Milk thistle-drug pharmacokinetic interactions in nonalcoholic steatohepatitis

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Milk thistle [Silybum marianum (L.) Gaertn. (Asteraceae)] has a wide safety margin which has led to an array of commercially available milk thistle products with different recommended doses and/or formulations designed to increase systemic concentrations of the major bioactive constituents, flavonolignans. Clinical milk thistle doses between 700 mg and 2,700 mg are currently under investigation for multiple diseases. These higher doses can produce micromolar plasma concentrations of the flavonolignans [1], and the flavonolignans are inhibitors of the organic anion transporting polypeptide (OATP) uptake transporters at low micromolar concentrations [2], but the effect of these higher doses on OATP substrate pharmacokinetics has not been tested. The OATPs are a superfamily of transporters that mediate the sodium-independent transport of a wide range of amphiphilic organic compounds, including tyrosine kinase inhibitors, hydroxymethylglutaryl-CoA reductase inhibitors (statins), angiotensin II receptor blockers, angiotensin converting enzyme inhibitors, chemotherapeutics, anti-viral drugs, and anti-diabetic agents [3]. The aims of this research were to determine the roles of OATPs/Oatps in flavonolignan disposition and in pharmacokinetic silymarin-drug interactions. The seven major flavonolignans from silymarin were determined to be substrates for OATP1B1, OATP1B3, and OATP2B1. Sprague Dawley rats were fed either a control diet or a NASH-inducing diet and administered pitavastatin (OATP/Oatp probe substrate) and silymarin via intravenous injection or oral gavage. Decreased protein expression of Oatp1b2 and Oatp1a4 in NASH animals increased flavonolignan area under the plasma concentration-time curve (AUC) and maximum plasma concentration. The combination of silymarin inhibition of Oatps and NASH-associated decrease in Oatp expression caused an additive increase in plasma pitavastatin AUC in the animals. The combination of silymarin and NASH is a probable clinical scenario that may affect pharmaceutical uptake, liver concentrations, biliary elimination, and pharmacodynamics.

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