Obesity represents a serious problem especially in American and European populations. Pharmacotherapy in combination with a reduced calorie diet is recommended for obese patients as a multi-modal approach to weight loss. Sibutramine hydrochloride monohydrate represents one of the few established and well-proven agents available for treatment of obesity. It is sold as a racemic mixture under the trade-name Meridia, Reductil or Lindaxa. It acts as a monoamine reuptake inhibitor. The weight loss of patients induced by sibutramine is thought to be due to a combination of serotonin- and noradrenaline-mediated mechanisms that increase both satiety and energy expenditure.

In organisms, sibutramine is rapidly demethylated to form metabolites M1 and M2. These metabolites contribute largely to the pharmacological effects of sibutramine and the pharmacokinetic characteristics of M1 and M2 were thoroughly studied in human plasma. Although sibutramine is widely used for the treatment of obesity almost ten years, the published information on the further metabolic fate of metabolites M1 and M2 as well as on the elimination of sibutramine from the body is almost exclusively limited to package inserts of the product. To address this issue we determined the routes of elimination of sibutramine in humans via urine. LC-API/MS was utilized for detection of unknown metabolites and subsequent tentative structural characterization.

Two phase I (M1 and M2) and eight phase II metabolites of sibutramine were found in human urine. Consecutive mono- and di-N-demethylation of sibutramine resulted in metabolites M1 and M2, which were found as minor metabolites. Carbamoyl glucuronides formed from metabolites M1, M2, and their hydroxylated analogs were the main metabolites of sibutramine. These metabolites were probably formed by the chemical reaction of the amine with CO_2 followed by enzymatic glucuronidation of the carbamate.

The results allowed us to insight into the biotransformation and elimination of sibutramine in humans and we present a new way for conjugation of sibutramine metabolites.

Sibutramine and both M1 and M2 metabolites are chiral compounds. The enantioselective pharmacodynamic profile of these enantiomers has been reported. The *R*-enantiomers act as more potent monoamine reuptake inhibitors than the *S*-enantiomers. One aim of this study was to evaluate the stereoselectivity in phase I of sibutramine biotransformation in rat and man. The *in vitro* formations of the main metabolites from *R*-, *S*- and *rac*-sibutramine were studied and compared. Primary cultures of rat hepatocytes, microsomal fraction of rat liver homogenates and microsomal fraction of human liver homogenates were used as model systems, respectively.

Only metabolites M1 and M2 were detected after incubation of sibutramine with rat liver microsomes regardless of the enantiomeric form of substrate used. We did not conclude the phase I biotransformation of sibutramine to be stereoselective from these data. On the other hand, pronounced stereoselectivity of sibutramine biotransformation was found in primary cultures of rat hepatocytes. While *R*-sibutramine incubation led to formation of two main metabolites (M1 and M2) only, incubation of *S*-sibutramine or *rac*-sibutramine (to a lesser extent) resulted in four major metabolites (M1, M2, M3 and M4) and 2-3 minor metabolites. *R*-sibutramine was found as enantiomer with less extensive biotransformation than the *S*-enantiomer by rat hepatocytes *in vitro*.

Metabolites M1 and M2 were detected as the only biotransformation products of sibutramine in human liver microsomes regardless of the enantiomeric form of substrate used. The main metabolite formed was M1. The results showed, that the phase I biotransformation of sibutramine is stereoselective and stereospecific in human liver microsomes. *R*-sibutramine was found as enantiomer with less extensive biotransformation than the *S*-enantiomer by human liver microsomes *in vitro*. Moreover, it was shown, that the chiral carbon atom configuration is retained during formation of M1 and that sibutramine did not undergo chiral inversion.

On the basis of these results, *R*-sibutramine could be considered as enantiomer with less extensive biotransformation than the *S*-enantiomer by rat hepatocytes and human liver microsomes *in vitro*. Lower biotransformation might mean slower deactivation, lower risk in drug-drug interactions and inter-individual variability. Moreover, it was reported that both *R*-desmethylsibutramine and *R*-didesmethylsibutramine were clearly more potent in depressing food intake and decreasing body weight than the *S*-enantiomers. Thus *R*-sibutramine might represent the more advantageous sibutramine enantiomer from pharmacokinetic as well as pharmacodynamic points of view. The results obtained *in vitro* should be considered as preliminary with respect to well-known *in vivo* stereoselective processes such as absorption, protein binding and elimination which altogether, in addition to metabolism, determine the final disposition of individual enantiomers.