CMRF final report for scientific advisory committee:

Drug Metabolism in Severe Chronic Obstructive Pulmonary Disease (Grant 06/2019)

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Abstract

Aims

To evaluate the effect of severe chronic obstructive pulmonary disease (COPD) on drug metabolism by comparing the pharmacokinetics of the modified 'Inje' drug cocktail in healthy participants and participants with severe COPD.

Methods

This was a single-centre pharmacokinetic study with 12 healthy participants and 7 participants with GOLD D COPD. Midazolam 1 mg, dextromethorphan 30 mg, losartan 25 mg, omeprazole 20 mg, caffeine 130 mg, and paracetamol 1000 mg were simultaneously administered to phenotype CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2, UGT1A6 and UGT1A9 enzymes respectively. Pharmacokinetic sampling was conducted over 8 hours.

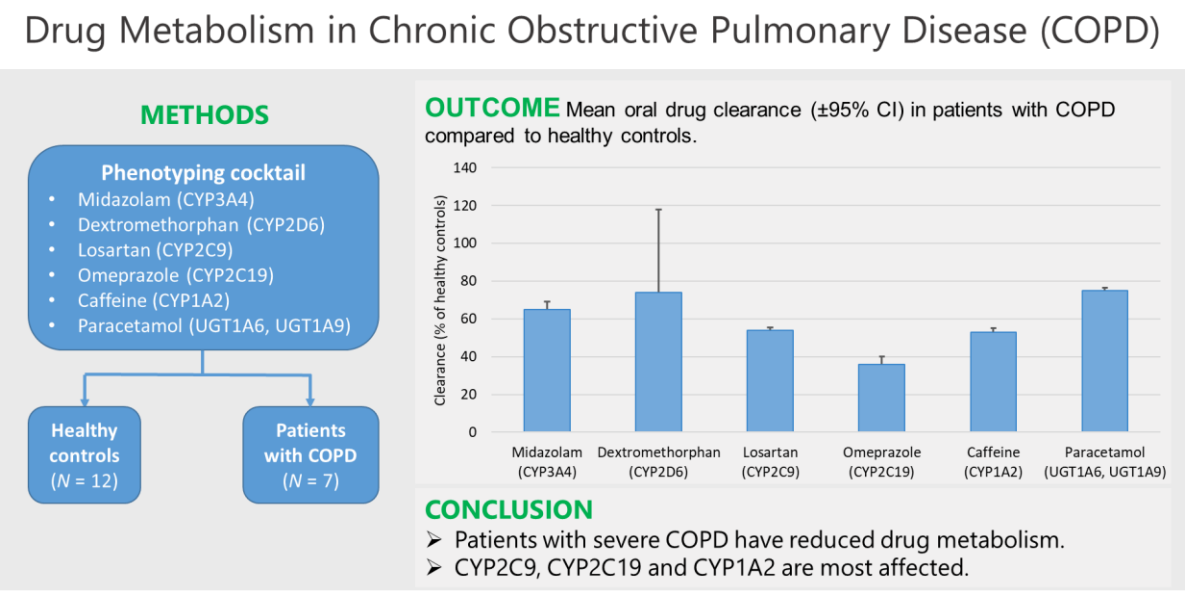
Results

COPD was associated with a reduction in oral clearance for all study drugs. The reduction (percentage, 95% CI) was greatest for omeprazole (65, 61 to 69), caffeine (48, 47 to 50), and losartan (47, 45 to 48). The change in clearance was statistically significant for all study drugs except dextromethorphan (*P*=0.5). There was a more than five-fold increase in AUC for omeprazole, and over two-fold increase for caffeine, losartan, and dextromethorphan. Midazolam and paracetamol metabolism appeared relatively preserved.

Conclusions

COPD is associated with a clinically significant reduction in dug clearance. This may be greatest for substrates of CYP2C19, CYP2C9 and CYP1A2. Empiric dose-reduction is suggested when prescribing for patients with COPD.

Graphical Abstract



Aims

The original aims of the project were:

- To quantify cytochrome P450-mediated (CYP450) drug metabolism in patients with severe COPD.
- To compare drug metabolism in patients with severe COPD to population controls.

No significant changes to these aims were made.

The primary outcome for the study was amended from area-under-the-plasma-concentration-time curve (AUC) to oral drug clearance (CL/F), which was originally a secondary outcome. This was because there was a larger than anticipated difference in weight between the body mass index (BMI) matched cohorts. Clearance can correct for weight, but it is not usual to express AUC as a function of weight. AUC was retained as a secondary outcome, alongside the other original secondary outcomes of half-life ($t_{1/2}$) maximum plasma concentration (C_{max}).

Results

Study procedures

The original target population was 12 healthy participants and 12 patients with severe COPD. Unfortunately, recruitment of patients with COPD was slower than anticipated and so a protocol amendment was approved to allow patients still smoking to be recruited. However, before recruitment of these additional patients could commence the COVID-19 pandemic forced the study to close early with 12 healthy participants and 7 patients with COPD recruited. The original study was powered to detect a 50% difference in clearance, the revised sample size was powered to detect a 70% difference with 80% power and 5% probability of type I error.

All participants completed the study protocol successfully, and no participants reported any adverse events.

Study outcomes

COPD was associated with a clinically meaningful reduction in drug metabolism. All six study drugs had statistically significant reductions in clearance, except for dextromethorphan (*P*=0.5). The full primary and secondary outcomes are shown in Table 1 and the mean plasma concentrations are shown in Figure 1.

Three drugs had a reduction in oral clearance of almost 50%: omeprazole, losartan, and caffeine. The greatest reduction in oral clearance was for omeprazole, with a reduction of 65%.

Clinical significance

There is very limited data on the effect of COPD, or indeed any chronic disease, on drug metabolism. This study demonstrates a reduction in clearance of close to 50% for two important CYP450 enzymes, and 65% for another major enzyme. A 50% reduction in clearance is of clinical significance for two reasons. Firstly, it results in a doubling of drug exposure for a given dose which is clearly of

clinical importance. Secondly, it is usually possible to reduce doses by 50% to compensate for this making it clinically feasible to change prescribing.

Smaller changes in clearance may clearly still be significant; some drugs have a narrow therapeutic index. The changes in CYP3A4, CYP2D6 and glucuronidation may be significant in this instance. Relevant clinical examples include clonazepam and midazolam (CYP3A4) and morphine (glucuronidation), which are all narrow therapeutic index drugs frequently used to treat symptoms of COPD. Dose reductions of less than 50% are sometimes limited by available tablet size, however.

COPD is associated with comorbidity and polypharmacy, and adverse drug reactions (ADRs). Many of these ADRs are related to inappropriate drug dosing for the patient's disease state. This study provides empiric evidence to support what has long been suspected, and to allow quantification of the theorised effect of COPD on drug metabolism. This allows clinicians to adjust doses in patients with severe COPD with more confidence.

COPD reduces drug metabolism, and substrates of CYP2C9, CYP2C19 and CYP1A2 are most vulnerable. Clinicians should consider empiric dose reduction for patients with severe COPD to avoid unnecessary ADRs.

Dissemination

We have published this study for publication in the British Journal of Clinical Pharmacology (impact factor 3.87, DOI: 10.1111/bcp.14862). A further paper detailed the laboratory methods has been submitted to the journal Therapeutic Drug Monitoring and we are awaiting reviewer feedback. We will notify CMRF of the outcome of this submission, and of any future presentations of the research.

Table 1. Pharmacokinetics of study drugs in healthy participants and participants with severe COPD.

	Healthy participants (*N* = 12), mean (SEM)	**Participants with COPD (*N* = 7), mean (SEM)**	***P* value**	**COPD pharmacokinetics *vs.* health pharmacokinetics, ratio (SEM)**
Midazolam (CYP3A4)				
AUC ($\mu g*h\ L^{-1}$)	16 (1)	32 (4)	0.006	1.99 (0.08)
C_{max} ($\mu g\ L^{-1}$)	7 (1)	11 (1)	0.02	1.64 (0.07)
$t_{1/2}$ (h)	2.9 (0.1)	5.0 (0.6)	0.01	1.70 (0.05)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	3.5 (0.2)	2.2 (0.3)	0.03	0.63 (0.01)
Dextromethorphan (CYP2D6)				
AUC ($\mu g*h\ L^{-1}$)	84 (48)	188 (145)	0.5	2.22 (4.58)
C_{max} ($\mu g\ L^{-1}$)	9 (4)	8 (5)	0.9	0.93 (0.46)
$t_{1/2}$ (h)	4.5 (0.7)	9.8 (2.8)	0.1	2.19 (0.5)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	213 (41)	153 (54)	0.5	0.72 (0.08)
Losartan (CYP2C9)				
AUC ($\mu g*h\ L^{-1}$)	237 (27)	546 (107)	0.03	2.30 (0.27)
C_{max} ($\mu g\ L^{-1}$)	71 (7)	214 (61)	0.06	3.03 (0.84)
$t_{1/2}$ (h)	1.6 (0.1)	1.5 (0.1)	0.4	0.90 (0.01)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	6.1 (0.4)	3.2 (0.3)	0.0009	0.53 (0.003)
Omeprazole (CYP2C19)				
AUC ($\mu g*h\ L^{-1}$)	1204 (234)	7051 (2677)	0.07	5.85 (6.23)
C_{max} ($\mu g\ L^{-1}$)	825 (138)	1876 (408)	0.04	2.27 (0.39)
$t_{1/2}$ (h)	0.9 (0.1)	2.0 (0.6)	0.09	2.35 (0.5)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	1.3 (0.2)	0.4 (0.1)	0.01	0.35 (0.01)
Caffeine (CYP1A2)				
AUC ($mg*h\ L^{-1}$)	21 (1)	52 (8)	0.007	2.53 (0.17)
C_{max} ($mg\ L^{-1}$)	2.8 (0.2)	6.3 (0.5)	0.0002	2.22 (0.04)
$t_{1/2}$ (h)	5.5 (0.4)	7.7 (1.5)	0.2	1.40 (0.09)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	0.3 (0.02)	0.2 (0.02)	0.0009	0.52 (0.005)
Paracetamol (UGT1A6, UGT1A9)				
AUC ($mg*h\ L^{-1}$)	45 (3)	75 (7)	0.005	1.66 (0.04)
C_{max} ($mg\ L^{-1}$)	14 (2)	23 (3)	0.008	0.17 (0.09)
$t_{1/2}$ (h)	2.7 (0.1)	2.4 (0.2)	0.2	0.89 (0.01)
CL/F ($L\ h^{-1}\ kg^{-0.67}$)	1.2 (0.04)	0.9 (0.06)	0.01	0.73 (0.003)

Figure 1. Study drug plasma concentrations (mean ± SEM) over time.