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GABAPENTIN FOR INTRACTABLE HICCUP

To the Editor:

We report a patient with a history of Guillain-Barré syndrome and metastatic gastric neoplasm who presented with intractable hiccup that successfully responded to treatment with gabapentin plus baclofen.

A 71-year-old man was hospitalized in December 2003 because of intractable hiccup and vomiting. Guillain-Barré syndrome was diagnosed in 1988 that caused bilateral lower limb, mild distal residual weakness and sensory loss. In May 2002, the patient had trouble swallowing liquids and food, and daylong hiccup started. A gastroscopy showed a gastric adenocarcinoma. Cancer infiltration of the anterior pillar of the diaphragm was noted at surgery. Chemotherapy and radiotherapy were started in July 2002. The hiccup persisted at a rate of 5 to 8 events per minute, with a total 3-hour hiccup-free interval. No specific therapy was initiated.

In March 2003, he was referred to a neurologist due to aggravation of his leg weakness. Relapse of Guillain-Barré syndrome was suspected, but the patient refused immunoglobulin therapy. The hiccup pattern persisted.

In November 2003, an abdominal computed tomographic (CT) scan revealed a lymphadenopathy over the left diaphragmatic pillar that was suggestive of metastatic origin. Hiccup bouts become continuous (10 to 15/min), usually leading to vomiting. He was unable to sleep and his nutritional condition was seriously affected. Oral deflazacort (30 mg/d) was started without improvement, and the patient was hospitalized.

Chest radiograph showed bibasal infiltrates suggestive of aspiration pneumonia, and abdominal CT scan revealed diaphragmatic neoplastic infiltration. A barium series of the upper gastrointestinal tract showed no structural abnormalities or fistulas.

Omeprazole (20 mg daily by mouth) and clorpromazine (25 mg three times daily) were initiated, but hiccup and vomiting persisted. Clorpromazine was withdrawn and baclofen (5 mg three times daily) was started. Baclofen was progressively increased to 15 mg three times daily, as the patient noted no improvement. Gabapentin (300 mg three times daily) was added. A day later, the hiccup ceased and the patient was able to eat. Sleep was restored. A week later the hiccup sporadically recurred, and gabapentin was increased to 400 mg daily. After 2 days, hiccup bouts resolved and the patient was transferred to the oncology department. Hiccup control remained unchanged 2 months later.

Chronic or "intractable" hiccup remains a diagnostic challenge for the clinician. It relates to a broad spectrum of underlying disorders (1). Although well-designed clinical studies are scarce, baclofen, a γ-aminobutyric acid (GABA) analogue leading to a perceptual blockage in synaptic transmission, is considered the cornerstone for the treatment of idiopathic intractable hiccup (2).

Gabapentin is structurally related to GABA. Nevertheless, it is not an inhibitor of GABA uptake or degradation, nor is it converted metabolically into GABA or a GABA agonist. Blood levels of gabapentin are quite predictable (about 3% circulates bound to plasma protein). It is not appreciably metabolized in humans and is eliminated by renal excretion as unchanged drug. The absence of liver metabolism is particularly useful in patients with cancer and metastatic spread. Dizziness, somnolence, and peripheral edema are the most frequent side effects (3).

Gabapentin has recently been suggested as a potential therapy for intractable hiccup. Seven cases have been reported (Table) (4,5). The mechanism by which gabapentin decreases hiccup is not well understood. It may selectively diminish calcium influx by inhibiting voltage-operated calcium channels in a subset of excitatory and inhibitory presynaptic terminals, thereby attenuating synaptic transmission (6). Indeed, gabapentin probably increases the endogenous release of GABA, modulating excitability of the diaphragm and the other inspiratory muscles (4,5). In this patient, the most probable cause for hiccup was the neoplastic infiltration of the diaphragm and thus gabapentin may have been useful for the former reason.

In summary, gabapentin should be considered as an alternative therapy to control intractable hiccup. It could be particularly useful in patients with solid malignancies, either alone or as an "add-on therapy" with baclofen.

Table. Characteristics of Patients with Chronic Hiccup Treated with Gabapentin

Age (ref.)	Sex	Related Condition	Medications	Duration of Hiccup (months)	Frequency (/min)	Previous Therapy	Gabapentin Dosage (3 times/d)	Treatment Combinations	Hiccup Outcome
62 (4)	M	Colon cancer Liver metastases	None	NR	Continuous	Metoclopramide Dexamethasone Chlorpromazine	300 mg	No	Relief
43 (4)	M	Pancreas cancer	None	NR	NR	Metoclopramide Haloperidol	300 mg 400 mg	No	Recurrence Resolution
51 (4)	M	Small-cell lung cancer Brain and liver metastases	Morphine	NR	NR	None	300 mg	No	Relief
75 (5)	M	CAD COPD Diabetes mellitus	Nitrates Verapamil Captopril Digoxin Ipratropium bromide Budesonide Insulin	96	30–40	Levomepromazine Promethazine Clorazepate Domperidone Cisapride Flunitrazepam Carbamazepine Lipoic acid Baclofen Hipnotic therapy Herbal remedies	400 mg	COG	Resolution
58 (5)	M	Alcoholism Hiatal hernia Reflux esophagitis Seminoma	Omeprazole Cisapride Pethidine Nortryptiline Doxepin Tiapride Mistletoe extract	32	6–20	Phrenicotomy Semifundoplication Acupuncture Herbal remedies	400 mg 400 mg	COG COBG	Recurrence Relief
55 (5)	M	Gastroesophageal reflux Duodenitis	Cisapride Amytriptiline	8	5	Triflupromazine Cisapride Pantoprazole Nordazepam Herbal remedies	400 mg	COG COBG	Recurrence Relief
74 (5)	M	Gastroesophageal reflux Axial hiatal hernia CAD Pulmonary embolism Recurrent deep venous thrombosis	Phenprocoumon Isosorbide dinitrate Verapamil Digoxin Carbamazepin Triflupromazine	12	20	Carbamazepine Triflupromazine Acupuncture	400 mg	COG	Resolution
71 (Present case)	M	Gastric cancer Guillain-Barré syndrome	Triazolam Folinic acid Phentanyl	20	10–15	Deflazacort Omeprazole Chlorpromazine Baclofen	300 mg 400 mg	OBG	Recurrence Resolution

C = cisapride (10 mg three times daily); CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; G = gabapentin; M = male; NR = not reported; O = omeprazole (20 mg/d); B = baclofen (15 mg three times daily).

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SUBERYTHEMAL ULTRAVIOLET EXPOSURE AND REDUCTION IN BLOOD PRESSURE

To the Editor:

Increased levels of blood pressure vary with latitude; toward the equator there is less hypertension (1). Krause et al attributed this effect to higher vitamin D levels found in sunnier climates (2).

This report examines potential alternative roles of ultraviolet (UV) exposure and whether a single exposure can achieve a reduction in blood pressure. Nineteen white and black normotensive and hypertensive (treated and untreated) volunteers were selected. The U.S. Food and Drug Administration has adopted categorizing different races and complexions into six skin types based upon ease of sunburn and propensity to develop pigmentation. Skin types I and II are the fairest and are at the greatest risk for sunlight-induced injury, whereas skin types V and VI are the darkest and have little risk for sunlight-induced injury. Selected volunteers ranged over the entire set of skin types based upon their inherent propensity to sunburn and tan. Two sources of exposure were used: two 250-watt infrared, reflectorized incandescent-type lamps; and a UV-A/UV-B phototherapy cabinet.

The protocol required a baseline blood pressure measurement followed by an infrared exposure of 8 minutes and 20 seconds that was immediately followed by blood pressure measurements at 0, 3, and 5 minutes. Following this, volunteers reentered the UV-A/UV-B cabinet to receive an exposure of a mixture of UV-B and UV-A radiation. Fair-skinned, white volunteers of skin types I and II received a 7.8 J/cm^2 exposure involving only the UV-A lamps, or 1.5 standard erythema doses, an erythemic effective exposure of 10 mJ/cm^2. It is approximately 1/2 of a minimal erythemal dose of a fair-skinned person. Skin types III and IV received the same 7.8 J/cm^2 dose from the UV-A lamps plus an additional 0.02 J/cm^2 dose from the UV-B lamps, or 2.25 standard erythema doses. For volunteers with skin types V and VI, the same 7.8 J/cm^2 dose was administered from the UV-A lamps, and a 0.04 J/cm^2 dose of UV-B radiation was administered, for a total of three standard erythema doses. Thus, the UV dose maintained constant UV-A dosage and varied the amount of erythemic UV-B dosage with the UV-B lamps. The UV doses administered were approximately equivalent to a 12- to 24-minute exposure of sunlight. The protocol was approved and monitored by our institutional review board.

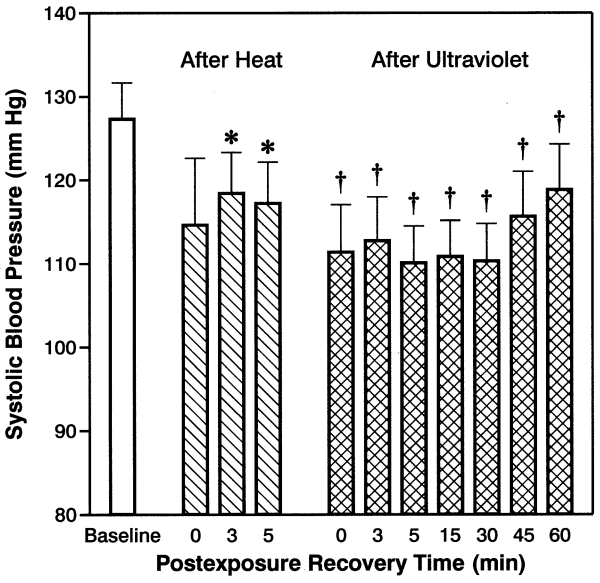

Figure. Statistically significant but modest decreases in systolic blood pressure were observed following exposure to infrared lamps at 3 and 5 minutes after exposure (*P <0.01). Following ultraviolet exposure, all volunteers showed a highly significant decrease in systolic blood pressure (†P <0.003). Bars indicate mean, error bars indicate SEM.

The Figure summarizes the study results. We did not observe any differences based on the sex, race, or