Pancuronium Bromide Enhances Atrioventricular Conduction in Halothane-anesthetized Dogs

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The effect of pancuronium bromide on atrioventricular conduction was studied by His-bundle electrocardiography during atrial pacing at different heart rates in halothane-anesthetized dogs. Pancuronium bromide, 0.1 mg/kg, uniformly enhanced atrioventricular conduction, as evidenced by decreased A–H interval (the time from the onset of the first high-frequency component of atrial depolarization to the His deflection). Wenckebach second-degree atrioventricular block appeared in five of 14 animals during atrial pacing with halothane anesthesia. This block was uniformly abolished by pancuronium. The enhancement of atrioventricular conduction may contribute to the development of tachyarrhythmias following administration of pancuronium in certain patients, particularly those who have atrial fibrillation or atrial flutter. (Key words: Neuromuscular relaxants, pancuronium; Heart, atrioventricular conduction; Heart, electrocardiography, bundle of His; Anesthetics, volatile, halothane; Heart, atrial pacing.)

PANCURONIUM, a nondepolarizing neuromuscular blocking agent, increases heart rate when administered to man during barbiturate–nitrous oxide and halothane anesthesia.[1–5] Studies in both animals[6] and man[1,3,5] have suggested that pancuronium has an atropine-like effect, and that the increase in heart rate depends upon the extent of vagolysis prior to pancuronium administration. Other investigators have not found similar increases in heart rate related to pancuronium administration to patients about to undergo cardiac surgery.[7–9] Several investigators have reported the occurrence of ventricular extrasystoles following administration of pancuronium.[4–5] A recent report described two patients in whom ventricular tachyarrhythmias developed when pancuronium was administered to facilitate mechanical ventilation.[10] The specific effect of pancuronium on atrioventricular (A–V) conduction, however, has not been reported. We used the technique of His-bundle electrocardiography[11–15] to evaluate the effect of pancuronium on A–V conduction in dogs anesthetized with halothane.

Methods

Fourteen unpremedicated mongrel dogs, weighing 14–24 kg, were anesthetized by inhalation of halothane†† and oxygen delivered via a standard circle absorber system from an Ohio anesthesia machine with a Fluomatic DRVl (Foregger) vaporizer. The tracheas were intubated without the use of muscle relaxants. Ventilation was controlled with an Ohio anesthesia ventilator. End-tidal carbon dioxide concentration was maintained between 4.3 and 4.8 per cent and end-tidal halothane was kept at 1 per cent using calibrated Beckman LB-2 infrared analyzers. The animals were kept normothermic throughout the study. Arterial blood was withdrawn at the beginning and end of each procedure and analyzed for P_{O_2}, P_{CO_2} and pH. Arterial blood was analyzed for halothane by gas chromatography using a Varian 1400 gas chromatograph and Se-30 column.

The anesthetized dog was secured in the supine position and bilateral femoral venous cutdowns were performed. Under fluoroscopic control, a tripolar catheter‡‡ was positioned across the tricuspid value such that a stable His-bundle electrogram was obtained, as evidenced by deflections representing depolarization potentials of the atrium, His bundle and ventricle (fig. 1A, bottom tracing). For atrial pacing a second tripolar catheter was passed via the opposite femoral vein and positioned near the junction of the superior vena cava and right atrium. A Medtronic 5837 R-wave-coupled pulse generator which delivers a square-wave monophasic pulse of 2-msec duration was used for all atrial pacing studies.

The His-bundle catheter electrodes were connected to an Ele-cath switch box that allowed selection of any combination of two electrodes. The output of the switch box was connected via a Burr-Brown isolation amplifier, ECG control unit, and interface unit to an Electronics for Medicine DR12 recorder. Band-width cutoff frequencies were 50 Hz to 400 Hz.

Arterial (aortic root) and left ventricular pressures

were recorded using a Model 350 Millar-tip transducer catheter introduced via the femoral artery. The catheter was connected to a DR-12 recorder via a pressure-signal conditioning unit.§§

After satisfactory anesthesia had been achieved and end-tidal carbon dioxide and halothane concentrations had been stable for at least 20 minutes, control His-bundle recordings were obtained. The right atrium was initially paced at 80, 100 or 120 beats/min, depending upon baseline heart rate, with increases of 20 beats/min to a maximum rate of 200 beats/min. Each paced rate was maintained continuously for 3 minutes with no evidence of loss of atrial capture before recordings were made. At least ten consecutive beats were recorded at a paper speed of 100 mm/sec. After recording at a paced rate of 200 beats/min, pacing was discontinued and at least 3 minutes allowed to elapse before baseline recordings were again obtained. Each animal was then given pancuronium bromide,¶¶ 0.1 mg/kg, intravenously. Three minutes after administration of the drug, baseline recordings were again obtained. Atrial pacing and recording was again performed as outlined above at rate increments of 20 beats/min to a rate of 200 beats/min. Pacing was then discontinued and the animals sacrificed by injection of potassium chloride, 40 mEq, intravenously.

The intervals recorded included the A-H interval (time from onset of the first high-frequency component of atrial depolarization to the His deflection) and the H-V interval (time from His deflection to onset of the first high-frequency component of ventricular depolarization). Arterial blood pressure and surface electrocardiogram, using the Frank X-Y-Z vectorcardiographic lead system, were also recorded at each paced rate.

The A-H and H-V intervals were measured and plotted against stepwise increases in heart rate produced by atrial pacing before and after pancuronium administration at each heart rate. All data were analyzed using Student's t test for paired data.

Results

Heart rate and mean arterial pressure increased after administration of pancuronium (table 1). The A-H interval of the His-bundle electrocardiogram decreased significantly, indicating enhancement of A-V conduction by pancuronium.

Atrial pacing prior to pancuronium administration resulted in a progressive increase in A-H interval, which plateaued, however, at paced rates above 140 beats/min. A Wenckebach second-degree A-V block appeared during rapid atrial pacing in five of 14 animals in the control experiments (fig. 1A). When the Wenckebach A-V block appeared it was uniformly abolished by pancuronium (fig. 1B).
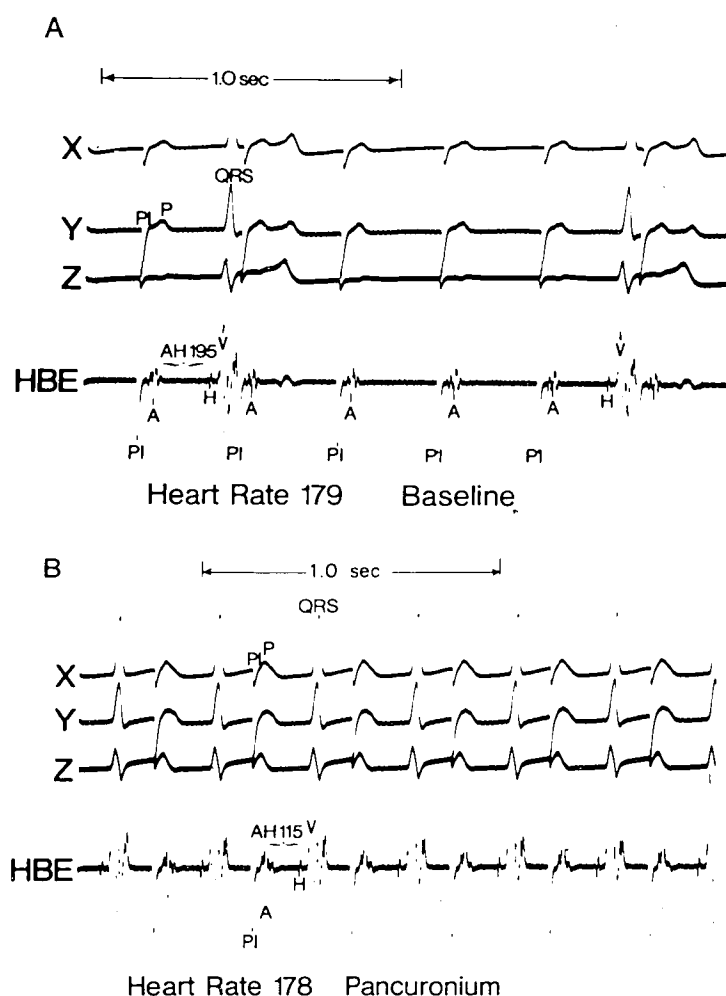
§§ Henry Koerner Research, Inc., Model 747.
¶¶ Supplied by Organon Laboratories.

FIG. 1. Surface electrocardiogram using the Frank X-Y-Z vectorcardiographic lead system and His bundle electrocardiograph (HBE) tracings before (A) and after (B) administration of pancuronium. At a paced rate of approximately 180 beats/min, note the development of an atrioventricular block in A. This atrioventricular block is abolished in B. AH = AH interval, PI = pacing impulse, A = atrial deflection, H = His deflection, V = ventricular deflection, P = P wave.

Following pancuronium administration, the A-H interval was significantly decreased at every incremental paced heart rate (fig. 2). The H-V (His-bundle to ventricle) conduction time was not changed in any experiment. Results of all other laboratory determinations were within normal limits.

Discussion

The P-R interval of the surface electrocardiogram measures A-V conduction time. The His-bundle electrocardiogram allows subdivision of the P-R interval into two components. Conduction time between the atrial depolarization potential and the His-bundle deflection (A-H interval) represents primarily impulse propagation in the region of the A-V node. Conduction to the distal bundle of His and Purkinje network (H-V interval) is measured
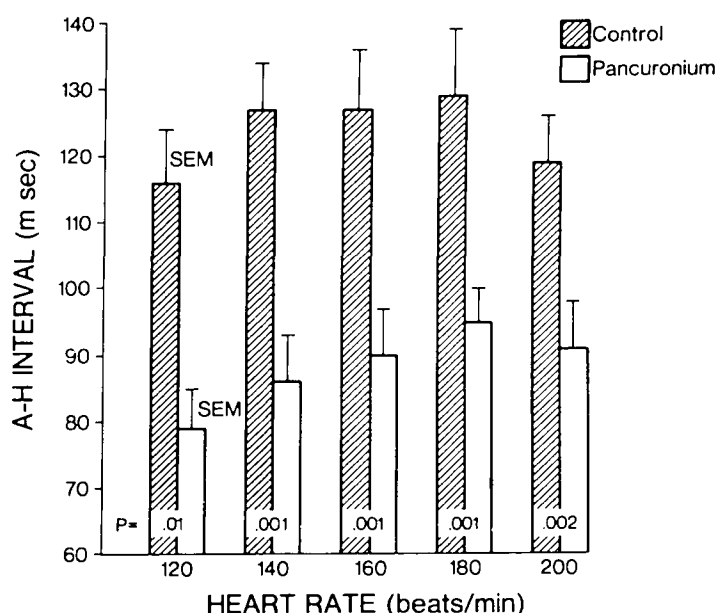
FIG. 2. Heart rate during incremental atrial pacing versus A-H interval in halothane-anesthetized dogs before and after pancuronium. Pancuronium decreased the A-H interval at every paced rate. N = 10 at HR 120 beats/min, N = 13 at HR 140 and 200 beats/min, n = 14 at HR 160 and 180 beats/min.

from the His deflection to the beginning of the QRS complex.[11,13–15] Atlee and Rusy[12] have described a dose-dependent depressant effect of halothane on A-V conduction. Additionally, increasing rates of atrial pacing have been shown to lengthen progressively the A-H interval in dogs[13] and in man.[14]

Our results confirm that pancuronium increased resting heart rate in animals anesthetized with halothane. Pancuronium also reverses the prolongation of the A-H interval produced by halothane anesthesia and rapid atrial pacing.

There are three possible mechanisms for these effects. Pancuronium may produce vagal inhibition or sympathetic stimulation, or act directly on the A-V node to enhance conduction. All of these mechanisms decrease A-V conduction time by shortening the A-H interval, which is the segment of the His-bundle electrocardiogram most susceptible to physiologic and pharmacologic interventions.[14,15]

Clinical and laboratory evidence suggests pancuronium has an atropine-like effect that can increase heart rate and, secondarily, mean arterial pressure and cardiac output, depending upon the extent of prior vagolysis. Thus, the greatest increase in heart rate following pancuronium would be anticipated in unpremedicated patients or those premedicated with scopolamine, a belladonna alkaloid with only a short-lived cardiac vagolytic effect.[16]

Further support for vagal inhibition by pancuronium has been provided by Duke et al.[17] They studied the reflex slowing the heart rate in response to increased systolic blood pressure produced by infusing angiotensin before and after pancuronium administration in unpremedicated patients anesthetized with methoxyflurane. Their results indicated that reflex slowing of heart rate occurred only at a higher systolic blood pressure following pancuronium, suggesting at least some inhibition of the vagally mediated baroreflex.

Another mechanism by which pancuronium could produce an increased heart rate is sympathetic stimulation. The effects of vagal inhibition and sympathetic stimulation on the His-bundle electrocardiogram are identical. Thus, the data reported in our study are not sufficient to conclude which mechanism may be responsible for the changes observed. The absence of an increase in peripheral vascular resistance associated with the increase in heart rate, blood pressure, and cardiac output with pancuronium[1,3,4] would indicate that systemic sympathetic stimulation does not occur. Both an increase[18] and no change[19] of blood catecholamine levels following pancuronium administration have been reported. Whether pancuronium causes selective cardiac sympathetic stimulation remains to be determined. Such an effect could explain the occurrence of ventricular extrasystoles and tachyarrhythmias. However, ventricular arrhythmias may also result from a relative increase in adrenergic influence on A-V conduction secondary to vagal inhibition. Pancuronium could also have a direct effect on the A-V node to decrease conduction time, but presently there are no experimental data relating to this question.

Several reports have not confirmed pancuronium-related tachycardia in patients undergoing cardiac surgery, regardless of premedication, and have advocated the use of pancuronium in patients who have heart disease.[7–9] The lack of an increase in heart rate in response to pancuronium in these patients may reflect a disturbance of the parasympathetic control mechanism of heart rate in patients who have heart disease or are chronically receiving digitalis or propranolol therapy. Experimental heart failure in animals and clinical heart failure in man markedly attenuate the parasympathetic regulation of sinoatrial node automaticity.[20]

TABLE 1. Effect of Pancuronium, 0.1 mg/kg, Prior to Atrial Pacing in Halothane-anesthetized Dogs*

	Heart Rate (Beats/Min)	Mean Arterial Pressure (torr)	A–H Interval (msec)
Control	(n = 14) 79 ± 5	(n = 12) 92 ± 5	(n = 14) 92 ± 5
After pancuronium, 0.1 mg/kg	(n = 14) 101 ± 5 (P < 0.000)	(n = 12) 111 ± 6 (P < 0.005)	(n = 14) 73 ± 3 (P < 0.000)

* Values are means ± SE.

This study has shown that pancuronium enhances atrioventricular conduction and increases heart rate by decreasing the A-H interval of the His-bundle electrocardiogram, which represents a decrease in conduction time from the sinoatrial node to the bundle of His. This effect may result from vagal inhibition or sympathetic stimulation. An increased ventricular rate in a patient who has heart disease can decrease cardiac output, blood pressure, and coronary blood flow. An excessive ventricular rate could occur, especially in patients who have atrial fibrillation or flutter, because the ventricular response to the rapid atrial impulses in these arrhythmias is determined by the degree of A-V conduction.[21] Patients with mitral stenosis, in whom ventricular filling time is dependent upon heart rate, may also be adversely affected. Because of this possibility, the use of pancuronium in patients with heart disease in whom an increase in heart rate would be harmful should be carefully considered, regardless of the mechanism.

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