phine and its disappearance following naloxone administration.

Somewhat puzzling is the fact that the full symptomatology only occurred following the second injection of epidural morphine, although motion sickness was already reported after the first injection. It should be recalled, however, that pruritus, a known side effect of extradural morphine, also appeared only after the second injection. The delayed appearance of the vestibular symptoms is best explained by the time lag that occurs between the injection of morphine into the epidural space and its intracranial spread,[7] in particular in the endolymphatic system, which is connected with the CSF.

There is experimental evidence that the intracerebroventricular or intrathecal administration of opioids possesses irritant properties.[8] In humans opioids have been shown to increase labyrinthine responsiveness,[9] and a potential role of endogenous opioid peptides in the pathogenesis of motion sickness has been suggested.[10] This suggestion is based on prophylactic and therapeutic effect of naloxone. These are indirect arguments, which coupled to the rapid and complete recovery following naloxone administration, argue for a direct pathogenic role of morphine in the manifestations presented by this patient.

Although lidocaine and bupivacaine, with their known CNS toxicity,[11] either alone or by interacting with morphine[12] might theoretically have played a role, the rather long delay between their administration and the symptomatology argue against such a role.

In conclusion, this case suggests that vestibular dysfunction may be added to the side effects associated with epidural morphine analgesia and can be rapidly reversed by naloxone administration.

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Transient Systemic Arterial Hypotension and Cutaneous Flushing in Response to Doxacurium Chloride

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Doxacurium chloride (BW A938U) is an investigational nondepolarizing neuromuscular blocking drug with a benzylisoquinolinium structure and a duration of action similar to that of pancuronium. Its ED_{95} for neuromuscular blockade is 0.03 mg/kg, and it does not release histamine in doses up to 0.08 mg/kg.[1] Clinical studies of doxacurium have demonstrated cardiovascular stability following administration in healthy patients,[2] in children,[3] and in patients anesthetized with sufentanil and midazolam undergoing cardiac surgery.[4] Fifty-five patients have received doxacurium at our hospital as participants in an institutionally approved investigation for patients undergoing cardiac or major vascular surgery. Forty-five cardiac surgical patients[5] and nine patients for abdominal aortic surgery received doxacurium without clinically significant

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hemodynamic effects. This case report details the adverse response of one patient to a 0.05 mg/kg iv bolus of doxacurium.

Report of a Case

A 76-yr-old, 65-kg male was admitted for elective repair of an asymptomatic abdominal aortic aneurysm. A pulsatile abdominal mass had been discovered on routine physical examination, and echocardiography revealed an infrarenal aortic aneurysm 8 cm in diameter. Past medical history was significant for emphysema due to 60–80 pack-years of cigarette smoking. Pulmonary function studies indicated severe chronic obstructive pulmonary disease (forced vital capacity [FVC] 2.25 l, FEV_1 0.71 l) with significant improvement following bronchodilator therapy (29% increase in FEV_1). His exercise tolerance was 1–2 flights of stairs. Other inactive past medical problems included recurrent bouts of sinusitis and peptic ulcer disease. There were no known allergies. His only medication was an oral theophylline preparation. Theo-dur®, 200 mg po bid (Key Pharmaceuticals, Kenilworth, New Jersey).

On physical examination, the patient was anxious, 175 cm in height, and 65 kg in weight. Chest examination was remarkable for diminished breath sounds bilaterally and increased anteroposterior chest diameter. The expiratory phase of respiration was moderately prolonged. The cardiac examination was normal. The abdominal examination was significant for a pulsatile mass in the epigastrium. Peripheral pulses were adequate.

Laboratory investigations showed electrolytes, creatinine, transaminase, alkaline phosphatase, albumin, and total serum protein levels all to be normal. Hemoglobin was 12.5 gm/dl, hematocrit was 38.1%, and platelet count was 213,000 mm^{-3}. The prothrombin time and the activated partial thromboplastin times were within the normal range. Arterial blood gases while breathing room air supplemented with 2 l/min oxygen *via* nasal cannulae were *p*H 7.35, Pa_{CO_2} 47 mmHg, and Pa_{O_2} 89 mmHg. The theophylline concentration was 2.1 μg/ml (subtherapeutic). The electrocardiogram showed normal sinus rhythm, right atrial hypertrophy, and poor R-wave progression over the precordium. A chest radiograph showed changes consistent with emphysema but no effusions or infiltrates.

On the morning of surgery, he received his usual oral theophylline preparation, and iv doses of metronidazole, 500 mg, and cefazolin, 1,000 mg, 2 h preoperatively. Preanesthetic medication consisted of diazepam, 5 mg po. He arrived in the operating room sedated and breathing comfortably, receiving supplementary oxygen, 2 l/min *via* nasal cannulae. Hemodynamic parameters are listed in table 1. Midazolam, 2 mg iv, was administered for further sedation. Two 14-G iv cannulae were inserted.

The patient breathed 100% oxygen for 5 min. Anesthesia was induced with fentanyl 30 μg/kg and an additional 2 mg of midazolam iv. Tracheal intubation was facilitated with succinylcholine, 1 mg/kg iv. There was no hemodynamic response to laryngoscopy or intubation. The lungs were mechanically ventilated with a tidal volume of 700 ml at a rate of 12/min. The peak inspiratory pressure was 26 cmH_2O and the I:E ratio was 1:2.5. Hemodynamic parameters are listed in table 1.

Seven minutes following tracheal intubation, doxacurium, 0.05 mg/kg, was given as an iv bolus over 10 s followed by a continuous saline flush for 20 s *via* the right atrial port of the pulmonary artery catheter. One minute after completion of the doxacurium dose, the MAP was declining rapidly. Table 1 details the hemodynamic response. Two minutes after doxacurium, cutaneous flushing was present. There was no change in the ventilatory inflation pressure, and no wheezing was appreciated on auscultation of the chest. Intravenous crystalloid replacement solution (Plasmalyte A, 500 ml) was rapidly infused, and ephedrine 40 mg iv and calcium chloride 500 mg iv were administered during the hypotensive episode. The MAP stabilized at 90 mmHg, and the cutaneous flushing faded over the next 5 min. Arterial blood gases drawn 6 min after doxacurium were *p*H 7.46, Pa_{CO_2} 36 mmHg, and Pa_{O_2} 578 mmHg on 100% oxygen. No electrocardiographic changes were noted.

Ten minutes after doxacurium, a 12-lead electrocardiogram still showed no changes from the electrocardiogram obtained on admission. No response to train-of-four stimulation applied to the left ulnar nerve was observed.

The surgical procedure began 20 min after resolution of the hypotensive episode. An aorto-biiliac prosthesis was inserted in 2 h, and the operative course was uneventful. The patient received an additional 30 μg/kg of fentanyl during the procedure. Hypertension was controlled with low inspired concentrations of isoflurane and an iv infusion of nitroglycerin. No further neuromuscular blocking drugs were administered during the procedure, and 2 twitches were observed following train-of-four stimulation upon completion of the surgery.

Ventilation was controlled until the following morning when ventilatory support was slowly discontinued. The trachea was extubated 20 h postoperatively. The subsequent postoperative course was uneventful, and the patient was discharged from the hospital on the seventh postoperative day. There were no sequelae from the hypotensive episode. The patient, the institutional review board, and the pharmaceutical company (Burroughs Wellcome Co., Research Triangle Park, North Carolina) were all informed of the suspected adverse response to doxacurium exhibited by this patient.

Discussion

Doxacurium chloride (BW A938U) is a potent and long-acting nondepolarizing neuromuscular blocking drug the iv bolus administration of which has not been

Table 1. Hemodynamic Parameters

Time	Preinduction	Postinduction	2 min post DOX	3 min post DOX	4 min post DOX	5 min post DOX
HR (beats/min)	72	72	70	70	72	78
MAP (mmHg)	102	88	40	42	45	108
MPAP (mmHg)	24	28	30	30	32	30
PCWP (mmHg)	11	18	—	—	—	22
RAP (mmHg)	6	13	15	15	15	18
CI ($l \cdot min^{-1} \cdot m^{-2}$)	2.95	2.11	—	—	—	2.68
SI (ml/m^2)	41	29	—	—	—	34
Treatment	—	—	Crystalloid infusion	Ephedrine 20 mg, $CaCl_2$ 500 mg	Ephedrine 20 mg	None

The hemodynamic response to one 0.05 mg/kg iv dose of doxacurium chloride (DOX).

previously reported to result in hypotension. Despite its benzylisoquinolinium structure (similar to *d*-tubocurarine and atracurium), histamine release has not been found at doses up to 2.7 times the ED_{95} for neuromuscular blockade (2.7×0.03 mg/kg = 0.08 mg/kg).[1] The current case report describes an episode of severe, transient systemic arterial hypotension associated with cutaneous flushing following a therapeutic (0.05 mg/kg) dose of doxacurium ($1.7 \times ED_{95}$).

The close temporal relationship of the hypotensive episode to the iv administration of this drug almost certainly implicates doxacurium as the cause. Two possible mechanisms for the reaction include histamine release due to a direct action of doxacurium on basophils and an anaphylactoid response.

Quaternary ammonium compounds, such as benzylisoquinoline muscle relaxants, are known to release histamine and other vasoactive substances from basophils.[6] The current, limited research experience with doxacurium and the difficulties with specimen handling, analysis, and interpretation of histamine assays do not preclude the possibility that doxacurium may release histamine. Patients with cardiovascular disease may be particularly susceptible to severe reactions from histamine-releasing drugs.[7] This patient's response to the systemic hypotension was atypical in that there was no reflex tachycardia. This might be explained by sinus node dysfunction due to cardiovascular disease or by the vagotonic effects of a high-dose fentanyl anesthetic. In the absence of a normal compensatory response (reflex tachycardia), direct histamine release could have explained the reaction.

The patient had no previous exposure to doxacurium, making an immunoglobin E-mediated anaphylactic response unlikely. However, this does not exclude an anaphylactoid reaction. In a series of 67 patients, 85% of life-threatening anaphylactoid reactions to muscle relaxants occurred with no previous exposure to the drug.[8] Crossed anaphylaxis to muscle relaxants has been proposed, and this may be due to a common hapten, such as the quaternary ammonium radical.[9] The lack of previous exposure in this case report suggests that doxacurium could have antigenic determinants in common with other drugs.

This patient had mildly elevated mean pulmonary arterial pressure (MPAP) prior to the induction of anesthesia. This was probably due to chronic obstructive pulmonary disease. The increases in MPAP, pulmonary capillary wedge pressure (PCWP) and right atrial pressure (RAP) following tracheal intubation are consistent with the effects of positive pressure ventilation and probably do not reflect true increases in transmural pressure. There were further slight increases in MPAP and RAP during the period of systemic arterial hypotension. This is consistent with either of the proposed mechanisms of the adverse reaction. Histamine release typically results in bronchospasm and elevations in MPAP. However, bronchospasm did not occur in this patient, despite the subtherapeutic theophylline level. A drug interaction between or among doxacurium and metronidazole, cefazolin, erythromycin, or theophylline cannot be excluded. It is unlikely that the benzyl alcohol preservative in the doxacurium vial was the cause of the reaction.[10]

In summary, a case of severe transient systemic arterial hypotension and cutaneous flushing in response to iv bolus administration of a clinically relevant dose (0.05 mg/kg) of doxacurium chloride has been described. The case is also remarkable for the lack of a compensatory tachycardia during the hypotensive episode.

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