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

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December 12, 2020

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.

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