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Clinical and Biochemical Studies of High-Dose Thymidine Treatment in Patients with Solid Tumors

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Summary. In a clinical study of high-dose thymidine (TdR) treatment, toxic effects, TdR metabolism, and the influence of TdR on pyrimidine and purine metabolism were examined. Ten patients with solid tumors were treated with continuous infusion of TdR at 34–75 g/m^2/day for 3 to 5 days. Hematologic toxicity occurred with 5-day TdR infusion at 75 g/m^2/day but not when plasma TdR concentration failed to reach millimolar levels. In three patients who received similar TdR doses, plasma TdR levels were related to elimination rates of TdR and its metabolites from plasma. In one patient in whom urinary excretion was studied, 100% of the TdR dose given was recovered in the form of TdR, thymine (Thy), β-aminoisobutyrate, and 5-hydroxymethyluracil (5-HMUra). The latter metabolite, which had not been previously described in high-dose TdR treatment, was also found in plasma at levels from 5% to 10% of those of TdR. No effects of high-dose TdR infusion on purine levels in plasma were observed, while a substantial increase in uracil levels was noted both in plasma and urine. These data provide further information on high-dose TdR treatment with regard to clinical, pharmacokinetic, and biochemical effects.

Key words: Thymidine – Thymidine toxicity – Thymidine pharmacokinetics – Thymidine metabolism – Pyrimidines

Introduction

Several studies on high-dose TdR treatment have been reported from the point of view of clinical effects and pharmacokinetics. These investigations have been reviewed extensively (Martin et al. 1980; Bruno et al. 1981; Schornagel et al. 1982). Most of these studies involved patients with hematologic malignancies and the administration of TdR as a constant i.v. infusion for several days at doses of 70–90 g/m^2/day. Antileukemic effects were described in several cases as a reduction in peripheral blast counts and occasionally clearing of blasts in the bone marrow. These responses were, however, short lived. Responses in the few patients with solid tumors studied were occasional and minor. Various forms of toxicity were recorded with myelosuppression appearing to be the dose-limiting toxicity. Pharmacokinetic studies of TdR infusion showed that doses of 75–90 g/m^2/day produce plasma TdR levels in the millimolar range. In these studies, the only metabolite of TdR that was examined was Thy. During constant infusion of TdR, Thy is also present in plasma at millimolar concentrations. At high doses, TdR is eliminated largely by the kidneys due to saturation of metabolic clearance. At the end of infusion, TdR disappears from plasma with a half-life of 80–100 min. So far clinical trials have not proved high-dose TdR to be an effective anticancer therapy. However, the use of TdR in modulating the activity of other antimetabolites may be more prospective (see review, Schornagel et al. 1982).

The present study provides a closer examination of some aspects of the clinical and biochemical characteristics of high-dose TdR infusion. Hematologic toxicity is assessed with regard to interpatient differences in TdR pharmacokinetics. TdR metabolism is studied beyond the breakdown of TdR to Thy. Effects of TdR on plasma levels of normal pyrimidines and purines are examined.

Materials and Methods

Patients

Ten patients, seven females and three males, with advanced-stage cancer were entered in the study. The median age was 59 years (range 45–75 years). The following tumor types were included: three head and neck cancers; two colon cancer; one soft tissue sarcoma; and four

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Table 1. Doses of TdR given to patients

Patient	TdR dose (g/m²/day)	Duration of infusion (days)
1	34	3
2	50	3
3	70	3
4	70	3
5	75	3
6	75	5
7	75	3.5[a]
8	75	5
9	75	5
10	75	5

[a] Infusion was terminated after 84 h due to anuria

Table 2. Hematologic toxicity of high-dose TdR infusion

Patient number[a]	Hb (m*M*) [b]Pre/ nadir	WBC (10^3/µl) Pre/nadir	Granulocytes (10^3/µl) Pre/nadir	Lymphocytes (10^3/µl) Pre/nadir	Platelets (10^3/µl) Pre/nadir
1	7.6/5.8	10.3/ 6.2	8.0/ 4.4	1.0/0.6	198/133
2	6.0/4.9	14.2/12.5	12.3/10.5	1.0/0.9	910/577
3	6.1/5.1	7.3/ 6.3	5.8/ 5.5	0.9/0.3	251/125
4	7.2/4.8	6.1/ 2.5	4.4/ 1.7	1.3/0.4	108/ 62
5	5.8/4.6	3.5/ 3.3	2.4/ 2.8	0.9/0.3	173/ 90
6	5.1/4.9	7.6/ 1.8	6.3/ 1.3	0.8/0.3	165/ 10
8	8.0/6.1	4.9/ 1.8	2.9/ 1.5	1.4/0.1	173/ 76
9	10.1/8.2	5.2/ 4.2	3.8/ 2.5	1.2/0.7	180/ 88
10	8.5/7.1	8.4/ 1.9	6.8/ 0.9	1.2/0.6	193/116

[a] Patient 7 was not evaluable
[b] Pre = pretreatment value

melanomas. Anamnesis was taken daily during treatment, while the patients underwent a physical examination at the same time. Pretreatment laboratory studies included: complete blood cell counts; urinalysis; and determination of serum creatinine, blood urea nitrogen, uric acid, serum electrolyte, glucose, calcium, phosphorus, bilirubin, alkaline phosphatase, gammaglutamyl-transpeptidase, serum glutamate-oxalate transaminase, serum glutamate pyruvate transaminase, lactate dehydrogenase, total protein, and serum protein fractions. Hematologic and biochemical studies were repeated daily during treatment and twice weekly following TdR infusion. Plasma and urine samples were collected before and during treatment for determination of TdR and TdR metabolites, other pyrimidines, and purines. Toxicity was assessed according to WHO criteria (Miller et al. 1981).

TdR Infusions

Isotonic solutions of TdR at physiologic pH were prepared by the Pharmacy Department of the University Hospital Utrecht. Preparations of 30–40 g/l TdR were made from analytical grade TdR (Sigma Chemical, St. Louis, Mo) and sterilized by autoclave, which is known to cause about 2% hydrolysis of TdR (Chiuten et al. 1980).

Treatment Schedule

TdR was administered as a continuous i.v. infusion via a long indwelling femoral vein catheter (16G) to avoid phlebitis. In all cases IVAC infusion rate control equipment was used. The initial two patients were given moderate doses of 34 and 50 g/m²/day, respectively, for 72 h, while subsequent patients received 70–75 g/m²/day for 72 or 120 h (Table 1). Additional courses were planned only in case there was no evidence of progressive disease at 3 weeks after treatment.

Assay of Bases and Nucleosides in Plasma and Urine

Plasma was separated from heparinized blood samples within 30 m by centrifugation at 5,000 xg at 4 °C. Plasma was deproteinized by addition of 2 volumes trichloroacetic acid and the supernatant was neutralized as described by Khym (1975). Urine samples were stored at −20 °C. Each 24-h volume was thawed and mixed and an aliquot was filtered through a C-25 Amicon cone to remove protein. Plasma extracts were analyzed for pyrimidine and purine bases and nucleosides by high pressure liquid chromatography (HPLC) as described previously (Leyva et al. 1980). Briefly, HPLC separation was carried out using columns packed with strong anion-exchange resins (Aminex A29 or A28; Bio-Rad Laboratories, Richmond, CA). Two isocratic elution systems, A and B, were used. The eluent consisted of 0.01 *M* sodium phosphate, 0.005 *M* citric acid, and ethanol. In system A, the eluent was at pH 8.8–9.2, contained 19% ethanol, and the column temperature was 70 °C, while in system B, the pH was 8.35, ethanol content was 28.5%, and operating temperature was 60 °C. HPLC instrumentation consisted of Perkin Elmer Series 2/2 pump, LC-15 UV detectors (254 and 280 nm), and Sigma 10 integrators. Samples of 10 to 50 µl were injected. Peaks were identified by retention time and spectral characteristics and quantified by peak height or area based on calibrations with known standard compounds. System A was used for fractionation of pyrimidines, whereas system B was better suited for fractionation of purines. Urine samples were analyzed for TdR and TdR metabolites by cation exchange chromatography as described by Van Gennip et al. (1980).

Results

Clinical Effects

Nine of ten patients were evaluable for toxicity. Patient 7 was excluded due to development of hypotension and anuria during treatment. Toxic effects, which were mild to moderate, were seen only in those patients who received 70 or 75 g/m²/day TdR. Myelosuppression was the most common toxicity (Table 2). We observed a median WBC nadir of 2.5×10^3/µl with granulocyte and lymphocyte nadirs of 1.7 and 0.3×10^3/µl, respectively. The median platelet nadir was 90×10^3/µl. Nonhematologic toxicity was observed mainly in the gastrointestinal tract and CNS and was generally not severe (grade 1 or 2). In this group of patients, one patient with melanoma had no change of disease after the first course of TdR, but refused further treatment. All other patients had progressive disease.

Plasma Concentrations of TdR and TdR Metabolites

Plasma TdR concentrations were determined at various time points during TdR infusion for all patients treated (Fig. 1). Pretreatment TdR concentration was consistently less than 1 µ*M*. Steady-state TdR levels in plasma were attained within 12 to 24 h after start of

infusion. Patients 1 and 2, who received 34 and 50 g/m^2/day doses, respectively, had mean TdR levels of about 0.5 mM during infusion. All other patients (excluding patient 7) who received TdR doses of 70 or 75 g/m^2/day, had mean plateau concentrations ranging from 0.67 to 1.76 mM (median: 1.34 mM). Among those patients who received 75 g/m^2/day TdR infusion for 5 days, patient 9 different appreciably with approximately twofold lower plasma TdR concentrations. In patient 7, plasma TdR levels continued to rise until termination of infusion, at which time the TdR levels had reached 7.51 mM.

Thy and 5-HMUra concentrations in plasma were also followed during TdR infusion (Table 3). The ratio of Thy to TdR during infusion varied from 0.6 to 2.8, while 5-HMUra plasma concentrations were about 5%–10% of TdR levels for all patients examined. Resolution of peaks of 5-HMUra and other pyrimidines from large peaks of TdR and Thy varied with pH of the eluent. Also, different lots of chromatographic resin gave slight differences in fractionation pattern of pyrimidines. Figure 2 shows HPLC tracings of representative plasma samples from different patients, obtained during TdR infusion. The presence of 5-HMUra is evident in each sample, while either uridine or uracil, but not both in the same chromatogram, is resolved sufficiently for quantification. 5-HMUra had retention times similar to either pseudouridine or 5-methyluridine standards. Identification of the major component fractionated between TdR and Thy as 5-HMUra was based on consistent agreement of retention time and 254/280 absorbance ratio with values obtained with the standard compound. In addition, cation-exchange chromatographic separations of urine of treated patients also showed the presence of a peak corresponding to 5-HMUra based on retention time and positive identification of isolated peak compound using 2-dimensional thin-layer chromatographic techniques as described by Van Gennip (1981).

For three patients, who received 5-day infusions of 75 g/m^2/day TdR, plasma disappearance of TdR and metabolites was examined following the end of infusion (Fig. 3). For patients 6, 8, and 9, initial half-life values of TdR were 2.3, 1.5, and 1.0 h, respectively. For the first 6–8 h after the end of infusion, an initial half-life for Thy was estimated at about 9 h. After 12 h, the rate of disappearance of Thy from plasma was similar to that of TdR; by 24 h after the end of infusion, both the Thy level and the TdR level returned to pretreatment values (<1 μM). In patient 9, Thy disappearance was also more rapid compared with patient 6. 5-HMUra levels in plasma increased slightly after the end of infusion, but declined rapidly to undetectable levels at 24 h postinfusion.

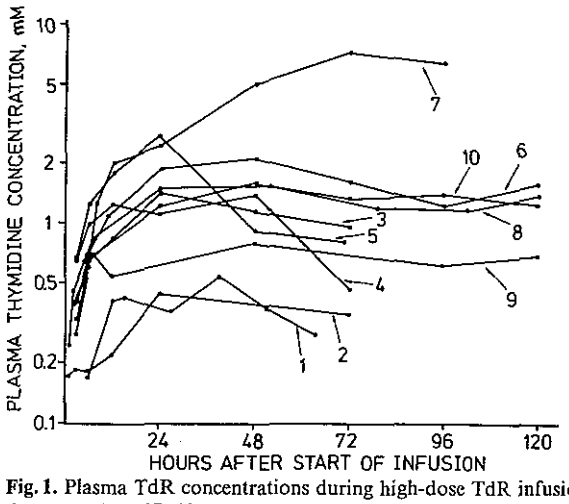

Fig. 1. Plasma TdR concentrations during high-dose TdR infusion. Curves are identified by patient number

Table 3. Steady-state plasma concentrations of TdR, Thy, and 5-HMUra during high-dose TdR infusion

Patient No.	Dose g/m^2/day	TdR (mM)	Thy (mM)	5-HMUra (μM)
1	34	0.40±0.09[a]	1.14±0.25	42± 21
2	50	0.32±0.09	0.89±0.08	15± 2
3	70	1.10±0.25	1.34±0.12	–[d]
4	70	1.25±0.13[b]	1.42±0.18	–
5	75	1.57±0.90	1.18±0.24	–
6	75	1.76±0.32	1.37±0.10	88± 8
7	75	2.10to7.51[c]	2.21to4.44	52to272
8	75	1.37±0.17	1.27±0.20	63± 5
9	75	0.67±0.05	1.08±0.03	33± 4
10	75	1.34±0.20	1.39±0.15	92

[a] Values given as mean±S.D. or as single determination
[b] Last day not included
[c] Values are given as ranges
[d] Not determined

In two patients, elimination of TdR and TdR metabolites from plasma followed a different course (data not shown). In patient 4, TdR levels declined from millimolar levels during the early part of the infusion period to 0.238 mM at the end of the infusion. Three days following the infusion, TdR concentration in plasma remained unchanged, while Thy levels decreased to 0.235 mM. The delay of TdR excretion in this patient could not be explained since there were no signs of renal or liver dysfunction. TdR infusion in patient 7 was discontinued at 84 h because of hypotension and anuria. The TdR, Thy, and 5 HMUra levels measured 72 h after start of infusion were 7.51, 4.44, and 0.272 mM, respectively (see Table 2). Over a period of 41 h following the end of the infusion, the plasma TdR concentration decreased gradually to 3 mM, while Thy and 5-HMUra levels remained essentially unchanged.

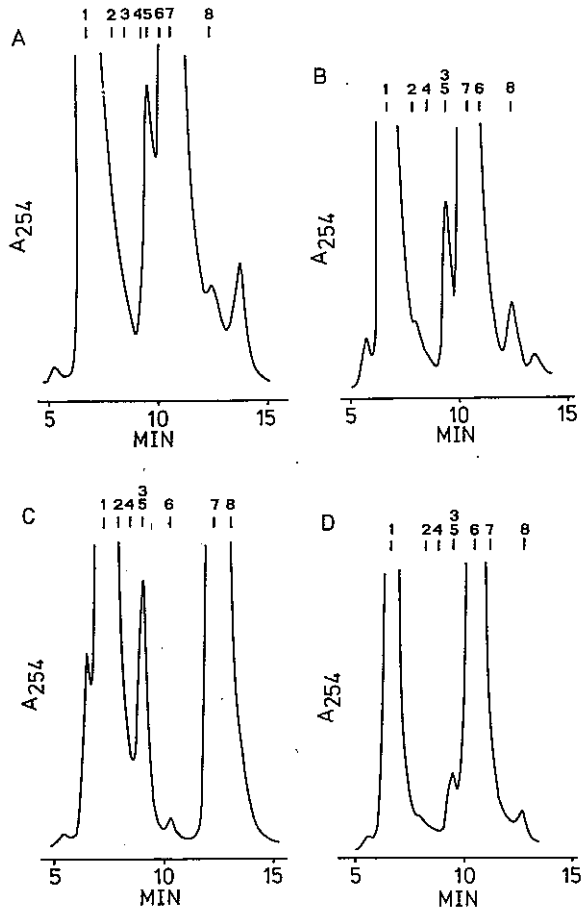

Fig. 2 A–D. Representative HPLC chromatograms of plasma samples during high-dose TdR infusion showing separations of TdR, Thy, and other pyrimidines. **A**, patient, 8; **B**, patient 9; **C**, patient 6; **D**, patient 2. Retention times of standard compounds are indicated above the chromatograms. *1* TdR; *2* deoxyuridine; *3* pseudouridine; *4* 5-methyluridine; *5* 5-HMUra; *6* uridine; *7* Thy; *8* uracil

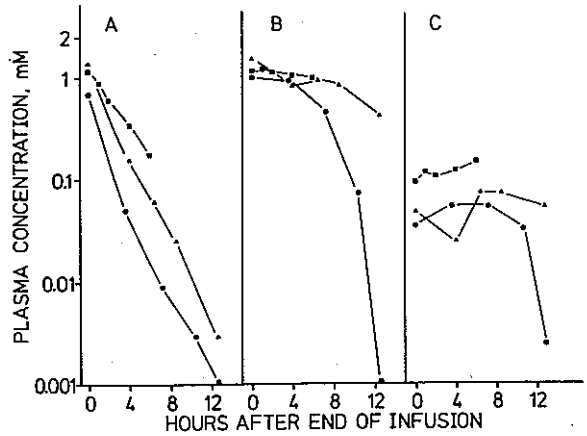

Fig. 3 A–C. Decline of plasma levels of TdR (**A**), Thy (**B**), and 5-HMUra (**C**) after the end of high-dose TdR infusion. ■ Patient 6; ▲ patient 8; ● patient 9

In patient 10, the clearance rate of TdR and Thy were determined by using average plasma concentrations over 24-h intervals and the input and the urine output over the same interval as described by Zaharko et al. (1979). Total body clearances (mean ± S.E.M. of three determinations at steady-state conditions) for TdR and Thy were 233 ± 12 and 227 ± 3 ml/min, respectively. Renal clearances for TdR and Thy were 71% and 22%, respectively, of total body clearances. These calculated values correspond well with the amounts of TdR and Thy recovered from the urine. Table 4 describes the urinary excretion of TdR, TdR metabolites, and uracil for patient 10. The TdR dose consisted of 2.50 mol administered over 5 days. Total recovery in urine was 2.53 mol in the form of 68% TdR, 22% Thy, 8.7% β-aminoisobutyrate, and 1.2% 5-HMUra.

Other Pyrimidines and Purines in Plasma

Uridine and uracil concentrations in plasma of some patients were determined during high-dose TdR treatment when TdR and Thy were below millimolar levels. For patients 6 and 7, plasma uridine concentrations before infusion and up to 6 h after the start of infusion (mean ± S.D. for 3 or 4 values at different time points) were 2.8 ± 0.5 and 2.6 ± 0.6 μ*M*, respectively. Subsequently, these levels increased during TdR infusion to 5.4 ± 1.3 and 7.6 ± 2.5 μ*M*, respectively. In patient 6, plasma uridine concentration returned to the pretreatment level in 1 to 3 days after the end of the infusion. In patients 1 and 2, uracil levels could be examined in plasma up to 7 h after the start of the TdR infusion. In these patients as in all others, the pretreatment level of uracil in plasma was 0.3 μ*M*. Uracil levels in patients 1 and 2 increased gradually to 3.5 and 8.5 μ*M*, respectively, while uridine levels were not altered. In patient 9, plasma uracil levels, which could be monitored throughout the infusion period, increased to 6.0 μ*M* during infusion and declined to undectable levels after infusion. Also enhanced urinary excretion of uracil was noted in patient 10 during TdR infusion (Table 4).

Plasma concentrations of purine bases and nucleosides were determined during TdR treatment. For patients 3 and 4, adenine, hypoxanthine, and inosine were measured in plasma (Table 5) using HPLC system B. The levels of these purines were below 5 μ*M* before and during TdR infusion and did not vary appreciably. Adenosine, guanosine, and guanine were not detectable (< 0.5 μ*M*). Using HPLC system A for examining primarily pyrimidine levels in plasma, we could monitor semiquantitatively hypoxanthine and inosine in plasma samples of other patients. It was ap-

Table 4. Urinary excretion of TdR and TdR metabolites and uracil during and following high-dose TdR treatment[a]

24-h Urine collection number	Period during infusion	mmol/24 h				
		TdR	Thy	5-HMUra	β-AIBA[b]	Uracil
0	Preinfusion	–[c]	–	–	–	0.03
1	1– 12 h	153	48	1.3	8.5	1.0
2	12– 36 h	264	79	5.2	23.0	0.9
3	36– 60 h	270	82	4.6	26.4	0.9
4	60– 84 h	403	117	5.5	46.0	1.2
5	84–108 h	383	125	6.6	45.8	1.3
6	108–120 h	257	89	6.1	35.8	1.3
7	Postinfusion	<1.0	9	2.3	37.2	0.8
8	Postinfusion	–	–	–	0.6	0.06

[a] Data are for patient 10 who received 75 g/m²/day TdR for 5 days
[b] β-AIBA = β-aminoisobutyrate
[c] Value less than 0.03 mmol/24 h

Table 5. Plasma concentrations of purines during and after 3-day TdR infusion at 70 g/m²/day[a]

Patient	Days after start of infusion	μM		
		Ade	Hyp	Ino
3	0	1.3	4.0	0.5
	0.5–3	0.5±0.3	4.8±1.0	1.0±0.5
	4 –6	<0.3	3.2±2.0	<0.3
4	0	0.9	2.3	1.0
	0.5–3	0.8±0.2	3.7±0.2	0.5±0.3
	6	0.4	1.4	0.4

[a] Values for adenine (Ade), hypoxanthine (Hyp), and inosine (Ino) are for single determinations or expressed as mean ± S.D. for three to four plasma samples taken on different days

parent that in other patients these latter purines did not vary in concentration more than twofold during TdR treatment.

Discussion

Various side effects including dose-limiting myelosuppression have been associated with high-dose TdR in reported clinical stu " (see reviews Martin et al. 1980; Bruno et al. 19 Schornagel et al. 1982), and those observed in the present study were in concurrence. Further, we noted that appreciable hematologic toxicity occurred with 5-day infusion of 75 g/m²/day TdR only when steady-state plasma TdR levels in the millimolar range were attained; in patient 9, lack of hematologic toxicity was coincident with twofold lower plasma TdR levels. Also, shorter infusion periods of similarly high doses of TdR had little or no effect on the hemopoietic system except when TdR excretion was abnormal as observed with patients 4 and 7.

Due to the ability of deoxycytidine to reverse TdR toxicity (Egan et al. 1981), deoxycytidine availability could influence the action of TdR. Plasma samples of patients before and during treatment contained <0.2 μM (A. Leyva, unpublished data). It is unlikely that any reversal of TdR activity by endogenous deoxycytidine accounted for the differential TdR toxicity observed in the present study.

It is apparent that high-dose TdR infusion may result in appreciable variability with regard to plasma nucleoside levels. Data from three patients treated with equivalent TdR doses showed that steady-state plasma levels of TdR were dependent on the plasma half-life. In patient 9, who had submillimolar plasma TdR levels during infusion, more rapid elimination from plasma of Thy and 5-HMUra as well as TdR, was evident. Zaharko et al. (1979) described a similar case where submillimolar plasma TdR concentrations could be ascribed to a comparatively short TdR plasma half-life.

Previously reported pharmacokinetic studies on high-dose TdR in man have described only Thy as a metabolite – TdR and Thy recovered in the urine were estimated to account for 58% to 82% of the total TdR body clearance (Zaharko et al. 1979). The present study indicates that the unaccounted remainder is largely the endproduct of TdR metabolism, β-aminoisobutyrate, and 5-HMUra. Other possible intermediates in the catabolic pathway between Thy and β-aminoisobutyrate were not determined in urine or plasma samples, but were probably in very low amounts. The oxidation of Thy to 5-HMUra is an alternative route to degradation of TdR to β-aminoisobutyrate (Fink et al. 1956). The formation of 5-HMUra is consistent with the apparent saturation of Thy catabolism and has recently been described in a child with a deficiency of dihydrothymine dehydroge-

nase accompanied by Thy and uracil overproduction (Wadman et al. 1983). Although a relatively small percentage of the TdR dose was found as 5-HMUra, the latter metabolite was present in plasma at substantial concentrations. To our knowledge there is no published information on 5-HMUra regarding potential biological effects. The role of this modified pyrimidene base in side effects observed with high-dose TdR infusion cannot be ruled out.

TdR infusion produces elevations in plasma uridine and uracil levels and enhances uracil excretion, suggesting inhibition of uridine catabolism by TdR or one of its metabolites. A likely explanation is that Thy inhibits uridine phosphorylase and competes with uracil for the common catabolic enzyme pyrimidine dehydrogenase. Notably, 5-fluorouracil likewise shares the same catabolic pathway and TdR treatment would also be expected to hinder 5-fluorouracil degradation and clearance from plasma. This is evident from clinical studies of TdR and 5-fluorouracil, which have demonstrated enhanced 5-fluorouracil toxicity as a result of increased plasma half-life of the pyrimidine analog (Kirkwood et al. 1980; Ohnuma et al. 1980).

Plasma purine levels in the patients studied were in the normal range (Leyva et al. 1980) and were not affected by high-dose TdR infusion. A marked alteration of purine metabolism by TdR was not apparent. However, this is assuming that such an effect would be reflected in changes in plasma purine concentration and would require corroboration by analysis of nucleotide pools in tissues.

The present study provides additional data on TdR toxicity, TdR metabolism, and effects of TdR on purine and pyrimidine metabolism in man. This information may be useful in further studies aimed at elucidating the limitations of high-dose TdR treatment or in studies on the combination of TdR with other antimetabolites.

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