Drug Metabolism in Severe Chronic Obstructive Pulmonary Disease: A Phenotyping 'Cocktail' Study

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The authors confirm that the Principal Investigator for this paper is Richard McNeill and that he had direct clinical responsibility for patients.

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What is Already Known About This Subject

- Chronic obstructive pulmonary disease (COPD) is a complex syndrome involving hypoxia, cor pulmonale, chronic inflammation and cachexia.
- When studied in isolation, hypoxia, heart failure, inflammation and cachexia have been associated with impaired CYP450 function.

What This Study Adds

- Severe COPD is associated with reduced drug metabolism.
- It provides empiric evidence for reduced starting doses when treating patients with severe COPD.

Abstract

Aims

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

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 and intensive pharmacokinetic sampling was conducted over 8 hours. Drug metabolism by CYP3A4, CYP2D6, CYP2C9, CYP2C19, CYP1A2, UGT1A6 and UGT1A9 in participants with COPD were compared with phenotypes in healthy controls.

Results

The oral clearance (95% CI) in participants with COPD relative to controls was: midazolam 63% (60-67%), dextromethorphan 72% (40-103%), losartan 53% (52-55%), omeprazole 35% (31-39%), caffeine 52% (50-53%), and paracetamol 73% (72-74%). There was a five-fold increase in AUC for omeprazole and approximately two-fold increases for caffeine, losartan, dextromethorphan, and midazolam. The AUC of paracetamol, which is mostly glucuronidated, was increased by about 60%.

Conclusion

Severe COPD is associated with a clinically significant reduction in drug clearance. This may be greater for cytochrome P450 substrates than for glucuronidated drugs. This supports reduced starting doses when prescribing for patients with severe COPD.

Introduction

Drug dosing in chronic disease is difficult. Dose adjustment is based on an estimate of drug clearance, but there is no reliable biomarker of drug metabolism and empiric data for most conditions is lacking. In chronic disease, lack of appropriate dose adjustment can lead to overdose and preventable adverse drug reactions [1,2].

Chronic obstructive pulmonary disease (COPD) affects up to 15% of the adult population, and is the fourth leading cause of death in New Zealand [3]. COPD is a complex disease state compromising hypoxia, hypercapnia, cor pulmonale, chronic inflammation and cachexia. These is reason to believe these pathological states could impair drug metabolism. Acute hypoxia can influence the expression of cytochrome P450 (CYP450) enzymes *in vitro* [4]. However, *in vivo* studies of patients with hypoxia have shown inconsistent effects on drug metabolism [5,6]. Heart failure can impair drug metabolism, but studies have focussed on primary cardiac failure rather than cor pulmonale [7]. CYP450 function is inhibited by iatrogenic and chronic inflammatory states *in vivo* [8]. Finally, cachexia reduces CYP450 function, but only malignant cachexia has been studied [9]. The pathophysiology of cachexia in COPD is distinct to that of malignancy [10]. However, there have been no studies to date to robustly evaluate this potential effect *in vivo*.

In the absence of reliable, *in vivo* biomarkers of drug-metabolising enzyme function, enzymes are phenotyped by administering probe drugs and measuring plasma concentrations over time [11]. 'Cocktails' of probe drugs can be used to phenotype multiple enzymes simultaneously [12]. This approach is most commonly used to evaluate drug-drug interactions [13], however it can also be used to evaluate the effects of disease on drug metabolism [14].

The aim of this study was to evaluate the effect of severe COPD on drug metabolism by comparing the pharmacokinetics of a phenotyping drug cocktail for CYP450 and glucuronidation in healthy participants and participants with severe COPD. The primary outcome was the oral clearance of each drug, and secondary outcomes were AUC, $t_{1/2}$ and C_{max}.

Methods

This was a single-centre pharmacokinetic study of 12 healthy participants and 7 participants with COPD. The study was conducted in accordance with Good Clinical Practice and local regulations. The protocol was approved by Health and Disability Ethics Committees of New Zealand (19/CEN/112; Ministry of Health, Wellington, NZ). The study was registered on www.anzctr.org.au (ACTRN12619000861156).

Study population

Participants with COPD were of GOLD D severity [15] and had previously taken part in clinical research. The control group were healthy volunteers. Exclusion criteria for both cohorts were: known sensitivity or contraindications to any of the study drugs, concomitant use of study drugs (except caffeine) or moderate or major inhibitors or inducers of cytochrome P450, smoking, liver cirrhosis, active hepatitis, active malignancy, exacerbation of COPD or oral corticosteroid use in the last 2 weeks, acute intercurrent illness, use of domiciliary oxygen, and pregnancy.

We considered a 50% difference in oral clearance to be clinically meaningful. Assuming a standard deviation of 0.5, the study required 17 healthy participants and 17 participants with COPD to detect a 50% change in oral clearance with 80% power and a 5% probability of type I error with a two-tailed t-test. The study closed early due to the COVID-19 pandemic and recruited 12 healthy participants and 7 participants with COPD. The revised sample size is powered to detect a 70% difference in oral clearance with the same probability of type I and II error.

Phenotyping cocktail

We used a modified 'Inje' cocktail to assess CYP450 function, using midazolam (CYP3A4), dextromethorphan (CYP2D6), losartan (CYP2C9), omeprazole (CYP2C19) and caffeine (CYP1A2) [13,16]. Paracetamol is metabolised predominantly by UDP-glucuronosyltransferase (UGT) isoforms UGT1A6 and UGT1A9 and by sulfation (SULT1A1 and SULT 1A3/4) [17,18] and has been used in a phenotyping cocktail [19]. We added paracetamol as a non-specific probe of glucuronidation as no specific, validated probes for UGT isoforms exist.

Each cohort received the cocktail as follows: 1 mg midazolam (Midazolam, Pfizer; 1 ml of 1 mg/ml diluted in 50 ml water), 30 mg dextromethorphan (Robitussin Dry Cough Forte, GSK; 10 ml of 3 mg/ml diluted in 50 ml water), 25 mg losartan (Losartan Actavis, Teva Pharma; 25 mg tablet), 20mg omeprazole (Omeprazole Actavis, Teva Pharma; 20 mg tablet) and caffeine/paracetamol 130 mg/1000 mg (Panadol Extra, GSK; two tablets of 65 mg/500 mg).

Study procedures

Screening physical examinations, vital signs, routine biochemistry (including creatinine, albumin, liver function tests, brain natriuretic protein (BNP), and C-reactive protein (CRP)), haematology (including international normalised ratio (INR)), and urinalysis were all performed within 28 days of dosing. For patients with COPD, most recent spirometry and modified Medical Research Council (mMRC) breathlessness score [15] were recorded. A focussed assessment of weight, vital signs, liver function tests including albumin, BNP, CRP, and INR was repeated on the study day for safety and to reassess the parameters most associated with drug metabolism at time of dosing. Values below the lower limit of quantitation (LLQ) were assigned the LLQ for the purpose of pooled analysis.

Participants omitted caffeine for 48 hours and were fasted for at least 8 hours prior to administration of the study drugs. Study drugs were administered in the research unit and participants remained there for a minimum of eight hours after dosing for clinical monitoring including blood pressure, oxygen saturations and subjective assessment of sedation.

Serum for analysis of study drugs was taken at baseline (prior to administration), 0.25, 0.5, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, and 8 hours post-administration.

Laboratory analysis

Measurements of the phenotyping cocktail drugs in serum were performed using two in-house developed and validated LC-MS/MS assays by Clinical Pharmacology, Department of Medicine, University of Otago-Christchurch. Briefly, plasma and urine samples were pre-treated with acetonitrile and then diluted with the mobile phase. The prepared samples were injected into two LC-MS/MS systems to analyse the cocktail drugs. Midazolam was analysed using the Agilent 6460 LC-MS/MS system. Caffeine, dextromethorphan, losartan, omeprazole, and paracetamol were analysed using the API 4000 LC-MS/MS system. The lower limits of the quantification in serum were 0.2 ng/mL for midazolam, 0.1 ng/mL for dextromethorphan, and 5.0 ng/mL for caffeine, losartan, omeprazole, and paracetamol. The intra- and inter-day coefficients of variation over the analysed concentration ranges for all the compounds were less than 10%.

Statistical analysis

$AUC_{(0\text{-}t)}$ was calculated using the trapezoidal method, and $AUC_{(t\text{-}inf)}$ extrapolated by C_{8h} / k. Where participants were non-adherent to caffeine abstinence, AUC for caffeine administration prior to the study drug was calculated using $C_{baseline}$ / k and subtracted from the total AUC. These descriptive analyses were undertaken in Microsoft Excel® for Microsoft 365. Mean values were compared between cohorts using Welch's unequal variances *t*-test (GraphPad Prism version 8.0.0 for Windows, GraphPad Software, San Diego, California USA, www.graphpad.com). Clearance was corrected for body weight using allometric scaling with an exponent of 0.67 [20].

Results

All participants successfully completed the study. There were no adverse events. The demographics and baseline characteristics of the participants are shown in Table 1. The mean concentration time curves of the probe drugs are shown in Figure 1. The AUC, C_{max}, $t_{1/2}$, and oral clearance of each study drug is shown in Table 2. In the participants with COPD the AUC increased by over five-fold for omeprazole and more than doubled for dextromethorphan, losartan, and caffeine. The reduction in oral clearance ranged from 65% for omeprazole to 27% for paracetamol. The reduction in oral clearance was statistically significant for all study drugs except dextromethorphan (P=0.5).

There was detectable caffeine at baseline in five health participants and seven participants with COPD. No other study drugs were detected at baseline. The extrapolated AUC from prior exposure was subtracted from the total AUC to control for the prior exposure; this was less than 10% of the AUC in all but three participants. More than 70% of the AUC was directly measured for all study drugs except for caffeine (63% in the healthy cohort and 56% in the cohort with COPD) and dextromethorphan in the cohort with COPD (49%). In all cases, there were sufficient observations to define the elimination constant (Figure 1).

Both study cohorts had similar body mass index (BMI), but healthy participants were younger and heavier (Table 1). The participants with COPD were not cachetic and had no evidence of daytime hypoxia.

Discussion

Severe COPD was associated with reduced oral drug clearance in this study. The weight adjusted clearance was decreased by 27%-65%, with the greatest effect seen for omeprazole (CYP2C19). The effect was not statistically significant for dextromethorphan due to high variance in both groups.

Drug metabolism in COPD is under researched. Previous studies were limited to single drugs, rather than a phenotyping cocktail. A previous studies examining fluticasone, a CYP3A4 substrate [21], found clearance was not significantly affected by COPD when administered intravenously to 10 patients with COPD and 13 age and sex matched healthy controls [22]. Bachmann *et al.* studied the pharmacokinetics of theophylline (a CYP1A2 probe [11]) in 13 patients with COPD and 14 healthy controls [23,24]. The mean oral clearance was modestly reduced from 3.4 L/hr to 2.8 L/hr (a reduction of 18%) between the healthy participants and those with COPD. We found a reduction of 48% in caffeine oral clearance in this study. These are broadly consistent with our findings, given the differences in probe drug and route of administration, in that the effect on CYP1A2 was greater than

that of CYP3A4. Our study used participants with severe COPD which may have magnified the effect of disease.

We found the effect of COPD to vary by drug metabolising enzyme. The Pittsburgh cocktail has been used to evaluate CYP2D6, CYP2C19, CYP1A2, and CYP2E1 in patients with varying degrees of liver impairment [14]. This has been the only other study to date to use this approach to fully characterise the effect of disease on drug metabolism. It was found that CYP2C19 was affected much earlier in the cirrhosis process, while CYP2E1 was the best preserved. This led the concept of a selective effect of disease on drug metabolising enzymes [25]. We also found that CYP2C19 was most affected, despite a different CYP2C19 probe. Glucuronidation was relatively preserved in the presence of COPD in this study. No previous studies have investigated paracetamol pharmacokinetics in patients with COPD compared to healthy subjects. Liver disease was originally believed to have limited effect on glucuronidation, however, it is now clear that it is preserved early in liver disease but significantly affected in advanced cirrhosis [25,26]. Interpreting the effect of disease on pharmacokinetics is complex as the probe drugs have different properties; for example, drugs with low oral bioavailability and high first pass metabolism are more sensitive to changes in metabolism than those with high bioavailability. It remains unclear, therefore, whether COPD selectively modulates drug metabolising enzymes or this is an artifact of different probe drugs.

Limitations

The main limitation of this study is the small sample size - recruitment of patients was ceased due to the COVID-19 pandemic. Despite the small sample size statistically significant changes were seen in patients with severe COPD. Participants were not matched by age, weight and sex. Age may partly account for some of the changes in clearance seen in this study. In considering this, oral drug clearance is most defined by intrinsic hepatic clearance which is only modestly affected by age [27–29]. Weight was controlled for by adjusting clearance for weight and body composition was accounted for by BMI matching. Sex is not expected to have a meaningful effect on CYP450 function after controlling for weight [30].

Clinical significance

COPD is associated with comorbidity and polypharmacy [31]. Adverse drug reactions are a common cause of morbidity in patients with COPD [32,33]. The reduction in drug clearance associated with COPD in this study places patients at risk of unintended over-exposure and adverse drug reactions [1,2].

The participants in this study were typical of ambulatory patients with COPD [34,35] and the healthy participants were typical of those used in pharmacokinetic studies to define doses. Hence, the changes may be broadly representative. Although GOLD D, the study participants were not hypoxic or cachetic, and had modest breathlessness scores. These patients were at the ‘mild’ end of the spectrum of GOLD D and it is possible that patients with more severe disease, such as those with daytime hypoxia, may have even greater reductions in drug metabolism.

“Start low and go slow” is a widely used clinical adage. This study supports that approach in patients with severe COPD.

Conclusion

COPD is associated with a reduction in oral drug clearance, with substrates of CYP450 more affected than substrates of UGTs. Clinicians should consider empiric dose-reduction and additional monitoring for adverse reactions when prescribing for patients with severe COPD. Further research is required to identify clinical factors most predictive of impaired drug metabolism, and to confirm a selective impact on specific drug metabolising enzymes.

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Conflict of interest

The authors have no conflicts of interest.

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Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

References

1. McDonnell PJ, Jacobs MR: Hospital Admissions Resulting from Preventable Adverse Drug Reactions. Ann Pharmacother 2002, 36:1331–1336.

2. Kongkaew C, Hann M, Mandal J, Williams SD, Metcalfe D, Noyce PR, Ashcroft DM: Risk factors for hospital admissions associated with adverse drug events. Pharmacotherapy 2013, 33:827–837.

3. Broad J, Jackson R: Chronic Obstructive Pulmonary Disease and Lung Cancer in New Zealand. Auckl UniServices Thorac Soc Aust New Zeal 2003,

4. du Souich P, Fradette C: The effect and clinical consequences of hypoxia on cytochrome P450, membrane carrier proteins activity and expression. Expert Opin Drug Metab Toxicol 2011, 7:1083–1100.

5. Taburet AM, Tollier C, Richard C: The Effect of Respiratory Disorders on Clinical Pharmacokinetic Variables. Clin Pharmacokinet 1990, 19:462–490.

6. Jurgens G, Christensen HR, Brosen K, Sonne J, Loft S, Olsen NV: Acute hypoxia and cytochrome P450–mediated hepatic drug metabolism in humans. Clin Pharmacol Ther 2002, 71:214–220.

7. Mangoni AA, Jarmuzewska EA: The influence of heart failure on the pharmacokinetics of cardiovascular and non-cardiovascular drugs: a critical appraisal of the evidence. Br J Clin Pharmacol 2018, 85:20–36.

8. Dumais G, Iovu M, du Souich P: Inflammatory reactions and drug response: Importance of cytochrome P450 and membrane transporters. Expert Rev Clin Pharmacol 2008, 1:627–647.

9. Trobec K, Kos MK, Von Haehling S, Springer J, Anker SD, Lainscak M: Pharmacokinetics of drugs in cachectic patients: A systematic review. PLoS One 2013, 8:1–12.

10. Sanders KJC, Kneppers AEM, van de Bool C, Langen RCJ, Schols AMWJ: Cachexia in chronic obstructive pulmonary disease: New insights and therapeutic perspective. J Cachexia Sarcopenia Muscle 2016, 7:5–22.

11. Keller GA, Gago MLF, Diez RA, Di Girolamo G: In vivo Phenotyping Methods: Cytochrome P450 Probes with Emphasis on the Cocktail Approach. Curr Pharm Des 2017, 23.

12. Frye RF, Matzke GR, Adedoyin A, Porter JA, Branch RA: Validation of the five-drug “Pittsburgh cocktail” approach for assessment of selective regulation of drug-metabolizing enzymes. Clin Pharmacol Ther 1997, 62:365–376.

13. Snyder BD, Rowland A, Polasek TM, Miners JO, Doogue MP: Evaluation of felodipine as a potential perpetrator of pharmacokinetic drug-drug interactions. Eur J Clin Pharmacol 2014, 70:1115–1122.

14. Frye RF, Zgheib NK, Matzke GR, Chaves-Gnecco D, Rabinovitz M, Shaikh OS, Branch RA: Liver disease selectively modulates cytochrome P450-mediated metabolism. Clin Pharmacol Ther 2006, 80:235–245.

15. Global Initiative for Chronic Obstructive Lung Disease (GOLD): Global strategy for the diagnosis, management, and prevention of Chronic Obstructive Pulmonary Disease - 2019 Report. Glob Initiat Chronic Obstr Lung Dis Inc 2019, doi:10.1109/EDPC.2012.6425109.

16. Ryu JY, Song IS, Sunwoo YE, Shon JH, Liu KH, Cha IJ, Shin JG: Development of the “Inje cocktail” for high-throughput evaluation of five human cytochrome P450 isoforms in vivo. Clin Pharmacol Ther 2007, 82:531–540.

17. Court MH, Duan SX, von Moltke LL, Greenblatt DJ, Patten CJ, Miners JO, Mackenzie PI: Interindividual variability in acetaminophen glucuronidation by human liver microsomes: identification of relevant acetaminophen UDP-glucuronosyltransferase isoforms. J Pharmacol Exp Ther 2001, 299:998–1006.

18. Zhao L, Pickering G: Paracetamol metabolism and related genetic differences. Drug Metab Rev 2011, 43:41–52.

19. Lenuzza N, Duval X, Nicolas G, Thévenot E, Job S, Videau O, Narjoz C, Loriot MA, Beaune P, Becquemont L, et al.: Safety and pharmacokinetics of the CIME combination of drugs and their metabolites after a single oral dosing in healthy volunteers. Eur J Drug Metab Pharmacokinet 2016, 41:125–138.

20. McLeay SC, Morrish GA, Kirkpatrick CMJ, Green B: The Relationship between Drug Clearance and Body Size. Clin Pharmacokinet 2012, 51:319–330.

21. Hughes SC, Shardlow PC, Hollis FJ, Scott RJ, Motivaras DS, Allen A, Rousell VM: Metabolism and Disposition of Fluticasone Furoate, an Enhanced-Affinity Glucocorticoid, in Humans. Drug Metab Dispos 2008, 36:2337–2344.

22. Singh S, Whale C, Houghton N, Daley-Yates P, Kirby S, Woodcock A: Pharmacokinetics and systemic effects of inhaled fluticasone propionate in chronic obstructive pulmonary disease. Br J Clin Pharmacol 2003, 55:375–381.

23. Bachmann K, Nunlee M, Martin M, Sullivan T, Jauregui L, DeSante K, Sides G: Changes Pharmacokinetics Treatment in the Steady-State of Theophylline with Dirithromycin. J Clin Pharmacol 1990, 30:1001–1005.

24. Bachmann K, Jauregui L, Sides G, Sullivan TJ: Steady-State Theophylline Treated Pharmacokinetics in COPD Patients With Dirithromycin. J Clin Pharmacol 1993, 33:861–865.

25. Verbeeck RK: Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. Eur J Clin Pharmacol 2008, 64:1147–1161.

26. Hoyumpa AM, Schenker S: Is glucuronidation truly preserved in patients with liver disease? Hepatology 1991, 13:786–795.

27. Butler JM, Begg EJ: Free drug metabolic clearance in elderly people. Clin Pharmacokinet 2008, 47:297–321.

28. McLean AJ, Le Couteur DG: Aging Biology and Geriatric Clinical Pharmacology. Pharmacol Rev 2004, 56:163–184.

29. Jensen BP, Chin PKL, Roberts RL, Begg EJ: Influence of adult age on the total and free clearance and protein binding of (R)- and (S)-warfarin. Br J Clin Pharmacol 2012, 74:797–805.

30. Bebia Z, Buch SC, Wilson JW, Frye RF, Romkes M, Cecchetti A, Chaves-gnecco D, Branch RA: Bioequivalence revisited : Influence of age and sex on CYP enzymes. Clin Pharmacol Ther 2004, 76:618–627.

31. Diez-Manglano J, Barquero-Romero J, Mena PA, Recio-Iglesias J, Cabrera-Aguilar J, Lopez-Garcia F, Viu RB, Soriano JB: Polypharmacy in patients hospitalised for acute exacerbation of COPD. Eur Respir J 2014, 44:791–794.

32. Adil MS, Amer Khan M, Nematullah Khan M, Sultan I, Aamer Khan M, Amir Ali S, Farooqui A: EMPADE study: Evaluation of medical prescriptions and adverse drug events in COPD patients admitted to intensive care unit. J Clin Diagnostic Res 2015, 9:FC05–FC08.

33. Hanlon P, Nicholl BI, Jani BD, McQueenie R, Lee D, Gallacher KI, Mair FS: Examining patterns of multimorbidity, polypharmacy and risk of adverse drug reactions in chronic obstructive pulmonary disease: A cross-sectional UK Biobank study. BMJ Open 2018, 8:1–11.

34. Kim S, Oh J, Kim Y Il, Ban HJ, Kwon YS, Oh IJ, Kim KS, Kim YC, Lim SC: Differences in classification of COPD group using COPD assessment test (CAT) or modified Medical Research Council (mMRC) dyspnea scores: A cross-sectional analyses. BMC Pulm Med 2013, 13:0–4.

35. Cheng SL, Lin CH, Wang CC, Chan MC, Hsu JY, Hang LW, Perng DW, Yu CJ, Wang HC: Comparison between COPD Assessment Test (CAT) and modified Medical Research Council (mMRC) dyspnea scores for evaluation of clinical symptoms, comorbidities and medical resources utilization in COPD patients. J Formos Med Assoc 2019, 118:429–435.

Tables and figures

Table 1. Summary of participant demographics and baseline characteristics

Demographics	Healthy participants (*N* = 12)	Participants with COPD (*N* = 7)	P-value
Age, years	26 (9)	71 (6)	<0.0001
Male sex, *N*	12	3	
Body mass index, kg m^{-2}	25 (2)	24 (2)	0.6
Height, cm	185 (8)	164 (8)	<0.0001
Weight, kg	86 (14)	66 (10)	0.003
White cell count, x10^{9}/L	5.6 (1.0)	7.0 (2.0)	0.1
C-reactive protein, mg/L	3 (0)	4 (2)	0.2
Brain natriuretic protein, pmol/L	5 (0)	42 (72)	0.2
Creatinine, µmol/L	95 (10)	85 (13)	0.1
Albumin, g/L	39 (2)	36 (3)	0.06
International normalised ratio	1.1 (0.1)	1.2 (0.4)	0.5
Bilirubin, umol/L	17 (8)	12 (8)	0.3
Gamma-glutamyl transferase, U/L	17 (13)	33 (19)	0.08
Aspartate aminotransferase, U/L	21 (4)	20 (6)	0.9
Alanine aminotransferase, U/L	19 (7)	17 (5)	0.6
Peripheral oxygen saturations, %	97 (1)	97 (2)	0.8
mMRC score, median (range)		2 (2-3)	
FEV_1, L		0.86 (0.34)	
FEV_1/FVC		0.34 (0.08)	

All data are presented as mean (standard deviation) unless otherwise stated. *N* = number of participants; mMRC = modified Medical Research Council; FEV_1 = forced expiratory volume in the first second; FVC = forced vital capacity.

Table 2. Pharmacokinetics of study drugs in healthy participants and participants with severe COPD.

	Healthy participants (*N* = 12), mean (95% CI)	**Participants with COPD (*N* = 7), mean (95% CI)**	***P* value**	**COPD pharmacokinetics *vs.* health pharmacokinetics, ratio (95% CI)**
Midazolam (CYP3A4)				
AUC ($\mu g^{*}h\ L^{-1}$)	16 (13, 19)	32 (24, 39)	0.006	1.99 (1.83, 2.16)
C_{max} ($\mu g\ L^{-1}$)	7 (6, 8)	11 (9, 14)	0.02	1.64 (1.52, 1.77)
$t_{1/2}$ (h)	2.9 (2.7, 3.2)	5.0 (3.9, 6.2)	0.01	1.70 (1.61, 1.79)
CL/F ($L\ h^{-1} kg^{-0.67}$)	3.5 (2.9, 4.0)	2.2 (1.4, 3.0)	0.03	0.63 (0.60, 0.67)
Dextromethorphan (CYP2D6)				
AUC ($\mu g^{*}h\ L^{-1}$)	84 (-10, 179)	188 (-97, 473)	0.5	2.22 (-6.76, 11.2)
C_{max} ($\mu g\ L^{-1}$)	9 (1, 17)	8 (-1, 18)	0.9	0.93 (0.04, 1.83)
$t_{1/2}$ (h)	4.5 (3.2, 5.8)	9.8 (4.3, 15.3)	0.1	2.19 (1.21, 3.18)
CL/F ($L\ h^{-1} kg^{-0.67}$)	213 (100, 326)	153 (6, 299)	0.5	0.72 (0.40, 1.03)
Losartan (CYP2C9)				
AUC ($\mu g^{*}h\ L^{-1}$)	237 (184, 290)	546 (336, 755)	0.03	2.30 (1.77, 2.84)
C_{max} ($\mu g\ L^{-1}$)	71 (57, 84)	214 (94, 334)	0.06	3.03 (1.38, 4.68)
$t_{1/2}$ (h)	1.6 (1.4, 1.8)	1.5 (1.2, 1.7)	0.4	0.90 (0.87, 0.92)
CL/F ($L\ h^{-1} kg^{-0.67}$)	6.1 (5.0, 7.2)	3.2 (2.5, 4.0)	0.0009	0.53 (0.52, 0.55)
Omeprazole (CYP2C19)				
AUC ($\mu g^{*}h\ L^{-1}$)	1204 (746, 1663)	7051 (1805, 12297)	0.07	5.85 (-6.36, 18.07)
C_{max} ($\mu g\ L^{-1}$)	825 (554, 1097)	1876 (1077, 2675)	0.04	2.27 (1.51, 3.04)
$t_{1/2}$ (h)	0.9 (0.7, 1.1)	2.0 (0.9, 3.1)	0.09	2.35 (1.37, 3.34)
CL/F ($L\ h^{-1} kg^{-0.67}$)	1.3 (0.8, 1.8)	0.4 (0.1, 0.8)	0.01	0.35 (0.31, 0.39)
Caffeine (CYP1A2)				
AUC ($mg^{*}h\ L^{-1}$)	21 (18, 23)	52 (37, 67)	0.007	2.53 (2.20, 2.85)
C_{max} ($mg\ L^{-1}$)	3 (3, 3)	6 (5, 7)	0.0002	2.22 (2.14, 2.30)
$t_{1/2}$ (h)	5.5 (4.6, 6.3)	7.7 (4.7, 10.7)	0.2	1.40 (1.22, 1.58)
CL/F ($L\ h^{-1} kg^{-0.67}$)	0.3 (0.3, 0.4)	0.2 (0.1, 0.2)	0.0009	0.52 (0.50, 0.53)
Paracetamol (UGT1A6, UGT1A9)				
AUC ($mg^{*}h\ L^{-1}$)	45 (39, 51)	75 (61, 90)	0.005	1.66 (1.59, 1.74)
C_{max} ($mg\ L^{-1}$)	14 (10, 17)	2 (-3, 8)	0.008	0.17 (0.09, 0.26)
$t_{1/2}$ (h)	2.7 (2.5, 2.9)	2.4 (2.0, 2.8)	0.2	0.89 (0.88, 0.90)
CL/F ($L\ h^{-1} kg^{-0.67}$)	1.2 (1.0, 1.3)	0.9 (0.7, 1.0)	0.01	0.73 (0.72, 0.74)

N = number of participants; CI = confidence interval.

Figure 1 title and legend.

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

Figure 1 legend: Concentration-time curves for study drugs in healthy participants (*N* = 12) and patients with severe COPD (*N* = 7) over eight hours after administration. Data are plotted on a linear scale.

<Figure submitted as separate file>