Isoproterenol Treatment of Visual Symptoms in Migraine

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SUMMARY Six patients with transient or permanent visual loss associated with migraine are presented. In 3 patients with monocular and one patient with binocular episodes of transient visual loss subsequent visual episodes were relieved by prompt inhalation of isoproterenol. The authors review the possible mechanisms of action of isoproterenol in migraine and present evidence to support the prophylactic use of isoproterenol to prevent transient and possible persistent visual loss in patients with migraine.

ALTERATIONS OF VISION have been reported by 10–15% of patients afflicted with migraine.1 Visual disturbances may occur immediately prior to or during the episode of severe headache. Symptoms described include homonymous hemianopia, unilateral or bilateral scintillating scotomata, micropsia, or macropsia, bilateral amaurosis or monocular amaurosis. Symptoms are often stereotyped and related to specific ocular or brain arterial territories.5, 6 While some have questioned the relationship of pure monocular amaurosis to migraine, adequate evidence has been presented in the literature confirming the existence of this relationship.1, 4, 5 The visual symptoms are almost always transient. However, several reports have emphasized permanent visual dysfunction in association with migraine and actual occlusions of the central retinal artery and its branches, as well as secondary partial or complete optic atrophy.5, 6

A variety of drugs have been employed to prevent migrainous head pain with reasonable success in most patients.10–18 Little attention, however, has been paid to the question of prevention of the associated visual symptoms, in part because they are usually transient and much less disturbing to the patient than the headache. Some patients are disturbed primarily by the transient visual symptoms and prevention of permanent sequellae, such as hemianopia, may be a major therapeutic concern. This report describes 4 patients with classical migraine and associated transient visual disturbances. Treatment of all these patients with isoproterenol at the onset of each subsequent episode prevented further visual dysfunction in 3 and reduced the incidence of visual disturbance in the fourth. Two additional untreated patients suffered permanent hemianopia. The pathophysiology and treatment of this serious complication of migraine is discussed.

Transient Visual Disturbances

Patient 1. A 53-year-old white female was seen at the Bellevue Hospital with complaint of 2 episodes of vision loss in the left eye during the previous week. Each episode began with throbbing pain in the left temporal area followed by gradual loss of vision moving from...
the nasal to the temporal field of the left eye and then disappearing after one hour. There had been a history of left temporal throbbing headaches since childhood. These were associated at times with scintillating scotomata in either eye, nausea, photophobia and stomach cramping. A very mild left hemiparesis had been noted since childhood, not clearly related to an episode of headache. The head pain in previous years had been minimally alleviated by Cafergot. There was no history of significant head trauma or hypertension. The patient had suffered from diabetes since childhood and was treated with NPH insulin. There was a strong family history of migraine. A very mild left hemiparesis was found on examination. All other clinical and laboratory studies were normal save for the presence of several microaneurysms in the left macular area.

The patient was advised to take 2 inspirations of 1% isoproterenol via a nembulizer with the onset of headache. She stated during subsequent follow up examinations that she suffered several headaches per week during a period of 2 months. On each occasion the isoproterenol was inspired at the onset of headache. There were no subsequent visual symptoms save for some photophobia. The throbbing head pain and nausea were unaffected by the medication.

**Patient 2.** A 21-year-old white male presented at the Bellevue Hospital with a history of 2 episodes of sudden and complete loss of vision in the right eye, each lasting approximately 5 minutes. Shortly after loss of vision in the right eye a throbbing temporal headache began in parallel with progressive return of vision. There was a 10 year history of throbbing temporal headaches weekly alternating from the left to the right side of the head lasting several hours. The headaches were associated with a prodrome of photophobia, nausea, and an indescribable "abnormal feeling." There was no history of significant head trauma, hypertension or diabetes mellitus. General physical, neurological and extensive laboratory examinations revealed no abnormalities.

The patient was instructed to take 2 inspirations of 1% isoproterenol via nembulizer at the onset of either nausea or the "peculiar abnormal feelings." During the next 6 months he reported that his weekly headache attacks had continued but none was associated with alterations in vision. It was also of interest that the head pains were considered to be "milder" after inspiration of isoproterenol.

**Patient 3.** A 28-year-old white female presented at the Bellevue Hospital with a complaint of a 15 minute attack of sudden and total vision loss in her left eye immediately following an occipital headache. There was a past history of throbbing headaches during the previous 5 years associated either with blurring of vision bilaterally or scintillating scotomata in the left eye. Since childhood visual acuity in the right eye had been 20/400. The patient denied having significant head trauma, hypertension or diabetes mellitus. An extensive general medical and neurological examination revealed only a best corrected visual acuity of 20/400 in the right eye and 20/20 in the left eye. There was a congenital right esotropia. There were no other abnormalities.

The patient was instructed to use a 1% isoproterenol nembulizer at the onset of headache. Five attacks of head pain occurred during the following month but there was no recurrence of blindness with the conscientious use of the medication. The headache itself was not affected by isoproterenol. Aspirin and other mild analgesic medications helped relieve the head pain. Approximately 3½ months after beginning isoproterenol therapy, attacks of blindness in the left eye recurred despite the medication.

**Comment.** The combination of headache and monocular visual compromise, as well as the histories of prior headache episodes, serves to distinguish these 3 patients from those suffering amaurosis fugax secondary to arterial-arterial embolization from proximal internal carotid artery atherosclerotic occlusive disease. None of the patients had a history of optic neuritis or drug abuse; nor was there evidence of systemic arteritis, arteriovenous malformation, brain tumor, demyelinating disease or central nervous system syphilis. The retinal microaneurysms found in Patient 1 were the only abnormal findings noted on ophthalmoscopy; these vascular lesions did not appear to be related to the symptom complex described. In no case was there evidence of optic atrophy, papillitis or papilledema. The prompt and continuing response of the monocular visual symptoms to isoproterenol was impressive. The lack of sustained relief from monocular visual disturbance after 3½ months in Patient 3 is notable. Since there was no continuous daily use of the medication, tachyphylaxis cannot be invoked as an explanation.

**Patient 4.** A 15-year-old white female was seen at the New York University Hospital for episodes of dizziness, headache and bilateral visual loss occurring at weekly intervals for approximately 5 months. Each episode was heralded by rotational vertigo followed by headache over the lateral aspect of the right supraorbital region and sudden bilateral loss of vision. After 30 seconds vision rapidly and completely returned. The right supraorbital headache subsided during the next hour. There was no past history of head trauma, hypertension or diabetes mellitus. No abnormalities were disclosed by physical and laboratory examinations.

The patient was asked to inhale 0.25% isoproterenol via a nembulizer at onset of her symptoms. Six episodes similar to those described above occurred during the next month. At the onset of 4 of the episodes the patient used the nembulizer and no visual symptoms occurred. Two attacks were untreated; during both of these episodes brief blindness recurred. It was of interest that the patient commented that the headaches were "more severe" when the isoproterenol was inhaled at the onset of the migrainous episode.

**Comment.** The bilateral visual symptoms in association with rotational vertigo strongly suggest that this patient's symptoms were related to dysfunction in the distribution of the vertebrobasilar arterial system. The patient's failure to employ isoproterenol...
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on 2 occasions with the concomitant recurrence of visual symptoms served to act as a control for the 4 treated episodes during which no visual symptoms occurred. The response pattern in all 4 patients strongly suggests that a therapeutic effect is provided by the medication in more than one cerebrovascular territory and that isoproterenol will prevent transient visual symptoms associated with migraine.

Permanent Visual Loss

During the past 12 years one of us (WH) has studied 2 young women who, in the course of severe headache, developed persistent homonymous hemianopsia. Both were seen first shortly after angiography had revealed stasis in end vessels appropriate to the visual radiations contralateral to the hemianopsia.

Patient 5. A 16-year-old schoolgirl presented with a 5 year history of headache in 1963. Bilateral frontal throbbing headaches usually occurred once or twice a month after excessive reading or watching television. There was no associated nausea, vomiting or photophobia. No visual or motor abnormalities occurred in the preheadache phase. During a school examination in 1963 she had a headache. The following morning, again during an examination, she had a bilateral frontal headache with anorexia. Five hours later the headache became throbbing and "terrible." It was associated with altered vision in the right visual field of sudden onset and a "sleepy" sensation in the right cheek, arm and leg. Two hours later intermittent periods of severe head pain would cause her to scream. By this time the sensory symptoms on the right side of the body had vanished but there was no change in the right visual field defect. She had nausea associated with brief episodes of vomiting. The patient required injections of meperidine and prochlorperazine for relief.

On admission to University Hospital the following day the blood pressure and pulse rate were normal. The neck was supple; temperature was 37.9°C. The only significant neurological finding was a right homonymous hemianopsia to confrontation. A tangent screen visual field examination (fig. 1) revealed a dense congruent right homonymous hemianopsia with sparing of the central 15 degrees of the right homonymous field. Uncorrected vision was 20/20 in the right eye and 20/30 in the left eye. A left carotid arteriogram performed 24 hours after onset of the hemianopsia revealed occlusion of the proximal portion of the calcaneous branches of the posterior cerebral artery with collateral filling of these vessels from the anterior and middle cerebral arteries (fig. 2). A lumbar puncture performed within 36 hours of the onset revealed crystal clear fluid under a pressure of 9mm/Hg; 3 red cells per cubic millimeter were present. No white cells were seen. The spinal fluid protein was 24mg/dl; cerebral spinal fluid culture and a serologic test for syphilis were negative. The erythrocyte sedimentation rate was 22mm/hr; a complete blood count and an extensive battery of blood chemistries revealed no abnormalities. An electroencephalogram exhibited a 1β-3 cycle per second slow wave focus in the left parietal occipital and left posterior temporal areas. One month later slow activity was still present in these areas. The patient's headache persisted intermittently for 3 weeks.

One year later the patient had a normal blood pressure and pulse rate and she was bright and alert. Ophthalmodynamometry demonstrated diastolic pressures of 47 grams in both eyes. There were no carotid or cerebral bruits. The dense right homonymous hemianopsia was still present. During the year after the severe headache the patient reported occasional unilateral headache, usually over the right or left eyebrow. The pain was "steady"; it usually responded to aspirin.

Patient 6. A 24-year-old woman with a family history of migraine presented with a 17-year history of bifrontal "plain" headaches usually induced by reading or writing. These occurred 2-3 times a week for periods of up to 2 hours and were relieved by aspirin. In April of 1963 a severe headache occurred. It began anterior to the right ear; was throbbing in character; and persisted for 15 minutes. There was no associated nausea or vomiting. Two similar headaches

FIGURE 1. Visual fields for Patient 5 showing right homonymous hemianopsia.
occurred 2 and 6 weeks later unaccompanied by pre-headache symptoms. Three months later the patient suddenly felt faint and nauseated. After a 2 hour rest she went to bed. While falling asleep she noted once again a severe throbbing pain in the right temple. This was associated with generalized visual blurring and a feeling of numbness of the left side of the body which subsided after 15 minutes. She was given a sleeping pill by her local physician and slept for a period of 12-14 hours. On awakening she noted some left sided numbness and found that she could not see to the left. Her vision was also "slightly blurred" in the right visual field.

On admission to University Hospital 24 hours after headache onset her blood pressure was 110/70; the pulse rate was 108/min associated with a sinus arrhythmia. Temperature was 37.9°C. The uncorrected vision was 20/25 in the right eye and 20/30 in the left eye. Neurological examination revealed a dense left homonymous hemianopsia to confrontation. The rest of the neurological examination was normal save for slightly diminished abdominal reflexes on the left. A lumbar puncture performed the day of admission revealed a pressure of 5mm/Hg. The fluid was crystal clear with a protein content of 56mg/dl. Three white cells and one red cell were noted per cubic millimeter. A spinal fluid serologic test for syphilis and culture were negative. The white blood count was 10,400/cumm with a normal differential. An electroencephalogram demonstrated an amplitude depression in the right posterior temporal occipital area.

Approximately 70 hours after onset, persistence of the headache and left homonymous hemianopsia led to the performance of a right carotid arteriogram (fig. 3) which revealed occlusion of a branch of the right posterior cerebral artery with meningeal-pial collateral circulation largely from the anterior cerebral artery. The headache persisted 6 more days. The left homonymous hemianopsia persisted unchanged (fig. 4). One year later the patient appeared well. However, the dense left homonymous hemianopsia had persisted.

Comment. It is of interest that the headache which preceded and paralleled the permanent hemianopic episodes in both of these young women was the most severe they had ever experienced. Both had suffered headaches since childhood but only Patient 6 suffered from headaches prior to the hemianopic episode which were clearly unilateral in character and only she had a strong family history of migraine. Both patients had neurological signs ipsilateral to their hemianopsia all of which were transient save for the hemianopsia. This is not uncommon.

Cerebral angiography was performed on both
patients within 3 days after onset of the persistent hemianopsia. In both cases branch occlusion of the posterior cerebral artery was demonstrated with retrograde filling in the late arterial phase. The pattern of occlusion and delayed retrograde collateral circulation to the distal territory of the occluded vessel is strikingly similar in both patients.

Discussion

Prevalence figures for migraine of up to 19% in men and 29% in women have been presented by Waters. Of these, 10% present with a history of associated neurologic deficits during an episode. The majority of the neurological symptoms in migraine involve the visual pathways including calcarine cortex and the retina. When hemianopic visual symptoms occur they may be associated with ipsilateral sensory symptoms and ipsilateral hemiplegia. The hemiplegic symptoms almost always clear completely. Hemianopic symptoms all too frequently persist. The relatively benign prognosis in patients with hemiplegic migraine may be due to the absence of persistent arterial occlusion as evidenced by cerebral angiographic studies in reported patients.

It is clear that "despite . . . observations suggesting dysfunction of autonomic, immunologic, hematologic, and humoral mechanisms, a direct relationship between these findings and the sequence of events occurring in migraine has not been established." A brief review of the possible mechanisms involved is indicated, however, to establish a basis for the apparent effectiveness of isoproterenol.

The classical studies of Schumacher and Wolff demonstrated that during pre-headache migrainous visual phenomena, the vasodilator amyl nitrite would reverse quadrant field defects if its administration was associated with a sustained normal level of blood pressure. This reversal of visual symptoms occurred within 10-12 seconds, suggesting a vasconstrictor mechanism causing cerebral ischemia. Subsequent studies by Marcussen and Wolff revealed that carbon dioxide, a potent cerebral vasodilator, inhaled in 10% concentration, produced transient clearing of visual disturbances in 5 patients during inhalation, with the return of visual symptoms to their previous intensity within 5 minutes after 10% carbon dioxide inhalation was discontinued.

Direct evidence of vasoconstriction during a migrainous attack was demonstrated by Dukes and Vieth. They described a right carotid arteriogram on a 44-year-old man. During the procedure the patient had both his customary migraine prodrome and subsequent headache period. During the course of the arteriogram scotomata in both visual fields occurred. Concurrently the anterior and middle cerebral arteries, previously visualized, were reduced to a faint trace with shunting to the posterior cerebral artery circulation. When the visual symptoms were maximal a further decrease in filling of the internal carotid system occurred. When prodromal symptoms had subsided after 30 minutes and a typical throbbing right frontal headache appeared, a third set of films demonstrated good intracranial filling of the internal carotid system with no vertebral filling apparent. Indirect evidence of vasoconstriction, using cerebral blood flow measurements, during migraine has also been observed.

These studies are, in part, the basis for the ongoing hypothesis that the visual symptomatology, as well as other focal neurologic signs of migraine, are related to reversible narrowing of arteries in specific cerebral arterial territories. Amyl nitrite and other vasodilators of the nitrite class have non-specific vasodilatory effects on cerebral vessels. The vasodilatory effects of carbon dioxide appear to be related to changes in extravascular, extracellular pH. Whatever the underlying cause of the focal vasoconstriction in migraine may be, it is antagonized by the non-specific effects of nitrites and an increased blood carbon dioxide tension.

In addition to the non-specific effects, cerebrovascular responses to neurotransmitters and pharmacological agents suggest the existence of various vasomotor receptors on the intracranial arteries of many mammalian species. In vitro, vasoconstriction of cat and human pial arteries induced by serotonin or alpha-adrenergic agents is abolished by methysergide.
and phenoxybenzamine respectively. β-adrenergic agents also reverse the vasoconstriction following serotonin application in human and cat pial arteries, in vitro. While β-adrenergic antagonists, propranolol and 1-N-isopropyl-p-nitrophenyl-ethanolamine (NPEA), block this vasoconstriction. In human basilar, middle cerebral and anterior cerebral arteries serotonin induced vasoconstriction is non-specifically antagonized by nitroglycerine.

Perivascular micro-application of norepinephrine to cat pial arteries and arterioles in vivo by Wahl and Kuschnisky resulted in 30% reductions in vascular diameter. Carbachol application resulted in 20% increases in vascular diameter. In a similar system this increase in vascular diameter was blocked by the β-adrenergic antagonist, propranolol. The evidence suggests that α-adrenergic receptors mediating constriction and β-adrenergic or cholinergic receptors mediating dilation of pial arteries can be demonstrated under in vivo conditions. Also, the fact that the constrictor effect of norepinephrine is attenuated by a decrease in K+ or H+ concentration or increased H+ concentration suggests one basis for the effect of carbon dioxide on visual symptoms in migraine described above.

With specific reference to the β-adrenergic agonist isoproterenol, some investigators have found only weak vascular reactions to its direct application. On the other hand O'Neill and Traysman have studied the effects of interarterial injection of 10 micrograms of isoproterenol into the carotid arteries of dogs. At this dose level a 200-250% increase in carotid blood flow was obtained which was significantly reduced in a graded dose related fashion with concurrent injections of the β antagonist, propranolol. In contrast, Melamed, et al. have reported direct evidence for the absence of β-adrenergic receptors in rat cerebral blood vessels.

The existence of β-adrenergic receptors such as those which might mediate the isoproterenol effect on vasoconstricted arteries in humans is still disputed. Another mechanism, however, to account for the effects of isoproterenol in our migraine patients may be offered.

With respect to vasoconstriction of cerebral vessels Flamm and co-workers noted that in various experimental conditions relaxation of both vascular and nonvascular smooth muscle had been shown to be associated with the rise of cyclic AMP and that β-adrenergic stimulation had been shown to produce increased levels of cyclic AMP. After isoproterenol administration cyclic AMP values as measured in the cat basilar arteries rose more than twofold over control values and also fourfold over those for the vasoconstricted state (P < 0.05). Whether or not isoproterenol has direct effects on normal, nonconstricted intracranial vessels via a specific β-adrenergic receptor, it appears to have a definite vasodilating effect on narrowed vessels. This effect may be mediated through the stimulation of adenylate cyclase to form cyclic AMP.

The mechanisms described, as well as the reported patient responses to isoproterenol, provide the basis for our therapeutic suggestion that whenever visual symptoms are prominent in migraine, either when they are transient and more disturbing than the headache itself or when they become more persistent than usual, that isoproterenol be administered to help prevent the permanent visual loss exhibited by patients 5 and 6. Isoproterenol therapy does not appear to consistently alter the intensity of the associated headache. Patients still have to use such analgesics as aspirin. Paradoxically, the combined use of aspirin and isoproterenol may, because of aspirin’s platelet inhibitory effects, act synergistically to prevent the most feared consequence of migraine, permanent visual loss.

References

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Isoproterenol treatment of visual symptoms in migraine.
M J Kupersmith, W K Hass and N E Chase

Stroke. 1979;10:299-305
doi: 10.1161/01.STR.10.3.299

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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