

Effects of Droperidol on Sympathetic Activity and Baroreflex Control of Heart Rate in Humans

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The effects of intravenous droperidol, 0.2 mg·kg⁻¹, on baroreflex control of heart rate and on plasma catecholamine levels were determined in 10 ASA physical status I unpremedicated patients. Baroreflex control of heart rate was assessed by a pressor test using phenylephrine. Plasma concentrations of norepinephrine and epinephrine were determined by high pressure liquid chromatography, and plasma droperidol concentrations were measured by radioimmunoassay, from blood samples withdrawn before baroreflex evaluation. All data were obtained before and 5, 10, and 15 min following droperidol administration. Baroreflex response was significantly decreased after droperidol at each time of the study with the maximal decrease (-47% from control) observed at 5 min. No resetting of baroreflex was present since the pulse interval at the reference pressure was unchanged. Plasma norepinephrine concentrations were moderately but significantly increased only at 5 min, while no significant change in epinephrine concentrations was observed. It is concluded that droperidol induces a moderate but sustained alteration of baroreflex function and a transient increase in plasma norepinephrine concentrations. (Key words: Anesthetics, intravenous: droperidol. Blood pressure: baroreceptor reflexes. Sympathetic nervous system: epinephrine; norepinephrine.)

CARDIOVASCULAR RESPONSES to anesthetic agents can be explained, at least in part, by their effects on sympathetic activity and baroreflex function. Thus, most anesthetics and anesthetic adjuvants,¹⁻³ except ketamine,⁴ decrease adrenergic activity and depress baroreflex control.^{3,5-9} By contrast, conflicting data regarding the effects of droperidol on sympathetic nervous system have been reported. For instance, although this agent has alpha-adrenergic-blocking properties,¹⁰ its administration in humans induces a decrease of blood pressure by lowering venous return and, consequently, cardiac output, and not by decreasing systemic vascular resistance.¹¹ In addition, it can produce a hypertensive crisis in some patients with pheochromocytoma,^{12,13} which has been attributed to a transient release of norepinephrine from sympathetic nerve endings.¹⁴ Since no data concerning the effects of droperidol in humans on sym-

pathetic activity and on baroreflex response are available, this study was designed to evaluate in humans the actions of intravenous droperidol alone on baroreflex control of heart rate and on plasma norepinephrine and epinephrine concentrations.

Methods

Ten patients (seven male, three female, 36 ± 9 yr of age), ASA physical status I and unpremedicated, were studied before their scheduled surgical procedure. Institutional approval was obtained, and all patients gave informed consent.

Upon the arrival of the patients in the operating room, a catheter was placed into the radial artery after lidocaine local anesthesia and an intravenous catheter was introduced into a forearm vein. Blood pressure was transduced with a Statham pressure transducer and recorded along the ECG on an Elema four channels recorder (Mingograph, Siemens). The sensitivity of baroreflex control of heart rate was assessed by the relationship existing between the value of systolic arterial pressure (SAP) and the succeeding R-R interval on the ECG, while blood pressure was pharmacologically increased with an intravenous bolus of phenylephrine (pressor test). The dose of phenylephrine was selected by a sensitivity testing to produce an increase in SAP of approximately 20 to 30 mmHg (50 to 200 µg). Three minutes later, the blood pressure had returned towards the pre-injection level. The same dose was used in each individual experiment during the entire study. The relationship between SAP and the succeeding R-R interval was plotted on a beat-to-beat basis during the increasing phase of blood pressure. The slope of the regression line, expressed in msec·mmHg⁻¹, calculated by least square analysis, was used as index of the gain of baroreflex function.¹⁵ Only complete sets of data with a correlation coefficient greater than 0.8 were included in this study. Resetting of baroreflex was determined by calculation of the pulse interval at the reference pressure, as previously described,⁵ and by calculation of systolic pressure of reference pulse interval. These parameters permit quantification of an eventual shift of the relationship between SAP and R-R interval.

Before each evaluation of baroreflex function, blood samples were withdrawn from the radial catheter for subsequent measurements of: 1) plasma norepinephrine

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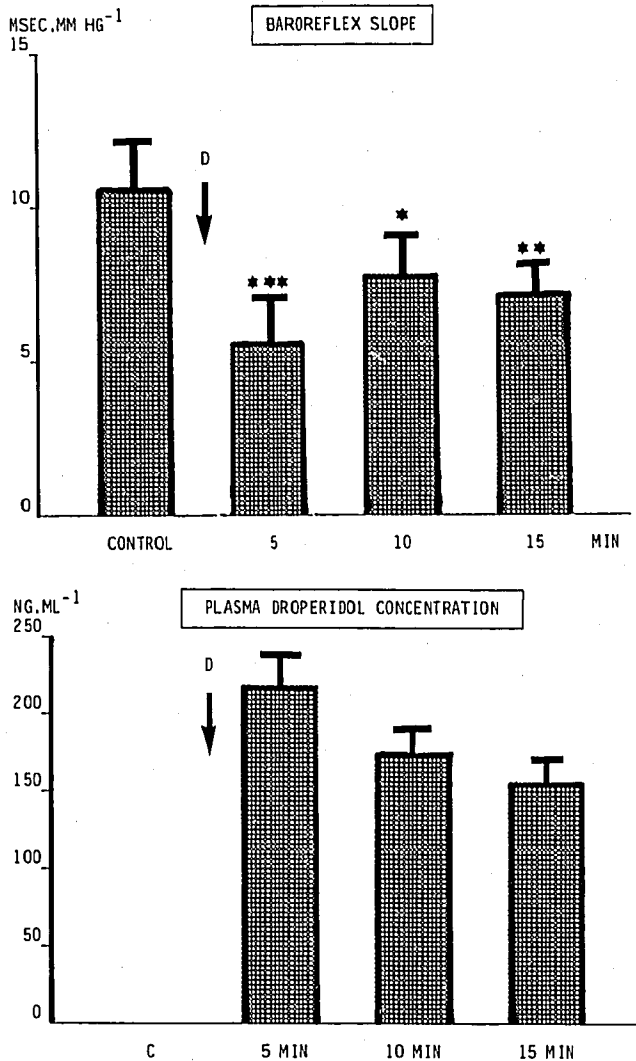


FIG. 1. Baroreflex slope and plasma droperidol concentrations (mean \pm SEM) plotted against time at each period of the study (C = control period); * $P < .05$, ** $P < .01$, *** $P < .001$ versus C.

and epinephrine concentrations using high-pressure liquid chromatography;¹⁶ 2) plasma droperidol concentration by radioimmunoassay, as recently reported;¹⁷ and 3) arterial blood gas tension with an ABL II blood gas analyzer.

TABLE 1. Pulse Interval and Systolic Arterial Pressure (SAP) at Reference Values (Mean \pm SEM)

	Control	5 Min	10 Min	15 Min
Pulse interval at reference SAP (msec)	833 \pm 70	771 \pm 50	815 \pm 58	833 \pm 80
SAP at reference pulse interval (mmHg)	138 \pm 4	150 \pm 9	138 \pm 5	135 \pm 6

Patients breathed room air enriched with nasal oxygen ($3 \text{ l} \cdot \text{min}^{-1}$) throughout the study. Baseline measurements (control) were performed 15 min after insertion of venous and arterial catheters to allow heart rate and blood pressure to return to stable resting levels. Then an intravenous bolus of droperidol, $0.2 \text{ mg} \cdot \text{kg}^{-1}$, was administered in less than 10 s, and measurements were repeated 5, 10, and 15 min after drug injection. Data are presented as mean \pm SEM. All values were compared to control using analysis of variance (ANOVA), followed by the Bonferoni method for paired comparison. Statistical significance was considered if $P < 0.05$.

Results

The baroreflex slope decreased significantly below baseline value 5, 10, and 15 min after droperidol administration (fig. 1). The maximal decrease (-47% from control) was observed at the time of the highest plasma droperidol concentration (5 min) (fig. 1). However, no significant relationship was found between plasma droperidol concentration and baroreflex slope. The pulse interval at reference pressure and systolic pressure at reference pulse interval were not significantly changed at any time of the study (table 1). Values of plasma norepinephrine and epinephrine concentrations before droperidol administration were in the range observed in our institution in normal unpremedicated patients at rest. Plasma norepinephrine concentration was significantly increased only at 5 min, while no significant change in epinephrine concentration was observed (fig. 2). Systolic arterial pressure was significantly decreased at each time of the study, while diastolic arterial pressure was unchanged (table 2). Heart rate was increased at 5 min, and then returned to control values at 10 and 15 min (table 2). Slight but significant increase in PaCO_2 and decrease in pHa were present at 15 min, while PaO_2 did not change (table 2).

Discussion

The present study allowed us to accurately determine the effects of droperidol on the sympathetic nervous system. An alteration of baroreflex control of heart rate followed droperidol iv administration. Thus, the negative feedback mechanism by which the baroreflex regulated the heart rate was decreased. Two experimental conditions which could have influenced baroreflex responses should be examined before interpretation of the results. First, baroreflex activity might be also affected by the effects of droperidol on ventilation. However, no change in PaO_2 occurred, and the increase in PaCO_2 was slight. Furthermore, Bristow *et al.* showed that PaCO_2 at 50 mmHg did not change baroreflex

slope.¹⁸ Second, the decrease of blood pressure induced by droperidol may have resulted in a depression of calculated baroreflex gain by a shift to a flat portion of the sigmoidal relationship between blood pressure and R-R interval, but blood pressure after droperidol remained in the physiologic range. No resetting of the baroreflex was present after droperidol administration, since the pulse interval at the reference pressure and blood pressure at the reference pulse interval were not significantly altered. Thus, the observed lower systolic arterial pressure following droperidol administration without a sustained change in heart rate could be explained mainly by the depression of baroreflex control of heart rate. The site of droperidol depression of the baroreflex system could be at one or at several components of the baroreflex arc, including the vagal pathway.¹⁹ In the present study, the effects of droperidol on the different levels of the baroreflex loop have not been assessed. Since a depression of baroreflex function occurs with most anesthetic agents, whatever their specific effects, it may be that the decrease of baroreflex control of heart rate would be a consequence of the action of droperidol on the central nervous system, as reported for barbiturates and halogenated anesthetics.⁶⁻⁸ Nevertheless, the extent of the changes was less than that observed previously reported with inhalation anesthetics.⁶⁻⁸ Although baroreflex control of heart rate was only investigated, it is likely that the acute regulation of circulatory homeostasis is probably depressed by droperidol, since a good correlation between each component of baroreflex responses has been reported.²⁰

The second main finding of this study is the transient and slight increase in plasma norepinephrine concentrations, while plasma epinephrine levels were unchanged. Plasma norepinephrine concentration is considered a reliable index of sympathetic activity, and its short half-life allowed examination of acute variations in adrenergic activity.²¹ By contrast, plasma epinephrine concentration reflects mainly adrenal activity. In this study, a discrepancy between plasma norepinephrine and epinephrine levels was observed. These findings suggest that the alteration of sympathetic activity by droperidol is not related to an effect on the central control of the adrenergic system, but, rather, on its pe-

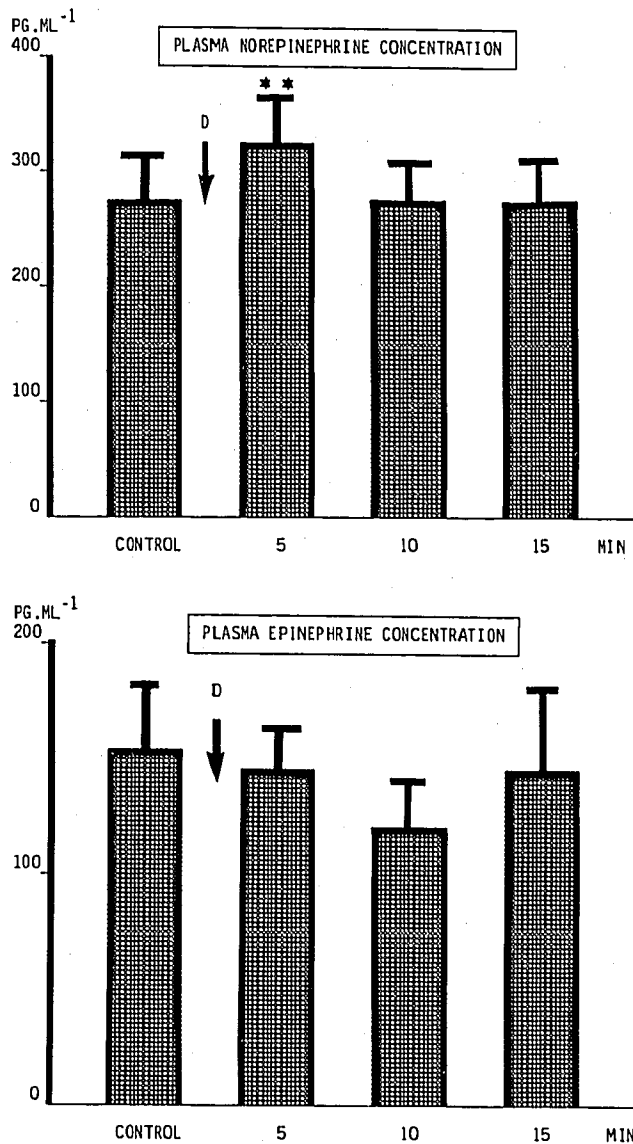


FIG. 2. Plasma norepinephrine and plasma epinephrine concentrations (mean \pm SEM) plotted against time at each period of the study (C = control period), * $P < .01$.

ripheral components. Indeed, Hyatt *et al.*¹⁴ have reported that droperidol produced a leakage of norepinephrine from presynaptic endings on an *in vitro* prepa-

TABLE 2. Hemodynamic Data and Blood Gas Tensions (Mean \pm SEM)

	Control	5 Min	10 Min	15 Min
Systolic arterial pressure (mmHg)	138 \pm 3	131 \pm 3*	131 \pm 3*	130 \pm 3*
Diastolic arterial pressure (mmHg)	73 \pm 2	71 \pm 3	68 \pm 3	70 \pm 3
Heart rate (beats \cdot min ⁻¹)	76 \pm 6	85 \pm 6*	79 \pm 4	78 \pm 4
Pa _{CO₂} (mmHg)	41.2 \pm 0.7	40.5 \pm 1.5	42 \pm 0.7	43.5 \pm 0.7*
Pa _{O₂} (mmHg)	139.5 \pm 20.2	135 \pm 16.5	123 \pm 10.5	128.2 \pm 12.7
pHa	7.39 \pm 0.01	7.39 \pm 0.01	7.38 \pm 0.01	7.37 \pm 0.01*

* $P < 0.01$ versus control.

ration using sympathetic synapses of the saphenous vein of dogs. The brief increase in plasma norepinephrine levels that we observed is likely related to this mechanism. These changes differ from those reported with other anesthetics,^{1,2} or with benzodiazepines,³ which produce a decrease of adrenergic activity during steady-state anesthesia. The transient increase in heart rate¹¹ observed in previous reports and in this study might be related to a release of norepinephrine, although the observed changes in plasma norepinephrine levels are small. Paradoxical hypertensive crises following administration of low doses of droperidol has been observed^{12,13} in some patients with pheochromocytoma. In these cases, a release of norepinephrine from much larger stores of norepinephrine than in normal subjects in the presynaptic endings²² could cause marked vasoconstriction blunting the alpha-adrenergic-blocking effects of droperidol.

In conclusion, droperidol produces an alteration of baroreflex activity and a brief increase in norepinephrine plasma levels. Consequently, the use of droperidol in patients with acute hypovolemia may be hazardous, although the action of droperidol on baroreflex function is less marked than that produced by volatile halogenated anesthetics.

The authors wish to thank Françoise Blanchet for her technical assistance with the measurements of blood gases.

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