

Oral Sodium Phenylbutyrate Therapy in Homozygous β Thalassemia: A Clinical Trial

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Butyrate analogues have been shown to increase fetal hemoglobin (HbF) production in vitro and in vivo. Sodium phenylbutyrate (SPB), an oral agent used to treat individuals with urea-cycle disorders, has been shown to increase HbF in nonanemic individuals and in individuals with sickle cell disease. We have treated eleven patients with homozygous β thalassemia (three transfusion dependent) and one sickle- β -thalassemia patient with 20 g/d (forty 500-mg tablets) of SPB for 41 to 460 days. All patients showed an increase in the percent of F reticulocytes associated with treatment, but only four patients responded by increasing their Hb levels by greater than 1 g/dL (mean increase, 2.1 g/dL; range, 1.2 to 2.8 g/dL). None of the transfusion-dependent thalassemia subjects responded. Increase in Hb was associated with an increase in red blood cell number (mean increase, $0.62 \times 10^{12}/L$), and mean corpuscular volume (mean increase, 6 fL). Changes in percent HbF, absolute HbF levels, or α - to non-

α -globin ratios as measured by levels of mRNA and globin protein in peripheral blood did not correlate with response to treatment. Response to treatment was not associated with the type of β -globin mutation, but baseline erythropoietin levels of greater than 120 mU/mL was seen in all responders and only two of eight nonresponders to SPB. Compliance with treatment was greater than 90% as measured by pill counts. Side effects of the drug included weight gain and/or edema caused by increase salt load in 2/12, transient epigastric discomfort in 7/12, and abnormal body odor in 3/12 subjects. Two splenectomized patients who were not on prophylactic antibiotics developed sepsis while on treatment. We conclude that SPB increases Hb in some patients with thalassemia, but the precise mechanism of action is unknown.

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HOMOZYGOUS β THALASSEMIA, a disease in which there is inadequate production of β globin leading to severe anemia, affects thousands of individuals worldwide. Current management of this condition includes the use of regular red blood cell (RBC) transfusions and iron chelation therapy. The development of an effective therapy to increase hemoglobin (Hb) levels in homozygous β thalassemia without the use of RBC transfusions could allow normal growth and development, whereas decreasing or eliminating transfusional iron overload, which remains the major cause of death, reduced life expectancy and morbidity in individuals with this disease.¹ Although bone marrow transplantation can achieve these aims,² it is not a therapeutic option for the majority of patients.

For some years, there has been interest in increasing γ -globin transcription and fetal Hb (HbF) production in patients with β hemoglobinopathies.^{3,4} For patients with homozygous β thalassemia, increased γ -globin production and a reduction in the ratio of α - to non- α -globin could reasonably be expected to ameliorate the severity of the anemia. To this end, trials of chemotherapeutic agents including 5-azacytidine^{3,5-7} and hydroxyurea^{3,8,9} have been conducted, but myelotoxicity, fears of long-term carcinogenesis, and only modest responses to treatment have limited the clinical usefulness of these agents. Erythropoietin has also been used, but responses to this therapy have been variable.^{10,11}

There is considerable evidence that butyrate analogues induce erythroid differentiation¹²⁻¹⁴ and stimulate HbF production in human erythroid progenitors in vitro.¹⁵⁻¹⁷ In vivo, these agents have also been shown to reactivate embryonic globin production in an avian model,¹⁸ delay the switch from fetal to adult globin in ovine fetuses,¹⁹ and to increase HbF production in adult primates.^{17,20-22}

In humans, several fatty acids including α amino-butyric acid,²³ arginine butyrate,^{24,25} isobutyramide,^{26,27} sodium phenylbutyrate,^{28,29} propionic acid,³⁰ and 2-propylpentanoic (di-propylacetic) acid (unpublished data) have now been shown to stimulate HbF production, suggesting that they may play a role in the treatment of the β -globin disorders. However, previous clinical trials of these agents in β -thalassemia have

been limited to relatively short-term trials of the intravenous agent, arginine butyrate,^{24,25,31} and oral isobutyramide.^{26,27}

Sodium phenylbutyrate is an orally administered agent originally developed to promote waste nitrogen excretion in the treatment of urea-cycle disorders³² and is currently used for this purpose in an Federal Drug Administration-approved phase III trial. Over 100 patient-years experience with this drug has now accumulated with no untoward effects being found. The finding of increased HbF levels in these patients²⁸ stimulated clinical trials of sodium phenylbutyrate in patients with β -hemoglobinopathies.

We report here the first long-term clinical trial of an orally administered fatty acid, sodium phenylbutyrate, in patients with homozygous β thalassemia. This represents the largest clinical trial of any Hb switching agent used in thalassemic patients to date.

PATIENTS AND METHODS

This study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins Medical Institutions and written informed consent was obtained from all patients. Eleven patients

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Table 1. Clinical Details of Patients Studied

Patient No.	Age (yrs)	Sex	β -Globin Mutations	Prestudy Hb (g/dL)
1	32.7	M	Codon 39/??	7.8†
2	26.5	F	Homozyg IVS1, nt 110	6.0
3	20.5	F	Homozyg IVS1, nt 110	6.9
4	32.2	F	Codon 39/IVS1, nt 1	7.4
5	36.7	F	Codon 39/IVS1, nt 1	6.5
6	20.6	M	Codon 39/IVS1, nt 6	8.1
7	42.3	F	IVS1, nt 6/??	4.5
8*	30.5	F	Codon 39/FR 5/6	5.5
9	24.8	M	Homozyg IVS1, nt 110	Transfused
10	26.9	F	Homozyg IVS1, nt 110	Transfused
11	25.1	M	IVS1, nt 1/IVS2, nt 745	Transfused
12	35.7	F	β^0 /IVS2, nt 745	8.2

All patients had normal α genes.

* Pretreated with 5-azacytidine.

† Transfused 6 and 3 weeks before study.

with homozygous β thalassemia and one patient with sickle β plus thalassemia were studied. Of the 11 patients with homozygous β thalassemia, 3 were receiving regular RBC transfusions and 8 were not. Of these 8, 4 had never received regular transfusions, 3 had discontinued regular transfusions because of severe RBC alloimmunization and one had discontinued transfusions to hasten the treatment of severe iron overload. All patients had previously undergone splenectomy. Details of each patient's age, β -globin mutations, α gene number and prestudy Hb are shown in Table 1.

Patients 1 through 7 and 9 through 12 commenced sodium phenylbutyrate therapy during a 21-day inpatient stay in the Johns Hopkins Hospital Clinical Research Unit. Patients 2 and 9 underwent the protocol on two occasions, recommencing sodium phenylbutyrate after 59 and 440 days off treatment. All received 20 g/d of sodium phenylbutyrate (10.6 to 13.8 g/m²/d) given as forty 500-mg tablets in three divided doses: 12 tablets were given with breakfast and 14 tablets with each of lunch and dinner. All were discharged home on medication and were followed from between 31 and 500 days as outpatients. Five of these patients continue on medication.

Patient 8, unable to be transfused because of severe alloimmunization, was receiving intravenous infusions of 5-azacytidine every 3 to 4 weeks⁷ before starting sodium phenylbutyrate therapy. Her therapy was initiated at a lower dose of 12 g/d (9.6 g/m²/d) during a 21-day inpatient stay at the National Institutes of Health, Bethesda, MD. The infusions of 5-azacytidine were subsequently discontinued and she continues on sodium phenylbutyrate alone.

All patients were documented to have normal RBC folate levels (and serum folate in the case of regularly transfused patients) before the commencement of therapy and received folic acid 1 mg/d orally while on the protocol.

Blood counts were determined using Coulter STK-S or STK-R counters (Coulter Immunology, Hialeah, FL) with manual spun Hb measurements being performed to overcome any artifactual elevation in automated Hb measurements caused by the presence of nucleated RBCs in the peripheral blood.³³ A Technicon H-1 counter was used for the determination of RBC mean corpuscular volume (MCV). Reticulocyte counts were measured with a Sysmex R-1000.³⁴ Percentages of HbF, F cells, and F reticulocytes were measured as previously described.³⁵ Globin-chain synthesis was measured by incubating peripheral blood (PB) with tritiated leucine using standard methods³⁶ with globin-chain separation being achieved by high-performance liquid chromatography. PB ratios of α , β - and γ -globin mRNA were measured using an RNAase protection assay (RPA II kit; Ambion, Inc, Austin, TX). ³²P-labeled RNA probes were made complimentary to a 130-bp segment of exon 1 of α globin, a 205-

bp segment of exon 2 of β globin and a 170-bp segment of exon 2 of γ globin. The protected fragments were separated by electrophoresis on an 8 mol/L urea 6% polyacrylamide gel, located by autoradiography and quantitated by counting the radioactivity of each isolated band in a scintillation counter. Levels of sodium phenylbutyrate, phenylacetate, and phenylacetylglutamine were measured in plasma and urine by previously described methods.³⁷

Data are expressed as mean \pm standard deviation (range) and were compared using the paired Student's *t*-test. Differences between observed and expected frequencies were compared using a chi-square test.

RESULTS

Changes in Hb. We divided the patients into two broad categories, responders and nonresponders, based on changes in Hb while on sodium phenylbutyrate therapy (Table 2). A response was defined as a sustained rise in Hb of greater than 1 g/dL. A sustained increase in Hb of 2.1 ± 0.7 g/dL (1.2 to 2.8 g/dL) was seen in 4 of the 8 (50%) patients with homozygous β thalassemia not on regular transfusion programs (Fig 1). Patient 4 showed a progressive increase in Hb over 350 days on therapy, with an acute episode of anemia related to septicemia at day 200 during which she was not transfused. Her Hb peaked at 10.2 g/dL on day 351 and then fell to around 9 g/dL when her dose of sodium phenylbutyrate was reduced by 25% to 15 g/d. Interestingly, her sibling, patient 5, also responded to sodium phenylbutyrate therapy with an increase in Hb of 1.8 g/dL over the first 140 days on therapy. Patient 8, who was receiving intravenous infusions of 5-azacytidine at the time sodium phenylbutyrate therapy was commenced, has shown a progressive increase in Hb over more than 450 days, interrupted by an acute episode of anemia related to a major gastrointestinal hemorrhage at day 220. She received two units of blood at this time. Her Hb has continued to increase allowing the 5-azacytidine infusions to be discontinued at day 280. Patient 3 showed an increase in Hb of 1.2 g/dL while on sodium phenylbutyrate, and her Hb had returned to pretreatment levels within 40 days after stopping therapy. Although this increase in Hb is only modest, in the other patients responding to therapy, Hb continued to increase for 500 days or more, suggesting that a trial of only 100 days of sodium phenylbutyrate therapy may have been inadequate to achieve the maximum possible response. Four of the eight nontransfused patients and all three previously regularly transfused patients showed no response to therapy (Table 2, Fig 2).

F reticulocyte response. All 12 patients showed an increase in the percentage of F reticulocytes after the commencement of sodium phenylbutyrate therapy, with levels at day 21 being $70\% \pm 74\%$ (mean \pm 1SD; range, 6% to 248%) above baseline levels ($P = .001$). In all patients, the increased level of F reticulocytes persisted as long as therapy was continued. In five of eight patients who discontinued sodium phenylbutyrate therapy, F reticulocytes decreased rapidly, but in three, nos. 1, 6, and 11, the F reticulocytes remained at the higher level for 4 weeks or more after the cessation of therapy. Two patients, 2 and 9, again showed an increase in F reticulocytes when therapy was recommenced. These changes suggest that the increase in F reticulocytes was directly related to the sodium phenylbutyrate therapy (Fig 3).

Table 2. Hb, RBC Count, and MCV Pre- and Post-Sodium Phenylbutyrate Therapy

Patient No.	Days Treated	Hb (g/dL)		RBC $\times 10^{12}/L$		MCV (fL)		Erythropoietin (mU/mL)	LDH 1 U/L		Indirect Bilirubin (mg/dL)		
		Pre	Post	Pre	Post	Pre	Post	Pre	Pre	Day 21	Pre	Day 21	
Nonresponders													
1*	323	7.8	5.1	2.95	2.87	85	81	96	334	237	4.8	3.5	
2	91	6.0	5.8	2.42	2.43	88	85	185	729	666	4.1	3.1	
	89	5.7	6.1	2.27	2.38	87	90	ND	ND	ND	ND	ND	
6	95	8.1	6.1	3.00	2.77	80	80	18	601	385	3.7	3.0	
7	97	4.5	5.0	2.55	2.50	73	75	104	340	148	4.6	1.7	
9*	39†	9.1	7.9	3.10	2.80	86	85	56	ND	ND	3.9	1.7	
	31†	9.0	8.8	3.15	3.10	86	88	44	214	251	2.5	2.5	
10*	86†	9.4	6.8	3.25	ND	84	90	25	144	210	1.1	0.9	
11*	71	8.4	5.0	2.90	1.71	88	96	240	302	371	1.3	1.4	
12	44	8.2	8.1	3.74	3.62	68	74	41	308	346	1.0	0.9	
Responders													
3	100	6.9	8.1	3.63	3.97	66	73	166	418	289	5.6	3.5	
4‡	490	7.4	10.2	2.58	3.36	86	94	3,882	440	259	3.3	1.7	
5‡	137	6.5	8.3	2.61	3.37	76	83	207	247	251	2.6	1.6	
8‡	468	5.5	8.3	1.91	2.49	93	97	682	531	422	4.3	4.6	

Abbreviation: ND, not done.

* Patient was transfused before commencing sodium phenylbutyrate.

† Patient was transfused while on sodium phenylbutyrate therapy.

‡ Patient continues on therapy.

Hemoglobin F response. Table 3 outlines the HbF response to sodium phenylbutyrate therapy in each patient, as measured by percentage of HbF, absolute HbF g/dL, and α /non- α ratios of both globin mRNA and globin-chain synthesis. In those patients responding to therapy, increase in total Hb was not solely explained by increased HbF. In those patients previously on regular transfusion programs, at termination of therapy both HbF% and absolute HbF levels were higher than at baseline, probably reflecting the reduced suppression of erythropoiesis related to fall in Hb and not being necessarily directly attributable to the sodium phenylbutyrate therapy. Ratios of α - to non- α -globin mRNA, measured before therapy and again at day 21 in all patients, showed no uniformity of response to sodium phenylbutyrate therapy,

nor was there any correlation between the change in globin mRNA ratios and peripheral Hb levels. Similarly, when repeated in three patients after more than 270 days on therapy, no correlation between ratios of globin mRNA and change in Hb could be shown. In addition to mRNA studies, in three patients, the production of α - and non- α -globin chains in PB reticulocytes was measured at day 0 and at day 21. Again, in these patients, neither ratios of globin mRNA nor globin-chain synthesis seemed related to changes in Hb on therapy.

Patient 12, with sickle β plus thalassemia, did not experience an increase in Hb and, therefore, was called a nonresponder. However, over the first 21 days of therapy, she did show an increase in F reticulocytes (14% to 34%) and F cells (13% to 20%) associated with an increase in HbF%

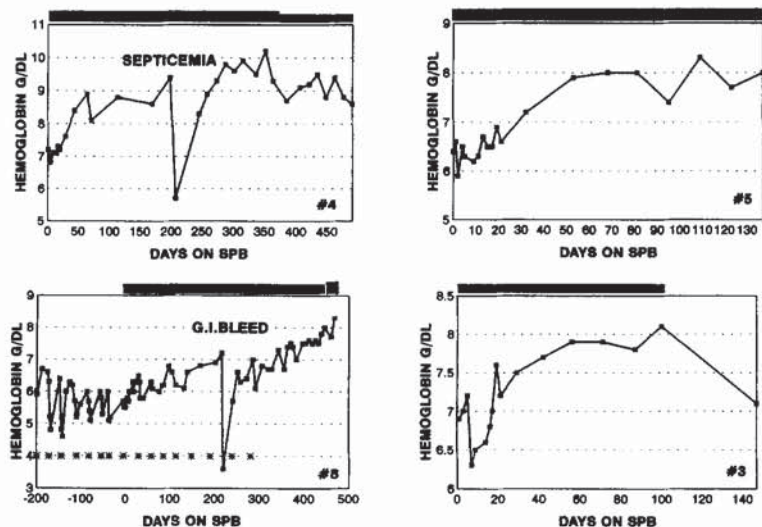


Fig 1. Hb in the four patients responding to sodium phenylbutyrate therapy: patient 4 (upper left), patient 5 (upper right), patient 8 (lower left), and patient 3 (lower right). (■), sodium phenylbutyrate therapy, with changes in the size of the bar corresponding to changes in dose. (*), intravenous infusions of 5-azacytidine.

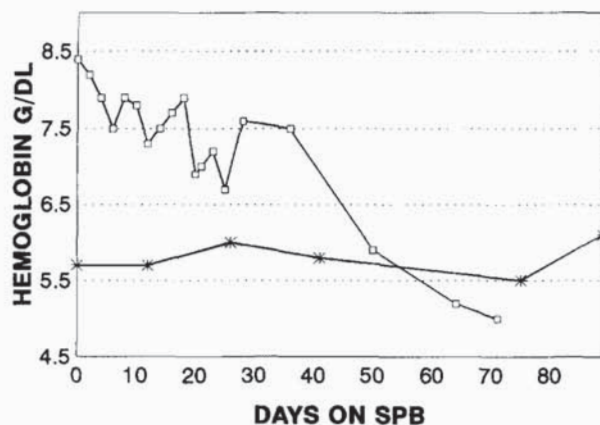


Fig 2. Hb in two patients who did not respond to therapy: patient 2 (*), who is not regularly transfused and patient 11 (□), who is transfusion-dependent.

(3.1% to 5.0%). This response to therapy is very similar to those previously seen in patients with homozygous sickle cell disease.²⁹ In sickle thalassemia, an increase in the percentage of HbF is probably a more desirable outcome than increase in Hb. Interestingly, while on therapy, her MCV increased from 67 fL to 74 fL and returned to its pretreatment value when sodium phenylbutyrate therapy was discontinued.

Indicators of hemolysis. The nine patients not on regular transfusion programs showed indirect evidence of a reduction in hemolysis, with significantly lower levels of serum lactate dehydrogenase ($P < .03$) and indirect bilirubin ($P = .0005$) when pretreatment levels were compared with those at day 21 (Table 2). This was not observed in the transfusion-dependent patients, possibly related to the mean fall in Hb of 2.0 g/dL, which occurred in these patients during the 21-day inpatient study period. In contrast, no significant difference was seen in Hb between baseline measurements and day 21 in those patients who were not regularly transfused.

Predictors of increased Hb in response to sodium phenylbutyrate therapy. Response to sodium phenylbutyrate therapy, as defined by a sustained increase in total Hb of greater than 1 g/dL above baseline, did not appear to be predicted by β -globin mutation; baseline percentage of HbF, absolute HbF, or F-reticulocyte levels; or baseline Hb or baseline α -to non- α -globin ratios. Similarly, significant falls in lactate dehydrogenase and indirect bilirubin, traditional measures of hemolysis, could be shown in all nontransfused patients with no differences being observed between responders and nonresponders. Interestingly, those patients with baseline erythropoietin levels greater than 120 mU/mL were significantly ($P < .05$) more likely to experience an increase in Hb (4/6) than those whose baseline erythropoietin level was below 120 mU/mL (0/6) (Table 2). A similar trend existed between baseline HbF percentage in those patients not receiving regular RBC transfusions and response to sodium phenylbutyrate therapy, although this did not reach statistical significance. Of the four patients with baseline HbF less than 40%, none responded to therapy. In contrast, four of the five patients with baseline HbF greater than 40% did respond ($P = .075$).

Compliance with sodium phenylbutyrate therapy. Sodium phenylbutyrate tablets were provided to the patients with a 25-day supply each time; a further supply was provided only when the patient specifically requested more tablets. In this way, compliance was calculated for each patient by comparing the number of tablets dispensed to that prescribed. Compliance with therapy was a problem in only one patient, no. 3, who abruptly discontinued therapy after 100 days, having been 95% compliant up until that time. For the patients as a group, compliance with medication was 97% \pm 3%.

Phenylbutyrate pharmacokinetics. Peak daytime levels of phenylbutyrate, phenylacetate, and phenylacetylglutamine ranged between 0.60 and 1.70 mmol/L, 0.50 and 1.50 mmol/L, and 0.56 and 2.67 mmol/L, respectively. Serial-fasting morning plasma levels of phenylacetate, measured in all patients, were less than 1.0 mmol/L and showed no progressive accumulation. Serial 24-hour urine collections performed in 9 of the 12 patients studied showed a mean excretion of 76% \pm 13% (53% to 97%) of the molar amount of sodium phenylbutyrate administered as urinary phenylacetylglutamine. Plasma glutamine levels, measured before therapy and again after 2, 9, and 21 days on therapy showed no evidence of glutamine depletion. These results are similar to those reported in patients with urea-cycle disorders^{32,37} and homozygous sickle cell disease²⁹ treated with sodium phenylbutyrate.

Adverse events occurring on therapy. The daily dose of 20 g of sodium phenylbutyrate contributes 2,460 mg (107 mmol) of sodium to the diet, a significant proportion of the recommended daily intake. While in the hospital, one of the twelve patients (no. 6) developed ankle edema associated with a 3.5% increase in body weight, which resolved spontaneously with dietary modification. After discharge from hospital, one patient (no. 1) required intermittent treatment with a thiazide diuretic and one (no. 8) required an increase in her previous diuretic dose to control peripheral edema. No patient developed hypertension. Epigastric discomfort after

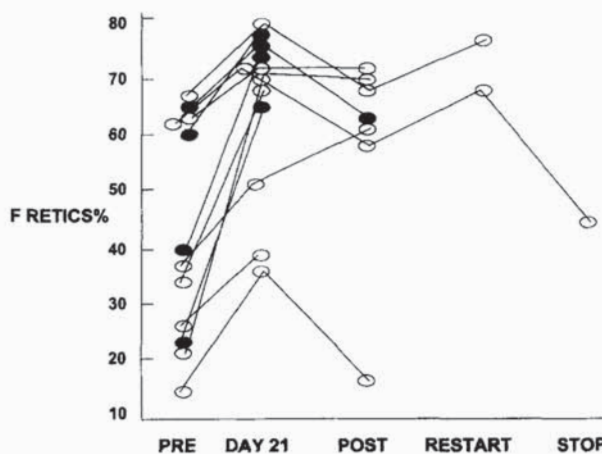


Fig 3. The percentage of F reticulocytes in individual patients before sodium phenylbutyrate therapy (PRE), after 21 days of therapy (DAY 21), at least 2 weeks after the cessation of therapy (POST), on restarting therapy (RESTART), and after again stopping therapy (STOP). (●), responders; (○), nonresponders.

Table 3. Percent HbF, Absolute HbF, and α /Non- α Ratios Pre- and Post-Sodium Phenylbutyrate Therapy

Patient No.	HbF (%)		AbsHbF (g/dL)		α /Non- α Ratio mRNA (mean \pm SD)			α /Non- α Ratio Globin		Hb Increase (g/dL)
	Pre	Post	Pre	Post	Pre	Day 21	Day 270	Pre	Post	
Nonresponders										
1*	13	27	1.0	1.4	1.7 \pm 0.2	2.6 \pm 0.3	2.0 \pm 0.3			-2.7
2	71	75	4.3	4.3	1.7 \pm 0.1	1.0 \pm 0.1				-0.2
	76	86	4.4	5.2						+0.4
6	21	50	1.8	3.2	2.9 \pm 0.1	1.8 \pm 0.1				-2.0
7	11	14	0.5	0.6	3.9 \pm 0.1	3.1 \pm 0.4		3.1	2.6	+0.5
9*	1	2	0.1	0.2	2.7 \pm 1.9	1.9 \pm 0.1				-1.2†
	2	1	0.2	0.1	1.8 \pm 0.2	2.6 \pm 0.2				-0.2†
10*	2			0.2	1.8 \pm 0.2	2.2 \pm 0.5				-2.6†
11*	13	59	1.1	3.0	2.0 \pm 0.3	0.7 \pm 0.1				-3.4
12	3.1	5.0	0.3	0.4	2.9 \pm 0.8	1.7 \pm 0.1		1.5	1.6	-0.1
Responders										
3	57	58	3.9	4.7	1.5 \pm 0.1	1.0 \pm 0.1				+1.2
4	90	84	7.5	8.6	1.7 \pm 0.2	2.6 \pm 0.3	1.7 \pm 0.1			+2.8
5	85	86	5.5	7.5	2.4 \pm 0.1	2.0 \pm 0.1		2.2	2.1	+1.8
8	82	83	4.9	6.7	1.5 \pm 0.2		2.2 \pm 0.1			+2.8

* Patient was transfused before commencing sodium phenylbutyrate.

† Patient was transfused while on sodium phenylbutyrate therapy.

the ingestion of the tablets was the most common adverse effect, being reported by seven of the twelve patients. Two patients, both splenectomized and not on regular penicillin prophylaxis, had nonfatal episodes of bacterial septicemia: patient 4 developed infection with *Streptococcus pneumoniae* at day 71 and *Plesiomonas shigelloides* at day 200, and patient no. 6 developed infection with *Staphylococcus epidermidis* related to an indwelling central venous catheter at day 24. Patient 8 suffered a hemorrhage from a gastric ulcer at day 220 soon after the commencement of aspirin therapy for long-standing pulmonary hypertension. Patient 1, who had spun Hb levels between 5.1 and 7.5 g/dL associated with marked erythroblastosis, developed spinal cord compression requiring irradiation at day 323 and ceased sodium phenylbutyrate therapy. Patient 10 developed a deep venous thrombosis at day 28 with a Hb 5.9 g/dL. Three patients experienced bad body odor while on therapy, which in one, no. 12, caused her to be unable to tolerate the medication long-term, even at half the usual dose. These complaints are probably related to the in vivo β oxidation of phenylbutyrate to phenylacetate, a compound with an offensive odor secreted as a defense mechanism by the stinkpot turtle.³⁸

DISCUSSION

This study shows that sodium phenylbutyrate can safely be administered to patients with homozygous β thalassemia and is well tolerated by the majority. The need to take 40 tablets daily, epigastric discomfort, and the body odor created in some patients are problematic. Poor compliance with this regimen, based on previous experience with this drug, was expected to be a frequent problem,²⁹ but surprisingly was not, possibly related to the fact that many of these patients had had prior experience with other cumbersome medical interventions including transfusion schedules and iron chelation therapy. However, the oral route of administration

has clear advantages over the intravenous route needed for arginine butyrate, particularly because all the evidence available suggests that in the management of the β hemoglobinopathies, these therapies, if effective, will be needed long-term.

We found that 36% (4/11) of all patients or 50% (4/8) of nontransfused patients responded to sodium phenylbutyrate when a response was defined as a sustained increase in Hb of more than 1 g/dL over pretreatment values. Clearly, sodium phenylbutyrate can increase Hb in some patients with homozygous β thalassemia, but is not effective in all of them. Although it seems evident that β -globin mutation alone does not predict response, the fact that two siblings treated in this study both responded to sodium phenylbutyrate therapy raises the possibility that some other genetic factor is involved. Other genetic factors linked and unlinked to the β -globin locus have been shown to effect HbF levels in normal individuals and patients with β hemoglobinopathies.^{39,40}

The failure of Hb to increase in patients showing a decrease in levels of lactate dehydrogenase and indirect bilirubin is disappointing and raises interesting questions as to the cause of these changes if not related to decreased hemolysis. Similarly, we have observed increased production in F reticulocytes in all patients treated with this agent to date and the persistence of levels of F reticulocytes higher than baseline in some patients up to a month or more after the cessation of therapy with an agent known to be rapidly metabolized and excreted. Similar observations have been reported after the use of arginine butyrate.^{24,27} This uniformity of F-reticulocyte response, persistence of response in some patients long after the cessation of therapy, and lack of correlation between changes in F reticulocytes and increased total Hb or increased absolute HbF production may indicate suboptimal increases in HbF insufficient to decrease ineffective erythropoiesis.

The lack of correlation between changes in α - to non-

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