A review of potential cardiac drug-drug interactions amongst patients presenting with cystic fibrosis exacerbation

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January 18, 2023

Abstract

Drug-drug interactions inducing adverse drug reactions remain a significant, avoidable health risk to cystic fibrosis (CF) patients. With increasingly complex CF exacerbation treatment regimens being used, the risk of clinically important drug-drug interactions has in turn increased. Cardiovascular medications have reportedly been commonly implicated in severe CF exacerbation drug-drug related reactions. Therefore, knowledge of these potential drug-drug interactions is essential for improvement of medication safety and preventing patient harm. Drug-drug interactions can be classified into either pharmacokinetic or pharmacodynamic. This article, using the British National Formulary, details the drug-drug interactions between commonly prescribed CF exacerbation medications and cardiac medications. For each respective drug-drug interaction, the potential consequence, management strategy and interaction severity have been described.

Introduction

When a patient with cystic fibrosis (CF) is diagnosed with an exacerbation, the next step may involve inpatient hospital admission with a complex treatment regimen. Commonly more than four medications are prescribed, which can facilitate an increased number of drug-drug interactions.[1]

Drug-drug interactions occur when the effect of one drug is impacted by the concurrent administration of another.[2] This causes either a favourable or unfavourable response. The favourable response increases the drug effectiveness; however, the potential unfavourable response is the toxic effects in the body.[3] The mechanisms of drug-drug interactions are split into either pharmacokinetic or pharmacodynamic interactions.

In pharmacokinetic drug-drug interactions, the plasma concentration of the interacting drugs may be increased or decreased. For pharmacodynamic drug-drug interactions, the interacting drugs may produce synergistic or antagonistic effects.[2,3] These respective drug-drug interactions can cause adverse drug effects.[4]

It has been well documented that drug-drug related interactions can cause severe adverse reactions resulting in serious harm to patients.[4] Studies have shown adverse drug reactions increase mortality, morbidity and are responsible for longer in-patient hospital stays.[5] The percentage of in-patient adverse drug reactions as a direct result from drug-drug interactions range from 3-5%.[5] Factors increasing the risk of drug-drug interactions include: age, polypharmacy and co-morbidities – in particular cardiovascular disease.[6,7]

With the average age of survival for cystic fibrosis increasing, the risk of cardiovascular disease in turn has increased.[8,9] It has been reported cardiovascular medications are commonly implicated in severe drug-drug related reactions.[6,10] Therefore, knowledge of these potential drug-drug interactions is essential for improvement of medication safety, as this is an example of avoidable patient harm. However, drug-drug interactions between CF exacerbation medications and cardiovascular medications are not well reported.

This article was written to highlight the potential drug-drug interactions and adverse effects between commonly prescribed medications used for a cystic fibrosis exacerbation and cardiovascular medications.

Tools Used

The British National Formulary (BNF) was used to research all potential drug-drug interactions.[11] The BNF is a pharmaceutical national formulary reference book used by medical professionals in the UK for prescribing advice and medication information.[11]

Potential drug-drug interactions

The recommended inpatient management of a CF exacerbation is well reported.[1] Patients are usually given antibiotics, steroids, bronchodilators, inhaled enzyme, continuation of CF transmembrane conductance regulator (CFTR) modulator therapy and physiotherapy.[1]

The most commonly prescribed medications used to treat a CF exacerbation and potential cardiac drug-drug interactions are enlisted in Table.1.[11]

A total of 54 potential drug-drug interactions were identified. For each drug-drug interaction, the respective potential consequence of the drug pairing is given, as well as the management strategy and severity of interaction.

Cystic Fibrosis Medication	**Cardiac medication interactions**	**Potential consequence**	**Management strategy**	**Severity**
Antibiotics	**Antibiotics**	**Antibiotics**	**Antibiotics**	**Antibiotics**
Meropenem with varborbactam	**Metoprolol**	Increases the concentration	Monitor for toxicity	U
Ceftazidime with avibactam	No interaction listed	No interaction listed	No interaction listed	No interaction listed
Cefoxitin	No interaction listed	No interaction listed	No interaction listed	No interaction listed
Tobramycin	**Digoxin**	Increases the concentration	Regular monitoring and dose adjustment recommended	+
	Furosemide & Torasemide	increases the risk of nephrotoxicity and ototoxicity	Advised to avoid	++
Colistimethate Sodium (Colomycin)	No interaction listed	No interaction listed	No interaction listed	No interaction listed
Piperacillin with tazobactam (Tazocin)	**Warfarin**	Alters the anti-coagulant effect of warfarin	Regular INR monitoring & dose adjustment advised	+++
Azithromycin	**Apixaban, Dabigatran & Edoxaban**	Predicted to increase the exposure	No recommendation given	++
	Digoxin	Increases concentration	Advised to monitor digoxin levels	+++
	Nadolol	Predicted to increase exposure	No recommendation given	++
	Ticagrelor	Increases the exposure	Advised to use with caution or avoid	+++

Cystic Fibrosis Medication	**Cardiac medication interactions**	**Potential consequence**	**Management strategy**	**Severity**
Minocycline	**Pravastatin, Rosuvastatin & Simvastatin**	Increased risk of hepatotoxicity	Advised to use with caution	U
	Warfarin	Increases the anti-coagulant effect of Warfarin	Advised to monitor INR	+++
Aztreonam	No interaction listed	No interaction listed	No interaction listed	No interaction listed
Bronchodilators	**Bronchodilators**	**Bronchodilators**	**Bronchodilators**	**Bronchodilators**
Salbutamol	**Bendroflumethiazide, Bumetanide, Chlortalidone, Furosemide, Indapamide, Metolazone, Torasemide**	Increases the risk of hypokalaemia	No recommendation given	U
	Digoxin	Increases the risk of digoxin toxicity	Advised to use with caution	+++
	Dronedarone, Flecainide, Quinine, Ranolazine, Sotalol	Predicted to cause hypokalaemia (potentially increasing the risk of torsade de pointes)	No recommendation given	+++
CFTR Modulators	**CFTR Modulators**	**CFTR Modulators**	**CFTR Modulators**	**CFTR Modulators**
Ivacaftor	**Dabigatran, Edoxaban & Rivaroxaban**	Predicated to increase the exposure	Advised to use with caution	++
	Digoxin	Slightly increases the exposure	Advised to use with caution	++
	Dronedarone	Increases exposure of Ivacaftor	Advised to use with caution	++
	Verapamil	Increases the exposure of Ivacaftor	Dose adjustment recommended	++
	Warfarin	Increases exposure	Advised to monitor INR	++
Ivacaftor with tezacaftor and Elexacaftor (Kaftrio)	**All interactions included above for Ivacaftor**	**All interactions included above for Ivacaftor**	**All interactions included above for Ivacaftor**	**All interactions included above for Ivacaftor**
	Atorvastatin, Pravastatin, Rosuvastatin & Simvastatin	Increases exposure	Advised to use with caution	++
	Diltiazem	Increases exposure	Advised to use with caution	+++
Enzymes	**Enzymes**	**Enzymes**	**Enzymes**	**Enzymes**

Cystic Fibrosis Medication	**Cardiac medication interactions**	**Potential consequence**	**Management strategy**	**Severity**
Dornase Alfa	No interaction listed	No interaction listed	No interaction listed	No interaction listed
Steroids	**Steroids**	**Steroids**	**Steroids**	**Steroids**
Prednisolone	**Amiodarone & Dronedarone**	Predicted to cause hypokalaemia & increases the risk of torsade de pointes.	No recommendation given	+++
	Aspirin	Increases concentration & risk of gastrointestinal bleeding	No recommendation given	++
	Bumetanide, Chlorothiazide, Chlortalidone, Furosemide, Indapamide, Metolazone & Torasemide	Increases the risk of hypokalaemia	Advised to use with caution	U
	Digoxin	Increases the risk of digoxin toxicity	Advised to use with caution	+++
	Nicorandil	Increases the risk of gastrointestinal perforation	Advised to use with caution	+++
	Ranolazine	Predicted to cause hypokalaemia & increases the risk of torsade de pointes	Advised to use with caution	+++
	Warfarin	Increases the effects of Warfarin	Advised to monitor INR	++

Table.1: Potential drug-drug interactions between medications commonly prescribed for cystic fibrosis exacerbation and cardiac medications.[11] The potentially hazardous effect, recommended management strategy and drug-drug interaction severity are listed. Regarding severity, '+' is mild, '++' is moderate, '+++' is severe and 'U' is unknown.

Discussion

Drug-drug interactions causing adverse drug reactions remain a significant, avoidable health risk to patients. The impact of drug-drug interactions can range from mild to fatal.[12] It has been reported most actual drug-drug interactions causing adverse drug reactions occur in a secondary care setting, resulting in a prolonged hospital stay.[5] This therefore emphasises the importance of drug-drug interactions recognition in health education.

This review revealed of the total drug-drug interactions identified, the majority of interactions were either moderate or severe severity (64%) – where 29% (16/54) were severe severity and 35% (19/54) were moderate severity. This appears to be consistent with world-wide studies conducted on drug-drug interactions.[13,14]

On review of the mechanisms of the drug-drug interactions, 87% (47/54) were pharmacokinetic driven reactions compared to 13% (7/54) pharmacodynamic driven reactions. These figures are consistent with

already published literature, which found drug-drug interactions mainly driven by pharmacokinetic type reactions.[15]

Cardiovascular medications that are frequently involved in severe drug-drug interactions include anti-arrhythmics [16], anti-platelets [17,18], and anti-coagulants[17,19]. Our review remains consistent with this, as the medications responsible for 'severe' drug-drug interactions with serious adverse effects included: anti-arrhythmics, digoxin, ticagrelor, nicorandil, ranolazine and warfarin; therefore, for patients already established on these respective medications, great care is recommended when prescribing CF exacerbation medications in order to reduce drug-related morbidity and mortality.

However, a limitation of this review is that not all the drug-drug interaction severities were known, and some drug-drug interactions still had no management recommendations. Second, potential drug-drug interactions that may arise given a certain drug combination was the main focus, not incidences of actual drug-drug interactions. An additional limitation of this review could be using one source of drug interaction checking methods.

Therefore, future research is required to validate the clinical consequences of these respective potential drug-drug interactions. It would also be interesting to see whether incidence rates of drug-drug interactions are consistent with similar world-wide studies already conducted into cardiovascular drug-drug interactions.

Conclusion

This article highlights cystic fibrosis patients are at risk of drug-drug interactions with cardiovascular medications. Therefore, this article emphasises the need for physicians to consider cardiovascular drug-drug interactions when planning the therapeutic regimen for CF exacerbation.

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