5-(m-Benzylxybenzyl)barbituric acid acyclonucleoside, a uridine phosphorylase inhibitor, and 2',3',5'-tri-O-acetyltudine, a prodrug of uridine, as modulators of plasma uridine concentration. Implications for chemotherapy.

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5-(m-Benzylxybenzyl)barbituric acid acyclonucleoside (BBBA), the most potent inhibitor known of uridine phosphorylase (UrdPase, EC 2.4.2.3), the enzyme responsible for uridine catabolism, and 2',3',5'-tri-O-acetyltudine (TAU), a prodrug of uridine, were used to investigate the possibility of improving the bioavailability of oral uridine in mice. Oral BBBA administered at 30, 60, 120, and 240 mg/kg increased the concentration of plasma uridine (2.6 +/- 0.7 microM) by 3.2-, 4.6-, 5.4-, and 7.2-fold, respectively. After administration of 120 and 240 mg/kg BBBA, plasma uridine concentration remained 3- and 6-fold, respectively, higher than the plasma concentration at zero time (C0) for over 8 hr. On the other hand, BBBA did not change the concentration of plasma uracil. TAU was far more superior than uridine in improving the bioavailability of plasma uridine. The relative bioavailability of plasma uridine released from oral TAU (53%) was 7-fold higher than that (7.7%) obtained by oral uridine. Oral TAU at 460, 1000, and 2000 mg/kg achieved area under the curve (AUC) values of plasma uridine of 82, 288, and 754 mumol.hr/L, respectively. Coadministration of BBBA with uridine or TAU further improved the bioavailability of plasma uridine resulting from the administration of either alone and reduced the Cmax and AUC of plasma uracil. Coadministration of BBBA at 30, 60, and 120 mg/kg improved the relative bioavailability of uridine released from 2000 mg/kg TAU (53%) by 1.7-, 2.7-, and 3.9-fold, respectively, while coadministration of the same doses of BBBA with an equimolar dose of uridine (1320 mg/kg) increased the relative bioavailability of oral uridine (7.7%) by 4.1-, 5.3-, and 7.8-fold, respectively. Moreover, the AUC and Cmax of plasma uridine after BBBA (120 mg/kg) coadministration with TAU were 3.5- and 11.5-fold, respectively, higher than those obtained from coadministration of BBBA with an equimolar dose of uridine. The exceptional effectiveness of the BBBA plus TAU combination in elevating and sustaining high plasma uridine concentration can be useful in the management of medical disorders that are remedied by administration of uridine as well as to rescue or protect from host-toxicities of various chemotherapeutic pyrimidine analogues.

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