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Fixed-dose combination products and unintended drug interactions: urgent need for pharmacogenetic evaluation

“We recommend that sponsors conduct clinical pharmacogenetic studies during the initial development phase of fixed-dose combinations and voluntarily submit findings to the regulatory agency in order to validate scientific arguments in favor of safety and effectiveness.”

Keywords: adverse events • drug interactions • fixed-dose combinations • pharmacogenetics • regulatory policy

Over the past 10+ years, we have been witness of a rapid progression in our understanding of the role of inheritance on the observed individual variance in drug responses and metabolism [1,2]. A relatively higher abundance of genetic polymorphisms of clinical interest are described at the level of drug metabolisms where up to 40% of phase I biotransformation of medically used drugs, including both drug elimination and activation of prodrugs, is mediated by enzymes with polymorphisms known to have a significant impact on their activity *in vivo*.

Well-known variable isoenzymes are the cytochrome-P450 enzymes CYP2D6, CYP2C9 and CYP2C19, which all constitute valid biomarkers for predicting clinical outcomes in humans [3–9]. Among the drugs with current pharmacogenetic-driven relabeling, the metabolizing enzymes are in a majority accounting for 80% of such revised labels by the US FDA (e.g., Warfarin and Irinotecan, among others). New genomic technologies are incorporated into the clinical development programs sponsored by big pharmaceutical companies. Guidance for industry was first issued in 2006 (reissued in 2007) encouraging sponsors to submit pharmacogenomic data in support of an application approval by the FDA [10]. In addition, a guideline on the use of pharmacogenetics in the evaluation of medicinal products (EMA/CHMP/37646/2009) was published

in December 2011 by the Committee for Medicinal Products for Human Use of the EMA [11].

Statement of the problem

These advances have not been applied to fixed-dose combinations (FDCs) or co-packaged versions of previously approved drug products [12–14]. The number of FDCs currently developed by pharmaceutical companies is considerable, and their future is looming large, as convenience and savings drive the bundling of different product classes into combination pills. Although some reports in the scientific literature suggest a better compliance as well as greater benefits with FDCs [15–19], it might also be a direct consequence of patent expirations for the individual components in the market. Since FDCs can indeed be patented as a novel chemical entity, they are developed as a way to extend proprietary rights and marketability of their own drug products, even after individual active ingredients and some medical uses thereof are off-patent.

For the purpose of this commentary, the term FDC drug product is defined as: “a drug product that according to its proposed labeling is for use only with another specified drug product where both are required to achieve the intended use, indication, or effect at a fixed ratio of doses. Usually, they are administered as a finished pharmaceutical product that contains two or more therapeutically

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active entities. This term does not include co-packaged versions of previously approved drug products.” Although FDCs were initially developed to target a single illness (i.e., antiretroviral combinations to fight AIDS), today they can also be used against multiple diseases or medical conditions [20–23]. For example, Caduet® (amlodipine besylate 2.5 mg/atorvastatin calcium 10 mg) is prescribed to treat hypercholesterolemia and high blood pressure and thus lower the risk of heart attacks and other deleterious cardiovascular events. Because FDCs would involve active ingredients that were regulated under different regulatory policies, they raise some challenging regulatory concerns. Differences in regulatory pathways can influence the regulatory processes for all aspects of product development, including clinical investigation.

“At present, an increasing proportion of drugs selected for development as fixed-dose combinations are metabolized (or requires activation) by polymorphic enzymes in the body.”

Safety of FDCs & role of pharmacogenetics

One misconception in the development of FDCs is the erroneous perception that their active ingredients are not likely to give rise to any significant ‘undue’ side event (including therapeutic failures, adverse effects or drug interactions with each other). It is because their applications are fully revised by the regulatory bodies and are usually formulated in combination products at doses of the active ingredients that are less than if they were prescribed separately. Lack of enough supportive data from proper pharmacogenetic studies of FDCs and their separate ingredients could nullify such an expectation.

At present, an increasing proportion of drugs selected for development as FDCs are metabolized (or requires activation) by polymorphic enzymes in the body. However, there is very little or no knowledge on any clinically relevant impact of their pharmacogenetics once the product is administered to the patient as the combination of two or more active ingredients and the potential for genotype-dependent drug interactions (Supplementary Table 1). This is particularly important for products under development when the altered enzyme(s) is (are) either an essential part of the primary pathway for eliminating both drugs from the body or a critical step in the onset of their drug actions. Either way, the expected therapeutic outcomes will be compromised due to an increased risk for drugs accumulation and toxicity or for subtherapeutic levels and inactivity, respectively. Not to mention when both drugs compete for the same metabolic pathway. Another aspect of this potential interaction could be revealed if the exposure to one of the drugs in the combination gives rise to either

an induction or an inhibition effect on the polymorphic enzyme. In this context, an intermediate metabolizer could turn out to be a poor metabolizer instead (phenocopy). Accordingly, pharmacogenetic-driven drug interactions at this pharmacokinetic level (metabolism) need further attention given their potential clinical consequences. That is, it is necessary to assess the effect of the different allelic variants on prodrug activations or drug clearance through the specific metabolic pathway related to the polymorphic gene(s).

FDC that does not meet a patient’s dose requirement (e.g., a poor metabolizer), with the patient receiving too much (or too little) of one of the active ingredients in the combination, will further limit the clinician’s ability to individualize the patient’s dosing regimen.

Nuedexta®: a case for deliberate drug interactions?

Approved by the US FDA in 2010, Nuedexta® (Avanir Pharmaceuticals, CA, USA) is used to treat pseudo-bulbar affect (PBA), involuntary outbursts of crying or laughing in patients with certain neurological disorders, including multiple sclerosis and amyotrophic lateral sclerosis (ALS, or Lou Gehrig’s disease). Nuedexta may also be used for off-label purposes in psychiatry. Developed by Avanir Pharmaceuticals, Nuedexta is a combination product containing 20 mg dextromethorphan hydrobromide (an uncompetitive NMDA receptor antagonist and sigma-1 agonist) and 10 mg quinidine sulfate (a CYP450 2D6 inhibitor) per capsule. Dextromethorphan affects the signals in the brain that trigger cough reflex and is generally used as an antitussive. Pharmacokinetically, dextromethorphan is a classic, major CYP2D6 substrate. Quinidine affects the electrical conduction in the heart and is generally used to treat cardiac arrhythmias. Interestingly, while the components of Nuedexta are classical drugs known for decades, their combination and its therapeutic indication are novel.

The quinidine in Nuedexta inhibits CYP2D6 in patients in whom CYP2D6 is not otherwise genetically absent or its activity otherwise pharmacologically inhibited. Because of this effect on CYP2D6, accumulation of parent drug and/or failure of active metabolite formation may increase the risk of side effects and/or reduce the efficacy of drugs used concomitantly with Nuedexta that are metabolized by CYP2D6. The quinidine component of Nuedexta is deliberately intended to inhibit CYP2D6, so that higher exposure to dextromethorphan can be achieved compared with when dextromethorphan is given alone. In fact, the quinidine component of Nuedexta is not therapeutic at all, but expected to contribute to the effectiveness of Nuedexta.

The drug label contains an explicit pharmacogenomics section stating: “The quinidine component of

Nuedexta is intended to inhibit CYP2D6 so that higher exposure to dextromethorphan can be achieved compared with when dextromethorphan is given alone. In those patients who may be at risk of significant toxicity due to quinidine, genotyping to determine if they are PMs should be considered prior to making the decision to treat with Nuedexta.” [24].

This guidance for pharmacogenetic testing in the drug label is noteworthy as a safeguard on the broad use of the drug for all patients. In CYP2D6 null or poor metabolizers, quinidine will have little if any CYP2D6 enzyme to inhibit, which would result in liberation of this agent in the circulation, to induce its pharmacological effect as arrhythmic agent, potentially dangerous. The same problem is likely in patients taking other psychiatric drugs that are dual substrates and inhibitors of CYP2D6, such as amitriptyline, fluoxetine and paroxetine. When Nuedexta is prescribed with drugs that inhibit or are extensively metabolized by CYP2D6, consideration should be given to initiating treatment with a lower dose. In ultrarapid metabolizers, quinidine is likely to have little effect at the dosage included in Nuedexta, thus disrupting the pharmacokinetic rationale for the drug combination in the first place.

For Nuedexta, both null/poor and ultrarapid metabolizers, patients at either extreme of the CYP2D6 functional spectrum, are being deliberately exposed to a dangerous drug combination and interaction. It would appear that pharmacogenetic testing should be a requirement for prescribing this drug, not merely a suggestion. The deliberate drug interaction pursued for Nuedexta works only for patients with normal (average) CYP2D6 functional status.

Conclusion

The present work discusses the urgent need for pharmacogenetic (PGt) evaluations of FDCs or co-pack-

aged versions of previously approved drug products, as their growing appeal will raise some challenging regulatory concerns. An example of the clinical consequences of inappropriate evaluations of these PGt risks is discussed. We concluded that the lack of enough supportive data from proper PGt studies of FDCs could nullify any expectation of developing safe products. We recommend that sponsors conduct clinical PGt studies during the initial development phase of FDCs and voluntarily submit findings to the regulatory agency in order to validate scientific arguments in favor of safety and effectiveness.

Future perspective

A rational approach is to be adopted by key players (i.e., industry, regulatory agency and researchers) through a thorough evaluation of the clinical relevance of any PGt effect on drug exposure as well as the benefits of applying individual genotyping in future clinical use of FDC products. This information is also expected to be used for decision-making on projected dosing schemes as well as to be reflected in drug labeling.

Supplementary data

To view the supplementary data that accompany this paper, please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/PGS.15.123

Financial & competing interests disclosure

This article was funded in part by the grant #SC1 HL123911 from the National Heart, Lung and Blood Institute (NHLBI, NIH). G Ruaño is founder and President of Genomas Inc. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Executive summary

- Currently, there is a lack of enough supportive data from proper pharmacogenetic (PGt) studies of fixed-dose combinations (FDCs) or co-packaged versions of previously approved drug products.
- Clinical PGt studies of FDCs should be conducted by sponsors during their initial development phases.
- Voluntary submission of collected PGt data to the regulatory agency should be encouraged in order to support scientific arguments in favor of safety and effectiveness of FDCs.
- The Nuedexta® example, portrayed as a case for deliberate PGt-driven drug interactions, makes a strong case for incorporating PGt evaluations in future regulatory policies.

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