A Phase I Clinical and Pharmacological Evaluation of Sodium Phenylbutyrate on an 120-h Infusion Schedule[1]

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ABSTRACT

Purpose: Sodium phenylbutyrate (PB) demonstrates potent differentiating capacity in multiple hematopoietic and solid tumor cell lines. We conducted a Phase I and pharmacokinetic study of PB by continuous infusion to characterize the maximum tolerated dose, toxicities, pharmacokinetics, and antitumor effects in patients with refractory solid tumors.

Patients and Methods: Patients were treated with a 120-h PB infusion every 21 days. The dose was escalated from 150 to 515 mg/kg/day. Pharmacokinetics were performed during and after the first infusion period using a validated high-performance liquid chromatographic assay and single compartmental pharmacokinetic model for PB and its principal metabolite, phenylacetate.

Results: A total of 24 patients were enrolled on study, with hormone refractory prostate cancer being the predominant tumor type. All patients were evaluable for toxicity and response. A total of 89 cycles were administered. The dose-limiting toxicity (DLT) was neuro-cortical, exemplified by excessive somnolence and confusion and accompanied by clinically significant hypokalemia, hyponatremia, and hyperuricemia. One patient at 515 mg/kg/day and another at 345 mg/kg/day experienced this DLT. Toxicity resolved ≤12 h of discontinuing the infusion. Other toxicities were mild, including fatigue and nausea. The maximum tolerated dose was 410 mg/kg/day for 5 days. Pharmacokinetics demonstrated that plasma clearance of PB increased in a continuous fashion beginning 24 h into the infusion. In individuals whose V_{max} for drug elimination was less than their drug-dosing rate, the active metabolite phenylacetate accumulated progressively. Plasma PB concentrations (at 410 mg/kg/day) remained above the targeted therapeutic threshold of 500 μmol/liter required for *in vitro* activity.

Conclusion: The DLT in this Phase I study for infusional PB given for 5 days every 21 days is neuro-cortical in nature. The recommended Phase II dose is 410 mg/kg/day for 120 h.

INTRODUCTION

Differentiation therapy for epithelial malignancies may potentially alter tumor growth and progression, slow or inhibit metastases, inhibit angiogenesis, and/or effect response to other forms of therapy (1–5). Nonretinoid agents such as hexamethylenebisacetamide and sodium butyrate have been evaluated clinically, but sustained systemic levels required for activity have not been achieved because of toxicity and/or lack of a suitable formulation (6–9). Sodium PB,[3] an aromatic fatty acid, is a lead candidate as a cancer differentiating agent and a histone deacetylase inhibitor (10–13). Sodium PB is the precursor to PA, and both compounds are potent differentiating agents *in vitro* (10–18). PA is formed by β-oxidation of PB (19). PB is Food and Drug Administration approved for children and adults with hyperammonemia associated with urea cycle disorders (recommended dose of 13 g/m^2/day) and has been used for adult patients with hyperammonemia secondary to high-dose chemotherapy for leukemia and transplant therapies (19–22). PB is also under investigation for cystic fibrosis and adrenal leukodystrophy.

Preclinical studies have looked at the ability of these drugs to alter gene expression and promote differentiation (23–25). In various tumor model systems, PA/PB can arrest cells in G_1-G_0 with induction of p21^{WAF1} and other cdk-2-associated cell cycle checkpoint proteins, alter expression of invasion products such as urokinase-plasminogen activator (UPA), induce apoptosis, inhibit telomerase, and increase MHC class I expression at concentrations of 500-2500 μmol/liter PB (23–31). Delay in tumor progression has been noticed in prostate and malignant glioma models (12, 16, 17). It should be noted that tumor markers, such as PSA, might not be the most accurate measurements of progressive disease in patients treated with PB, as a rise in tumor markers may signal cell differentiation rather than

[3] The abbreviations used are: PB, phenylbutyrate; PA, phenylacetate; PG, phenylacetylglutamine; PSA, prostate-specific antigen; MTD, maximum tolerated dose; NCI, National Cancer Institute; DLT, dose-limiting toxicity; PCA, prostate cancer.

disease progression. Proposed mechanisms of action to elicit these effects include modification of lipid metabolism, activation of the peroxisome proliferator activator receptor, maintenance of histone acetylation through inhibition of histone deacetylase, inhibition of protein isoprenylation, and/or glutamine starvation (10, 27–31). There may be other cellular and molecular effects of PB that contribute to its antitumor activity.

In addition to all of the potential cellular and molecular effects, PB is minimally toxic in children with urea cycle disorders and hemoglobinopathies (31). Serum concentrations of PB have been reported in the range (500–2500 μmol/liter) required for *in vitro* effects of growth arrest and differentiation. Preclinical data from our laboratory and others suggest PB may be more potent and produce more molecular effects than PA (12). PB has activity similar to butyrate (induction of apoptosis and histone acetylation) that PA may not possess. For these reasons, Phase I studies of PB were initiated.

The purpose of this Phase I trial was to determine the MTD and toxicity profile of PB administered i.v. as an 120-h infusion every 21 days and to describe the pharmacokinetic behavior of this novel agent in patients with refractory solid tumors.

PATIENTS AND METHODS

Patient Eligibility

The protocol was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine. Male and female patients ≥18 years of age with a histologically or cytologically documented diagnosis of cancer (solid tumor or lymphoma) refractory to conventional therapeutic modalities were eligible. All patients enrolled onto the study had progressing, evaluable, or measurable disease. Patients were required to have an Eastern Cooperative Oncology Group performance status of 0, 1, or 2 and a life expectancy of ≥3 months. Patients were not to have had major surgery, radiotherapy, or chemotherapy in ≤28 days and were to be fully recovered from the toxicity of prior therapy. Patients with prostate cancer were allowed to continue on a leutenizing hormone releasing hormone (LHRH) agonist. A 4–6-week period of antiandrogen (flutamide and bicalutamide) withdrawal and evidence of PSA progression was required of all men on an antiandrogen before entry. Patients that previously received suramin were eligible if their suramin level was <50 μg/ml. Adequate organ function was required at study entry: WBC > 2,000 or absolute neutrophil count (ANC) > 1,500/mm^3, platelets > 100,000/mm^3, and hemoglobin > 9 g/dl, a serum creatinine < 2 mg/dl, total bilirubin < 1.5, and aspartate aminotransferase/alanine aminotransferase < 1.5 × the upper limit of normal, left ventricular ejection fraction (LVEF) by MUGA or echocardiogram > 40% and no history of congestive heart failure (CHF) requiring hospitalization, or uncontrolled hypertension (diastolic blood pressure (BP) >110 mmHg) and a forced expiratory volume (FEV)$_1$ > 1.5 liter/min. Patients with obstructive uropathy were eligible if obstruction was relieved by nephrostomy or other appropriate intervention. Patients were required to give informed consent with understanding of the investigational nature of the treatment and its potential risks. Patients were ineligible if they had an active infectious process, including HIV or viral hepatitis; a malignant brain tumor, or known central nervous system metastases even if treated previously and not clinically active; an active seizure disorder; or a baseline dementia with mini-mental score < 23 (32). Pregnant or nursing females were ineligible. Patients with requirement for steroids for any reason, including previous suramin therapy, were excluded because of concerns about potential interference with the mechanism of action of PB.

Pretreatment Evaluation

Patients were assessed before receiving the first dose of PB with a complete history, including prescription and nonprescription drug history, physical exam with a thorough neurological examination, including a mini-mental status examination (32), and performance status assessment. Documentation of evaluable or measurable disease was performed ≤4 weeks of initiation of therapy. Pretreatment laboratory evaluations included a complete blood count with platelet and differential, chemistry panel (including electrolytes, creatinine, bilirubin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, uric acid, total protein, albumin, calcium, phosphorous, and magnesium), partial thromboplastin time and prothrombin time, urinalysis, human chorionic gonadotropin (if woman of childbearing age), EKG, MUGA or echocardiogram for LVEF, spirometry with lung volumes, chest roentgenogram (or chest computed tomography if part of the tumor assessment), appropriate tumor marker (*i.e.,* PSA, CA-125, CA15-3, and CA19-9), and a suramin level, if the patient had been treated previously with suramin.

Evaluation During Therapy

Patients were monitored with laboratory and clinical evaluations weekly by an investigator or research nurse while on study. The history and physical was performed at the beginning of each 5-day infusion. Patients were also seen as needed for additional toxicity assessment. Toxicity was graded using the NCI common toxicity criteria, version 2.0. Tumor markers were assessed monthly. Evaluation of measurable and evaluable disease was performed after each two cycles of therapy. Documentation of performance status was required with all visits. Complete response was defined as the disappearance of all clinical evidence of active tumor and symptoms for ≥1 month. Partial response required a >50% decrease in the sum of the products of the perpendicular tumor diameters of all measurable lesions for ≥4 weeks without simultaneous increase in the size of any lesion or appearance of any new lesion. Progressive disease was defined as a >25% increase in the size of any measurable lesion or the appearance of any new lesion. Stable disease represented a response less than a partial response or growth less than progressive disease. Changes in tumor markers did not factor in to the definition of response, *e.g.,* a rising PSA did not define progression. Changes in PSA are merely descriptive.

Treatment Plan

The Investigational Drug Branch of the NCI received phenylbutyric acid, sodium salt (National Service Center number 657802; EL532) from Elan Pharmaceutical Research Corp., Gainesville, GA. PB was formulated in 50-ml glass vials containing 40% viscous solution of sodium PB in sterile water (400

mg/ml). The sodium content of one vial was 4.9 grams of sodium. PB was provided for the patients on this study by the Division of Cancer Treatment, NCI.

Patients were admitted to the General Clinical Research Center of the Johns Hopkins Hospital for each course of therapy. PB was administered as a continuous i.v. infusion (centrally or peripherally) for 120 h every 21 days. A course was defined as the 21-day cycle, consisting of the 5-day infusion and 16 days of rest. The infusional starting dose was 150 mg/kg/day for 5 days, a dose below that shown previously to be safe in children with urea cycle disorders. Subsequent dose levels were 225, 285, 345, 410, and 515 mg/kg/day for 5 days. Doses could be escalated within individual patients if 3 patients at the next higher dose level had received therapy for >1 month without DLT. Patients remained on study until evidence of progressive disease, severe DLT, or patient request to discontinue therapy. DLT was defined using the NCI common toxicity criteria, as neurotoxicity $\geq$ grade 2 or any other toxicity $\geq$ grade 3. A registered nutritionist met with every patient to discuss salt intake and to provide recommendations of lowering sodium intake while receiving PB.

Cohorts of 4 patients were initially enrolled at each dose level to fully evaluate the central nervous system toxicity and to gather more pharmacokinetic data. If no patients in a cohort experienced a DLT during the initial 3-week observation period, the dose was escalated, and the next cohort was commenced. If 1 of 4 patients experienced a DLT, 2 additional patients were added at that dose level. If 2 patients experienced a DLT at any dose level, no additional patients were enrolled at that dose level, and an additional 2 patients were entered at the next lower dose level. Dose escalation could occur once all 4 patients in a given cohort were treated, and at least 2 patients had completed one course (21 days) with the 3rd and 4th patients $\geq$1 week into therapy without meeting criteria for the MTD. Although the study was not designed to escalate doses within patients, in-trapatient dose escalation was allowed. A patient who received at least two courses of treatment without toxicity (except alo-pecia) greater than grade II at a given dose level could have their subsequent treatments at the next higher dose level. Before such an escalation could occur, 2 PB-naïve patients must have com-pleted at least one course (22 days) at the next higher dose level without any DLT. The MTD was defined as that dose level at which consistent, definable toxicity occurs that is reversible and does not subject patients to excessive risk or discomfort.

Patients who received $\geq$1 day of PB were assessable for toxicity, but only those patients who received one full 21-day course of PB were assessable for response. Patients for whom a drug was held because of DLT still had to complete the full 21-day observation period. Any patient who experienced DLT and recovered fully from that toxicity could resume PB at the next lower dose level; however, for MTD determination, pa-tients were included only at their initial, higher dose level. Patients who did not recover fully from DLT $\leq$14 days or had a DLT at a subsequent lower dose were taken off study. The study was defined as complete for a given patient if the patient did not recover fully from a DLT $\leq$14 days or had a DLT at a subsequent lower dose. Patients were also removed from the study if they had evidence of progressive disease or if the patient requested to be taken off the study.

Table 1 Gradient profile for HPLC

Time (min)	A (%)	B (%)	C (%)
0.00	47.5	5.0	47.5
20.00	38.5	23.0	38.5
23.00	38.5	23.0	38.5
35.00	27.5	45.0	27.5
35.01	5.0	90.0	5.0
38.00	5.0	90.0	5.0
38.01	47.5	5.0	47.5
45.00	47.5	5.0	47.5

Recognizing that the recommended Phase II dose is often one dose level below the MTD, the recommended Phase II dose was to be dictated by toxicities, patient tolerability, and plasma levels achieved. An objective of this study was to achieve a range of plasma levels that may be clinically relevant as dictated by preclinical models.

Pharmacokinetic Study

Pharmacokinetic Sampling. Drug disposition studies were performed during the first course of treatment. Blood specimens were collected before the start of the infusion, at 0.5, 1, 2, 4, 6, 12, 24, 36, 48, 60, and 96 h during the infusion and just before completion of the infusion (120 h). Postinfusion specimens were obtained at 0.5, 1, 2, 4, 8, and 24 h as measured from the end of the infusion. Urine specimens (every 24 h) were collected between 0 and 24 h and between 96 and 120 h as measured from the start of the infusion.

Analytic Assay. Plasma PB, PA, and PG concentrations were determined in all blood specimens by reverse-phase high-performance liquid chromatography assay. These methods have not been published previously. Plasma (200 μl) containing compound was transferred to a microcentrifuge tube, followed by the addition of 50 μl of 10% perchloric acid (Sigma Chem-ical Co., St. Louis, MO) for protein extraction. The samples were vortexed and centrifuged (International Equipment Co., Needham Heights, MA) at 4°C at 8500 rpm for 10 min. After centrifugation, 150 μl of supernatant was added to 5 μl of super-saturated potassium bicarbonate solution for neutraliza-tion and centrifuged again at 4°C at 8500 rpm for 10 min. All of the supernatant was transferred to an autosampler vial for anal-ysis. The chromatographic apparatus consisted of a Hewlett Packard Series II 1090 Liquid Chromatographic (Hewlett Pack-ard Corp., Palo Alto, CA) with an autosampler compartment, solvent delivery system, and a diode-array UV absorbance de-tector with a resolution of 2 nm. The absorbance wavelength was 208 nm (bandwidth, 10 nm) with a reference wavelength of 400 nm (bandwidth, 80 nm). Mobile phase A consisted of 100% deionized water (Milli-Q^{UV} Plus; Millipore Corp., Bedford, MA) with 0.005 M phosphoric acid (Sigma Chemical Co.) buffer. Mobile phase B consisted of 100% high-performance liquid chromatography grade acetonitrile (J. T. Baker, Phillips-burg, NJ) with 0.005 M phosphoric acid buffer, and mobile phase C was identical to mobile phase A. All mobile phases were run at a flow rate of 1 ml/min for a run time of 45 min at the gradient profile listed on Table 1.

A Waters Nova-Pak C$_{18}$ guard column was placed in line before the analytical column. The samples were injected onto a
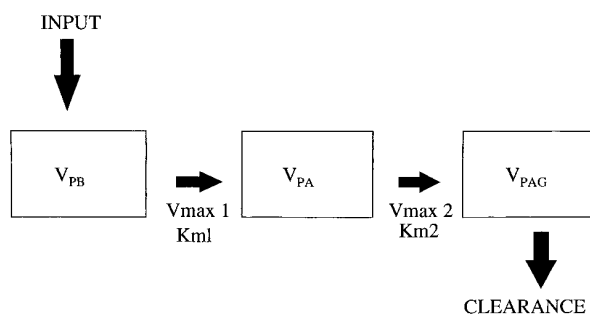
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Fig. 1 Single compartment model of PB disposition. PB is β-oxidized to PA, and glutamine binds PA to form PG, which is cleared in the urine. The disposition model for these three compounds is defined by a specific V_{max} and km for the disposition of one compound to another.

reverse-phase (Waters Bond-Pak C_{18}, 3.9 × 300 mm; Millipore Corp) column, which was maintained at 60°C. PA, PB, and PG had retention times of ~18.2, 31.4, and 10.2 min, respectively. Chromatographic peak area was used for quantitation by linear regression analysis. The lower limit of detection for the assay was 5 µg/ml. Quality control samples were assayed at concentrations of 15, 35, and 85 µg/ml, and the inter-day coefficients of variation were 11% for PA, <7% for PB, and <11% for PG. One set of quality control samples were placed before the calibration standards, before the patient samples, and then immediately after the patient samples were assayed. Samples from 1 patient were assayed with each analytical run. Each analytical run was equivalent to ~26 h; autosampler stability for 35 h demonstrated that metabolites are stable for this period of time with a <10% change (loss or gain) in concentration. The lower limit of quantitation was 5 µg/ml for PA and PG and 10 µg/ml for PB. PG concentrations were determined in the urine specimens, and the amount of PG excreted during the urine collection period was calculated as concentration × urine volume. The accuracy of the assay was 93–98% with precision of the assay to ≤1–4%.

Pharmacokinetic Methods. The plasma PB disposition curves were analyzed in two ways: (*a*) individual subject disposition curves were fit by nonlinear regression (PCNONLIN; Scientific Consulting, Apex, NC) using a pharmacokinetic model consisting of a single distribution compartment and a first-order elimination process that increases in magnitude in an exponential fashion beginning 24 h after the institution of drug therapy, *i.e.,* clearance rate(t > 24 h) = clearance rate(t = 0)×exp[kinc×(t − 24 h)], where kinc is the rate constant of the exponential process; and (*b*) the data were analyzed using a pharmacokinetic model consisting of a single distribution compartment and a Michaelis-Menten-type saturable elimination process in which V_{max} increases in magnitude in an exponential fashion beginning 24 h after the institution of drug therapy. For this model, the disposition curves were analyzed by nonlinear mixed effect modeling (P-Pharm; MicroPharm International, Champs-sur-Marne, France). With this software, population parameter values were estimated using an EM-type iterative algorithm, and individual subject parameter values were estimated by MAP Bayesian fitting.

The plasma PA and PG disposition curves were also ana-

Table 2 Patient characteristics

Total patients[a]	24
Male	23
Female	1
Diagnosis	
Prostate, hormone-refractory	19
Kidney	3
Melanoma	1
Endometrium	1
Performance status	
0	5
1	18
2	1
Prior therapy	
Chemotherapy, XRT, hormone	7
XRT,[b] hormone	6
Hormone	4
Chemotherapy, hormone	3
Chemotherapy, radiation	1
Immunotherapy only	1
Chemotherapy, immunotherapy	1
No therapy	1

[a] Age: range, 48–80, median, 66.
[b] XRT, X-ray therapy.

lyzed by nonlinear mixed effect modeling. In the pharmacokinetic models used, PA was modeled as arising from PB via the Michaelis-Menten-type saturable elimination process for PB (Fig. 1). PG was modeled as arising from PA via a Michaelis-Menten-type saturable process. For both species, it was assumed that biotransformation was complete. PA was modeled as distributing in a single compartment with elimination solely via the process that gives rise to PG. The V_{max} of this elimination process was treated as increasing in an exponential fashion beginning 24 h after the institution of drug therapy. PG was modeled as distributing in a single compartment with first-order elimination. In one model, the elimination was treated as time invariant, and in another, it was modeled as increasing in an exponential fashion beginning 24 h after the institution of drug therapy.

Urine clearance rates of PG were calculated as the amount of PG excreted in the urine during the period of urine collection divided by the area under the PG plasma disposition curve during the same period of time. The areas were determined using a linear trapezoidal rule.

RESULTS

Patients (24) were enrolled at six dose levels. Patient characteristics are listed in Table 2. A total of 89 full cycles of treatment were administered. All patients were evaluable for toxicity and response assessment. The majority of patients were men with advanced hormone refractory prostate cancer. Over half of the patients had received previous chemotherapy. One patient with renal cell cancer had had no previous therapy, and 4 men with prostate cancer received PB as their first therapy in the hormone refractory state. The median number of courses per patient was four (range, one to eight) for an average time on trial of 84 days.

Patients (21) were withdrawn from therapy secondary to progressive disease documented by radiograph or symptoms.

Table 3 No. of patients with grade 3 or 4 toxicity by dose level

	150 mg/kg/d	225 mg/kg/d	285 mg/kg/d	345 mg/kg/d	410 mg/kg/d	515 mg/kg/d
Neurocortical				1		1[a]
Hypokalemia						1[a]
Hyperuricemia						1[a]
Nausea						1[a]
Neutropenia	1[b]					
Fatigue					2[c]	

[a] Toxicities occurred in the same patient.
[b] Lasted 2 days only.
[c] Felt to be related to disease progression rather than drug.

One patient refused additional therapy after six cycles for personal reasons despite continued stable disease. Another patient discontinued therapy secondary to toxicity during his first cycle of therapy at 410 mg/kg/day. Lastly, 1 patient had toxicity at two different dose levels despite dose reduction and met criteria for withdrawal secondary to toxicity. This patient had a 10% decline in his PSA and subjective improvement in bone pain over the two cycles that he received therapy.

Three patients had their dose escalated during the course of therapy. Two of these patients remained on the study for a total of eight cycles. In fact, 1 of these patients had his dose increased twice from 150 mg/kg/day (dose level 1) to 285 mg/kg/day (dose level 3). Two patients had their dose reduced secondary to toxicity at their starting dose during cycle 1. The starting doses for these patients were 345 and 515 mg/kg/day. No patient at 410 mg/kg/day had their dose reduced or escalated and was determined to be the recommended Phase II dose. Table 3 describes all grades 3 and 4 toxicities during the study period.

Neuro-cortical Toxicity. DLT was neuro-cortical in nature. One patient on 515 mg/kg/day experienced grade 3 neuro-cortical toxicity ≤48 h of the start of drug infusion. The toxicity was exemplified by excessive somnolence and confusion and was accompanied by metabolic changes consisting of grade 4 hypokalemia (2.1 mmol/liter), grade 3 hyponatremia (128 mmol/liter), grade 2 hypocalcemia (7.9 mg/dl), and grade 4 hyperuricemia (15.2 mg/dl). The metabolic nadirs occurred 4 days after initiation of infusion. The patient also had grade 3 nausea before the decline in mental status. Full recovery and return to baseline clinical state occurred ≤10–12 h after discontinuation of the drug at approximately the same time as the electrolyte abnormalities returned to normal values after aggressive repletion. The patient received a second cycle at the next lower dose and experienced a similar toxicity syndrome on rechallenge. An additional patient developed grade 3 neuro-cortical toxicity at the 345 mg/kg/day dose. This was not accompanied by electrolyte abnormalities and occurred at 96 h into the infusion. The symptoms resolved 10–12 h after discontinuing the drug. A 3rd patient developed grade 2 neuro-cortical toxicity with only grade 1 hyponatremia and hypocalcemia at 410 mg/kg/day. This patient was not rechallenged at a lower dose because he developed obstructive urinary symptoms and was taken off study for progression of disease. Of note, plasma ammonia levels in the grade 3 toxicity patients remained in the normal range.

Patients with nausea had more sedating effects from anti-emetics, such as the phenothiazines (prochloperazine). This observation led to the use of nonsedating antiemetics such as the serotonin 5-HT3 receptor antagonists, ondansetron and granisetron. Patients had less sedation and minimal emesis with this change in antiemetic.

Hematological Toxicity. No dose-limiting hematological toxicity was noted. Minor decreases in hematocrit were noted over the course of therapy. No platelet toxicities were noted in any patient. One patient had a transient grade 3 neutropenia (absolute neutrophil count of 600) noted at dose level 1 that resolved in 2 days. No other declines in total white cell count or in subpopulations were noted.

Nonhematological Toxicity. Patients experienced mild grade 2 nausea at the higher dose levels, in particular, the 410 mg/kg/day dose. Fatigue was dose related as well. Grade 2 fatigue was noted in 1 patient at 345 mg/kg/day and 2 patients at 410 mg/kg/day. Grade 3 fatigue was noted in 2 of 7 patients receiving 410 mg/kg/day infusions. This degree of fatigue was not felt to be drug related but rather attributable to tumor progression. In fact, the 2 patients with grade 3 fatigue did not receive a rechallenge with PB as they were taken off study for progressive disease. Of note, 7 (38%) of the patients with bony metastatic PCA experienced a flare in bone pain that started on discontinuation of the infusion and persisted for 48 h. Only the 2 patients with grade 3 neuro-cortical toxicity developed the characteristic odor of PA. The ability to detect the odor also resolved promptly with discontinuation of the study drug.

Pharmacokinetics and Pharmacodynamics. Of 24 patients enrolled in the study, 1 patient had incomplete blood sampling for pharmacokinetic data analysis, and 2 patients did not have adequate plasma sample volumes to allow determination of PA and PG concentrations. These 3 patients were excluded from the pharmacokinetic data analysis.

In the majority of the patients, the plasma PB disposition curves were characterized by a rise to an apparent plateau achieved by 4–6 h into the infusion. However, a number of the subjects had curves that showed a substantial decline in PB concentrations starting around 24 h into the infusion and continuing throughout the remainder of the infusion. This pattern was seen in 0 of 4 patients 150 mg/kg/day, 0 of 4 patients at 225 mg/kg/day, 1 of 4 patients at 285 mg/kg/day, 3 of 4 patients at 345 mg/kg/day, 5 of 7 patients at 410 mg/kg/day, and 0 of 1 patient at 515 mg/kg/day. This pattern suggested that the plasma clearance of PB increased in a continuous fashion beginning 24 h into the infusion. Fig. 2 demonstrates the PB disposition pattern for 2 patients, 1 at 225 mg/kg/day and the other at 515 mg/kg/day. This feature was incorporated in the pharmacokinetic models used to describe the disposition curves.

Individual subject PB disposition curve analysis using a pharmacokinetic model with first-order elimination showed an inverse relationship between clearance rate and dose, suggesting that a model with saturable elimination would be more appropriate. In the model that was used in the population pharmacokinetic analysis of PB disposition, elimination was modeled as being Michaelis-Menten in character. The population pharmacokinetic estimates for PB disposition are listed in Table 4. The mean kinc value of 0.0029/h equates to a 1.32-fold increase in V_{max} by 120 h into the infusion.

The population pharmacokinetic estimates for PA and PG

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