Personal Observation: Intravenous Aminophylline Treatment for Migraine

Michael Kenyon MD, Barry Phillips MD, Christiaan DeWit MBChB

Migraine is common condition, often affecting young patients and causing disruption in the home and workplace alike. The impact of patients presenting to emergency room services with intractable headache is significant, often tying up space and resources in the tedious wait for a narcotic and sedative “cure.” In Canada alone, 3.2 million adults suffer from migraines, and the condition costs the Canadian economy an estimated $500 million annually. Absenteeism and loss of productivity resulting from migraines cost $20 every second.1

Mills Memorial Hospital is a regional referral centre in Terrace, British Columbia, serving a population of 70,000 people. Between June 2011 and January 2012, 21 patients came to the emergency room (ER) suffering from symptoms compatible with migraine headache as defined by International Headache Society criteria.2 These patients had failed to achieve results from standard outpatient therapy, and the internal medicine service was consulted.

We care for patients in the ER and the intensive care unit (ICU): we also supervise patients undergoing nuclear cardiology testing (stress and dipyridamole methoxyisobutylisonitrile [MIBI]). As such, we have experience in the administration of intravenous (IV) dipyridamole, an arterial vasodilator that can induce a vascular headache in 20% of subjects. Standard therapy for this common side effect is the administration of 50–250 mg (usual dose = 100 mg) of IV aminophylline, given by IV push over a 30- to 60-second period.3 This protocol almost always brings about rapid and persistent relief of headache, without significant adverse effects.4

We postulated that the administration of IV aminophylline would be effective in the treatment of the vasodilatory component of spontaneous migraine complex.3–9 Aminophylline is a competitive non-selective phosphodiesterase inhibitor and adenosine antagonist. It has been shown in dipyridamole (Persantine) MIBI studies that dipyridamole administration inhibits adenosine deaminase in red-cell membranes, increasing blood levels of adenosine. This induces coronary vasodilation through a low-affinity interaction with the A2a receptor. The antidote, aminophylline, preferentially binds to this receptor, displacing adenosine and curtailing its effect.3,4

Aminophylline has traditionally and principally been used as an intravenously or orally administered bronchodilator in asthmatics. Caution in its use should be observed in patients with active peptic ulceration, a low seizure threshold, hypokalemia, tachyarrhythmias, and acute congestive heart failure (CHF). It is contraindicated in acute porphyria and in patients with a sensitivity to methylxanthine products.10,11

In keeping with our practice in the cardiodiagnostic laboratory, we monitored the electrocardiograms (ECGs) and blood pressures of all patients during the administration of this drug. For safety, all treatments were administered in a monitored setting to patients under direct observation in the ER by nursing and physician staff.4

Often, migraine patients presenting to the ER have tried various standard therapies, including antiemetics, analgesics, caffeine/ergot preparations, triptans, beta blockers, acetaminophen-codeine preparations, and nonsteroidal anti-inflammatory agents. It is common for these patients to receive parenteral narcotics and antiemetics and be cared for in a dark, quiet room for several hours in an otherwise-busy ER.12

Methods
We report 21 cases observed over a 7-month period; all of these patients attended the ER. Each patient met the International Headache Society criteria for migraine headache and had failed standard outpatient therapy with conventional treatments. All

About the Authors
Michael Kenyon (near right) and Barry Phillips (far right) are internists, and Christiaan DeWit is an emergency room physician, all practising at Mills Memorial Hospital, in Terrace, British Columbia. Correspondence may be directed to: zulus5@shaw.ca
underwent a complete history and physical examination and had an appropriate laboratory profile performed. We explained the rationale of aminophylline treatment and our experience with it as a safe, readily available treatment for dipyridamole-induced vascular headache in our most medically frail cardiac patients. All gave informed consent to this modest dose of a safe and well-known therapeutic agent, albeit for the unlabelled indication of spontaneous migraine outside of the Nuclear Medicine Laboratory.

Results and Discussion
Aminophylline is a cheap, genericized, readily available medication with known pharmacokinetic properties. It has not been studied as an IV therapy for refractory migraine. An extensive literature review on Google, Medline, and PubMed confirmed this. (We did get interesting “hits” for its use in post-lumbar puncture headache13 and in “myocardial migraine.”14) In this observation of 21 patients, aminophylline proved to be a highly effective intervention. After the completion of a 20-minute infusion of aminophylline, 17 of 21 patients had a substantial or complete relief of their headache and were fit for discharge from the ED, two were felt to have treatment failure, and two had partial relief. We noted that patients with localizing symptoms and signs did well uniformly. (Our sample size was small, but this was also something more objective to measure.)

As this was an observational study, it did not incorporate formal long-term follow-up interviews with this patient group; however, we have not been made aware of any subsequent adverse outcome by our family or ER doctors or at follow-up chart reviews (computerized, regional), and there is an impression that there is reduced “rebound effect” compared with several other standard therapies.

We believe our experience with this inexpensive, safe, and easily accessible medication offers promise for a formal randomized double-blind trial in a sizable cohort of migraine patients. Oral and suppository routes for aminophylline therapy for migraine might also be explored. We hope that this approach might afford prompt relief of symptoms for a difficult-to-treat condition, and may allow early and safe discharge from congested ERs. We feel that a randomized, double-blind, controlled trial is indicated, with the approval of our local ethics board.

References

Appendix: Case Reports

Case 1
S.M. was a 40-year-old female migraineur of many years. On her 3rd day of “usual, severe migraine,” and unresponsive to a range of standard therapies, she experienced a rapid, significant (80–90%) relief of the headache with 100 mg aminophylline IV over 20 minutes. The relief was dramatic and rapid, with nausea and photophobia completely cured immediately before the infusion was finished. There were no side effects. She was able to return to work immediately post-treatment.

She subsequently had a second episode, identically relieved by the same treatment, except that the aminophylline was infused over 10 minutes. Once again, she was able to return to work, unlike with other treatments she has tried in the past. She has also observed that the frequency of episodes has diminished after these treatments, as compared to previous experience (no “rebound” phenomenon).

Case 2
P.L. was a 52-year-old female homemaker with frequent hemiplegic migraine, complex migraine; she was a frequent recipient of narcotics. Presenting with a hemiplegic episode lasting > 6 hours, accompanied by dysarthria, photophobia, phonophobia, and paresthesia affecting the right side, she was
given 100 mg aminophylline IV over 2 minutes with complete relief of her symptoms within 10 minutes, but she experienced tremor and tachycardia.

She has subsequently had far fewer visits to the ER. She has not experienced side effects when given 100 mg aminophylline in a mini-bag IV over 20 minutes. She has usually asked for aminophylline treatment specifically and has not required narcotics again (> 5 months).

**Case 3**
W.O. was a 44-year-old female homemaker who presented with status migrainosus, semi-continuous clusters over 35 days. She had right-sided ptosis, dysesthesia in the right side of her face, shoulder/arm, and foot, photophobia, and severe headache. Computed tomography (CT) showed a right parietal cavernous hemangioma that was felt to be unrelated to her symptoms and signs, and she was screened by neurology and neuro-ophthalmology in Vancouver, who did not find any structural disease. Most standard migraine therapy had been tried and failed.

She received 100 mg of aminophylline and experienced almost total relief by 20 minutes. A second dose of 100 mg was given with complete relief. The patient had been seen in ER several times in the previous 6 months with headache/migraine. For 4 months since treatment, she has not required ER treatment again. She has had one visit with the visiting neurology service as an outpatient at the 3-month mark.

**Case 4**
S.B., a 19-year-old female telephone operator, presented with 5 hours’ left retro-orbital headache, facial dysesthesia, and a “leaden” left leg that made her feel “off-balance.” She has had complete relief on two separate ER visits with aminophylline 100 mg IV infusion over 20 minutes.

**Case 5**
P.H., a 65-year-old female teacher, took early retirement because of migraines. She was allergic to narcotics, took standard migraine therapy, including ergot, and had a long history with neurology with a multi-faceted treatment approach, including onabotulinumtoxinA (Botox), etc. She presented to the ER with one of her usual refractory migraines for approximately 24 hours, despite all usual standard therapy. Usually the migraine lasted 4–5 days. Headache pain was 10/10, and she complained of photophobia, phonophobia, emesis, and incapacitation. She was given 100 mg aminophylline over 20 minutes.

Details from the case notes are as follows: “Apart from feeling slightly jittery at the end of the 20 minutes, there were no other side-effects. At the 5-minute mark her nausea disappeared, at the 10-minute mark her headache was down from 10/10 to 1/10, and at the 20 minute, mark she had no further visual disturbance. She says this is the best she has felt this far into a migraine in her life. She was discharged after removal of her IV. Her usual pattern is two episodes a month, but she has had only one episode in 2 months since treatment.” (Again, there seems to be no “rebound.”)

**Case 6**
K.C. was a 32-year-old female with a 2-year history of headache following two motor vehicle accidents. Her father had ocular migraine. The patient had had extensive neurological review and treatment at headache clinics. Her headache was thought to be multifactorial – mainly post-traumatic. She has rarely experienced auras.

On this occasion, there was peri-orbital pain, photophobia, phonophobia, nausea, and pain in her neck and shoulders. Her headache had lasted 72 hours. She had tried several therapies without relief, including anti-inflammatories and narcotics. She was nervous to take any more narcotics because she did her own childcare without support. Both the patient and physician were doubtful that there would be benefit.

Surprisingly, after a 20-minute 100 mg aminophylline infusion IV, the patient had an 80% response. She was able to drive home and do her own childcare and go to work. There were no side effects (importantly for her, no sedation). On a second occasion, this treatment was less effective.

**Case 7**
M.S., a 31-year-old First Nations female with a strong background history of migraine, presented with left arm and leg weakness following a night of heavy alcohol intake, and marked left-sided hyperesthesia, and pain, including headache and marked nausea.

The reflexes on the left were somewhat brisk despite a history of <12 hours of deficit. The patient had normal CT scans, with and without contrast, of the brain. There was no history of seizure or loss of consciousness. General internal medicine consult was requested as the patient had significant hemiparesis, was unable to stand or even turn herself over in bed, and the two radiologists could not agree as to whether or not there was any ischemia on the CT scan. It was felt that the hyperesthesia and brisk reflexes were more consistent with migraine. The patient had never previously experienced hemiplegic migraine.

At this point, 100 mg aminophylline was given IV infusion over 20 minutes. At the 5-minute mark, the nausea disappeared. At the 10-minute mark the headache had gone from 8/10 to
0/10. At the 20-minute mark, she could move her left left foot and left hand. By 30 minutes, she could stand and had the full use of her left hand. There was mild numbness in the left fourth and fifth fingers. At one hour, the patient was completely back to normal and was discharged.

**Case 8**

M.S., a 45-year-old male, reported a migraine for the previous 3 days. He was uncertain if he could complete his work shift (he was a nurse). He was experiencing a moderate bifrontal headache, nausea, photophobia, and slight tinnitus. He was given aminophylline 100 mg IV over 10 minutes. All symptoms disappeared in 8 minutes, just prior to the completion of the infusion. There was no change in his pulse or blood pressure prior to or upon completion of the infusion.

**Case 9**

J.D., a 35-year-old female with a long history of migraine events, presented with a 2-day history of headache, pain behind the right eye, and severe photophobia but no nausea. She had taken ketorolac tromethamine (Toradol) 2 hours earlier, but her headache was still severe. She was given 100 mg of aminophylline IV over 10 minutes. Headache and photobia were gone 5 minutes into the infusion.

**Case 10**

T.C. was a 23-year-old First Nations female with a history of migraine. She presented to the ER with blurred vision, tingling fingers, vomiting, and a bitemporal throbbing headache. Aminophylline IV was given over 20 minutes, and the symptoms abolished 12 minutes into the infusion.

**Case 11**

K.O. was a 22-year-old normotensive female who was also 34 weeks’ pregnant, with no proteinuria. Over 24 hours, she had an 8/10, throbbing headache with severe photophobia, dizziness, and scotomata. There was no meningism and no focal deficit, and she was afebrile and having a normal pregnancy.

She was not able to take ergot (definitively contraindicated in pregnancy – in the product monograph), and triptans were relatively contra-indicated in this patient (see Olesen C, Steffensen FH, Sorensen HT, et al. Pregnancy outcome following prescription for sumatriptan. Headache 2000;40:20–24).

She had already had a significant quantity of narcotics, to the point that obesity and related respiratory issues were becoming a concern. She also had severe nausea and emesis. The patient was referred to one of us by the obstetrician who had already done a head CT (because of a suspected subarachnoid bleed), which was normal. Options were limited. The obstetrician felt that all usual, acceptable therapies had been explored, and that the patient’s ongoing nausea, anorexia, emesis, and excessive analgesic requirements were starting to pose a threat to feto-maternal well-being.

Aminophylline is category “C” in pregnancy (no adequate human studies – no proven teratogenicity). The drug is (historically) used for asthma in pregnancy, but has been supplanted by more effective new medications. The obstetrician and patient agreed to her receiving a treatment of aminophylline 100 mg infused by IV over 20 minutes. The patient’s nausea was gone by 5 minutes, and her headache and photophobia were gone by 20 minutes.

The patient had originally arrived incapacitated from a neighboring town by ambulance for a head CT based on the persistence and severity of her neurological symptoms. Her condition was felt to pose a threat to the health of both mother and fetus. The patient went home direct with her own family 1 hour after treatment. No recurrence was noted at follow-up.

**Case 12**

T.D. was a 42-year-old female with a history of migraines. She presented with a 2-day history of headache with nausea, weakness, and vertigo. Paresthesia in the right arm, neck, and leg was followed by numbness for about 4 hours and 30 minutes. Power, tone, and reflexes were normal. Her CT was normal. The patient was given 100 mg aminophylline IV over 20 minutes and experienced complete relief.

**Case 13**

M.B. was a 46-year-old man who presented after 48 hours of a pounding headache with photophobia, nausea, and vomiting. Usually the patient responded to rizatriptan (Maxalt), but not this time. This migraine also did not have the usual aura. The patient was dysarthric.

He was given 100 mg aminophylline IV over 20 minutes. The patient had some relief at 12 minutes but relapsed with movement. This case was considered an aminophylline failure.

**Case 14**

S.C. was a 40-year-old 40 First Nations female with a history of migraine. She presented to the ER with headache of 8 hours’ duration. She had pain on moving her head, nausea, and photophobia. She was given 100 mg IV aminophylline over 10 minutes, and the headache was gone 8 minutes into the infusion. There was no change in blood pressure or pulse prior to and at the completion of the infusion.
**Case 15**

H.W. was a 56-year-old First Nations female. She had a severe cardiomyopathy. This patient was receiving nuclear simulated stress testing with dipyridamole, but she already had a bifrontal headache for 2 days prior to the testing. Dipyridamole was infused over 4 minutes as per the usual nuclear medicine protocol, and she developed an additional occipital headache of some severity. Aminophylline 100 mg IV push was given over 1 minute, and both headaches completely resolved 90 seconds later. The improvement was sustained. Photophobia and nausea also resolved along with the headache.

**Case 16**

C.S. was a 24-year-old female with a history of migraine for years. She had been in bed at home with a severe headache for 24 hours, photophobia, and nausea. As treatment, 100 mg of IV aminophylline was given over 10 minutes. All symptoms resolved 7 minutes into the infusion.

**Case 17**

R.P. was a 42-year-old First Nations female with a history of migraine and sciatic leg pain for years. She presented with a migraine of 3 days’ duration after a few days of a head cold and possible “sinus pain.” The patient tried self-medication with acetaminophen with no benefit. She did experience vomiting and photophobia.

She indicated she usually needed a narcotic injection of meperidine, which would relieve the sciatic pain as well. Because of that statement, we felt she might be a narcotic seeker. We (the nurses, emergency physician, and internal medicine consultant) were all surprised when the headache and photophobia and nausea disappeared immediately after 100 mg of aminophylline was infused over 10 minutes. Immediate relief occurred just as the infusion was finished. There was some delay in starting the aminophylline infusion, and normal saline was infused over 40 minutes.

To start, there was no significant relief of symptoms, and then the aminophylline was infused over the 10 minutes with the complete relief of migraine symptoms. The patient did not then want a narcotic injection and was discharged.

**Case 18**

T.S., a 57-year-old male, presented in the ER with a 3-day history of a severe right-sided headache mainly behind the right eye, which he self-diagnosed as a sinus infection. He asked an emergency physician for a CT scan of the sinuses, which demonstrated some slight mucosal thickening but no blockage. He asked for and had received 50 mg of prednisone and also received the antibiotic ceftriaxone for 3 days. He still had the severe headache and was slightly nauseated. He indicated that a few years prior in the United States, he had received similar treatment and that had cured his sinus headache after several days. This time there was no fever, and his white cell count was just at the upper limit of normal even considering he was taking prednisone (which can raise the white cell neutrophil count itself). It was mentioned that we were using the old drug aminophylline for some headaches, particularly migraine, and he wanted to try it even though he felt this was not a migraine and he had no history of migraine except for a prior history of recurrent severe sinusitis lasting several days. He was familiar with aminophylline as he had used it decades ago for asthma attacks. Thus, 100 mg of aminophylline was infused over 10 minutes and partial relief was obtained within 10 minutes.

Two thirds of the headache was gone but one third remained. He felt so much better that he wanted to be discharged and go back to work. Prednisone was discontinued, and it was also suggested that antibiotics be discontinued in 3 more days. We feel this headache might have been a migraine rather than a sinus infection.

**Case 19**

C.Z. was a 33-year-old female with long history of migraines that were now occurring almost monthly. She presented to the ER with a headache for 24 hours. Pain was a 9 out of 10 in severity. She would not look at the examiner and wanted complete darkness because of photophobia. She was severely nauseated. She kept her eyes closed and her head was flexed, with her hands holding a cold cloth on her forehead. Aminophylline 100 mg was given over 10 minutes with partial relief of all symptoms. She stated that the headache was 50% relieved in 10 minutes and perhaps two thirds gone 10 minutes after that. She still had slight but lesser nausea. She was given ativan 1 mg sublingually and 1 mg to take at home. She was, after the aminophylline, given maxeran 10 mg. She was happy to go home less than 1 hour after arrival. She left by taxi as she had arrived by taxi and the symptoms had been too severe for her to drive.

**Case 20**

K.S. was a 44-year-old female. This patient had experienced repetitive migraines for a long time, and for years she had attended the ER for injections of the narcotic meperidine (Demerol) and the antiemetic dimenhydrinate (Gravol) if her migraine was prolonged. This headache was right frontal and “pounding,” and pain was mainly behind the right eye but was also generalized somewhat and throbbing. She was vomiting...
and had severe photophobia. Aminophylline was given, 100 mg over 10 minutes, and after the infusion the pain behind the right eye was immediately relieved; but she still felt nauseated and had only a one third relief of the headache and wanted the demerol and gravol. She left with her husband.

**Case 21**

C.B. was a female with a history of migraine. She presented with a severe (8/10) right-sided headache, accompanied by nausea, photophobia, dizziness, left facial and right arm dysesthesias, whose onset occurred during a morning yoga class. It was not her usual migraine. There were some scotomata at onset. These were worse by afternoon, and she was referred by her general practitioner from a neighbouring town by ambulance for CT scanning of the brain, which was normal. She was referred to one of us for review.

She received 100 mg of aminophylline IV over 20 minutes. The nausea relieved within 8 minutes, and photophobia was gone within 20 minutes. By 1 hour, she was completely back to normal and walked out of the ER saying, “It’s a miracle!”

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**World Health Day Focuses on Hypertension**

Each year on April 7, the World Health Organization (WHO) focuses on a major health issue to celebrate World Health Day. Hypertension was selected for 2013 (http://www.who.int/world-health-day/en/).

Slightly more than half of heart disease and stroke is attributed to increased blood pressure (BP >115/70 mm Hg), with about half of BP-related disease occurring in those with increased but still normal BP. Thus, about 9.4 million deaths per year are caused by increased BP, which is also the leading risk for disability worldwide. WHO wants to focus global attention on the causes and adverse outcomes of hypertension, encouraging people to have healthy behaviours and regular BP checks, and to motivate governments to create healthy environments that prevent hypertension.

Although Canada has a lower prevalence of hypertension and higher rates of diagnosis, treatment, and control than are seen in most countries (and thus a lower disease burden from hypertension), still much work needs to be done. A Hypertension Framework was created to guide national efforts for prevention and control, and CSIM has joined a coalition of national health care and scientific organizations (Canadian Hypertension Advisory Committee) to help implement the Hypertension Framework.

Medical specialists can play important roles. As clinicians, we can both educate other health care professionals in best practices and lead by example to ensure our patients are systematically screened for hypertension and that those with hypertension are optimally managed. We can also focus efforts on documented clinical care “gaps.” Currently, about one in three adult Canadians with hypertension are “uncontrolled” — more often systolic than diastolic BP and more often older women than men. Lack of awareness of having hypertension is most common in the young adult, with men more likely to be undiagnosed than women. Also, most vascular risks apart from BP are not well controlled in people with hypertension.

The Hypertension Advisory Committee, recognizing that up to 80% of hypertension is caused by obesity and unhealthy diets, has prioritized the development of healthy eating policy statements that, if implemented, could markedly prevent and control much of hypertension and also reduce health care costs. CSIM has been actively supporting healthy public policy statements, and individual members can play important roles in advocating for the implementation of these policies. This is particularly important as current federal and provincial governments are predominantly relying on the food industry to voluntary self-regulate, despite the long-term and consistent failure of that industry to do so in a manner that promotes public health. It is time for a paradigm shift to prioritize the health of Canadians by ensuring we have a healthy environment both for ourselves and future generations. Internists can help lead this important change.

Norm Campbell MD

**References**
