Comparison of the effects of clonidine, loperamide and metoclopramide in two models of gastric emptying in the rat.

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Abstract

Several methods are used to evaluate gastric emptying (GE) in rats, which is an important endpoint in preclinical drug development. Although phenol red model or monitoring of plasma acetaminophen levels are well-established procedures for GE assessment, their capacity to detect the effects of pharmacological agents has rarely been compared. This study was therefore designed to evaluate clonidine with loperamide and metoclopramide in the two test models. Rats were administered phenol red or acetaminophen test meals. The remaining amount of phenol red in the stomach or the time course of plasma acetaminophen levels was then measured. In the phenol red test, loperamide (8 mg/kg, p.o.) and clonidine (100 μg/kg, s.c.) decreased GE (-88% and -42%, P < 0.001 and P < 0.01, respectively). Metoclopramide (10 mg/kg, s.c.) accelerated GE (+42%, P < 0.01). Loperamide reduced acetaminophen plasma levels (-45% at T15 min, P < 0.05), suggesting a delayed GE. Clonidine and metoclopramide increased acetaminophen plasma levels (+115% and +152% at T15 min, P < 0.05 and P < 0.001, respectively), suggesting an accelerated GE. The three substances did not affect plasma acetaminophen levels when acetaminophen was subcutaneously injected, thereby suggesting that acetaminophen metabolism/excretion was not modified. Whereas the phenol red test allows the evaluation of GE at a single time point, the measurement of plasma acetaminophen levels over the time would appear more informative. Nevertheless, the fact that clonidine, in contrast to expectation, increased plasma acetaminophen levels, suggests that data obtained with the acetaminophen method should be interpreted with caution for new chemical entities susceptible to modify absorption of acetaminophen from the small intestine.