

Acetaminophen toxicity in lymphocytes heterozygous for glutathione synthetase deficiency.

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We have studied the effects of acetaminophen metabolites generated by a murine hepatic microsomal system on lymphocytes from two subjects heterozygous for glutathione synthetase deficiency. Heterozygous cells exhibited greater dose-related toxicity than controls. Following a 2-h incubation with acetaminophen and the microsomal system, cells were washed and incubated for 16 h in the presence or absence of N-acetylcysteine, the standard antidote for acetaminophen toxicity. In control cells, glutathione content was replenished to nearly base-line values and toxicity was prevented. N-Acetylcysteine thus prevented toxicity even after covalent binding of acetaminophen metabolites had occurred. Heterozygous cells failed to use N-acetylcysteine as efficiently to resynthesize glutathione, and the cells were not protected from acetaminophen toxicity. Heterozygotes may be at increased risk of toxicity from drugs whose metabolites are detoxified by glutathione conjugation.

