We conducted a trial of oral acetazolamide for the treatment of cryptococcal meningitis in 22 Thai adults with headache and an opening cerebrospinal fluid pressure of \( \geq 200\) mm H\(_2\)O. The trial was terminated prematurely because patients who received acetazolamide developed significantly lower venous bicarbonate levels and higher chloride levels and had more-frequent serious adverse events than did subjects who received placebo.

Cryptococcal meningitis–associated mortality, visual loss, and severe headache have been attributed to elevated intracranial pressure [1–4]. The optimum management of elevated intracranial pressure in affected patients is uncertain, but repeated lumbar punctures, lumbar drains, ventriculoperitoneal shunts, and therapy with steroids, mannitol, or acetazolamide have been performed at admission, headache, a Glasgow Coma Score of \( \leq 11\), normal serum electrolyte and creatinine levels at admission, and weight of \( \geq 35\) kg. Patients were excluded if they were pregnant or breast-feeding or if they had known hypersensitivity to sulfonamides, contraindications for acetazolamide therapy, a systolic blood pressure of \(<100\) mm Hg, a known intracerebral lesion, or an infection other than cryptococcosis and HIV infection. No patient received antiretroviral therapy, CD4 lymphocyte counts could not be determined, and cerebral CT scanning was not performed.

Lumbar puncture was performed using 18-G spinal needles, and CSF opening pressures were recorded using disposable manometers. All patients received standard dosages of amphotericin B (1 mg/kg per day [Fungizone; Squibb]). Patients were randomized in groups of 10 to receive either oral acetazolamide (250 mg per tablet [Glaupax; Ercopharm]) or an identical appearing placebo that was made of lactose, starch, and magnesium stearate. For patients who weighed >45 kg, the starting dosage was 1 tablet given every 6 h. The dose interval was reduced according to serum creatinine level, as follows: the interval was reduced to 12 h for patients with a serum creatinine level of 186–266 \( \mu \)M and to 24 h for those with a serum cre-
The primary outcome measures were CSF opening pressure, headache severity, and serum potassium and bicarbonate levels. We aimed to include 60 patients in the trial, because this allowed a difference in the proportion of patients with pressures remaining $>200$ mm H$_2$O at 14 days of 80% and 40% to be detected with 95% confidence and 80% power, as well as a 10% drop-out rate. An interim analysis was planned after 30 patients were enrolled. Pulse, blood pressure, respiratory rate, Glasgow Coma Score, Headache Visual Analogue Score, and Karnofsky score were recorded every morning. The Headache Visual Analogue Score was determined by showing the patient a 12-inch ruler and asking him/her to assign a number to rate the headache, with 0 representing no headache and 12 representing the worst headache that the patient could imagine. Lumbar punctures were repeated on the second, fourth, seventh, and 14th day after commencement of the acetazolamide/placebo regimen (and on other days at the discretion of the responsible physician); CSF opening and closing pressures and the volume of CSF removed were measured. Before each lumbar puncture was performed, the levels of serum electrolytes, bicarbonate, creatinine, and urea were measured. CSF yeast cell counts on India ink, WBC count, protein level, and glucose level were measured.

Statistical analysis was performed with SPSS, version 9.0 (SPSS), using nonparametric tests (Mann-Whitney U test and Spearman rank correlation test). The study was approved by the Ethical and Scientific Review Committee of the Ministry of Public Health, Royal Government of Thailand (Bangkok).

**Results.** Twenty-four patients (10 in Ubon Ratchatani and 14 in Khon Kaen) were enrolled in the study. Two patients were withdrawn from the study because they were found to be underweight (both received acetazolamide, which was stopped after 1 day in 1 patient who did not have adverse effects and after 6 days in 1 patient who became acidic and who was taken home against medical advice). Because a high prevalence of severe acidosis was encountered, the data were reviewed by an external monitor after 24 patients had been recruited; he advised termination of the study.

The enrolled patients were well matched by the randomization (table 1). All patients but 1, for whom no cause of immunodeficiency could be found, were HIV infected. Amphotericin B therapy was continued until discharge from the hospital or for a maximum of 14 days. The median daily doses of acetazolamide were 20.4 mg/kg (range, 15.4–22.7 mg/kg) and 17.5 mg/kg (range, 12.5–20.6 mg/kg) on the first and 14th day, respectively ($P = .11$). All patients received acetaminophen, 6 received nonsteroidal or opiate analgesics, 19 received oral potassium supplements, 5 received metoclopramide, 5 received sodium bicarbonate, and 1 received intravenous and intraocular dexamethasone for the management of visual loss.

Intracranial pressure did not decrease and the Karnofsky score did not improve between study admission and day 14 of treatment in either group or for all patients combined ($P > .2$; figure 1, table 1). The headache score improved significantly over the course of the 14 days ($P = .002$), but there was no significant difference between the 2 treatment groups.

Five patients (all of whom were in the acetazolamide treatment arm) developed serious adverse events, defined as events attributable to the drug that caused significant morbidity, risk of death, or death itself. Two patients died: one died on day 13 after having visual loss, and the other died on day 7 after developing acidosis, acidotic breathing, and coma. In addition, 1 patient developed visual loss, 1 developed a peripheral sensory neuropathy, and 1 developed severe symptomatic acidosis with acidotic breathing, despite attempted correction. The median serum bicarbonate levels for these 5 patients on the day that the first severe adverse event was recorded (+/− 1 day) was 13.1 mM (range, 6.5–16.0 mM).

Patients in the acetazolamide group consistently developed a severe hyperchloremic acidosis, which was apparent by day 2 (median serum bicarbonate levels in the placebo and acetazolamide groups, 18.7 mM and 16.1 mM, respectively; $P = .024$). The serum bicarbonate level was significantly lower in the acetazolamide group than it was in the placebo group on days 4, 7, and 10 (data not shown), as well as on day 14. Nine (41%) of 22 patients (7 patients [78%] in the acetazolamide group and 2 [22%] in the placebo group) had a serum bicarbonate level of $\leq 15$ mEq/L on $\geq 1$ day. In 6 of the 9 cases, the acidosis appeared to be asymptomatic, but the symptoms could have been clinically masked by meningitis and HIV infection. There was a positive linear correlation between serum bicarbonate level and serum potassium level ($P = .002$; $R^2 = 0.4$) on day 4, but not on subsequent days ($P > .1$).

Twelve patients were evaluable on day 14. The shorter duration of hospital stay in the acetazolamide group was a result of death and of patients being taken home by relatives who believed that the patients’ conditions were not improving. There was no significant relationship between the change in CSF opening pressure and the change in serum bicarbonate level from the day of admission to day 14.

**Discussion.** This evaluation of acetazolamide for the treatment of elevated intracranial pressure complicating cryptococcal meningitis was terminated prematurely, because indepen-
Table 1. Admission and outcome variables of Thai patients who received either acetazolamide or placebo in a trial of oral acetazolamide for the treatment of elevated intracranial pressure in cryptococcal meningitis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo group</th>
<th>Acetazolamide group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At study admission</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No. male/no. female</td>
<td>5/5</td>
<td>9/3</td>
<td>.7</td>
</tr>
<tr>
<td>Age, years</td>
<td>29 (21–52)</td>
<td>28 (22–38)</td>
<td>.7</td>
</tr>
<tr>
<td>HVAS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.5 (5–12)</td>
<td>8.5 (5–12)</td>
<td>.3</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>20 (20–24)</td>
<td>20 (18–24)</td>
<td>.8</td>
</tr>
<tr>
<td>Karnofsky score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>65 (50–70)</td>
<td>60 (20–80)</td>
<td>.9</td>
</tr>
<tr>
<td><strong>Serum values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium, mM</td>
<td>3.8 (3.0–4.0)</td>
<td>4.1 (3.0–5.0)</td>
<td>.2</td>
</tr>
<tr>
<td>Creatinine, μM</td>
<td>89 (53–177)</td>
<td>89 (62–177)</td>
<td>.9</td>
</tr>
<tr>
<td>Bicarbonate, mM</td>
<td>22.0 (16.0–30.0)</td>
<td>21.0 (16.0–31.0)</td>
<td>.8</td>
</tr>
<tr>
<td>Chloride, mM</td>
<td>105 (92–114)</td>
<td>100 (92–116)</td>
<td>.9</td>
</tr>
<tr>
<td><strong>CSF values</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yeast count, ×10&lt;sup&gt;4&lt;/sup&gt; cells/mL</td>
<td>1785 (109–2550)</td>
<td>1250 (372–11,000)</td>
<td>.3</td>
</tr>
<tr>
<td>Glucose, mM</td>
<td>2.6 (0.7–4.0)</td>
<td>2.4 (1.4–3.4)</td>
<td>.8</td>
</tr>
<tr>
<td>Protein, g/L</td>
<td>0.8 (0.2–3.0)</td>
<td>0.6 (0.2–4.9)</td>
<td>.7</td>
</tr>
<tr>
<td>Opening pressure, mm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>322 (210–800)</td>
<td>365 (210–800)</td>
<td>.9</td>
</tr>
<tr>
<td>Closing pressure, mm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>165 (100–250)</td>
<td>185 (110–360)</td>
<td>.3</td>
</tr>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td>10</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>No. of days in hospital</td>
<td>14 (8–23)</td>
<td>12.5 (4–14)</td>
<td>.02</td>
</tr>
<tr>
<td>Total volume of CSF removed, mL</td>
<td>32.5 (3–92)</td>
<td>30.9 (3–92)</td>
<td>.9</td>
</tr>
<tr>
<td>No. of patients with severe adverse events</td>
<td>0</td>
<td>5</td>
<td>.04</td>
</tr>
<tr>
<td>No. of deaths by day 14</td>
<td>0</td>
<td>2</td>
<td>.5</td>
</tr>
<tr>
<td><strong>At day 14</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opening pressure, mm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>205 (70–629)</td>
<td>410 (60–540)</td>
<td>.6</td>
</tr>
<tr>
<td>Closing pressure, mm H&lt;sub&gt;2&lt;/sub&gt;O</td>
<td>95 (50–190)</td>
<td>120 (50–170)</td>
<td>1.0</td>
</tr>
<tr>
<td>Total volume of CSF removed, mL</td>
<td>9.5 (2–18)</td>
<td>10.3 (0.5–14.0)</td>
<td>1.0</td>
</tr>
<tr>
<td>HVAS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.0 (0–5)</td>
<td>3.0 (1–8)</td>
<td>.6</td>
</tr>
<tr>
<td>Karnofsky score&lt;sup&gt;b&lt;/sup&gt;</td>
<td>70 (50–80)</td>
<td>70 (50–80)</td>
<td>1.0</td>
</tr>
<tr>
<td>Respiratory rate, breaths/min</td>
<td>20 (20–24)</td>
<td>20 (20–24)</td>
<td>.7</td>
</tr>
<tr>
<td>Serum values</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Potassium, mM</td>
<td>3.2 (3.1–4.7)</td>
<td>3.0 (2.6–4.4)</td>
<td>.5</td>
</tr>
<tr>
<td>Serum creatinine, μM</td>
<td>106 (97–177)</td>
<td>89 (89–115)</td>
<td>.2</td>
</tr>
<tr>
<td>Serum bicarbonate, mM</td>
<td>20.6 (15.7–26.0)</td>
<td>15.7 (11.6–16.0)</td>
<td>.018</td>
</tr>
<tr>
<td>Serum chloride, mM</td>
<td>101 (100–106)</td>
<td>110 (109–117)</td>
<td>.003</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median (range), unless otherwise indicated. HVAS, Headache Visual Analogue Score.
<sup>a</sup> Of a possible score of 12.
<sup>b</sup> Of a possible score of 100.

...dent review strongly suggested that acetazolamide therapy was harmful, with an excess of severe acidosis and adverse events. This study has insufficient power to characterize the effect, if any, of acetazolamide on intracranial pressure, headache, or Karnofsky score. The severity of the acidosis, combined with hypokalemia, suggests that acetazolamide has an additive or synergistic toxicity with amphotericin B resulting from renal tubular dysfunction.

The antisecretory effects of acetazolamide may be insufficient to reduce intracranial pressure in the face of severe outflow...
Figure 1. Relationship between number of days (0, 2, 4, 7, 10, and 14) since the commencement of acetazolamide/placebo treatment and CSF opening pressure at lumbar puncture (top) and serum bicarbonate level (bottom) for subjects who received either acetazolamide or placebo. Lines, median values; boxes, 25th and 75th percentiles; whiskers, tenth and 90th percentiles.

obstruction (caused by cryptococci or capsular polysaccharide) of CSF drainage through the arachnoid villi [2]. Acetazolamide should not be used in combination with amphotericin B for the treatment of cryptococcal meningitis. This study does not address whether acetazolamide may be beneficial for patients receiving lipid formulations of amphotericin B; for HIV-negative patients; for the palliation of symptoms of elevated intracranial pressure, if used in areas where amphotericin B is not affordable [10]; or after the amphotericin B course has finished.

Cryptococcal meningitis remains a serious, common HIV-associated infection in tropical regions. There is urgent need for clinical trials to test whether interventions, such as frequent lumbar punctures with large-bore needles, placement of lumbar drains, or steroid therapy, are beneficial for the treatment of elevated intracranial pressure associated with cryptococcal meningitis.

Acknowledgments

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References