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Drug interactions in times of Covid-19, a not-so-imaginary case

Danny Ziv, Pharm.D

The impact of drug-gene interactions and drug-drug-gene interactions on patients' wellbeing

Drug–drug interactions (DDIs) are a well-known cause of drug-related problems (DRPs), but two other relatively newly described types of interactions are also involved in causing DRPs: Drug–gene interactions and drug–drug–gene interactions. Both are considered to have a significant impact on patients' wellbeing and treatment outcome.

- A drug–gene interaction - describes an instance where a patient's genetic CYP450 type affects the patient's ability to metabolize a certain drug (e.g., CYP2D6 poor metabolizer)
- A drug–drug–gene interaction - occurs when the patient's CYP450 type and a different drug in the patient's regimen (e.g., a CYP2D6 inhibitor) both affect the patient's ability to metabolize a certain drug.

The actual extent of these types of interactions has not yet been widely described in the medical literature. As a result, very few databases can provide healthcare providers with relevant information on such cases, resulting in possible new DRPs, thereby affecting patients' health and outcomes.

For example, hydroxychloroquine, one of the most used experimental drugs for treating hospitalized patients with Covid-19 (Survey: Hydroxychloroquine use fairly common in COVID-19) inhibits cytochrome P450 enzyme 2D6 (CYP2D6), most likely by competitive inhibition.

As the result of genetic polymorphism, the expression of CYP2D6 varies among individuals. Up to 13.5% of Americans present an increased functionality of CYP2D6 ("ultra-rapid" metabolizer phenotype) which may lead to decreased drug efficacy. A similar percentage have gene mutations causing loss of functionality, which may lead to an increased risk of drug toxicity ("poor" metabolizer phenotype).

Case essentials:

Age: 70
Gender: Female
Medical conditions: Mild hyperlipidemia, hypertension, migraine, osteoporosis, Covid-19
Patient-specific factors: CYP2D6 ultra-rapid metabolizer

Drug-drug-gene interaction can result in serious outcome

A 70-year-old patient diagnosed with mild hyperlipidemia, hypertension and migraine was prescribed a relatively high dose of 200 mg of metoprolol (one of the 10 most prescribed drugs in the US), to be consumed twice daily, on a regular basis. Additionally, the patient has been taking 10 mg of atorvastatin daily to control her lipid levels. She is clinically stable. Migraine attacks occur approximately once per month, blood pressure and heart rate are 117/83 mmHg, with 57 beats per minute (BPM) respectively. Her LDL levels are constantly below 100 mg/dl. She is a known CYP2D6 ultra-rapid metabolizer, as confirmed in a recent genetic test that she had performed on her own initiative when considering antidepressant treatment.

This patient had also tested positive for Covid-19. As she presented moderate symptoms, she was hospitalized in an isolated department, special for Covid-19 patients. Since she presented typical respiratory symptoms (without needing ventilation) and according to common practice these days, her doctors decided to begin a course of hydroxychloroquine. Before prescribing the hydroxychloroquine, the cautious physician double-checked for possible drug interactions, using one of the most widely spread legacy drug interaction systems. The review did not result in any alerts regarding any issues or risks with this patient's drug combination.

Over the next few days, the patient noticed a decrease in her blood pressure results, although the medical team was not concerned. A few days into her hospital stay, while going to the bathroom, she fell. The fall fractured her hip due to an underlying undiagnosed osteoporosis. While measuring her vital signs afterwards, the medical team found that she suffered from severe hypotension (83/56 mmHg) and bradycardia (43 BPM). Trying to figure out what has led to the fall, the team first suspected that her symptoms and dizziness were caused by the known, common side effects of hydroxychloroquine therapy. However, after consulting with colleagues and investing in some more extensive background reading, the physicians realized that there was an interaction between hydroxychloroquine and metoprolol, affected by both the patient's genetic profile and the fact that hydroxychloroquine is a CYP2D6 inhibitor.

How using Seegnal could have influenced the chosen medication therapy

If the physicians would have used Seegnal, a smart patient-specific, off-the-shelf software, to assess this patient's treatment, Seegnal would have immediately alerted the physicians regarding the important issues arising from this patient's specific combination of genetic profile and the suggested drug therapy. The dangerous drug-related problems resulting from treatment could thus have been easily avoided.

How?

Seegnal's evidence-based data clearly shows that hydroxychloroquine increases systemic exposure to orally administered metoprolol [e.g., Br J Clin Pharmacol. 2000 Jun;49(6):549-54]. Additionally, it is common practice to use CYP2D6 inhibitors as an effective tool in normalizing the metabolic status of CYP2D6 ultra-rapid metabolizers. Thus, it is very likely that once this patient's CYP2D6 activity was inhibited by hydroxychloroquine, the relatively high dose of metoprolol would become excessive and could lead to the observed side effects and outcome. Seegnal's smart, patented algorithms gauge all available patient-specific parameters and, in this case, would have alerted the physician to consider a different drug combination, modify the metoprolol dose, or at least instruct the patient to monitor heart rate and blood pressure.

The physicians decided to change the patient's medication regimen by removing hydroxychloroquine and switching to a different treatment for Covid-19. Within a few days, all related adverse effects were completely cleared. The patient's blood pressure and heart rate values returned to normal, although the consequences of the hip fracture will remain for a long time.

Drug-drug-gene interactions play a key role in everyday patient care

The above is an example of the involvement of drug-drug-gene interactions in everyday patient care. There is significant potential for hydroxychloroquine to affect and interact with other CYP2D6 substrates, such as opioids, carvedilol and others, which may result in serious clinical consequences for patients who are taking these drugs regularly.

Another insight is that hydroxychloroquine and other off-label experimental drugs currently used for Covid-19-positive patients should only be administered in an appropriate setting, such as clinical trials, and are generally not recommended for use outside a hospital setting. Recently, the World Health Organization (WHO) announced that due to safety concerns, it is temporarily halting a clinical trial of hydroxychloroquine for treatment of Covid-19 patients.

This case study also serves as an example of the importance of patients' knowledge of their genetic profile and informing their healthcare providers about it.

ABOUT SEEGNAL

Seegnal eHealth Ltd. was established with the goal of globally disrupting the clinician-medication-patient value chain by introducing revolutionary concepts, new knowledge, and advanced technologies, generating both value and safety.

Seegnal is a smart and intuitive clinical decision support platform that empowers clinicians to quickly vand effectively manage and resolve patient-specific Drug-Related Problems (DRPs - the 4th leading cause of death in the US alone).

Seegnal interfaces with the EMR at the point of care and harnesses the widest scope of DRP-related information, generating an additional 50% of unique data (which legacy systems either don't recognize or address), while delivering groundbreaking accuracy (sensitivity and specificity) of about 95%. The platform diminishes alert fatigue (~ 6% alert load vs. legacy systems) and is intuitive and easy to use, requiring only 5-10 seconds for DRP detection, prioritization, and resolution.

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