# Sodium Benzoate in the Treatment of Acute Hepatic Encephalopathy: A Double-blind Randomized Trial

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**A prospective randomized double-blind study was conducted to evaluate the efficacy of sodium benzoate in the treatment of acute portal-systemic encephalopathy. Seventy-four consecutive patients with cirrhosis or surgical portasystemic anastamosis and hepatic encephalopathy of less than 7 days duration were randomized to receive lactulose (dose adjusted for 2 or 3 semiformed stools/day) or sodium benzoate (5 gm twice daily). Assessment of response included mental status, asterixis, arterial ammonia level, electroencephalogram and number-connection test. Each was given a score between 0 and 4+. A portal-systemic encephalopathy index was calculated with these scores. Visual, auditory and somatosensory evoked potentials and a battery of psychometric tests for intelligence and memory were also performed to assess improvement. Thirty-eight patients received sodium benzoate; 36 took lactulose. Thirty patients (80%) receiving sodium benzoate and 29 (81%) receiving lactulose recovered; the remaining patients died. Improvement in portal-systemic encephalopathy parameters occurred in both treatment groups and was similar ($p > 0.1$). Electroencephalogram and evoked potentials were not as helpful as mental status in assessing of recovery. Psychometric test scores remained abnormal after recovery of mental status (21 to 42 days) and were probably too sensitive for monitoring of these patients. The incidence of side effects was similar in the two treatment groups. The cost of lactulose for one course of therapy was 30 times that of sodium benzoate. We conclude that sodium benzoate is a safe and effective alternative to lactulose in the treatment of acute portasystemic encephalopathy. (HEPATOLOGY 1992;16:138-144.)**

Portal-systemic encephalopathy (PSE) in patients with chronic liver disease may be mediated by various factors (1, 2). Elevation of blood ammonia has been considered an important factor in its pathogenesis (3). Conventional therapy for PSE is aimed at lowering blood ammonia through measures including a decrease in colonic urea-splitting bacteria (antibiotics) and a lowering of colonic pH (lactulose, acidifying enemas) (4). The role of lactulose in the treatment of encephalopathy in chronic liver disease has been well established (5, 6). However, lactulose is expensive and not easily available in India; it cannot be administered parenterally and is associated with undesirable adverse effects. Sodium benzoate, a commonly used food preservative, has been shown recently to be useful in the treatment of chronic PSE because of its ammonia-lowering potential (7, 8). Sodium benzoate is nontoxic, inexpensive and easily available. Its role has not been evaluated in acute PSE. Hence we performed a double-blind randomized study comparing sodium benzoate and lactulose in the treatment of acute PSE.

## PATIENTS AND METHODS

The study population consisted of consecutive patients with hepatic encephalopathy admitted to the gastroenterology ward. All patients were diagnosed as having cirrhosis or had a surgical portal-systemic anastomosis. The diagnosis of cirrhosis was made by liver biopsy or clinical criteria (9) when liver biopsy was not possible. All patients showed clinical evidence of hepatic encephalopathy of less than 7 days' duration. Encephalopathy could have been precipitated by nitrogenous substances (dietary proteins, diuretic drugs, gastrointestinal bleeding) or idiopathic (endogenous) factors. Patients were excluded if they underwent treatment with lactulose for 24 hr or more before entry into the study or had active gastrointestinal bleeding, history of neurological disease other than hepatic encephalopathy or refusal to enter into a study protocol by the responsible next of kin. The use of sodium benzoate in patients with hepatic encephalopathy was approved by the hospital ethics committee.

***Study Design.*** Patients were assigned to sodium benzoate or lactulose therapy by the sealed-envelope technique. Each episode of PSE was considered a distinct event and randomized to one of the two treatment protocols. Double blinding was achieved by administration of solutions of sodium benzoate or lactulose by an independent health care worker. The assessment of the response was done by using the portal-systemic parameters *(vide infra)* by one of the authors (S. S.) who was not aware of the group to which the patient was assigned.

***Treatment Schedule.*** Both compounds (lactulose and sodium benzoate) were administered as solutions. They were given orally or, if necessary, through a nasogastric tube. Lactulose was administered in an initial dose of 30 ml every 8 hr; the dosage was then adjusted once in 24 hr to result in

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3 semiformed stools/day. Sodium benzoate was administered at a dose of 5 gm twice daily (each dose dissolved in 30 ml of tap water). Treatment was continued until the patients experienced complete clinical recovery.

Standard treatment of patients with acute encephalopathy was continued in both groups and included twice-daily bowel washes with tap water, maintenance of fluid and electrolyte levels, intake of at least 800 calories/day and restriction of the oral intake of proteins to 20 gm/day in patients in whom oral intake was possible. Additional measures of treatment included antibiotic drugs for control of infection, diuretic drugs to control ascites and maintain a urinary output of more than 800 ml/24 hr and therapeutic paracentesis if required. Parenteral nutrition was not administered to any patient.

***Parameters of PSE.*** On admission to the hospital, patients underwent physical, neurological and psychometric assessment. The parameters used to assess the response to therapy included mental status, results of psychometric testing, electroencephalogram (EEG), arterial ammonia levels and presence of asterixis. These were assigned scores as described earlier (10).

Mental state was graded from alertness to coma (0 to 4+) by the West Haven criteria for grading of PSE (10):

0 = normal mentation; 1 = inability to perform manipulation and sequencing tasks, shortened attention span; 2 = disorientation to time, place and person; 3 = semistupor or somnolence, confusion, gross disorientation, bizarre behavior; 4 = coma (tests of mental function not possible).

The presence of asterixis was determined by extending the patient's arms and forearms (with the wrist dorsiflexed) for at least 30 sec. The scores assigned were as follows (10): grade 0 = no flapping motions; grade 1 = rare flapping motions; grade 2 = occasional irregular flaps; grade 3 = frequent flaps; grade 4 = almost continuous flapping movements.

A battery of psychometric tests for intelligence and memory was performed with the Indian version of psychometric testing (11). Tests for memory included those for verbal memory with homogeneous and heterogeneous interference and for nonverbal memory for designs with and without interference. Tests for intelligence included the identification of logical relationships and reasoning, the conceptual analogy test and maze learning. The results were scored on a scale of 0 to 4, with increasing scores assigned as the number of errors increased. The tests of memory and intelligence were scored from 0 to 4 for each of the tests performed. The best score possible was 0, which indicated correct performance of all six tests of memory and eight tests of intelligence. The worst possible scores would be 24 for memory and 32 for intelligence, indicating inability to perform or error in performance of all the tests. In addition, the standard psychometric tests used by other authors were performed, including the number-connection test, five-pointed star construction, the serial-seven subtraction and the backward counting tests (5). The error scores and time taken for these were compared in the two treatment groups and before and after therapy. The results of the number-connection test were graded as described by other authors based on the time in seconds necessary to complete the test (10): grade 0 = less than 30 sec; grade 1 = 31 to 51 sec; grade 2 = 51 to 80 sec; grade 3 = 81 to 120 sec; grade 4 = longer than 120 sec or patient unable to perform the test.

Arterial ammonia levels were estimated by the enzymatic method and graded as follows (10): grade 0 = less than 90 μg%; grade 1 = 91 to 120 μg%; grade 2 = 121 to 150 μg%; grade 3 = 151 to 180 μg%; grade 4 = greater than 180 μg%. Normal range was 60 to 90 μg%).

EEGs were recorded with a Nihon-Kohden 16-channel international 10-20 electrode placement system (Nihon-Kohden Corp., Tokyo, Japan). They were graded as follows (10): grade 0 = normal alpha rhythm of less than 9.0 cycles/sec (cps); grade $1^+$ = 7 to 8.9 cycles/sec; grade $2^+$ = 5 to 6.9 cycles/sec; grade $3^+$ = 3 to 4.9 cycles/sec; grade $4^+$ = 2.9 cycles/sec or less.

EEGs were recorded on entry or within 48 hr of entry in patients considered clinically fit to be transferred to the electrophysiology laboratory.

***PSE Index.*** Each of the above parameters was arbitrarily weighed in proportion to its importance. Mental status was assigned a factor of 3; each of the other categories received a factor of 1. Thus mental status had a maximum potential score of 12, whereas each of the other parameters had a maximum potential score of 4. The total of the weighted scores, the maximum of which is 28, was termed the PSE sum. The PSE sums were not always comparable because asterixis and the trailmaking test were not possible in comatose patients and EEGs were not always performed. Consequently, PSE index (PSEI) was calculated as the ratio of the PSE sum to the highest possible PSE sum. The PSEI allows comparative evaluation of PSE before and after therapy in the two treatment groups.

***Evoked Potentials.*** Visual, somatosensory and auditory evoked potentials were recorded when possible in patients before and after therapy with a Nicolet 1170 clinical averaging system (Nicolet Instrument Corp., WI). Each side was tested separately. At least two reproducible recordings ($< 0.08$ msec difference in interwave latencies), were obtained for each of the evoked potentials. All latencies were calculated from cursor values as measured on a cathode-ray oscilloscope display. The latency periods and amplitudes were compared between the two treatment groups, each treatment group before and after therapy and with those of a matched healthy control population.

***Therapeutic Response.*** Therapeutic success was defined as (a) sustained improvement of one grade in mental status in less than 48 hr or (b) improvement of more than two grades in mental status. Complete response was defined as recovery to normal mental status with no evidence of asterixis. Partial response was defined as improvement in mental status by at least two grades without normalization. Time elapsed before response was also recorded in each patient. Therapeutic failure was defined as (a) no change in mental state after 48 hr of therapy; (b) sustained deterioration of one grade in mental state during 48 hr of therapy; (c) deterioration of two grades in mental state; and (d) death in coma despite treatment.

In patients who showed therapeutic failure, the codes were broken and patients receiving sodium benzoate were started on lactulose. Patients treated with lactulose who deteriorated clinically continued with the same treatment.

***Follow-up.*** Clinical evaluation and neurological assessment for the grade of mental status was made every 2 hr until the patient had improved to grade $2^+$ status. Detailed assessments were made every 48 hr by one of the authors (S.S.), who was blinded to the treatment schedule. Arterial ammonia level was estimated at entry, after 72 hr and after recovery in patients who survived. Patients were treated with the assigned drug until they demonstrated a mental score of 0 and had no clinical evidence of encephalopathy.

***Cost Analysis.*** The cost of lactulose (Duphalac; Duphar B.V., Laboratories, The Netherlands) and of sodium benzoate (Dey Pharmaceuticals) were calculated in the local currency, and the costs were compared.

***Analysis.*** The changes in the different parameters before and after treatment were compared. The changes observed

TABLE 1. Clinical and demographic features

| Characteristics | Sodium Benzoate | Lactulose |
|---|---|---|
| No. of patients | 38 | 36 |
| M/F | 30/8 | 26/10 |
| Age (yr)[a] | 35.6 ± 18.4 | 37.9 ± 12.8 |
| Diagnosis | | |
| Posthepatitic cirrhosis | 25 | 27 |
| Alcoholic cirrhosis | 10 | 8 |
| Portacaval shunt[b] | 3 | 1 |
| Duration of encephalopathy before entry (days)[a] | 3.4 ± 1.6 | 2.9 ± 2.4 |
| Grade of encephalopathy | | |
| II | 4 | 6 |
| III | 19 | 18 |
| IV | 15 | 12 |
| Child score | | |
| B | 20 | 19 |
| C | 18 | 17 |
| Prior encephalopathy[c] | 3 (3) | 3 (4) |

[a]Data expressed as mean ± S.E.M.

[b]Noncirrhotic fibrosis in two; cirrhosis in two; no significant differences between the two treatment groups.

[c]Numbers in parentheses refer to number of episodes of encephalopathy in the patients before inclusion in the study.

were also compared between the two groups. The comparison of data in the same group before and after treatment was made with Student's paired *t* test. Comparison of results between the two treatment groups was made by Student's *t* test for unpaired data. Qualitative variables were compared by the $\chi^2$ test.

## RESULTS

Between January 1990 and June 1991, 132 patients with cirrhosis and hepatic encephalopathy were admitted to the gastroenterology ward. Seventy-four patients were inducted into the study. Others were excluded because of continued upper gastrointestinal bleeding (26 patients), sepsis (16 patients), severe hyponatremia (4 patients) or azotemia (12 patients).

The clinical and demographic features of the two groups were similar (Table 1). Patients were entered in the study within a week of onset of encephalopathy. Most of the patients (64) were in grade 3 or grade 4 encephalopathy. Diuretic drugs had been administered for control of ascites in 24 (63.2%) patients taking sodium benzoate and in 19 (52.8%) taking lactulose before entry.

Thirty (80%) patients receiving sodium benzoate and 29 (81%) patients receiving lactulose recovered with therapy ($p > 0.1$). The pathogenesis of underlying liver disease and duration of encephalopathy, before entry into the study did not influence the results. Grade of encephalopathy was inversely related to the response to treatment in both groups. The duration of therapy before complete clinical recovery was 11.6 ± 6.4 days in the sodium benzoate group and 12.8 ± 9.1 days in the lactulose group ($p > 0.1$). The rates of recovery in mental status and asterixis were similar in the two treatment groups. Three patients in the sodium benzoate group and one patient in the lactulose group continued in grade $1^+$ mental status despite therapy for 21 days. At this writing, these patients are continuing with the assigned treatment and are in follow-up. Two patients treated with sodium benzoate exhibited progressive worsening of their mental status while undergoing therapy. These two patients were switched over to lactulose and the data were censored up to the commencement of therapy with sodium benzoate. One of these patients showed improvement but the other patient died. Sodium benzoate therapy failed in nine patients (eight deaths and one response to lactulose). A similar response was observed with lactulose therapy. Four patients deteriorated from grade 3 to grade 4 mental status and died; three other patients who were in grade 4 mental state also died.

***Biochemical Tests.*** Arterial ammonia concentrations in acute encephalopathy at admission did not correlate with the grade of encephalopathy, but the levels were elevated in most patients in both groups (sodium benzoate, 36 of 38; lactulose, 33 of 36). After recovery, normal levels were found in 34 of 36 patients treated with sodium benzoate and in 31 of 33 patients treated with lactulose. The mean level of arterial ammonia in healthy controls was 21.6 ± 8.6 μg%.

Mild elevation of serum sodium was observed in patients treated with sodium benzoate (123 ± 22 mEq/L before and 138 ± 14 mEq/L after therapy). Other hematological, kidney function and liver function parameters did not show any significant changes ($p > 0.1$) after therapy (Table 2).

***Psychometric Tests.*** Standard tests, including the number-connection test, five-pointed star construction, serial-seven subtraction and backward counting could not be performed by 14 of 24 patients (58.3%) even after recovery. All patients showed impaired performance in the Indian version of the psychometric tests. After treatment with both sodium benzoate and lactulose, significant improvement ($p < 0.001$) in the scores of the tests of intelligence and memory was observed (Table 3). However, even after recovery of mental status and disappearance of asterixis, these tests remained abnormal for 3 to 6 wk in patients in both treatment groups. We continue to follow these patients.

***EEG Abnormalities.*** EEGs were performed in 24 patients on entry (sodium benzoate, 11; lactulose, 13). It could not be performed in others because of logistical reasons. These included difficulty in transferring the sick patients to the electrophysiology laboratory, movement artifacts distorting the EEG recordings or death before the study could be performed.

A normal α-rhythm (9 to 13 cycles/sec) was found in three patients in each of the two groups before therapy. Slow waves (< 8 cycles/sec) were found in 8 patients in the sodium benzoate group and 10 patients in the lactulose group before therapy. After recovery, repeat EEGs were performed in nine patients receiving sodium benzoate and in eight patients receiving lactulose. The changes in the two treatment groups were similar

**TABLE 2. Laboratory parameters**

| Measurement | Sodium benzoate (n = 32) | | Lactulose (n = 26) | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Hemoglobin (gm%) | 8.4 ± 2.8[a] | 9.1 ± 2.4 | 7.8 ± 4.6 | 8.2 ± 2.9 |
| TLC (per $mm^3$) | 9,600 ± 1,400 | 10,100 ± 2,400 | 8,600 ± 1,200 | 9,200 ± 1,100 |
| Blood urea (mg%) | 36.8 ± 11.2 | 32.4 ± 12.4 | 35.6 ± 9.8 | 31.4 ± 11.4 |
| Serum creatinine (mg%) | 1.1 ± 0.9 | 0.9 ± 1.2 | 0.8 ± 1.1 | 0.9 ± 1.0 |
| Serum bilirubin (mg%) | 3.4 ± 3.9 | 2.8 ± 3.6 | 3.2 ± 4.6 | 2.8 ± 4.1 |
| Serum sodium (mEq/L) | 123 ± 22 | 138 ± 14[b] | 119 ± 12 | 121 ± 16 |
| ALT (KU/dl) | 46 ± 12 | 48 ± 13 | 39 ± 16 | 41 ± 12 |
| Serum albumin (gm/dl) | 2.4 ± 1.8 | 2.2 ± 1.3 | 2.3 ± 1.3 | 2.2 ± 1.1 |
| Prothrombin time (msec) | 9.6 ± 10.4 | 11.4 ± 14.6 | 10.4 ± 11.2 | 12.4 ± 9.8 |
| Arterial ammonia (μg/dl)[c] | 64.6 ± 34.2 | 28.4 ± 12.6 | 72.4 ± 41.6 | 18.6 ± 24.2 |

TLC = total leukocyte count.
[a]Data expressed as mean ± S.E.M.
[b]$p < 0.05$ before and after treatment.
[c]Levels significantly lower after treatment in both treatment groups ($p < 0.001$). No other parameters showed significant differences.

**TABLE 3. Psychometric tests**

| Test | Sodium benzoate | | Lactulose | |
|---|---|---|---|---|
| | Before TRT (n = 21) | After TRT (n = 18) | Before TRT (n = 19) | After TRT (n = 17) |
| Memory (n = 6)[a, b] | 21.1 ± 2.1 | 8.6 ± 6.4 | 22.4 ± 1.8 | 11.6 ± 4.2 |
| Intelligence (n = 8)[a, b] | 28.4 ± 1.6 | 11.2 ± 4.6 | 26.8 ± 2.6 | 12.8 ± 5.9 |
| Maze test[c] | – | 5[d] | – | 4[d] |
| Backward counting | – | 2[a] | – | 2[d] |
| Reitans number-connection Test | – | 4[d] | – | 3[d] |
| Five-pointed star | – | 6[d] | – | 4[d] |

[a]$p < 0.001$ before and after treatment in the two treatment groups. Before-treatment and after-treatment scores in the two groups were similar ($p > 0.1$).
[b]Data expressed as mean ± S.E.M.
[c]$p < 0.05$ before and after treatment in the two groups.
[d]Number of patients successfully performing the test.

($p > 0.1$) and normal patterns were seen in seven patients in the sodium benzoate group and in five patients in the lactulose group after recovery. However, one patient receiving sodium benzoate and three patients taking lactulose showed persistence of slow waves on EEG 1 wk after clinical recovery. None of the patients showed the three cycles/sec pattern.

***PSEI.*** The parameters constituting the PSEI showed a significant improvement with therapy in the two groups of patients (Table 4). PSEI on admission was an indicator of the final outcome of the patients; an index less than 0.8 predicted a mortality of 95% and an index less than 0.2 predicted survival in 92% of patients.

***Evoked Potentials.*** The latency and amplitude of the recordings in the two treatment groups before and after treatment are shown in tables 5-7. It was found that the brainstem auditory evoked potential (BAEP) was more sensitive than visual evoked potential (VEP) and somatosensory evoked potential (SSEP) in the assessment of PSE. Abnormal VEP latency was seen in two patients in the sodium benzoate group and in three patients in the lactulose group. These patterns showed a reversal to normal after 7 days of treatment. The SSEP was normal in both treatment groups before and after therapy and was noncontributory in the monitoring of these patients. The BAEP interpeak latencies were abnormal in patients with encephalopathy and the interpeak latency between III and V was the most sensitive parameter. These became normal with therapy.

***Treatment and Complications.*** The mean dose of lactulose used was 66.8 ± 24.8 ml/day for 8.8 ± 7.1 days. The dosage of sodium benzoate used was 5 gm twice daily for 7.9 ± 6.4 days. Diarrhea with a stool frequency of more than 4 episodes/day occurred in 12 (33%) patients; flatulence occurred in 18 (50%) patients treated with lactulose. None of the patients treated with lactulose experienced dehydration or electrolyte abnormality. Of the 38 patients treated with sodium benzoate, 15 (39.4%) experienced nausea, 10 (25.8%) experienced vomiting and 10 (25.8%) experienced epigastric discomfort. Administration of ranitodine (150 mg) twice daily controlled these symptoms. Reduction in the dosage of sodium benzoate, however, did not result in amelioration of the gastrointestinal symptoms. Additional treatment measures in the patients included the use of antibiotics for control of infection (pneumonitis,

**TABLE 4. Changes in PSE parameters before and after treatment**

| PSE parameters | Sodium benzoate | | Lactulose | |
|---|---|---|---|---|
| | Before | After | Before | After |
| Mental status (0-4) | 3.3 ± 0.13 (38)[a] | 0.13 ± 0.34[b] (30) | 3.6 ± 0.4 (36) | 0.1 ± 0.3[b] (29) |
| Asterixis (0-4) | 3.6 ± 0.5 (23) | 0.1 ± 0.2[b] (30) | 3.5 ± 0.6 (24) | 0.2 ± 0.6[b] (29) |
| Number-connection test (0-4) | 3.9 ± 0.25 (18) | 2.1 ± 1.1[c] (12) | 3.8 ± 0.8 (17) | 1.9 ± 1.3[c] (12) |
| Arterial ammonia (0-4) | 2.1 ± 0.9 (38) | 1.1 ± 0.8[c] (30) | 1.9 ± 0.6 (36) | 0.9 ± 0.3[c] (29) |
| EEG (0-4) | 1.6 ± 0.8 (11) | 1.4 ± 0.4[c] (8) | 1.8 ± 0.9 (13) | 1.5 ± 0.8[c] (10) |
| PSEI | 0.61 ± 0.08 | 0.2 ± 0.01[b] | 0.68 ± 0.06 | 0.19 ± 0.02[b] |

[a]All values expressed as mean ± S.D.; figures in parenthesis indicate number of patients in whom the tests could be performed.
[b]Values significantly different before and after treatment ($p < 0.01$).
[c]Values significantly different before and after treatment ($p < 0.05$).

**TABLE 5. VEPs (P100)**

| Characteristics | Normal (n = 20) | Sodium benzoate | | Lactulose | |
|---|---|---|---|---|---|
| | | Before (n = 14) | After (n = 11) | Before (n = 12) | After (n = 15) |
| Latency (msec) | 93.22 ± 5.43[a] | 101.6 ± 12.6[b] | 98.8 ± 8.6 | 102.6 ± 9.6[b] | 98.6 ± 9.8 |
| Amplitude (uv) | 7.2 ± 2.65 | 7.4 ± 2.1 | 7.3 ± 2.4 | 6.8 ± 2.5 | 7.1 ± 3.4 |

P100 = first positive wave that occurs normally at 100 msec after the visual stimulus.
[a]Data expressed as mean ± S.D.
[b]$p < 0.05$ before and after treatment.

**TABLE 6. BAEPs**

| Interpeak latencies | Normal (n = 20) | Sodium benzoate | | Lactulose | |
|---|---|---|---|---|---|
| | | Before (n = 14) | After (n = 11) | Before (n = 12) | After (n = 11) |
| I-III | 2.12 ± 0.14[a] | 2.3 ± 0.10 | 2.2 ± 0.09 | 2.21 ± 0.11 | 2.11 ± 0.12 |
| I-V | 3.86 ± 0.24 | 4.1 ± 0.8 | 4.0 ± 0.9 | 4.10 ± 1.0 | 3.80 ± 0.6 |
| III-V | 1.77 ± 0.24 | 2.5 ± 0.08[b] | 1.9 ± 0.3 | 2.6 ± 0.10[b] | 1.80 ± 0.08 |

[a]Data expressed as mean ± S.D.
[b]$p < 0.01$ before and after treatment.

**TABLE 7. SSEPs (n = 19)**

| Characteristics | Normal (n = 20) | Sodium benzoate | | Lactulose | |
|---|---|---|---|---|---|
| | | Before (n = 14) | After (n = 11) | Before (n = 12) | After (n = 11) |
| Latency (msec) | 19.9 ± 0.6[a] | 19.8 ± 0.9 | 19.6 ± 0.6 | 19.6 ± 0.6 | 19.1 ± 0.9 |
| Amplitude (μV) | 0.8 ± 0.01 | 0.7 ± 0.06 | 0.8 ± 0.09 | 0.82 ± 0.06 | 0.79 ± 0.13 |

[a]Data expressed as mean ± S.D.

bacterial peritonitis urinary infection) in seven patients receiving sodium benzoate and in one patient taking lactulose. Diuretic therapy was continued for control of ascites and maintenance of adequate urine output in 14 patients taking sodium benzoate and 12 patients taking lactulose. Therapeutic paracentesis was not performed, and parenteral nutrition was not administered to any of these patients. Before inclusion in the study, six (15.8%) patients taking sodium benzoate and eight (22.2%) taking lactulose had been treated with parenteral fluids and bowel washes. In the remaining patients, tap water enemas and the specific treatment assigned (sodium benzoate or lactulose) were started simultaneously.

Analysis of the response to treatment (clinical features, biochemical profile, electrophysiological changes) in patients with cirrhosis was similar to those with noncirrhotic portal hypertension and portacaval shunts. Hence these patients were analyzed together.

***Mortality.*** Eight patients taking sodium benzoate and seven patients taking lactulose died during treatment (Table 8). The mortality rates in the two groups were similar ($p > 0.1$). Patients in Child class C had significantly higher mortality than did those in Child class B ($p < 0.01$). The mortality rates of patients in grade III or IV mental status were higher than in those in grade II ($p < 0.05$). The causes of death in the two treatment groups were also similar.

***Cost Analysis.*** The cost of lactulose for the duration of

therapy was 30 times that of sodium benzoate in the local currency ($p < 0.001$).

## DISCUSSION

This study has shown that sodium benzoate is effective in the treatment of acute episodes of hepatic encephalopathy in patients with cirrhosis or portal-systemic shunts. Objective and statistically significant improvement in mental state, neurological abnormalities and intellectual abilities and reduction in arterial ammonia concentration occurred with sodium benzoate therapy. These observations were based on objective evaluation of each of these parameters by an observer (S.S.) who was blinded to the therapy being administered. Improvement in mental status and asterixis was found in 30 (80%) patients receiving sodium benzoate treatment. These results were similar to those previously reported on the efficacy of sodium benzoate in chronic portal-systemic encephalopathy (7, 8). No reports have been made of sodium benzoate therapy in acute hepatic encephalopathy in patients with cirrhosis. Lactulose and lactitol have been successfully used in the treatment of acute hepatic encephalopathy in cirrhotic patients (12-14). Both these drugs have been found to result in clinical improvement in 69% to 82% of patients (12, 13), similar to our experience with sodium benzoate and lactulose.

In this study, patients in different grades of encephalopathy had shown similar results with the two treatment modalities. As expected from earlier experience (15), increasing grades of encephalopathy were associated with increasing mortality. Duration of therapy before recovery of mental status was similar in the two treatment groups. Complete recovery of mental status was, however, not found in three patients in the sodium benzoate group and in one patient in the lactulose group. Asterixis disappeared earlier than did recovery of mental status in all patients.

A significant improvement in arterial ammonia level was seen in our patients with either treatment modality. The ammonia levels in our patients and in the control subjects were lower than in the Western patients with cirrhosis (10). This may be because of the lower body mass index, lower protein intake or the predominantly vegetarian eating habits of Indian subjects. A fall in PSEI was associated with a decrease in the arterial ammonia. However, the grade of encephalopathy did not correlate with arterial ammonia, which is consistent with previous reports on patients with hepatic encephalopathy (16).

The standard psychometric tests, which included the number-connection test, the five-pointed star construction, serial-seven subtraction and the backward counting test could not be performed in 14 (30%) patients undergoing sodium benzoate therapy or in 26 (29%) patients undergoing lactulose therapy even after recovery of mental status. The Indian version of the tests for intelligence and memory showed a significant improvement with therapy. However, they continued to remain abnormal for 3 to 6 wk. This may be due to persistence of subclinical PSE in these patients (17).

**TABLE 8. Mortality in the two treatment groups**

| Characteristics | Sodium benzoate (n = 8) | Lactulose (n = 7) |
|---|---|---|
| Child score | | |
| B | 1 | 0 |
| C | 7 | 7 |
| Grade of coma at entry | | |
| II | 0 | 0 |
| III | 3 | 2 |
| IV | 5 | 5 |
| Cause of death | | |
| Gastrointestinal bleeding | 1 | 1 |
| Spontaneous bacterial peritonitis | 2 | 1 |
| Refractory hypotension | 3 | 2 |
| Azotemia | 1 | 2 |
| Aspiration pneumonitis | 1 | 1 |

These tests may therefore be too sensitive and not relevant in routine monitoring of patients with PSE.

Abnormal EEGs with slow waves were seen in 8 (72.7%) patients in the sodium benzoate group and in 10 (77%) patients in the lactulose group. The classical 3 cycles/sec EEG pattern reported in patients with hepatic encephalopathy (18) was not seen in any of our patients. A similar observation has been made by other authors (18). Normal EEGs were found after recovery in five (83%) of six patients in the sodium benzoate group and in five (62.5%) of eight patients in the lactulose group. Persistence of slow waves was found in the remaining patients despite normal mental status; this persistence was similar to that reported earlier (19). Previous studies of hepatic encephalopathy with the PSEI have not attempted to define its prognostic value (4-8, 10-12). This is the first study to show that cut-off values can be defined to predict the final outcome of these patients' clinical courses.

VEP and SSEP were not helpful in this study for evaluation of patients with PSE on therapy. An abnormal latency of VEP was seen in 4 (29%) of 14 and in 5 (42%) of 12 patients undergoing sodium benzoate and lactulose therapy, respectively. After recovery, the latencies were similar to the control values. BAEPs were more sensitive than VEPs or SSEPs in the evaluation of PSE. The interpeak latency between mental status classes III and V was significantly higher in patients with PSE than in control subjects. A similar degree of improvement in interpeak latency was observed in our patients in the two treatment groups. These results were similar to those of earlier studies on evoked potentials in PSE (20-22). The amplitudes of evoked potentials in patients receiving either therapy were similar to those of the control subjects. A comparative evaluation of VEP, SSEP, and BAEP in patients with subclinical encephalopathy had also suggested that the latter was the most sensitive investigation (23). Thus evoked potentials were not found to be of as much value as clinical evaluation in the monitoring of these patients in this study.

All the patients had been given enemas twice daily. It

could therefore be suggested that protein restriction and bowel cleansing resulted in the improvement. Previous studies have shown, however, that tap water enemas alone are not very effective in the treatment of acute PSE and resulted in only a 20% success rate (19). Hence additional measures are required for the treatment of acute PSE. Indeed, none of the patients who had been treated with parenteral fluids and cleaning enemas alone before inclusion in this study had shown improvement until the specific measures (sodium benzoate or lactulose) were started. It was also observed that the response to therapy was similar in patients with cirrhosis and in those with portacaval shunts. Hence exclusion of these patients would not alter the results.

The incidence of adverse effects was similar in the two treatment groups. However, upper-gastrointestinal symptoms such as dyspepsia were more common with sodium benzoate than with lactulose. These were easily controlled by simultaneous histamine-2 receptor blockade. Only modest elevation of serum sodium was observed despite administration of a sodium salt of benzoate in a cirrhotic patient. This resulted in no untoward effects. These results were similar to those found in previous reports on the safety of sodium benzoate (7, 24). Lactulose was associated with lower-gastrointestinal symptoms such as flatulence and diarrhea. The mortality rates were similar in the two treatment groups; they correlated with the grade of encephalopathy and the Child score.

Sodium benzoate has been used in the treatment of hyperammonemia in children (24, 25). It acts by decreasing the ammonia levels in blood by utilizing alternative pathways of waste nitrogen excretion (26). The possibility of nitrogen compounds other than urea serving as waste nitrogen products was shown for the first time in 1914 (27). Benzoate binds to nitrogenous compounds glycine and glutamine to form hippurate that is excreted in the urine (7).

A cost-benefit analysis showed that for a similar efficacy, lactulose is 30 times more expensive than sodium benzoate. Furthermore, sodium benzoate is manufactured in India and is freely available.

We conclude that sodium benzoate is a safe and effective alternative to lactulose in the treatment of acute hepatic encephalopathy in cirrhotic patients.

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