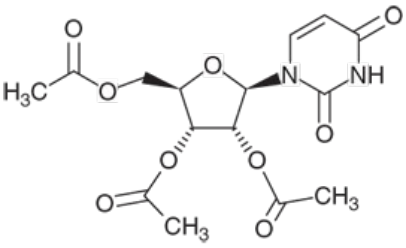
Chapter A14: Uridine Triacetate

Silas W. Smith

INTRODUCTION



Uridine triacetate (2′,3′,5′-tri-*O*-acetyluridine) is used to treat cases of toxicity from fluoropyrimidines such as fluorouracil and fluorouracil prodrugs such as capecitabine and tegafur. Uridine triacetate is a prodrug that is taken orally to provide uridine as a source for uridine triphosphate for endogenous RNA incorporation.

HISTORY

In 1950, leucovorin (folinic acid) successfully mitigated chemotherapeutic toxicity from aminopterin and methotrexate, for which folate antidotal therapy was inefficacious.[39] Fluorouracil (5-FU) synthesis and its antitumor activity were reported in 1957.[18] A decade later, the concept of leucovorin "rescue" emerged to mitigate toxicity from higher methotrexate chemotherapy doses.[27] However, in 1982 leucovorin was reported to paradoxically both increase 5-FU chemotherapeutic efficacy as well as cytotoxicity in humans by increasing inhibition of thymidylate synthase.[30] Additional studies in 1982 reported successful use of uridine to "rescue" mice from lethal 5-FU doses, as well as the ability to deliver higher 5-FU chemotherapeutic doses with concomitant uridine.[25,32] Human phase 1 uridine rescue trials soon followed in 1984.[28] Intravenous uridine was associated with severe phlebitis when administered peripherally and with cellulitis and thrombosis when given centrally.[41,42] This necessitated a shift toward oral administration. However, oral uridine was limited by poor bioavailability.[43] To prevent uridine catabolism by uridine phosphorylase and increase lipophilicity, uridine was modified to uridine triacetate in the late 1980s[45] and introduced in mice in 1996.[4] Phase 1 human studies of oral uridine, then also known as PN401, were reported soon after in 1997.[22] Meanwhile, capecitabine, which was synthesized in the early 1990s and patented abroad in 1992, underwent pilot/phase 1 studies in 1996 and received US market approval in 1998.[3,5,17] The FDA designated uridine triacetate an orphan product in 2009, and ultimately granted marketing approval in January 2015 to treat 5-FU or capecitabine overdose and early-onset, severe or life-threatening toxicity.[6]

PHARMACOLOGY

Chemistry/Preparation

Uracil (demethylated thymine) is a naturally occurring pyrimidine and one of the 4 fundamental bases of ribonucleic acid (RNA). Uracil has a molecular weight of 112.1 Da. Uridine is uracil attached by a β-N_1-glycosidic bond to a ribose ring. Uridine triacetate (or triacetyluridine) is uridine that has been triacetylated at the 2′,3′, and 5′ positions. Uridine triacetate has a molecular weight of 370.3 Da.

Mechanism of Action

Uridine as uridine triphosphate is an essential component of RNA, while uridine as uridine diphosphate glucose is an important precursor to glycogen synthesis.[48] Mechanisms of toxicity by the fluoropyrimidines (5-FU, capecitabine, tegafur, and floxuridine) are reviewed in Chap. 51 and summarized in Fig. 51–2. The 5-FU metabolite fluorouridine triphosphate (FUTP) is incorporated in RNA. Uridine triacetate, once absorbed and metabolized, supplies uridine, which can serve as a source for uridine triphosphate to compete with FUTP for RNA incorporation.[26] The enzyme thymidylate synthase generates deoxythymidine monophosphate (dTMP), which is necessary for DNA synthesis, from deoxyuridine monophosphate (dUMP). Uridine triacetate does not reverse inhibition of thymidylate synthase by the 5-FU metabolite fluorodeoxyuridine monophosphate (5-FdUMP), nor does it reverse incorporation of fluorodeoxyuridine triphosphate into DNA, as uridine is not present in DNA.

Related Agents

Various uridine formulations that are marketed as dietary supplements are available but they are not recommended to treat fluoropyrimidine toxicity because of a lack of quality control. Uridine triacetate is also packaged as branded Xuriden for treatment of hereditary orotic aciduria (HOA), at a dose that is different than for fluoropyrimidine toxicity.[47]

Pharmacokinetics and Pharmacodynamics

The pool of physiologically available uridine arises both from pyrimidine salvage pathways and through the de novo synthesis of uridine monophosphate (UMP) by the enzyme uridine monophosphate synthetase (UMPS). Uridine monophosphate synthetase catalyzes UMP generation from orotate and phosphoribosylpyrophosphate (PRPP), which is itself a product of the pentose phosphate pathway.[48] Uridine phosphorylase metabolizes uridine to uracil, and uracil is further degraded to dihydrouracil, 3-ureidopropionate, and ultimately to β-alanine by dihydropyrimidine dehydrogenase, dihydropyrimidinase, and β-ureidopropionase, respectively.[48] Unlike uracil, uridine is not a substrate for dihydropyrimidine dehydrogenase (DPD), the enzyme responsible in humans for metabolizing approximately 80% of 5-FU.[9,37]

In one of the earliest studies in a small group of 7 healthy volunteers, baseline uridine concentrations were 2.32 ± 0.58 μmol/L in plasma, and 10.44 ± 5.06 μmol/L in bone marrow.[14] Other studies found human plasma physiological uridine concentrations more typically ranging from 3 to 8 μmol/L.[28,48] When given in only trace amounts, radiolabeled uridine elimination was triphasic, with initial half-lives of 0.57±0.28 and 1.79±0.62 minutes, and a terminal half-life of 17.5±7.3 minutes.[14] This rapid elimination could be slightly altered with increasing dose. Intravenous uridine bolused at large doses of 1 to 12 g/m^2 cleared from the plasma in a biphasic manner with an initial half-life of 25±8 minutes and a terminal half-life of 118 minutes.[28] Uridine concentrations increased linearly with increased IV doses.[28] The volume of distribution (V_d) of uridine averaged 0.481±0.07 L/kg with trace amounts and 0.634 L/kg, with large IV doses.[14,28] The goal of sustained serum uridine concentrations higher than 70 μmol/L, which are needed to expand intestinal and bone marrow nucleotide pools and to prevent toxicity,[26,31] was explored in several pharmacokinetic evaluations. Continuous uridine infusions of 1 and 2.5 g/m^2/hour increased plasma uridine concentrations to steady-state concentrations of 500 and 1,000 μmol/L, respectively.[42] Intermittent 3-hour dosing of 3 g/m^2 (the maximum tolerated dose) created peak and nadir concentrations of 846 to 1,306 μmol/L and 138 to 335 μmol/L, respectively.[42] When uridine was changed to the oral route to mitigate safety concerns with the intravenous product, with single uridine doses from 0.3 to 12 g/m^2, bioavailability was extremely poor and ranged from only 5.8% to 9.9%.[43] At the maximum tolerated single oral dose of 8 to 12 g/m^2, plasma uridine concentrations reached 60 to 80 μmol/L; however, at the maximum tolerated multiple-dose regimen of 5 g/m^2, steady-state concentrations were only approximately 50 μmol/L.[43] Uridine's oral dosing limitations were confirmed in a separate study in which oral dosing of uridine 8 g/m^2 yielded mean trough concentrations of only 42.9±18 μmol/L.[40]

The significant pharmacokinetic limitations of rapid uridine plasma clearance and poor bioavailability, as well as poor oral tolerance and the safety issues surrounding intravenous administration, prompted evaluation of uridine delivery as a uridine triacetate prodrug.[4]

Uridine triacetate has several pharmacokinetic advantages. It is more lipophilic than uridine and does not require the pyrimidine transporter for absorption, which results in enhanced transport across the gastrointestinal mucosa.[19,22] Additionally, uridine triacetate is not a substrate for uridine phosphorylase, thus mitigating catabolism.[19]

Following absorption, uridine triacetate is deacetylated by nonspecific esterases to uridine and acetate. Mouse studies demonstrated that uridine

triacetate had decreased first-pass effects that increased uridine bioavailability from 7% to 53% and decreased time to maximum plasma concentrations (ie, to 507 µmol/L at 0.4 hours, compared to only 20 µmol/L at one hour with uridine).[4] Subsequent human evaluations demonstrated that oral uridine triacetate doses of 3.3 g produced average uridine trough values of 37.3 µmol/L and 6.6 g doses produced average trough values of 50.8 µmol/L.[22] With intensive dosing (6 g every 2 hours for 3 doses followed by 6 g every 6 hours for 15 doses), the mean C_{max} was 259.33 µmol/L 2 hours after the third intensive dose, and this was then maintained above 100 µmol/L for more than 6 hours.[19] Following single and repeat dosing every 8 hours of a proprietary supplement that contained 0.58 g (1.61% by weight) uridine and 5.4 g uridine triacetate (15.0% by weight), the peak plasma uridine concentrations one to 2 hours later were 150.9±39.3 µmol/L with single dosing and 161.4±31.5 µmol/L with repeat dosing.[46] In clinical trials with current labeled dosing of 10 g for adults and 6 g/m^2 for children, the maximum uridine concentrations occurred after 2 to 3 hours, with a half-life of 2 to 2.6 hours.[21] Plasma uridine concentrations were 99 to 119 µmol/L after the first dose and rose to 153 to 160 µmol/L after the final dose.[6]

ROLE IN FLUOROPYRIMIDINE TOXICITY

Previous therapy for fluoropyrimidine toxicity was limited to supportive care, included discontinuing drugs that impaired fluoropyrimidine clearance, ECG and cardiovascular monitoring, volume resuscitation, electrolyte repletion, antiemetics and antidiarrheals, colony-stimulating factors, broad-spectrum antibiotics, glutamine enteral supplementation, and ACE inhibitors (for 5-FU-related cardiac dysfunction).[1,2,15] Despite these measures, toxicity was often severe, including bone marrow suppression (with neutropenia, infection, and sepsis), gastrointestinal toxicity (with mucositis, stomatitis, vomiting, transaminitis, and severe diarrhea), volume depletion, acute kidney injury, cardiotoxicity (dysrhythmias, congestive heart failure, and hemorrhagic pericarditis), neurotoxicity, mutisystem organ failure, and death. Uridine triacetate rescue offers a novel antidotal mechanism to mitigate fluoropyrimidine toxicity. Hematopoietic and gastrointestinal mucosal progenitors efficiently incorporate exogenous uridine by the salvage pathway, compared to solid tumors, which favor de novo synthesis, providing an explanation for the effectiveness of exogenous uridine in competing with FUTP in normal tissues.[37]

Animal Studies

In the first mice studies, intraperitoneal (IP) uridine at 1, 5, or 10 g/kg/day produced 100% survival from previously lethal doses of 5-FU (up to 800 mg/kg), although it was ineffective against higher fluorouracil doses (1,000 or 1,200 mg/kg).[25] With 2 doses of uridine 3.5 g/kg IP, the median lethal dose (LD_{50}) of fluorouracil was increased by 68% from 190 to 320 mg/kg.[32] Furthermore, in mice with tumors given uridine rescue, the maximum tolerated dose of fluorouracil was doubled from 40 to 80 mg/kg without attendant toxicity as well as improved efficacy.[32] In another mouse study using uridine rescue with multiple doses ranging from 1.5 to 3.5 g/kg, high-dose fluorouracil 100 mg/kg/week could be extended to very-high-dose 200 or 225 mg/kg/week, with improved chemotherapeutic efficacy.[34] In mice treated with the maximum tolerated single dose of 5-FU (200 mg/kg) followed in 24 hours by a 5-day rescue uridine infusion of 5 g/kg/day, bone marrow cellularity declines were blunted and recovery was hastened significantly.[24] Mitigation of 5-FU toxicity in doses up to 800 mg/kg with this regimen was also reconfirmed.[24] In combination chemotherapy experiments of methotrexate and 5-FU in which leucovorin intended for methotrexate rescue potentially worsened 5-FU toxicity, uridine rescue permitted an increase in 5-FU doses from 100 mg/kg that was associated with a 60% mortality to 5-FU doses of 150 mg/kg with only 6% mortality.[33] Two IV uridine (3.5 g/kg) doses at 2 and 20 hours after 5-FU dose permitted 5-FU increases from 100 mg/kg to 250 and 300 mg/kg and blunted the leukocyte and erythrocyte nadirs.[35,36] In an attempt to shift to oral regimens, doses of 4 g/kg oral uridine in mice were comparable IP rescue of 5-FU at doses of 150 mg/kg as part of a multidrug chemotherapeutic regimen, which was an increase by more than 50% of the maximum tolerated weekly dose.[31] The addition of a uridine phosphorylase inhibitor in order to sustain uridine concentrations was able to further lower the oral rescue dose to 2 g/kg without compromising efficacy.[31]

The limitations of uridine alone in oral or IV formulation, including its rapid plasma clearance, led to exploration of oral prodrugs in an effort to sustain therapeutic plasma concentrations. Both immediate (at 2 hours) and delayed administration of uridine triacetate (as late as 48 hours) were evaluated, with successful doubling of the maximum tolerated 5-FU dose from 100 mg/kg/week to 200 mg/kg/week.[38] To explore the window of efficacy of uridine triacetate resuscitation, mice were given a lethal dose of 300 mg/kg of 5-FU IP followed by uridine triacetate (2 g/kg orally every 8 hours for 15 doses) at 24, 48, 72, and 96 hours after 5-FU.[9] Survival rates were 90% at 24 hours, which declined to 60%, 30%, and 20% with each subsequent day's delay in administration.[9]

Because many cases of 5-FU toxicity are associated with DPD deficiencies and delayed 5-FU clearance, an animal model was created to mimic DPD deficiency. In mice given the lethal combination of 100 mg/kg 5-FU and the DPD dehydrogenase inhibitor 5-ethynyluracil (2 mg/kg) survival was 80%, 40%, 50%, and 20% after rescue at 24, 48, 72, and 96 hours after 5-FU, respectively.[44] This demonstrated efficacy even in the setting of compromised 5-FU elimination.

Human Studies

In the first phase 1 study exploring uridine, one or 2 doses of uridine 5 to 6 g/m^2 as a one-hour infusion after fluorouracil administration provided insufficient uridine to eliminate 5-FU toxicity as the 5-FU dose was increased from 550 to 800 mg/m^2.[28] The second phase 1 uridine trial included 20 patients treated with methotrexate (250 mg/m^2), 5-FU, leucovorin, and PALA, an inhibitor of the de novo pathway for the pyrimidine biosynthesis.[23] Fluorouracil doses started at 600 mg/m^2 (the prior maximum tolerated dose) and were escalated by 50 mg/m^2 until toxicity was reached. Because of high fevers with continuous uridine, uridine was given at 3 g/m^2 per hour for 3 hours on and then 3 hours off for a total of 72 hours of infusion. With the concomitant chemotherapy, the 5-FU dose could be increased to 750 mg/m^2 with uridine rescue with severe mucositis in only one patient and no decrease in functional status.[23] The oral route and additional supplementation were later explored in the last phase 1 uridine study with doses of 8 g/m^2 provided every 6 hours for 12 doses.[40] With this oral uridine schedule, the maximum tolerated dose of 5-FU could be increased 45% from 1.1 to 1.6 g/m^2 in patients also receiving methotrexate, and by 33% from 0.9 to 1.2 g/m^2 in patients receiving both methotrexate and doxorubicin.[40]

In the first phase 1 trial of uridine triacetate, in which 38 patients were rescued at 24 hours with 6 g as a tablet or 6.6 g as a suspension every 6 hours for 10 doses, the tolerated 5-FU dose could be increased from 0.6 to 1 g/m^2.[22] In a second phase 1 trial, 6 g of uridine triacetate was given as a rescue at 8 hours after 5-FU administration and then every 8 hours for 8 doses (48 g). When 5-FU dose-limiting toxicity was reached, intensive uridine triacetate (6 g) was given every 2 hours for 3 doses, and then every 6 hours for 15 doses.[19] Fluorouracil at 1.0 g/m^2 was tolerated without toxicity with uridine triacetate rescue, and the 5-FU dose could be consistently elevated further to 1.25 g/m^2 with intensive rescue. Fluorouracil doses as high as 1.95 g/m^2 were possible, but with hematologic toxicity occurring at this dose.[19] In a phase 2 trial, 65 patients with gastric carcinoma were administered 1.2 g/m^2 of 5-FU (twice the usual dose) with leucovorin, followed by 6 g of uridine triacetate every 8 hours, with rescue at 8 hours after 5-FU, for a total of 8 doses (48 g).[16] This normally toxic 5-FU dose, which leads to 3- to 5-fold increases in 5-FU systemic exposure, was tolerated with no episodes of severe stomatitis or diarrhea, and only a 20% incidence of moderate or severe neutropenia.[16]

The pivotal efficacy trials of uridine triacetate were 2 compassionate-use studies that were summarized in 2 publications and analyses by the FDA. Those included WELL401, an open-label, single-arm, multicenter emergency use study and collection of single-patient INDs, and 401.10.001, an open-label expanded access protocol.[7,8,21,29] In these trials of 173 total patients, 142 patients had documented overdose (136 by 5-FU at 1.9 to 576 times the planned infusion rate or doses up to 10 times the intended dose and 6 by capecitabine 7,000 to 2,800 mg), an additional 26 patients had rapid onset of toxicity (severe or life-threatening toxicities within 96 hours following the end of 5-FU administration), at least one of whom was DPD deficient, and 5 were lost to follow-up.[29]There were 6 pediatric patients, of whom 3 had ingested capecitabine unintentionally. Treatment included uridine triacetate 10 g or 6.2 g/m^2 orally every 6 hours for 20 doses. Historical controls—albeit confounded by publication, reporting, and litigation bias—included 47 cases from the FDA (eg, the Manufacturers and User Facility Device Experience Database and Adverse Event Databases), ISMP (Institute for Safe Medication Practices), the medical and gray literature, and forensic cases, which included 25 patients with available data for 5-FU administered dose, 5-FU time and rate of administration, and the patient outcomes.[29] The primary outcome, survival to 30 days or chemotherapy resumption, was achieved overall in 158 of 168 patients (94%), with an additional 5 lost to follow-up, which included 137 of 142 patients (96%) with overdose and 21 of 26 (81%) with early-onset toxicity. Not all of these patients had expected lethality based on the infusion rate and dose. Efficacy in late administration after more than 96 hours was significantly diminished. In the 8 patients in the early toxicity cohort who had therapy initiated after 96 hours following 5-FU exposure, only 3 survived (37.5% survival).[29] Acknowledging the aforementioned limitations of historical controls, the historical cohort patients—who appeared to be comparable to the overdose patients treated with uridine triacetate as ascertained in the FDA medical review—experienced only a 16% survival (4 of 25 patients) when treated with supportive care alone.[8,21] The FDA separately reviewed the Adverse Event Reporting System for postmarketing fatal cases of fluoropyrimidine toxicity. There were 203 cases in the past 50 years (58 5-FU cases and 145 capecitabine cases), many of which were similar in their early-onset, severe, or life-threatening toxicity presentation, which ultimately all resulted in death despite supportive care.[21] In a separate phase 3 trial for which outcomes data are not yet available (NCT00024427), 2 patients with DPD deficiency were identified who had

received high-dose 1.4 g/m^2 5-FU followed by 8 doses of uridine triacetate every 8 hours.[37] One patient developed severe thrombocytopenia and rash and survived, whereas the other patient died with a perforated duodenal ulcer and candidemia, highlighting the risk that the DPD genetic deficiency presents to patients.[37] There are no data on uridine triacetate efficacy in overdose of tegafur, a 5-FU prodrug, although it would be reasonable to provide uridine triacetate in this circumstance.

ADVERSE EFFECTS AND SAFETY ISSUES

The most common adverse events observed in the clinical trials of uridine triacetate were vomiting (8.1%), nausea (4.6%), and diarrhea (3.5%).[29] These adverse effects are also consistent with those in patients receiving fluoropyrimidine chemotherapy both therapeutically and in overdose.[29] Of 135 patients in the pivotal studies, 3 patients had to discontinue uridine triacetate because of adverse effects within 30 days.[8] Safety data can also be gathered from use of uridine triacetate in additional patient populations. FDA reviews identified uridine triacetate use in 4 patients with hereditary orotic aciduria (HOA), 53 adults with diabetic neuropathy; 30 patients (22 children and 8 adults) with mitochondrial and metabolic disorders; 46 healthy subjects, 148 patients (6 children and 142 adults) at risk of 5-fluorouracil (5-FU) toxicity, and 288 subjects receiving high-dose 5-FU.[12,13] Providing boundaries for safe dosing regimens, the doses studied included 120 mg/kg/day for 9 months in HOA; 4 or 8 g/day for 6 to 12 months in diabetic neuropathy; 33 to 300 mg/kg/day for up to 18 years in patients with mitochondrial and metabolic disorders; and doses of 6 to 40 g/day for 5 days in 5-FU toxicity.[13] Only “non-serious” gastrointestinal adverse effects were identified, which were attributed to an undisclosed excipient that was demonstrated to be in an earlier uridine triacetate formulation.[11] No treatment discontinuations occurred in HOA clinical trials for adverse events or for any other reason. Diarrhea was reported in patients administered doses of uridine triacetate greater than 4 g/day.[11] Regarding QT interval prolongation hERG potassium channel current inhibition was reported in vitro with uridine triacetate but not with uridine, but not at physiologically relevant concentrations, and no cardiac toxicity was observed in dog or rat studies.[8,9,13] In vitro, no significant CYP450 enzyme interactions were found with uridine or uridine triacetate.[7,10] Uridine triacetate is a weak P-glycoprotein substrate and inhibitor in vitro, and the potential for local inhibition at the gut level could not be excluded.[13]

PREGNANCY AND LACTATION

There are insufficient data on the use of uridine triacetate during pregnancy to inform the risks of birth defects or miscarriage. Animal studies did not demonstrate toxicity when uridine triacetate was provided at one-half the human dose.[6] The presence of uridine triacetate in human milk is unstudied.

DOSING AND ADMINISTRATION

Uridine triacetate dosing in adults is 10 g (1 packet) orally every 6 hours for a total of 20 doses, without regard to meals.[6] The pediatric dose is 6.2 g/m^2 up to the adult maximum, and a table for the conversion of grams to graduated teaspoons for children is provided in the prescribing information.[6] - Uridine triacetate is mixed with 3 to 4 ounces of soft foods (such as applesauce, pudding, or yogurt) and ingested within 30 minutes, along with 4 ounces of water.[6] We recommend that a 5-HT$_3$-receptor antagonist be given an antiemetic such as ondanstron, 20 to 30 minutes prior to each dose to prevent vomiting. If vomiting occurs within 2 hours of the last dose, the entire dose is given within 15 minutes of vomiting and the next dose is given at the next scheduled interval. In the event the patient cannot tolerate the oral route (eg, severe mucositis), then we recommend that uridine triacetate be given by nasogastric or gastrostomy tube. If provided via this route, then 4 ounces of a food starch–based thickening product in water should be stirred briskly until the thickener has dissolved, and the contents of one full 10-g packet of uridine triacetate granules that have been crushed to a fine powder added to the reconstituted food starch–based thickening product.[6] For pediatric patients receiving less than 10 g, the mixture should be prepared at a ratio of no greater than 1 g per 10 mL of reconstituted food starch–based thickening product and mix thoroughly.[6] The nasogastric or gastrostomy tube should be flushed with water following administration. Although uridine triacetate absorption is unaffected by food, medicines such as bismuth, cholestyramine, Kaopectolin, and sucralfate interfere with absorption.[8]

FORMULATION AND ACQUISITION

Uridine triacetate granules contain 10 g of orange-flavored, white to off-white oral granules in single-dose packets. Inactive ingredients include

ethylcellulose (0.309 g), Opadry Clear (a proprietary dispersion of hydroxypropylmethylcellulose and Macrogol, 0.077 g), and natural orange juice - flavor (0.131 g). Uridine triacetate is supplied as a full course of therapy with 20 single-dose packets per carton, as well as a "24-Hour Pack" containing 4 single-dose packets per carton. The manufacturer-supplied contact number for ordering uridine triacetate is 1-844-293-0007.[20]

SUMMARY

- Uridine triacetate is a uridine prodrug that is the recommended treatment for toxicity from fluoropyrimidines such as fluorouracil and its prodrugs pecitabine and Tegafur.
- Uridine triacetate should be started as early as possible after recognition of overdose or early toxicity, as efficacy declines with delay to administration.
- The antidote must be given orally or by nasogastric or gastrostomy tube.

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