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Pharmacokinetics of m-chlorophenylpiperazine after intravenous and oral administration in healthy male volunteers: implication for the pharmacodynamic profile.

Feuchtl A, Bagli M, Stephan R, Frahnert C, Kölsch H, Kühn KU, Rao ML.

Department of Psychiatry, University of Bonn, Germany.

Abstract

INTRODUCTION: Serotonin plays an important role in psychiatric diseases, most notably in depression and anxiety. Seven different major serotonin receptor subtypes have been described. Receptor-selective agonists and antagonists have been searched for to find a suitable drug to test the in vivo receptor sensitivity. Different serotonin receptor subtypes take part in the control of neuroendocrine function. m-Chlorophenylpiperazine (mCPP) acts as an agonist to serotonin 2C, 1A, 1B, and 1D receptor subtypes and is applied in challenge tests. The object of this study was to develop a pharmacokinetic-pharmacodynamic model to describe the effects of mCPP on pituitary hormone secretion. METHODS: The hormone and mCPP plasma concentrations were determined after intravenous and oral administration of mCPP to 12 healthy men. The kinetic parameters of mCPP were compared to the drug's effect on hormonal response. RESULTS: After mCPP treatment, ACTH, cortisol, and prolactin levels were significantly increased compared to placebo. There was also a significant increase in clinical response (anxiety, shivering, dizziness, heightened sensitivity toward light and noise, and fear of losing control). Maximum mCPP concentrations varied 2.3-fold after intravenous infusion and 8-fold after oral administration. The absolute bioavailability ranged from 12% to 84%. mCPP's elimination half-life ranged from 2.4 h to 6.8 h after intravenous infusion and from 2.6 h to 6.1 h after oral application. However, the kinetic data as well as the pharmacodynamic response varied to an extent that precluded pharmacokinetic-pharmacodynamic modeling. The wide interindividual variability in mCPP's disposition kinetics could not be fully explained by genetic variation of the mCPP-metabolizing enzyme cytochrome P4502D6, which was determined in all probands. DISCUSSION: Other factors contributing to the variability in disposition kinetics could not be ruled out in this study, suggesting that mCPP is not a suitable model drug to test serotonin 2C receptor activity in vivo.

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