Increased Gastrointestinal Absorption of Large Molecules in Patients after 5-Fluorouracil Therapy for Metastatic Colon Carcinoma

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ABSTRACT

Chemotherapeutic agents may damage gastrointestinal epithelium and thereby impair the mucosal barrier to bacteria and their products. In order to obtain an objective measurement of gastrointestinal permeability to large molecules, we measured urinary excretion of [14C]polyvinylpyrrolidone administered p.o. (mean molecular weight 11,000) and tobramycin (molecular weight 467) in ten patients receiving 5-fluorouracil therapy for metastatic cancer of the colon. Base-line absorption of [14C]polyvinylpyrrolidone was 0.013 to 0.048% of the administered dose. Dose-related increases in absorption (range, two to 20 fold) occurred after 5-fluorouracil administration, but the dose response differed markedly between individuals. Absorption was maximal 8 to 15 days after the start of therapy, was correlated in time but not necessarily in severity with the presence of gastrointestinal symptoms, and was unaffected by oral nonabsorbable antibiotics. Tobramycin excretion was 8.5 times greater than [14C]polyvinylpyrrolidone excretion, but the two were highly correlated in simultaneous determinations (r, 0.93; p, <0.001). With the exception of an episode of Escherichia coli bacteremia, infections coincided not with maximal [14C]polyvinylpyrrolidone absorption but with maximal granulocytopenia 17 to 24 days after the start of therapy. The gastrointestinal absorption of polyvinylpyrrolidone provides an objective measurement of mucosal integrity which may have applications in assessing the gastrointestinal toxicity of other cytotoxic agents.

INTRODUCTION

Patients who receive cancer therapy are at high risk for developing fever and infection. Although the magnitude of this risk has been related to the degree of granulocytopenia (2, 3, 8, 12, 17), several observations suggest that GI damage may also be an important predisposing factor. Frequently, no focus for fever or bacteremia is clinically apparent in the granulocytopenic patient (12, 16, 17, 34, 37). It has been postulated that this syndrome may be caused by viable bacteria or their products leaking across damaged bowel epithelium (17). Evidence for this hypothesis includes the common finding of gross GI ulcerations at autopsy (17, 35), the high frequency of bacte-

remia with gram-negative enteric bacilli, and the isolation of the same organism from the GI tract and blood (37). Clinical investigations of bowel permeability to luminal macromolecules and microorganisms have been limited by the lack of an adequate methodology. An ideal macromolecular marker should be nontoxic, nonimmunogenic, and inert to digestion. It should be minimally absorbed from the normal GI tract and not metabolized. Finally, the marker should be promptly excreted so that GI permeability can be estimated from urinary excretion after dose p.o. Previously used markers such as bovine serum albumin (43), horseradish peroxidase (42), and inulin (21) do not meet these criteria. Polyethylene glycol has been used as a permeability probe in humans, but the molecular weight of this material ranges from 232 to 594, which is considerably smaller than most biologically important macromolecules (6, 7). PVP, on the other hand, meets most of the proposed criteria (14, 45). [14C]PVP is not metabolized after parenteral administration to humans (27) and that the rate of urinary excretion of PVP depends on its molecular weight: components smaller than 40,000 daltons are excreted within 2 to 3 days; components between 40,000 and 100,000 daltons are excreted slowly over weeks to months; and components larger than 100,000 daltons may be retained for months to years by the reticuloendothelial system (27).

We therefore, prepared [14C]PVP of restricted molecular-weight range (mean molecular weight 11,000) and examined its absorption after parenteral administration p.o. in patients receiving 5-FU therapy for metastatic colorectal cancer. We also measured the absorption of "nonabsorbable" antibiotic, tobramycin (molecular weight 467), which was given p.o. with some of the treatment courses. We sought to determine whether reproducible increases in [14C]PVP absorption occurred after 5-FU therapy, whether these increases could be prevented by oral nonabsorbable antibiotics, and whether they could be related to the occurrence of fever and gram-negative bacteremia.

MATERIALS AND METHODS

Patient Selection. Ten patients with metastatic colonic carcinoma who had undergone resection of their primary lesion without requiring a colostomy were selected for study. After

1 Present in part at the 69th Annual Meeting of the American Association for Cancer Research, Inc., Washington, D.C., April 1978 (33). This work was supported by grants from the American Cancer Society (PDT-115), from the S. Burt Wolbach Fund, and by Contract 1-CM-67037 of the National Cancer Institute.

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3 The abbreviations used are: GI, gastrointestinal; PVP, polyvinylpyrrolidone; 5-FUra, 5-fluorouracil; PBS, phosphate-buffered saline containing 0.006 M sodium phosphate and 0.9% sodium chloride at pH 7.4.

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written informed consent was obtained, the patients were treated with escalating doses of 5-FUra ranging from 12 to 19.5 mg/kg i.v. bolus daily for 5 days repeated in a 28-day cycle. Patients received nonabsorbable antibiotics [tobramycin (400 mg), vancomycin (1 g), and nystatin (1.5 million units)] each 3 times/day p.o. for the first 15 days of alternate courses of 5-FUra in order to determine if the GI toxicity of 5-FUra could be diminished. The timing of antibiotics was chosen to coincide with the anticipated period of GI toxicity.

Ten μCi of fractionated [14C]PVP (see below) and 750 mg of carmine-red transit-time marker were administered p.o. after an 8-hr fast at weekly intervals. Serial 24-hr urine and stool collections were obtained beginning immediately after each dose. The color, frequency, and consistency of the stools were recorded by the patient. Urinary and fecal excretions of [14C]-PVP were expressed as a percentage of the administered dose. Symptoms and signs of mucositis, vomiting, abdominal pain, diarrhea, neurological symptoms, fever, and infection were evaluated at each clinic visit. Complete blood counts were obtained weekly or more frequently during periods of thrombocytopenia and granulocytopenia.

Quantitative Assays. [14C]PVP was measured in aqueous solutions using Aquasol (New England Nuclear, Boston, Mass.) with an internal standard of [14C]PVP in duplicate samples for quench correction. Stool samples and tissue samples were first digested by the method of Mahin and Lofberg (22). Samples were counted in a Packard Model 3000 liquid scintillation counter to an error of 5% or less.

Dextran was measured using the anthrone reaction (32). Tobramycin in serum and urine was measured with a radioenzymatic assay (36).

Fractionation of [14C]PVP. Unlabeled PVP (Plasdone C-15, Lot G207-45) and [14C]PVP (Lot 3710, 9.4 mCi/g) with a k-value of 17.8 and a mean molecular weight of 11,000 were obtained from L. Blecher, GAF Corporation, N. Y. Because the molecular weight range of unfractonated [14C]PVP was large, low- and high-molecular-weight components were removed by membrane filtration to obtain a product with a narrower molecular weight range. An Amicon Model 202-stirred ultrafiltration cell was used in the diafiltration mode. Ten mCi of [14C]PVP in 20 ml of PBS were diafiltered with 10 volumes of PBS under nitrogen at 55 psi, using a UM20 followed by an XM50 membrane filter. The exclusion limits of these filters for globular proteins are 20,000 and 50,000 daltons, respectively. The low-molecular-weight fraction (UM20 filtrate), the intermediate-molecular-weight fraction (XM50 filtrate), and the high-molecular-weight fraction (XM50 retained) constituted 14.9, 65.8 and 13.8% of the original product, respectively. The intermediate-molecular-weight fraction was used in subsequent experiments. Since equal amounts of high- and low-molecular-weight components were removed, the mean molecular weight of the fractionated [14C]PVP was assumed to be similar to that of the starting material (measured by viscometer).

Molecular Size Distribution of [14C]PVP. The molecular size distribution of the [14C]PVP fractions was assessed by gel filtration chromatography (Chart 1A). One-ml samples were applied to a 2.2-cm-diameter column packed to a bed height of 50 cm with Sephadex G-100 gel in PBS containing 0.5% PVP, eluted at 3 ml/hr/sq cm at 4°, and collected in 1.8-ml fractions. The elution peaks of dextran T-10 (mean molecular weight 10,400), dextran T-40 (mean molecular weight 39,500),...
and blue dextran (mean molecular weight $2 \times 10^6$) obtained from Pharmacia Fine Chemicals, Inc., are indicated in Chart 1. The void volume and total volume were 61 and 178 ml, respectively. The intermediate-molecular-weight fraction of $[^{14}C]PVP$ eluted between the peaks of dextran T-40 and T-10.

**Urinary Excretion and Tissue Retention of $[^{14}C]PVP$.** To document that absorbed $[^{14}C]PVP$ is rapidly and completely excreted in the urine, 3 female white rabbits weighing 3.5 to 4 kg were given fractionated $[^{14}C]PVP$ (1 μCi/kg) i.v. via the central ear vein, and serial 24-hr urine collections were obtained for 14 days. The animals were sacrificed 2, 6, and 12 weeks after receiving the injection, and radioactivity in tissues was determined. The animals excreted a mean of 72% of the fractionated $[^{14}C]PVP$ in 24 hr, 89.3% in 48 hr, and 93.7% in 14 days. The $[^{14}C]PVP$ was transiently retained in tissues with the highest concentrations in liver and spleen (Table 1). By 12 weeks, tissue concentrations had fallen to background levels.

**Effect of Unlabeled PVP Adsorption of $[^{14}C]PVP$.** To determine whether $[^{14}C]PVP$ is degraded in or adsorbed to stool, 3 fresh stool specimens from normal volunteers were homogenized in PBS (10% w/v) with and without unlabeled PVP at a final concentration of 0.5%. Fractionated $[^{14}C]PVP$ at a concentration of $2.5 \times 10^5$ dPM/ml was incubated with each sample for 18 hr at 37°C. Homogenates were centrifuged at 12,000 x g, and supernatants and pellets were assayed for $[^{14}C]$. The supernatants from homogenates in PBS alone contained 11.6 and supernatants from homogenates containing 0.5% unlabeled PVP showed no change in molecular weight distribution from the starting material. These results indicate that $[^{14}C]PVP$ is not degraded in stool but that high-molecular-weight components are preferentially adsorbed to stool solids.

### RESULTS

**Time Course of Urinary and Fecal Excretion of $[^{14}C]PVP$ Administered p.o. in Humans.** Detailed studies of the excretion of $[^{14}C]PVP$ were performed in 3 patients receiving 5-FUra therapy. The study illustrated in Chart 2 is typical in that most of the urinary $[^{14}C]PVP$ excretion occurred during the first 24 hr after each p.o. $[^{14}C]PVP$ dose. Stool excretion was 100% of the dose 4 to 5 days after administration. Large increments in
stool excretion corresponded with the appearance of the carmine-red transit-time marker. The patient was constipated during the first week of 5-FUra therapy with a transit time of 4 days and had one to 4 unformed stools per day during the second week with a transit time of 6 hr. This patient is representative of most patients in having an increase in \([^{14}C]PVP\) excretion during the second week despite a decrease in the transit time. Subsequent analyses consider only the \([^{14}C]PVP\) excreted in the urine during the first 24 hr after each dose.

**Base-line Absorption of \([^{14}C]PVP\).** Base-line urinary excretion of \([^{14}C]PVP\) was measured 1 week before beginning 5-FUra or at least 5 weeks after the last dose of 5-FUra. Values ranged from 0.013 to 0.048% (mean, 0.030%) of the administered dose. One patient was studied prior to 5-FUra therapy during 5 consecutive weeks while receiving oral nonabsorbable antibiotics during the second and third weeks (Chart 3). \([^{14}C]PVP\) absorption ranged from 0.019 to 0.031% without appreciable changes occurring during antibiotic treatment.

**Effect of 5-FUra on \([^{14}C]PVP\) Absorption.** Chart 4 illustrates changes in weekly urinary \([^{14}C]PVP\) excretion in a patient receiving 2 courses of 5-FUra therapy with and without oral nonabsorbable antibiotics. Base-line excretion was 0.039% of the dose. This patient absorbed and excreted unusually large amounts of \([^{14}C]PVP\) showing a slight increase on Day 1 of 5-FUra therapy and a maximum of more than 0.7% of the dose on Day 8. Excretion promptly returned toward normal by Day 15. Antibiotics had no effect on the changes in GI permeability to \([^{14}C]PVP\). Urinary excretion of tobramycin (mg/24 hr) paralleled \([^{14}C]PVP\) excretion.

Chart 5 illustrates \([^{14}C]PVP\) absorption and granulocyte counts in another patient during 4 courses of 5-FUra escalating in dose from 12 to 18 mg/kg i.v. daily. Again, GI permeability to \([^{14}C]PVP\) was maximal on Day 8 of each course and increased with increasing dosage of 5-FUra. The only exception occurred during the second course when maximal permeability occurred on Day 15 concurrently with symptoms of abdominal cramps and diarrhea. Microscopic examination of stool revealed many yeasts and pseudomyelia, and cultures yielded >10^8 candida per g of stool. The symptoms abated with oral nystatin, and \([^{14}C]PVP\) excretion returned toward base-line. Thereafter, nystatin was routinely added to the oral nonabsorbable antibiotics.

Other patients who received escalating doses of 5-FUra also absorbed progressively larger quantities of \([^{14}C]PVP\), but the dose-response curves of individual patients differed markedly (Chart 6). Chart 6 also illustrates that at any given dose of 5-FU, treatment with oral nonabsorbable antibiotics (•) did not alter \([^{14}C]PVP\) absorption.

**Effect of 5-FUra on Tobramycin Absorption.** During 10 courses of 5-FUra therapy in which oral nonabsorbable antibiotics were administered, serial 24-hr urine collections were obtained for 15 to 18 days. Chart 7A illustrates urinary tobramycin excretion in a typical patient showing maximal excretion between Days 6 and 11. Chart 7B illustrates the patient who developed candida gastroenteritis showing a peak in tobramycin excretion on Day 7 followed by a second higher peak on Day 11 at the onset of enteritis. The increases in tobramycin excretion paralleled those in \([^{14}C]PVP\) excretion in this patient (Chart 5, Course 2).

In all patients, urinary tobramycin excretion increased rapidly during 5-FUra therapy and reached a maximum between 3 and 11 days after onset of treatment (median, 6 days). Maximum urinary excretion averaged 27 mg/day (range, 5.8 to 167.2 mg/day) which represented 2.3% of the administered dose (range, 0.48 to 13.9%). One patient (Chart 4) had serum tobramycin levels of 2 μg/ml 8 days after 5-FUra therapy. In other patients, serum levels were <0.5 μg/ml. In 26 simultaneous measurements, tobramycin excretion was 8.5 times higher than \([^{14}C]PVP\) excretion (both expressed as a fraction of the administered dose), but the 2 were correlated highly with each other (r, 0.934; p, <0.001).

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**Charts:**
- Chart 3: Urinary excretion of \([^{14}C]PVP\) after p.o. administration measured weekly during 5 consecutive weeks. During the second and third weeks, the patient received nonabsorbable antibiotics p.o.: tobramycin (T); vancomycin (V); and nystatin (N). Bars, \([^{14}C]PVP\) excreted in the urine during the first 24 hr after each dose of \([^{14}C]PVP\).
- Chart 4: Urinary excretion of \([^{14}C]PVP\) after p.o. administration measured weekly during 2 courses of 5-FUra therapy at a dose of 12 mg/kg/day for 5 days. Bars, \([^{14}C]PVP\) excreted in the urine during the 24 hr after each dose of \([^{14}C]PVP\). Tobramycin (T) and vancomycin (V) were given p.o. during the first 15 days of the first course. Numbers in parentheses, mg of urinary tobramycin excretion per 24 hr; x, granulocyte counts.
- Chart 5: \([^{14}C]PVP\) absorption and granulocyte counts in another patient during 4 courses of 5-FUra escalating in dose from 12 to 18 mg/kg i.v. daily. Again, GI permeability to \([^{14}C]PVP\) was maximal on Day 8 of each course and increased with increasing dosage of 5-FUra. The only exception occurred during the second course when maximal permeability occurred on Day 15 concurrently with symptoms of abdominal cramps and diarrhea. Microscopic examination of stool revealed many yeasts and pseudomyelia, and cultures yielded >10^8 candida per g of stool. The symptoms abated with oral nystatin, and \([^{14}C]PVP\) excretion returned toward base-line. Thereafter, nystatin was routinely added to the oral nonabsorbable antibiotics.

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Observed increases in urinary [14C]PVP excretion were observed in patients receiving 5-FU therapy. These increases over baseline absorption were apparent on the first day of treatment and reached a maximum 8 or 15 days after the beginning of treatment. This time course is similar to that of histological changes observed on rectal and colonic biopsies in patients receiving 5-FUra (13, 23, 24).

The timing of urinary [14C]PVP excretion suggested that it is absorbed primarily in the upper bowel. Patients with transit times > 24 hr excreted most of the label during the first 24 hr after the dose (Chart 2). Studies with other markers such as polyethylene glycol (6, 7) and horseradish peroxidase (42) have demonstrated a gradient in the permeability of the GI mucosa in humans and animals with the highest permeability in the upper small bowel and the lowest permeability in the colon.

The size of [14C]PVP excreted in the urine during the first 24 hr after a dose was smaller than the administered material (Chart 1C). Although degradation did not occur, low-molecular-weight components may have been selected at several stages in the process of absorption and excretion. High-molecular-weight components were preferentially adsorbed to stool solids and were therefore less available for diffusion across the bowel mucosa. Preferential permeation by lower-molecular-weight components may also occur at the level of the GI mucosa and at the level of the glomerular basement membrane. After i.v. administration of [14C]PVP to rabbits, lower-molecular-weight components were excreted more rapidly, producing a shift in the molecular weight distribution of [14C]PVP excreted during the first 24 hr after the dose (data not shown).

GI permeability to [14C]PVP could be related to clinical observations including GI symptoms, the effect of oral nonabsorbable antibiotics, and the occurrence of infections. Maximal [14C]PVP absorption usually occurred at the same time as did GI symptoms (Table 2). However, in individual patients, the degree of GI permeability did not correlate with the severity of the symptoms. For example, 2 patients with high [14C]PVP permeability had minimal stomatitis and diarrhea, and one

**Toxicity of 5-FUra Therapy.** Table 2 summarizes the temporal relationships of the toxicities of 5-FUra. In most patients, GI symptoms, most often stomatitis, were maximal between Days 4 and 10, but the severity of symptoms did not necessarily parallel GI permeability as measured by [14C]PVP excretion. Granulocytopenia, on the other hand, was usually most severe between Days 18 and 24 (Charts 4 and 5; Table 2). In addition to the 35 courses of therapy summarized in Table 2, 12 additional courses during which [14C]PVP was not administered were evaluated for granulocytopenia and infection. During 27 episodes of severe granulocytopenia (<100/cu mm), we observed only 7 minor infections (skin, 3; pharyngitis, 2; urinary tract infection, 1; enteritis, 1) and 2 bacteremias (Staphylococcus aureus, one; and Escherichia coli, one). The timing of infections coincided with granulocytopenia and not with maximal GI permeability (Table 2). The patient with E. coli bacteremia was unique because maximal GI permeability occurred 3 weeks after 5-FUra, coinciding with the nadir of granulocytopenia (Chart 8).

**DISCUSSION**

Reproducible increases in urinary [14C]PVP excretion were observed during 4 courses of 5-FUra increasing in dosage from 12 to 18 mg/kg/day. Bars, [14C]PVP excreted in urine during the first 24 hr after each dose of [14C]PVP. Tobramycin (T) and vancomycin (V) were given p.o. during the first 15 days of Courses 2, 4, and 6. Nystatin (N) was added p.o. on Day 11 of Course 2 to treat symptomatic candida enteritis, and it was included in subsequent courses from the beginning of therapy. Numbers in parentheses, urinary tobramycin excretion per 24 hr. Antibiotics p.o. were discontinued on Day 5 of Course 6 because of severe vomiting. X, granulocyte counts.

**Chart 5.** Urinary excretion of [14C]PVP after p.o. administration measured weekly during 4 courses of 5-FUra increasing in dosage from 12 to 18 mg/kg/day. Bars, [14C]PVP excreted in urine during the first 24 hr after each dose of [14C]PVP. Tobramycin (T) and vancomycin (V) were given p.o. during the first 15 days of Courses 2, 4, and 6. Nystatin (N) was added p.o. on Day 11 of Course 2 to treat symptomatic candida enteritis, and it was included in subsequent courses from the beginning of therapy. Numbers in parentheses, urinary tobramycin excretion per 24 hr. Antibiotics p.o. were discontinued on Day 5 of Course 6 because of severe vomiting. X, granulocyte counts.

**Chart 6.** Relationship between 5-FUra dose and maximum urinary excretion of [14C]PVP administered p.o. Each point represents the maximum [14C]PVP excretion, expressed as fold increase over the patient's base-line, observed after a course of 5-FUra therapy at the indicated dose given with (O) or without (C) nonabsorbable antibiotics p.o. Repeated studies in the same patient are connected.
patient with low \([^{14}C]\text{PVP}\) permeability developed severe oral mucositis which was dose limiting. Thus, the sensitivity of various levels of GI tract to 5-FUra appears to vary between individuals (Chart 6), and the severity of oral lesions does not necessarily correlate with damage at lower levels.

Previous studies have documented that oral aminoglycosides may produce steatorrhea and morphological changes in the bowel (29). We observed occasional increases in stool frequency in patients on the oral nonabsorbable antibiotics but noted no changes in permeability to \([^{14}C]\text{PVP}\) except in the patient who developed candida enteritis. The increase in GI permeability induced by 5-FUra was not prevented by antibiotics, corroborating our clinical impression that antibiotics did not reduce the GI toxicity of this agent.

Infectious episodes did not occur during the usual period of maximal GI permeability but 7 to 10 days later coincident with the nadir in granulocyte count. The majority of infections were minor, and we observed no unexplained fevers during 27 episodes of severe granulocytopenia. Although this may be partly related to the relatively brief duration of granulocytopenia (usually 3 to 7 days), it may also be due to the temporal dissociation of GI permeability and granulocytopenia after 5-FUra therapy. It is possible that granulocytopenia alone poses a relatively low risk but that granulocytopenia concurrent with mucosal damage is associated with a high risk of fever and enteric bacillemia. Support for this hypothesis is provided by the single patient who developed E. coli bacteremia. This patient was unique in that she had maximal GI permeability and severe granulocytopenia simultaneously at the time of sepsis.

The timing and magnitude of \([^{14}C]\text{PVP}\) absorption correlated highly with the absorption of oral tobramycin given as part of oral nonabsorbable antibiotic regimen. The absorption of aminoglycosides administered oral is < 1% of the dose in normal individuals, but patients with underlying GI disease, including that induced by chemotherapeutic agents, may absorb larger amounts (4, 25, 28). Most of our patients had urinary tobramycin levels >5 \(\mu\)g/ml which are sufficient to inhibit common urinary pathogens, and one patient (Chart 4) had therapeutic serum tobramycin levels. This finding emphasizes that signs of antibiotic toxicity should be carefully monitored when oral "nonabsorbable" antibiotics are given together with radiation or chemotherapy which damage the GI tract, particularly if renal function is impaired. In addition, these findings raise the possibility that oral "nonabsorbable" antibiotics exert part of their therapeutic effects by providing systemic levels of antibiotics, especially at times when the GI barrier function is impaired.
We conclude that [14C]PVP is a useful macromolecular permeability probe which has provided an objective and reproducible measure of the integrity of the mucosal barrier after 5-FUra therapy. The measurements substantiated our clinical impression that oral nonabsorbable antibiotics do not decrease the Gl toxicity of 5-FUra and documented a temporal dissociation between the Gl toxicity and marrow suppression due to this agent. The hypothesis that concurrent Gl toxicity and marrow suppression are associated with a high risk of bacteremia due to endogenous bowel flora needs further study in high-risk patients such as those receiving intensive chemotherapy for acute leukemia. The objective assessment of Gl barrier function with [14C]PVP could be used for monitoring the toxicity of other chemotherapeutic agents (13, 23, 24, 35, 38, 39) or radiation therapy (5, 30, 41) and for the investigation of a variety of diseases in which the Gl absorption of endotoxin or other microbial antigens plays a role (1, 9, 11, 15, 19, 20, 31, 41, 44).

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