307, upper CL 0.958) in the treatment of gastroparesis in response to metoclopramide is not easily explained other than through a possible alteration of the function of $\alpha 1$ adrenergic receptors hypothetically interacting with dopamine or serotonin receptors.

Second, three SNPs in the *CYP2D6* gene are associated with adverse effects. This is possibly the easiest association to understand; *CYP2D6* participates in the hepatic metabolism and elimination of over 100 drugs (10). *CYP2D6* metabolism can be classified as ultra-rapid, extensive, intermediate or poor, according to the number of functional alleles (>3–0). Among Asian groups, poor metabolizers constitute ~1%, and among white populations, 5–10% are poor metabolizers (11,12). The most common nonfunctional alleles (associated with poor metabolizer status) are *CYP2D6**3, *CYP2D6**4, *CYP2D6**5, and *CYP2D6**6. Metoclopramide is metabolized predominantly by *CYP2D6* (and to a lesser extent by *CYP1A2*); poor metabolizers may therefore have high circulating and tissue concentrations of drug that may result in adverse effects. For example, two patients who developed acute dystonia on metoclopramide treatment were homozygous for inactive *CYP2D6* alleles [*CYP2D6**4/*4 and *CYP2D6**4/*5 (13)].

In this study, the rs1080985 SNP (located in an intron) in the *CYP2D6* gene is associated with protection against adverse effects of metoclopramide [odds ratio 0.508 (confidence interval lower limit 0.261, upper limit 0.985), p=0.045]; this is biologically plausible since the SNP results in ultra-rapid metabolizer status which would result in lower tissue levels of the drug (14).

The SNP, rs16947 (Cys245Arg) in *CYP2D6* gene is associated with protection against adverse events on treatment with metoclopramide (odds ratio 0.467, CI lower limit 0.267,

upper limit 0.817; $p=0.0076$). One report suggests the SNP is associated with poor CYP2D6 metabolism of ophthalmic timolol, resulting in bradycardia (15). Poor metabolism of metoclopramide would be expected to induce more adverse effects, not to reduce the odds for developing adverse effects.

Conversely, rs3892097 SNP (located in an intron) in *CYP2D6* is associated with greater propensity for adverse effects of metoclopramide (odds ratio 2.134, CI lower limit 1.001, upper limit 4.55; $p=0.0497$). This SNP, designated *CYP2D6*4*, is associated with reduced function and, therefore, the observed increase in adverse effects is attributable to this genetic variation.

One dimension of CYP2D6 function that is not addressed is the potential for drug interactions as a result of (typically) drug-induced inhibition of CYP2D6. Commonly used drug inhibitors of CYP2D6 are antidepressants and antiemetics (e.g., bupropion, duloxetine, fluoxetine, paroxetine, perphenazine, diphenhydramine) that are often co-administered in patients with gastroparesis. Other drug classes affected by CYP2D6 metabolism include antipsychotics, opioids, antiarrhythmics, and beta-adrenoceptor antagonists (16,17). Indeed, metoclopramide itself is a CYP2D6 inhibitor!

Third, an association was found between the genetic variant rs3815459 in *KCNH2* and adverse effects with metoclopramide. This same SNP was previously reported to be associated with efficacy in response to the dopaminergic agent, domperidone (9). It is somewhat surprising that the same SNP would be associated with efficacy of one dopamine antagonist (domperidone) and with reduced side effects of a second dopamine antagonist (metoclopramide). These potassium channels also might predispose individuals to cardiac arrhythmias. It is unclear whether the patients treated with metoclopramide in this study had cardiac arrhythmias, since that level of detail is not available in the paper and the sample size is too small to identify a statistically significant association, specifically with cardiac arrhythmia. Associations of metoclopramide and cardiac arrhythmias and propensity to prolong QTc interval are well documented in the literature (18,19).

Fourth, variation in *HTR4* gene (rs9325104) protected against adverse effects of metoclopramide in patients with gastroparesis (odds ratio 0.399, lower CL 0.191, upper CL 0.835; $p=0.026$). One report suggests non-significant association with schizophrenia, but the effects of the SNP on the function of the receptor were unclear (20), and the biological basis for the reduced adverse effects with metoclopramide treatment is unclear. The 5-HT₄ receptors are involved in stimulation of gastrointestinal muscle, brain neurons, cardiac muscle and aldosterone-secreting cells in the adrenal gland. In fact, the same SNP in the *HTR4* gene may have been associated with efficacy in response to metoclopramide [estimate 0.524 ± 0.296 (SEM), $p=0.0769$], suggesting that the variant is associated with a gain of function that enhances efficacy of metoclopramide by stimulating gastrointestinal 5-HT₄ receptors.

Genetic variation in the function of the D₃ receptors may predispose individuals to develop tardive dyskinesia when receiving neuroleptic drugs. Accili et al. (21) found that dopamine D₃ receptor (*DRD3*) knockout mice exhibited increased locomotor behavior during a test of exploration. The *DRD3* Ser9Gly gene polymorphism (rs6280) results in higher dopamine binding affinity to D₃ receptors (22). This appears to have a strong correlation with development and intensity of tardive dyskinesia symptoms (23). A meta-analysis has demonstrated that antipsychotic medication-associated tardive dyskinesia is more likely to occur in patients with the *DRD3* Ser9Gly gene polymorphism [odds ratio 1.39, 95% CI, 1.07–1.81 (24)]. In the Parkman et al. study, variation in the *DRD3* rs7625282 (which results in an intronic A/G variation in the *DRD3* gene on human chromosome 3) was not

associated with efficacy or adverse effects; the association with this SNP in *DRD3* would really need to be studied in patients with tardive dyskinesia on metoclopramide to appraise the potential role of the SNP.

In summary, the authors are to be congratulated for conducting this study and for acknowledging its limitations. The study poses several hypotheses or questions that may be the subject of future research as new formulations of metoclopramide are being developed. However, there are general principles that deserve consideration. First, all prescribers, including gastroenterologists, need to become more cognizant of the potential of pharmacogenetics to alter efficacy and to influence the occurrence of side effects. In an era when patients will have access and control of their electronic medical record, a one-time genotyping of CYP2D6, 3A4 and 2C19 appears to be advisable so that an electronic “prompt” of potential drug interaction with other medications, or potential for lack of efficacy, or induction of adverse effects would be provided to the prescriber. The dictum should be, “the right drug at the right dose for the right patient”. Second, regulatory agencies and clinical trialists need to include CYP pharmacogenetics in clinical trials in order to more critically and intelligently appraise adverse effects of medications on the basis of biological, interindividual variation in absorption, membrane transfer, metabolism or drug targets such as receptors. This “renaissance” is essential if our patients are going to benefit from novel medications before drugs such as cisapride, alosetron and tegaserod are prematurely withdrawn. Similarly, it is hoped that black box warnings from regulatory agencies will benefit from information based on pharmacogenetics, so that the right medication can be chosen for the right patient at the right dose instead of general prohibition or recommendations that are not based on consideration of genetic variation and its impact on efficacy and safety.

Acknowledgments

Funding: Supported in part by research grant DK-RO1-067071 to Dr. Camilleri from National Institutes of Health.

Abbreviations

5-HT 5-hydroxytryptamine or serotonin

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