Alternation of the pharmacokinetics of theophyline by rutaecarpine, an alkaloid of the medical herb Evodia rutaecarpa, in rats.

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Abstract

Rutaecarpine is a main active alkaloid present in the medicinal herb, Evodia rutaecarpa. The cytochrome P450 (CYP) 1A2 substrate, theophylline, is an important therapeutic agent for the treatment of asthma, but has a narrow therapeutic index. To evaluate the pharmacokinetic interaction of theophylline with rutaecarpine, the effects of rutaecarpine on CYP1A2 activity and theophylline pharmacokinetics were investigated. Oral treatment of Sprague-Dawley rats with 50 mg kg-1 rutaecarpine for three days through a gastrogavage caused a 4- and 3-fold increase in liver microsomal 7-ethoxyresorufin O-deethylation (EROD) and 7-methoxyresorufin O-demethylation activity, respectively. In the kidney, rutaecarpine treatment caused a 3-fold increase in EROD activity. In the lungs, EROD activity was elevated from an undetectable to a detectable level by rutaecarpine. Pharmacokinetic parameters of theophylline were determined using a microdialysis sampling method. Rutaecarpine pre-treatment increased the clearance of theophylline in a dose-dependent manner. Pre-treatment of rats with 50 mg kg-1 rutaecarpine caused a 3-fold increase in theophylline clearance and a 70%, 68% and 68% decrease in the area under the concentration-time curve (AUC), mean residence time (MRT) and half-life, respectively. These results demonstrated that rutaecarpine treatment elevated CYP1A2 catalytic activity and theophylline excretion in rats. In patients taking theophylline, adverse effects might be noticed when a rutaecarpine-containing herbal preparation is used concomitantly.