Bradycardia and Hypotension Associated with Baclofen Used during General Anesthesia


Baclofen, a gamma aminobutyric acid (GABA) analogue, is the most commonly prescribed drug used for the treatment of spasticity resulting from disease or injury of the spinal cord.1 It is particularly effective in treating flexor spasms and concomitant pain, clonus, and muscle rigidity associated with multiple sclerosis. In addition, baclofen has analgesic activity in rats, cats, and monkeys.2 The CNS possesses receptors that probably are activated by baclofen, influencing the processing of nociceptive stimuli, and resulting in analgesia.3 This baclofen-sensitive system coexists along with an opiate-sensitive system in modulating pain perception.4 In addition, there may be synergism in analgesic effect between opiates and baclofen.4 We began to investigate this proposed analgesic synergism by comparing the effects of baclofen or placebo given before narcotic-based general anesthesia for elective thoracic surgery. Our intention was to compare hemodynamic responses to surgery, severity of postoperative pain, and ease with which this pain could be relieved. However, a dangerous hemodynamic complication, severe bradycardia and hypotension, occurred in the patients who received baclofen.

METHODS

The study was approved by the Mayo Clinic Human Studies Committee and patients who participated gave informed consent. Patients with evidence of cardiac, nervous system, cerebrovascular, hepatic, or renal system disease were excluded. ASA Class II patients scheduled for elective thoracotomy were randomized to receive either 30 mg baclofen orally (a dose used clinically in the treatment of flexor spasm) and im morphine, 0.1 mg/kg, or placebo orally and morphine approximately 90 min prior to surgery. Placebo tablets were prepared by Giba-Geigy® and were identical in appearance to baclofen tablets. Anesthesia consisted of etomidate 0.3–0.4 mg/kg and fentanyl 5 µg/kg given iv, and isoflurane in oxygen and air, FIO2 0.6–1.0. Atracurium, 0.4 mg/kg, was given iv for muscle relaxation. Inspired isoflurane concentration was adjusted to maintain arterial pressure within 20% of that measured during the preoperative visit. Monitoring included ECG and intraarterial blood pressure, and these values were recorded intermittently. Arterial blood gases were measured approximately every 30 min. End-expired isoflurane was measured using a Beckman LB2® analyzer. Hemodynamic data were recorded on the patient's arrival in the operating room, following anesthetic induction, and following anesthetic induction, during endotracheal intubation, during antiseptic skin prep prior to incision, 3 min following skin incision, and 3 min following rib retraction once the chest had been opened. End-expired isoflurane concentration was measured in five patients.

Eight patients were studied. These included six patients in the double-blind part of the investigation and two patients in a pilot, nonblinded, preliminary study. These two patients received baclofen and morphine premedication and the standard anesthetic; however, pancuronium, 0.05 mg/kg, and metocurine, 0.1 mg/kg, were used for muscle relaxation and not atracurium.

RESULTS

Six patients participated in the randomized study. Three received baclofen premedication and subsequently, during thoracotomy, developed severe bradycardia and hypotension. Bradycardia progressed to virtual asystole in one patient.

Table 1 shows the hemodynamic course of the six study patients. End-tidal isoflurane concentrations also are listed. Table 2 indicates the time elapsed between anesthetic induction and bradycardia-hypotension and between baclofen administration and bradycardia-hypotension. Patients A, B, and C received placebo premedication. Patient A was a 62-year-old, 84-kg man who underwent wedge excision of a benign caseating granuloma; patient B was a 51-year-old, 78-kg man who underwent pneumonectomy for squamous cell carcinoma; and patient C was a 64-year-old, 60-kg woman who had an open-lung biopsy. Anesthesia, surgery, and recovery were uneventful for these placebo patients. Patients X, Y, and Z received baclofen. Their intraoperative courses are described.
CASE REPORTS

Patient X was a 27-year-old, 55-kg woman with metastatic fibroblastic osteosarcoma scheduled for wedge resection of nodules in her left lung. She had had a past below-knee amputation and previous wedge excision of pulmonary nodes (anesthesia and surgical course being unremarkable on both occasions). Anesthesia and surgery were uneventful until the chest was opened and the ribs were retracted, when she suddenly developed a sinus bradycardia of approximately 10–20 beats/min, accompanied by an arterial pressure of about 60/30 mmHg. Ephedrine, 12.5 mg, and atropine, 0.4 mg, were given iv immediately and were followed by sinus tachycardia and mild hypertension.

Patient Y was a 51-year-old man who had primary squamous cell carcinoma of the left upper lobe scheduled for lobectomy, but with no other significant medical or surgical history. His resting heart rate was 58 beats/min the evening before surgery. It was 50 beats/min on arrival in the operating room and remained relatively slow at 49 beats/min following skin incision. Following rib retraction, the patient abruptly developed a supraventricular bradycardia of about 20 beats/min accompanied by an arterial blood pressure of approximately 70/40 mmHg. Ephedrine, 12.5 mg, and atropine, 0.4 mg, were administered iv and hemodynamics restored to normal.

Patient Z was a 66-year-old, 82-kg man with a left upper lobe nodule subsequently determined to be a hamartoma. He had mild hypertension treated with a thiazide diuretic and propranolol, 10 mg, three times per day. Propranolol had been discontinued by the patient 36 h prior to surgery. Anesthesia and surgery were uneventful until rib retraction when he developed a sinus bradycardia of approximately 30–40 beats/min. Atropine, 0.4 mg, was given iv, but heart rate slowed further and a sinus pause of about 8–10 s occurred. Preparations were made to begin internal cardiac massage, and epinephrine, 200 µg, was given iv. However, a slow junctional rhythm occurred spontaneously and was followed by tachycardia and hypertension.

Two patients, the pilot study group, received the standard anesthetic, pancuronium–metocurine–induced muscle relaxation and baclofen; both had an uneventful surgical and postoperative course. However, there had been a delay of 6 h between baclofen administration and anesthetic induction in one patient.

DISCUSSION

Baclofen does not have pronounced cardiovascular effects in awake man, although a mild hypotensive effect occurs occasionally.6 Cardiovascular depression or dysrhythmias during anesthesia in patients receiving baclofen have not been reported. However, baclofen recently has replaced diazepam as the most frequently prescribed drug for the management of skeletal muscle spasm.7 Therefore, it is inevitable that some patients taking baclofen also will receive general anesthesia.

We are unsure of the mechanism producing bradycardia and hypotension in our patients. In experimental animals, baclofen can both decrease and increase heart rate and arterial blood pressure. Hypertension and tachycardia occur in awake and anesthetized rats,8,9 while intracerebroventricular administration of baclofen in the pentobarbital-anesthetized cat produces hypotension and bradycardia.10 Baclofen is structurally similar to GABA and is thought to act in part by stimulating central nervous system GABA receptors.1 General anesthetics may act via potentiation of GABA action on synaptic transmission.11 Central nervous system GABA may have an important role in controlling cardiovascular tone.12–17 GABA and drugs that stimulate GABA receptors cause a decrease in heart rate and arterial pressure in anesthetized animals.12–14 These responses are mediated by a reduction in sym-

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TABLE 1. Heart Rate (beats/min), Blood Pressure (mmHg), and End-expired Isoflurane Concentration (%) in Patients Who Received Placebo or Baclofen

<table>
<thead>
<tr>
<th>Patients</th>
<th>Preanesthetic Induction</th>
<th>Postinduction</th>
<th>1 Min after Endotracheal Intubation</th>
<th>Antisecpic Skin Prep</th>
<th>3 Min after Skin Incision</th>
<th>Rib Retraction</th>
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<tbody>
<tr>
<td></td>
<td>HR BP</td>
<td>HR BP</td>
<td>HR BP</td>
<td>HR BP Isoflurane</td>
<td>HR BP Isoflurane</td>
<td>HR BP</td>
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<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>69 155/75</td>
<td>56 125/70</td>
<td>59 170/95</td>
<td>53 130/80 0.29</td>
<td>60 155/90 0.85</td>
<td>65 140/90</td>
</tr>
<tr>
<td>B</td>
<td>76 160/85</td>
<td>72 125/65</td>
<td>88 170/105</td>
<td>68 115/70 0.36</td>
<td>82 150/100 2.63</td>
<td>90 130/85</td>
</tr>
<tr>
<td>C</td>
<td>64 160/60</td>
<td>55 130/60</td>
<td>66 150/70</td>
<td>54 110/55</td>
<td>56 165/90</td>
<td>70 120/70</td>
</tr>
<tr>
<td>Baclofen</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>X</td>
<td>66 130/60</td>
<td>63 125/60</td>
<td>55 145/80</td>
<td>60 120/50 0.30</td>
<td>62 140/80 1.43</td>
<td>10–20*</td>
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<tr>
<td>Y</td>
<td>50 135/65</td>
<td>48 120/55</td>
<td>68 150/80</td>
<td>46 115/60 0.21</td>
<td>49 155/80 1.14</td>
<td>20*</td>
</tr>
<tr>
<td>Z</td>
<td>76 140/90</td>
<td>70 120/70</td>
<td>96 170/100</td>
<td>65 110/70 0.45</td>
<td>70 140/85 1.39</td>
<td>70/40*</td>
</tr>
</tbody>
</table>

— Value not measured.
* Approximate value.
† Bradycardia <20 beats/min followed by an episode of asystole

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TABLE 2. Time Elapsed Between Anesthetic Induction and Cardiovacular Collapse and Between Preoperative Baclofen Administration and Cardiovacular Collapse

<table>
<thead>
<tr>
<th>Patient</th>
<th>Time Elapsed Between Induction and Bradycardia-Hypotension (min)</th>
<th>Time Elapsed Between Baclofen Administration and Bradycardia-Hypotension (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>46</td>
<td>2</td>
</tr>
<tr>
<td>Y</td>
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<td>Z</td>
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pathetic outflow to the vasculature and heart. Drugs that antagonize the effects of GABA cause an increase in arterial blood pressure and heart rate. A decrease in CNS sympathetic outflow mediated via a GABAergic, backlofen-sensitive system would help to explain our observations.

Factors other than baclofen could be responsible for the bradycardia-hypotension we observed. Surgical stimulation, rib manipulation, rib retraction, and pleural stretching all can cause hypotension and bradycardia by stimulating reflex vagal activity, especially in patients who have not received atropine premedication. However, profound bradycardia, hypotension, and virtual asystole do not commonly occur in relatively healthy patients during elective thoracotomy unless some other factor is operating. Our control group consisted of three patients, but perhaps an alternative control group could be considered to be the many patients who have undergone similar surgery under similar anesthesia at this institution without cardiovascular collapse. Bradycardia may be caused by narcotics. Fentanyl induces a heart rate slowing via central vagal nuclei stimulation; however, this response usually occurs following drug administration rather than completely unheralded 30–40 min later. In clinical practice, pancuronium often is used to partially antagonize this tendency toward bradycardia; however, all patients who suffered the adverse response received atracurium, a muscle relaxant without vagolytic properties. Severe bradycardia has been reported following narcotic-atacurium anesthesia. Perhaps pancuronium offered some protection from bradycardia; however, this suggestion is speculative because patient numbers were so small.

It is surprising that the first manifestation of this proposed baclofen effect occurred during rib retraction rather than earlier in the anesthetic and surgical course; but peak plasma baclofen levels do not occur until approximately 2 h following oral baclofen, a time that would coincide in our patients with bradycardia and hypotension (table 2). Baclofen is rapidly and virtually completely absorbed from the gastrointestinal tract. A 30-mg oral dose in healthy, fasting volunteers produces a peak plasma level of approximately 600 ng/ml 1–½ to 2–½ h following administration. (Therapeutic plasma levels are considered to be 80–400 ng/ml). Elimination half-life is about 3 to 6 h. Seventy to 80% is excreted unchanged in the urine, and the rest is eliminated in the feces; about 15% is deaminated in the liver.

We suggest that baclofen in dosages that are used clinically in the management of muscle spasm may, during general anesthesia and surgery, disturb autonomic control of the circulation. Our findings were reported to the Federal Drug Administration, Ciba-Geigy, and the institutional Human Studies Committee. We recommend that when anesthetizing such patients, the possibility of severe bradycardia and hypotension should be anticipated and that drugs appropriate for treating this emergency should be readily available. In addition, it may be advisable to discontinue baclofen therapy prior to anesthesia and surgery. The question concerning potentiation of narcotic analgesia remains unanswered.

References


Pulmonary Artery Catheter Migration during Cardiac Surgery

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METHODS

Sixteen men and five women patients scheduled for elective coronary artery bypass surgery were studied. A 7.5F quadruple-lumen pulmonary artery catheter was inserted by the Seldinger technique through the right internal jugular vein and advanced to a wedge position using a 1.5-ml balloon inflation volume. An external sterile shield containing approximately 15 cm of catheter allowed subsequent sterile catheter manipulations during the operation. Each catheter was secured to the patient's forehead to prevent its accidental migration, and the length of catheter at the distal end of the introducer was measured.

Anteroposterior chest radiographs were obtained at four intervals: after endotracheal intubation (baseline) (fig. 1a), after the initiation of cardiopulmonary bypass (fig. 1b), after anterior retraction of the ventricular apex during bypass using a Janke-Barron heart support (fig. 1c), and after chest closure (fig. 1d). Only those patients with the catheter positioned in the right pulmonary artery were studied. Radiographs were taken at end-expiration except during bypass, when the lungs were allowed to deflate passively.

Radiographic determination of catheter placement was made by locating the catheter tip relative to a zero point, defined as the point at which the catheter in the pulmonary artery visually intersected the portion of the catheter in the superior vena cava (fig. 1a). Catheter tip location

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Fig. 1. Radiographs of a Group 1 patient showing catheter tip placement after A. endotracheal intubation (arrowhead indicates zero point, open arrow indicates catheter tip); B. onset of cardiopulmonary bypass, note that catheter tip has passed beneath retractor flange (open arrow); C. anterior retraction of the ventricular apex (catheter tip remains behind retractor flange); and D. chest closure (open arrow indicates catheter tip). Following cardiopulmonary bypass, the pulmonary artery catheter appeared permanently wedged and required 5-cm catheter withdrawal to obtain a satisfactory tracing between C and D intervals.