Treatment of cerebral vasospasm from subarachnoid hemorrhage with isoproterenol and lidocaine hydrochloride

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Initial experience with intravenously administered isoproterenol and lidocaine hydrochloride in 14 patients with severe spasm from subarachnoid hemorrhage is summarized. All patients were actively deteriorating from progressive spasm without other major complications; 12 of 14 improved, and two died. The method of treatment, results, and rationale for this method of therapy are discussed.

Key Words • aneurysm • subarachnoid hemorrhage • cerebral vasospasm • isoproterenol • lidocaine hydrochloride

The sudden deterioration in a postoperative patient following an apparently successful clipping of an anterior aneurysm prompted an emergency trial of the agents reported in this study. The initial and continued success resulted in a group which now justifies a preliminary communication. The patients in this group represent primarily a problem of progressive vasospasm; the other causes for deterioration, such as communicating hydrocephalus, edema, or surgical trauma, were eliminated by diagnostic studies or were considered of secondary importance in the particular cases evaluated.

Methods

Each patient undergoing this form of management had constant cardiac monitoring either in the cardiac intensive care unit or in the neurosurgical intensive care unit. Isoproterenol (Isuprel) was administered intravenously in an initial dose of 0.4 to 0.8 mg in 150 ml of 5% glucose in water at a rate of 10 to 20 microdrops/min; this represented approximately 150 ml of solution every 8 hours. Through a separate intravenous unit in the opposite arm, lidocaine hydrochloride (Xylocaine) was administered in a dose of 2 gm in 450 ml of 5% glucose in 0.20% saline with 20 mEq of potassium added to the solution. This was given at the rate of 20 microdrops/min and approached a total of 450 ml/24 hr.

There was considerable variation from one patient to another in regard to their individual response to isoproterenol. If premature ventricular contractions occurred or the pulse rate exceeded 140/min, the concentration or rate of administration of
Thoralf M. Sundt, Burton M. Onofrio and John Merideth

the drug was decreased. The lidocaine was given at a constant rate of 20 microdrops/min but the rate was increased if premature contractions occurred from the isoproterenol.

Most patients did not receive dexamethasone or other steroids, and no dehydrating agents were used. Except for antibiotics, which were not used routinely, the patients received no other medications except codeine, aspirin, or antacids. As the patient's condition stabilized or improved, the concentration and the rate of administration of lidocaine and isoproterenol were gradually decreased over a period of 24 to 48 hours. Duration of treatment varied from 48 hours to 9 days.

Representative Case Reports

Case 1

A 46-year-old woman (Grade 2 according to the classification of Botterell, et al.) underwent operation for an anterior communicating aneurysm 6 days after hemorrhage. Signs, symptoms, and angiographic evidence of severe spasm developed 14 hours postoperatively. Over a period of 3 hours the patient showed evidence of left decortication and right decerebration. A combined drip of isoproterenol and lidocaine was instituted. Within 12 hours the patient's neurological condition had improved to the point where she moved the left side voluntarily, while the right-sided signs indicated decortication. The drip was continued for 5 days, during which time the patient improved daily. At the time the medication was discontinued she had good use of all limbs except the right leg, which was still weak. The patient was discharged 3 weeks postoperatively, neurologically normal except for slight weakness in the right foot. A follow-up examination 1 month later revealed normal mentality, personality, and memory, and no focal neurological deficits.

Case 11

A 38-year-old woman with a right middle cerebral artery trifurcation aneurysm was initially treated conservatively because of severe spasm on the preoperative angiogram. Twelve days after the hemorrhage she suddenly developed a profound left hemiplegia and homonymous hemianopsia without increasing headache or alteration in the level of consciousness. A Scoville clip was applied to the aneurysm; when the patient recovered from anesthesia, the hemiplegia was unchanged. An infusion of isoproterenol and lidocaine was instituted and continued over a period of 4 days; during this time the hemiplegia and homonymous hemianopsia improved. During the next month the hemiparesis continued to improve so that by the time of discharge her chief neurological abnormality was minimal decrease in the rate of alternating motions possible in the left hand. Eventually the patient made a complete neurological recovery.

Results

The patients in this group are not typical of patients with aneurysms in general but rather are representative of those with spasm as a major complication. Only five of the 14 patients treated were Grade 1 or 2 candidates at the time of operation, all were women, and all had neurological deficits at the time therapy was instituted. As we gained confidence in the regimen and realized that the blood pressure seldom increased, an occasional patient was treated prior to elective clipping of the aneurysm. The cases are summarized in Table 1.

One immediate dramatic result occurred with treatment: a total hemiplegia and homonymous hemianopsia with a forced ocular deviation to the side of spasm changed to near-normal neurological function within 18 hours after the therapy had been instituted; improvement was obvious within 1 hour after the drip had been started. The pattern of improvement was much less dramatic in most patients and the two cases reported are typical of the group as a whole. The initial response was an apparent arrest of progressive deterioration, while definite improvement was not noted for 4 to 8 hours.

Discussion

Several years ago, Garrett suggested using isoproterenol, a drug frequently used in cardiac surgery, for postoperative cerebral vasospasm. The drug was given an initial trial but cardiac irregularities made it extremely difficult to control the medication.
Effect of beta adrenergic drugs on cerebral vasospasm from SAH

### TABLE 1
Summary of cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs)</th>
<th>Treatment Date</th>
<th>Location of Aneurysm*</th>
<th>Grade†</th>
<th>Response to Isoproterenol</th>
<th>Final Result</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>46</td>
<td>9/70</td>
<td>ACA</td>
<td>2</td>
<td>good</td>
<td>excellent</td>
<td>complete recovery</td>
</tr>
<tr>
<td>2</td>
<td>65</td>
<td>9/70</td>
<td>ICA</td>
<td>4</td>
<td>discontinued</td>
<td>death</td>
<td>could not tolerate drug (arrhythmias)</td>
</tr>
<tr>
<td>3</td>
<td>50</td>
<td>12/70</td>
<td>MCA</td>
<td>1</td>
<td>good</td>
<td>excellent</td>
<td>only minor deficit when drip instituted</td>
</tr>
<tr>
<td>4</td>
<td>65</td>
<td>12/70</td>
<td>basilar</td>
<td>4</td>
<td>good</td>
<td>fair</td>
<td>good immediate improvement but limited rehabilitation</td>
</tr>
<tr>
<td>5</td>
<td>55</td>
<td>12/70</td>
<td>ACA</td>
<td>3</td>
<td>good</td>
<td>excellent</td>
<td>full employment</td>
</tr>
<tr>
<td>6</td>
<td>55</td>
<td>1/71</td>
<td>MCA</td>
<td>1</td>
<td>fair</td>
<td>excellent</td>
<td>——</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>3/71</td>
<td>ICA</td>
<td>2</td>
<td>excellent</td>
<td>excellent</td>
<td>dramatic improvement</td>
</tr>
<tr>
<td>8</td>
<td>47</td>
<td>5/71</td>
<td>MCA</td>
<td>3</td>
<td>good</td>
<td>death</td>
<td>good initial response to drug regimen; died when discontinued</td>
</tr>
<tr>
<td>9</td>
<td>60</td>
<td>4/71</td>
<td>ACA</td>
<td>3</td>
<td>fair</td>
<td>good</td>
<td>good immediate result but less than complete recovery</td>
</tr>
<tr>
<td>10</td>
<td>38</td>
<td>6/71</td>
<td>ACA</td>
<td>3</td>
<td>good</td>
<td>excellent</td>
<td>——</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>6/71</td>
<td>MCA</td>
<td>3</td>
<td>good</td>
<td>excellent</td>
<td>complete recovery</td>
</tr>
<tr>
<td>12</td>
<td>63</td>
<td>3/72</td>
<td>ICA</td>
<td>2</td>
<td>good</td>
<td>excellent</td>
<td>deteriorated after angiogram</td>
</tr>
<tr>
<td>13</td>
<td>65</td>
<td>2/72</td>
<td>ACA</td>
<td>4</td>
<td>fair</td>
<td>death</td>
<td>stable on drip, died thereafter; no operation</td>
</tr>
<tr>
<td>14</td>
<td>71</td>
<td>3/72</td>
<td>ACA</td>
<td>3</td>
<td>excellent</td>
<td>fair</td>
<td>on drip 8 days preop</td>
</tr>
</tbody>
</table>

*ACA = anterior communicating artery; ICA = internal carotid artery; MCA = middle cerebral artery.
†Preoperative condition of patient graded according to the classification of Botterell, et al.

and at that time there was not sufficient information in the literature to justify further investigation.

**Rationale for Treatment**

Since the initial trial, a number of studies have indicated the potential importance of the neuronal supply of cerebral vessels. It is now clear that the cerebral blood vessels contain both alpha and beta adrenergic endings; beta adrenergic drugs cause vasodilatation in vivo and in vitro in vessels with myogenic tone. Fluorescent microscopic observations have expanded the knowledge derived from earlier observations under the light microscope and, more recently, with the electron microscope. The conducting vessels in the subarachnoid space have a rich adrenergic nerve supply; after sympathectomy or subarachnoid hemorrhage, there is a loss of fluorescence, indicating inactivation of the granulated vesicles, certainly significant in peripheral arterial beds and very possibly in the brain. Granulated vesicles are important not only for the metabolism, production, storage, and release of norepinephrine but also for the control of function. In contrast with cholinergic

_J. Neurosurg. / Volume 38 / May, 1973_
endings, in which the purpose of enzyme function is to destroy the free acetylcholine, the limited duration of action of the adrenergic endings is thought to be related to the prompt re-uptake of norepinephrine by the granulated vesicles. After sympathectomy, the granulated vesicles can no longer take up circulating catecholamines; the effector organ with its functional alpha or beta adrenergic endings is sensitized to circulating catecholamines, explaining the "Cannon effect." Symon12 postulated such a sensitization after subarachnoid hemorrhage.

Pharmacology of Isoproterenol

Isoproterenol is almost purely a beta adrenergic drug and therefore its action is similar in many respects to that of alpha blockers. Although it tends to decrease the peripheral blood pressure slightly, this is in part compensated for by increased cardiac output. In contrast to the effect of an alpha blocking agent, that of isoproterenol is acutely sensitive to the rate of administration and is easily controlled or terminated. Thus, some of the undesirable side effects of peripheral hypotension found with alpha blocking agents are not encountered with isoproterenol. Isoproterenol acts as follows: 1) it increases the heart rate, reinforces myocardial contractility, and increases cardiac output; 2) it dilates peripheral arterioles and decreases the arterial pressure; and 3) it decreases the venous reservoir, with a marked increase in venous return to the heart.

The chief risk of using isoproterenol in man is the creation of cardiac arrhythmias. In the presence of preexisting cardiac damage, the drug can cause cardiac irregularities and premature ventricular or atrial contractions. These can be controlled in part with lidocaine, but some patients cannot tolerate the drug in the dosage used here. In addition to cardiac irregularities, isoproterenol may produce sinus tachycardia which is not altered by lidocaine.

Pharmacology of Lidocaine

Lidocaine hydrochloride is a potent local anesthetic that decreases electrical excitability of the myocardium and its conducting system. It is used intravenously to control cardiac irregularities. It tends to decrease the force of myocardial contraction and causes mild direct peripheral arteriolar dilatation. In large dosages such as those used in this study, patients can become somewhat sedated or narcotized, making neurological evaluation difficult; this has not yet occurred in our series.

References


This investigation was supported in part by Research Grant NS-6663 from the National Institutes of Health, U. S. Public Health Service, and the Lieutenant Colonel John R. Tesch Memorial Fund for Research of Cerebral Vasospasm.

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560 J. Neurosurg. / Volume 38 / May, 1973