Modulation of 5-Fluorouracil in Mice Using Uridine Diphosphoglucose

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ABSTRACT

Uridine diphosphoglucose (UDPG) is a precursor of uridine that can be used as a rescuing agent from 5-fluorouracil (5FU) toxicity. Four doses of UDPG (2000 mg/kg i.p. or p.o. at 2, 6, 24, and 30 h after SFU bolus) allowed the escalation of a weekly bolus of 5FU from 100 mg/kg (5FU100) to 150 mg/kg (5FU150) in healthy and tumor-bearing BALB/c, C57/B1, and CD8F1 (BALB/c × DBA/8) mice. 5FU150 without rescuing agents is not tolerated by the animals. When followed by UDPG, on the contrary, it is possible to increase the dose of 5FU even when it is modulated by leucovorin. Toxicity was the same for 5FU100 and 5FU150 + UDPG, and the nadir values (expressed as a percentage of pretreatment values) were 83 and 85% for weight, 45 and 45% for hematocrit, and 45 and 61% for leukocytes, respectively. Platelets were not affected by treatment.

A protective effect was also shown for the gastrointestinal tract. The enzymes thymidine kinase, maltase, and sucrase were measured in the intestinal mucosa at different times after 5FU treatment with or without UDPG rescue. Even if the nadir values in enzyme activities were similar in mice receiving or not receiving UDPG, the pattern of recovery showed that cell repopulation was more rapid in the group treated with UDPG.

5FU150 + UDPG had enhanced antitumor activity against CD8F1 mammary carcinoma and against the resistant tumor Colon 26 (tumor doubling time 1.9 days for controls, 8.5 days for 5FU100, 13.7 days for 5FU150 + UDPG, and 15.9 days for 5FU150 + leucovorin + UDPG). We demonstrated that UDPG administered at 2, 24, and 30 h after 5FU100 does not reduce the antitumor activity of SFU in two sensitive tumors (Colon 38 and Colon 26-10).

In conclusion, UDPG is a promising rescuing agent for 5FU; it reduces the toxic side effects and increases the therapeutic index.

INTRODUCTION

5FU is an essential element in the treatment of several tumors, and different attempts have been made to improve the effectiveness of this drug. The complex intracellular metabolism of 5FU makes it a suitable candidate for modulation (1). Encouraging results have been obtained with several agents (2), and the association of 5FU with LV is at present the most widely used treatment for advanced colorectal cancer.

Similar to what is observed with other anticancer agents, it is possible to enhance the activity of 5FU by increasing the dose. In the mouse, the administration of high doses of 5FU has been associated with an increased incorporation of fluoronucleotides in RNA (3), and a dose-response effect has been demonstrated in the clinic for 5FU alone (4) and for the combination of SFU with modulating agents (5-7). Dose escalation, however, is generally prevented by the appearance of toxic side effects that primarily involve the bone marrow and the GI tract.

Biochemical modulation can be used not only to improve the antiproliferative effect of 5FU but also to reduce the toxicity of 5FU on normal tissues. Among the different compounds tested, the most interesting results have been obtained with Urd (2, 8). Urd rescue from the activity of 5FU has been evaluated extensively in preclinical systems (9-13). In clinical trials, the results were encouraging, but toxic side effects of Urd appeared after parenteral and oral administration (14, 15). For this reason, additional studies have been started to find a more suitable molecule that is equally effective in rescuing from SFU toxicity, but without the side effects of Urd (16, 17).

UDPG is a physiological substance that is normally used in biochemical reactions as a donor of phosphorylated sugars or as a precursor of glucuronic acid. It can also be converted into Urd, uridine diphosphoglucose, Urd, uridine; LV: leucovorin; MTD: maximum tolerated dose; TD: doubling time; TK: thymidine kinase; GI: gastrointestinal.

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protective activity of UDPG from 5FU side effects in terms of systemic, hematological, and GI toxicity. Furthermore, we tested the combination of 5FU and UDPG in different tumor models, both sensitive and resistant to 5FU, to determine the optimal rescuing schedule to avoid the risk of reducing the antitumor activity of 5FU.

MATERIALS AND METHODS

Chemicals. 5FU was obtained from Hoffman-La Roche (Mijdrecht, the Netherlands). LV was prepared by the pharmacy department of the Free University Hospital (Amsterdam, the Netherlands). UDPG was provided by Boehringer-Mannheim Italia (Monza, Italy). All drugs were given as i.p. bolus injections, except for experiments performed on CDF8F1 (BALB/c × DBA/8) mice. All other chemicals are commercially available.

Toxicity Studies. Female BALB/c or C57/BI mice of 8–10 weeks were obtained from Harlan/Cpb (Zeist, the Netherlands) and maintained in the Clinical Animal Laboratory of the Free University. All experiments were performed in agreement with the rules for animal welfare established by the local committee. CDF8F1 mice hosting first-generation transplants of CDF8F1 mammary carcinoma were used in a different set of experiments on oral UDPG.

Systemic toxicity studies were carried out in healthy female C57/BI and BALB/c mice. Parameters used to define the MTD were weight loss not greater than 15% (the initial weight of the mice was 20–23 g) and/or lethality less than 10%.

5FU was administered at the MTD as defined during the systemic toxicity studies (100 mg/kg for 5FU alone and 150 mg/kg when it was followed by UDPG rescue). LV was injected i.p. in two doses of 50 mg/kg; one dose was given 1 h before 5FU administration and one dose was given together with 5FU (12). Oral UDPG was given to CDF8F1 mice at a dose of 1950 mg/kg 2.5 h after 5FU administration, then five doses of 2600 mg/kg q 8 h. Parenteral UDPG was initially given at a dose of 2000 mg/kg, repeated four times at 2, 6, 24, and 30 h after 5FU administration. In a later phase of the study, the injection at 6 h was omitted.

Investigations on hematological toxicity were performed as described previously (12). Blood was drawn from the retro-orbital plexus with heparinized capillaries after slight ether anesthesia. Initial values (mean ± SD for five animals) for hematological parameters were: hematocrit, 42 ± 1.2%; leukocytes, 4700 ± 600 cells/ml; and platelets, 4.5 ± 0.6 × 100,000 cells/ml.

GI toxicity was studied as described previously (20). 5FU was administered once as an i.p. bolus at a dose of 200 mg/kg. Briefly, mice treated with 5FU with or without UDPG rescue were sacrificed at different time points. The small intestine was removed, washed with normal saline containing 1 mM DTT, and frozen in liquid nitrogen. After homogenization, TK activity was determined by measuring the conversion of 2-[14C]thymidine to 2-[14C]thymidine-monophosphate; sucrose and malate activity and protein content were determined according to published methods (20).

Antitumor Activity. Antitumor activity was studied on the murine colon carcinomas Colon 26 and Colon 26-10 maintained in female BALB/c mice, Colon 38 maintained in C57/BI mice as described previously (12), and on mammary tumor CDF8F1 (18). Tumors were transplanted s.c. in the thoracic region on each flank of the animals. Tumor size was measured sequentially twice weekly using a caliper, and the volume was calculated as length × width × height × 0.5. The evaluation of antitumor activity was based on the ratio of the mean volume of treated tumors and the mean volume of control tumors. The growth delay factor was calculated from the median tumor TD of the tumors of treated mice and control mice according to the following formula: growth delay factor = (TDtreated − TDcontrols)/TDcontrols. For Colon 26, TDcontrols, is about 3 days, whereas it is 4.5 days for Colon 26-10 and 5 days for Colon 38 (11). Treatment was started when the tumors had reached a size of 50–150 mm³ (approximately 10 days for Colon 26 and Colon 26-10 and 18 days for Colon 38). For CDF8F1 tumors, only the final weight of the tumor (measured 6 days after the third course of treatment) was considered.

Analysis of Plasma Concentrations of UDPG and Urd. Plasma was obtained from heparinized blood drawn from the retro-orbital plexus. Plasma was deproteinized by addition of cold trichloroacetic acid to a final concentration of 8% and by keeping it on ice for 15 min. After centrifugation (5000 × g for 15 min), the supernatant was neutralized by mixing with two volumes of triocylamine-freon (1:4) and centrifuged, and the aqueous part was recovered and stored at −20°C (21).

High-performance liquid chromatography analysis was performed isocratically on a C18-μBondapack column with 50 mmol/l KH2PO4, 5 mmol/l tetrabutyl ammonium hydrogen sulphate, and 2% methanol (v/v, pH 3.5), flow rate 1 ml/min. Peaks were detected by UV analysis at 254 and 280 nm. Retention times were 3.70 min for uracil, 4.60 min for Urd, and 13.60 min for UDPG. Concentrations were calculated from the integrated peaks using an AXXIOM system (Separations, the Netherlands).

RESULTS

UDPG Schedule. UDPG can be administered according to several schedules, p.o. or i.p. We tested different rescuing regimens to identify the optimal one. In the first set of experiments, UDPG was given p.o. over 2 days as described in “Materials and Methods,” then we used the parenteral administration of UDPG at similar time points (2, 6, 24, and 30 h after 5FU injection). In the course of our research, however, it became clear that it was possible to eliminate the dose at 6 h with no reduction in the rescuing effect of the treatment. Because this protocol was also more similar to that already used with Urd (9, 11), only data from BALB/c and C57/BI mice that received this rescuing regimen are reported in this paper. CDF8F1 mice received the oral rescue regimen.

Systemic Toxicity. The toxicity of different doses of 5FU, with or without UDPG rescue, was studied in healthy BALB/c mice. The results for the systemic toxicity (weight loss) are shown in Fig. 1. The MTD of 5FU with no rescue, given as a weekly bolus repeated two or three times, was 100 mg/kg in both BALB/c and C57/BI mice. This dose was well tolerated by the animals, and it caused a maximum weight loss of ~15%. A dose of 150 mg/kg was lethal by day 12, but it could be safely administered when it was followed by UDPG rescue. The max-
A dose of 150 mg/kg 5FU was considered the MTD for the combination, and 5FU_{150} + UDPG was used in the studies on hematological toxicity and on antitumor activity. In mice, the systemic toxicity of 5FU was not enhanced by the addition of L.V., and the same dose of 5FU could also be used when modulation with L.V. was used (12).

**Hematological Toxicity.** These studies were performed in healthy BALB/c mice by comparison of the standard MTD of 5FU (100 mg/kg) with 5FU_{150} + UDPG. Results expressed as a percentage of the initial value are shown in Fig. 2. 5FU administration caused a sharp decrease in hematocrit, with a nadir value of 42.8 at day 21 for 5FU_{150} and of 58.3 at day 15 for 5FU_{150} + UDPG. Changes in WBCs were quite similar, with nadirs of 49.3 and 62.7, respectively, at day 16. In both cases, an overshoot was observed after the end of treatment. Platelets were not reduced in either case, but a striking rebound was observed 2 weeks after the first dose for both protocols.

**GI Toxicity.** The effect of UDPG on the GI toxicity of 5FU was evaluated by measuring the protein content of the intestinal wall and the activity of enzymatic markers of cell proliferation (TK) and of enterocytic differentiation (sucrase and maltase) in the mucosa.

The mucosa of the small intestine was damaged to a similar extent by 5FU treatment, independent of UDPG administration, but the rescuing protocol allowed a faster recovery of cell functions. The decrease in TK activity is very fast (6–24 h) and is followed by a rebound, whereas digestive enzymes (maltase and sucrase) decrease more slowly and reach a nadir only on day 3. This suggests that their change depends on the antiproliferative effect of 5FU that inhibits the replacement of functionally mature enterocytes. Results are shown in Fig. 3.

Cell proliferation was estimated by measuring TK, and this parameter gave the best indication of the protective activity of UDPG. After a short-lasting reduction in the proliferative activity, the mucosa of mice receiving UDPG was actively regenerating already on day 4 (P < 0.01 both versus controls and versus animals not treated with UDPG). On day 7, TK activity in mice treated with UDPG was within normal ranges, whereas it was still high in mice that were not rescued (P < 0.01 both versus controls and versus animals treated with UDPG).

The protein content was initially slightly increased, then it was significantly reduced in both treatment groups. In animals receiving UDPG, however, protein content was normal on day 4, when in the other group it was still significantly lower than that of the controls.

The time course of the markers of enterocytic differentiation was similar to that of the protein content. Sucrase was lower.
than controls on day 2, but in the group of mice treated with UDPG, it was within the normal range already on day 3, when it was still low in the other group. Maltase was lower than controls on day 7 in the group not receiving UDPG.

**Antitumor Activity.** The therapeutic efficacy of the different doses of 5FU, followed by UDPG rescue when required, was studied in three sensitive tumors (Colon 26-10, Colon 38, and CD8F1) and in the resistant tumor Colon 26.

In Colon 26, maintained in BALB/c mice, we studied the ability of 5FU100 + UDPG to give a better therapeutic effect compared to 5FU100 (Fig. 4). The untreated controls presented rapid growth, the tumors caused cachexia, and the survival was very short. 5FU100 reduced the growth rate only for a limited time. The higher dose of 5FU gave better results, and these were further improved by combination with LV (see Table 1). These data prove that high-dose 5FU with UDPG rescue actually presents a better antitumor activity. These results were confirmed in Colon 26-10 and in CD8F1; tumor growth was more effectively inhibited by high-dose 5FU with UDPG rescue compared to standard treatment.

To exclude the possibility that UDPG rescue might be interfering with the antitumor activity of 5FU, we compared 5FU at the standard dose (100 mg/kg) with or without UDPG in the sensitive tumors Colon 26-10 and Colon 38. Colon 38 tumors in mice treated with 5FU100 and those of mice treated with 5FU100 + UDPG do not show any significant difference in growth rate (Fig. 5) nor in the parameters used for the evaluation of the treatment effects (see Table 1). However, some preliminary experiments in Colon 26-10 and Colon 38 showed that in Colon 26-10, it was indeed possible to reduce the activity of 5FU when an additional injection of UDPG was given after 6 h. However, this did not occur with Colon 38. We tested different schedules and determined that by skipping the dose of UDPG after 6 h, there was no risk of tumor protection.

**Analysis of Plasma Concentrations.** We measured the plasma concentration of UDPG and of Urd at several time points after the administration of a bolus of UDPG at a dose of 2000 mg/kg (Fig. 6). Peak plasma concentrations were 424 ± 161 mM at 10 min for UDPG and 164 ± 13 mM at 20 min for Urd.
DISCUSSION

UDPG rescue enhanced the therapeutic efficacy of 5FU in resistant tumors because a higher dose of 5FU can be administered to mice. UDPG reduced the systemic and hematological toxicity of this drug. In 5FU-sensitive tumors, the antitumor activity was not affected, even when the standard dose of 5FU was followed by rescue. The better therapeutic effect of high-dose 5FU with UDPG rescue could be further improved by combination with LV.

Previous experiments on the modulation of 5FU or 5'-deoxy-5-fluorouridine with the simultaneous administration of nucleosides not only increased the activity but also the toxicity of the treatment (22, 23). On the other hand, it was possible to increase the dose of 5FU when a rescuing protocol was used (9, 11, 24). The administration of an excess of Urd shortly after 5FU theoretically might reduce the antitumor activity (25), but a protective effect of UDPG on the tumor was specifically excluded.

The final dose and the schedule selected for UDPG rescue were based on previous data (19) and on the experience with the p.o., i.p., and i.v. administration of Urd (11). UDPG was used more efficiently than Urd because the dose of UDPG was lower than that of Urd, especially when calculated on a molar basis: 2000 versus 3500 mg/kg and 3.2 versus 14.3 mmol/kg, with cumulative doses of 9.6 mmol for UDPG and 28.6 mmol for Urd. In previous studies, it was observed that high-dose Urd would result in plasma levels of ~20 mM (26), but rescue was also possible at lower concentrations of Urd (~100 μM; Refs. 8, 11, and 27) when maintained for a longer period. Also, in some initial experiments on Urd rescue, the prolonged administration of low doses proved to be as efficient as bolus injections of high doses (9, 10). Although the measurement of plasma Urd levels is indicative of the tissue distribution, concentrative mechanisms for Urd are present and may alter its concentration in tissues (28). We therefore selected a lower dose for each rescuing injection but repeated it until 30 h after 5FU administration.

Similar to Urd, several protocols of UDPG administration could rescue mice from 5FU-induced toxicity, which allowed a 50% increase in the MTD (19). The increased therapeutic index of high-dose 5FU with UDPG (present study) is in agreement with clinical evidence of a dose-response relationship for antitumor activity for both 5FU alone (4) and 5FU modulated with LV (6, 7). The possibility of increasing the dose of 5FU when followed by Urd rescue in patients has also been demonstrated (15, 25, 27, 29). Unfortunately, the clinical use of Urd is hampered by the presence of specific toxic side effects, phlebitis and fever, after continuous infusions, whereas oral administration caused diarrhea (8). Fever was also observed in rabbits (30, 31), whereas in mice, high-dose Urd caused hyperthermia (21). This effect could be partially prevented by inhibition of Urd-phosphorylase with benzylacyclicuridine (21). No evidence of alterations of body temperature was seen in mice throughout the experiments described in the present paper with UDPG used at the indicated dose.

<table>
<thead>
<tr>
<th>Tumor ID</th>
<th>GDF</th>
<th>T/C</th>
<th>Tumor TD</th>
<th>Survival</th>
<th>Minimum weight</th>
<th>Tumor weight</th>
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<tr>
<td>Colon 26 Controls</td>
<td>3.4</td>
<td>42</td>
<td>1.9</td>
<td>24</td>
<td>84.3 ± 12.9</td>
<td>286.7</td>
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<td>5-FU&lt;sub&gt;100&lt;/sub&gt;</td>
<td>6.1</td>
<td>47</td>
<td>13.8</td>
<td>35</td>
<td>92.3 ± 5.1</td>
<td>218.4</td>
</tr>
<tr>
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<td>7.2</td>
<td>38</td>
<td>15.9</td>
<td>31</td>
<td>89.3 ± 11.2</td>
<td>151</td>
</tr>
<tr>
<td>Colon 26-10 Controls</td>
<td>3.8</td>
<td>23&lt;sup&gt;e&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5-FU&lt;sub&gt;100&lt;/sub&gt;</td>
<td>NR</td>
<td>28</td>
<td>NR</td>
<td>32&lt;sup&gt;e&lt;/sup&gt;</td>
<td>85.5 ± 8.8</td>
<td>272</td>
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<td>2.2</td>
<td>16.5</td>
<td>12.1</td>
<td>32&lt;sup&gt;e&lt;/sup&gt;</td>
<td>97.2 ± 3.2</td>
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<td>Colon 38 Controls</td>
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<td>28.7</td>
<td>61&lt;sup&gt;e&lt;/sup&gt;</td>
<td>94.9 ± 2.2</td>
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<tr>
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<td>6</td>
<td>2.8</td>
<td>27</td>
<td>61&lt;sup&gt;e&lt;/sup&gt;</td>
<td>87.7 ± 7.8</td>
<td>65.2</td>
</tr>
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<sup>a</sup> GDF, growth delay factor. NR, not reached.
<sup>b</sup> The mean volume of the tumors of treated mice divided by the values obtained for control animals (%). The maximal T/C is given: for Colon 26 tumors, calculation is limited to the period that control mice can be kept in experiment (see also Fig. 4).
<sup>c</sup> Tumor TD is calculated from the first day of treatment.
<sup>d</sup> Survival is calculated from the day of tumor transplantation.
<sup>e</sup> Weight in milligrams 6 days after the third course of treatment. For Colon 26, Colon 26-10, and Colon 38, the weight was estimated from the volume (assuming 1000 mm<sup>3</sup> = 1 g); for some tumors, the weight of controls is not given due to short survival of controls (Colon 26) or to sacrifice of the mice when tumor volume exceeded 1000 mm<sup>3</sup>.
<sup>f</sup> Mice were sacrificed when tumor size was >1000 mm<sup>3</sup>. Mice bearing Colon 26 were sacrificed 1 day before suspected death due to cachexia.
<sup>g</sup> UDPG given orally (see Materials and Methods<sup>h</sup>).

After 60 min, Urd was ~50 mM, whereas the parent compound was no more detectable.
UDPG Modulation of 5FU in Mice

An increase in antitumor activity was obtained not only in sensitive tumor lines (Colon 26-10 and Colon 38) but, more importantly, also in the resistant tumor Colon 26. This is in contrast to results obtained with LV modulation in which, in vitro, an enhancing effect could only be obtained on lines “intrinsically sensitive to 5FU” (32). It is also important to note that nucleotide metabolism varies in the different tissues and may specifically affect the rescuing activity of Urd on normal tissues and not on tumors. Colon 38, for example, has been reported to possess a limited concentrating capacity for Urd (26, 28, 33); therefore, it was very important to verify that our rescuing protocol did not affect the antitumor activity of 5FU in this tumor.

In a previous study, it was demonstrated that Urd could reduce the toxicity of the standard dose of 5FU (11), but this is the first description of the hematological toxicity of 5FU150 compared to 5FU100. The pattern of toxicity of 5FU100 is similar to that of 5FU150 with UDPG, but the recovery tended to be more rapid with a rescue protocol. Contrary to what is commonly observed in clinical practice, in mice 5FU caused a significant decrease in hematocrit (11) but did not cause a substantial decrease in platelets. Also, in the clinical application, Urd rescue was successful in reducing leucopenia, but thrombocytopenia could not be reduced (15).

GI toxicity remains an important drawback to the use of high-dose 5FU; therefore, we studied the effect of UDPG rescue on the damage caused by 5FU on the intestinal mucosa of mice. The dose of 5FU was slightly higher in this set of experiments (200 mg/kg) and has been selected according to previous results as a dose that would induce significant changes in all aspects of mucosal proliferation and function (20). Although the combination of 5FU with the rescuing agent did not prevent GI toxicity, the quick recovery of cell proliferation (already evident at 72 h) resulted in a faster normalization of intestinal functions as indicated by the recovery in maltase and sucrase activity. The protective effect on the GI mucosa is particularly relevant for the clinical use of 5FU modulated with LV. The combination of myelosuppression and extensive mucosal damage was in fact responsible for several episodes of life-threatening toxicity observed in the early use of this combination (34).

UDPG is an effective rescuing agent from the toxicity of 5FU, allowing a 50% increase in dose intensity. It did not interfere with the antitumor activity of 5FU and did not cause any of the toxic side effects of Urd. Its clinical use in combination with high-dose 5FU may improve the activity of 5FU as a single agent and of the combination 5FU-LV that represents the most widely used treatment for advanced colorectal carcinoma.

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