Measurement of Anti-Arrhythmic Potency of Drugs in Man: Effects of Dehydrobenzperidol

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The anti-arrhythmic action of dehydrobenzperidol (DBP) (droperidol) was studied during cyclopropane anesthesia in nine normal female patients during elective surgical operations. Cardiac rhythm was monitored by means of electrocardiography. Ventricular arrhythmias were produced by the intravenous infusion of epinephrine at a low, constant rate. The rate just sufficient to initiate an arrhythmia was defined as the "threshold." The principal finding was that DBP in a dose of 0.2 mg./kg. doubled the arrhythmic threshold.

Among the various pharmacologic agents used in the operating room, perhaps none is more difficult to evaluate than an anti-arrhythmic drug. Species differences render animal data suspect. Indeed, much of the literature dealing with cardiac rhythm during anesthesia consists of argument concerning what findings are typical. This results largely from the use of different techniques, in various species, by different investigators. The cat, used for many years as reference animal, was ultimately found [1] not to resemble most other species in its responses to chloroform. The dog, which Meek and associates believed to resemble man physiologically, almost never develops a cardiac arrhythmia during the inhalation of cyclopropane alone; this was the genesis of the experiment on cyclopropane-epinephrine (injected) arrhythmias. An additional complexity was that the arrhythmic threshold in various animals ranged so widely that it was necessary to administer a dose of epinephrine (10 μg./kg. in 30 seconds) probably exceeding the maximal secretory capacity of an animal's own adrenal medulla [2]—in order to be certain of achieving a positive result in the preponderance of a given animal population. Understandably, this dose was excessive in many instances, and not a few animals exhibited ventricular fibrillation.[3]

The belief arose—largely from the results of giving such large doses of epinephrine to animals—that any attempt to provoke arrhythmias during anesthesia in man would be hazardous. Yet the alternative—that of trying to study "spontaneous arrhythmias"—is probably doomed to failure because of their evanescent nature.

It occurred to us that there was no *a priori* reason to fear the effect of an intravenous infusion of epinephrine which was *just adequate* to provoke an arrhythmia.[•] Using a calibrated constant-rate infusion pump and continuous observation of the ECG, we developed a method which we believed to be objective, accurate and safe for determining the "arrhythmic threshold" in any subject under specified conditions. With this information at hand the effects of drugs could be established

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• It is not commonly realized that catecholamine infusion can be of definite value during anesthesia produced by anesthetics which "sensitize" the myocardium, nor that such controlled administrations are safe in the sense of failing to produce ungovernable cardiac arrhythmias.[4] Indeed, we know of only one report in the entire literature of ventricular fibrillation following injection of a catecholamine in an anesthetized patient. This occurred during cyclopropane anesthesia after the intravenous injection of an enormous overdose of epinephrine (400 μg.), which was apparently given in error.[5]

by determining the threshold level before and following pharmacological intervention.

In the present study, this method was applied to investigate a possible anti-arrhythmic action of the usual doses of dehydrobenzperidol (DBP) (droperidol) in man, since Yelnosky and associates [6] had previously suggested such an action at much higher doses in the dog. It was found that DBP had only a weak action, but that this could easily be demonstrated by the present method.

Methods

Nine normal female patients scheduled for elective operation were studied; † they ranged in age from 29 to 51 years, weighed between 118 and 204 pounds, and were physically normal except for obesity in subjects 1 and 11. They were scheduled for minor gynecologic or dental procedures under general anesthesia.

Lead 2 of the electrocardiogram was monitored by means of an ORM 1 Cardioscope and recorded intermittently on a Sanborn Visette. Needle electrodes were used. Anesthesia was induced with cyclopropane in oxygen. The level of anesthesia was deepened and the trachea intubated with the aid of succinyldicholine (40–60 mg. intravenously). Ventilation was controlled with intermittent positive pressure breathing. One-half hour elapsed between intubation of the trachea and the first measurements. During this time a steady state of anesthesia was approached with respect both to clinical signs and the concentration of cyclopropane in end-expired gas, the latter measured by the method of Linde and Price.[7] Cyclopropane was chosen as the anesthetic because it produces a higher degree of "sensitization" to catecholamines than the other inhalational anesthetics commonly used.

Epinephrine was administered intravenously ranging in concentration from 2 to 12 mg./liter in a solution of physiological saline. The solutions were made up freshly for each study and in later studies at frequent intervals throughout the period of observation. The epinephrine-containing solutions were infused by means of a Harvard Pump which produced a constant administration rate ranging from 3.6 to 26.1 μg./minute. All doses and concentrations of epinephrine are expressed in terms of the base.

The method of determining the threshold for production of ventricular arrhythmias ‡ was as follows. An initial injection at a rate of 4 μg./minute was first tried. If this did not produce an arrhythmia within 5 minutes, the infusion was terminated and restarted at a higher rate following a pause of 5 to 10 minutes. In general, rates were increased in increments of 50 per cent until an arrhythmia was observed. In every case determination of the arrhythmic threshold was repeated at least once in order to ascertain that the value was reproducible. In about half the cases the arrhythmia threshold increased with repeated doses of epinephrine until the higher rates of administration were reached. Therefore, in 3 cases we elected to continue testing for threshold to epinephrine without the administration of DBP in order to establish whether the method was feasible or whether it would be limited by the development of tachyphylaxis as has been reported.[8] In the remaining 6 cases, after determination of the arrhythmia threshold, DBP was administered intravenously in single doses ranging from 0.15 to 0.20 mg./kg. (mean 0.18) of body weight. Fifteen to 30 minutes later the arrhythmic threshold was re-established. In later cases a new epinephrine solution was prepared to estimate the threshold following administration of the drug. In the last 2 cases ascorbic acid, 1 mg./2 μg.

† The problem of obtaining valid consent always exists in an experiment performed on human beings. Despite the fact that all of our subjects were interviewed before the study and the procedure explained, we believe that an informed consent cannot be obtained for a study of this type, because of the impossibility of transmitting to a patient both the relevant information and the *background* needed to analyze and evaluate such information. Instead, we have accepted the role of guarantor of the patient's rights and safety: (1) only physical status I is acceptable; (2) inhaled cyclopropane concentration must not range beyond 20–30 per cent; (3) respiratory acidosis must be prevented; (4) starting dose and rate of administration of epinephrine must be the minimal one, 3.6 μg./minute in these experiments; (5) the infusion is terminated when an arrhythmia appears.

‡ The end point for an arrhythmia was taken as bigeminy or trigeminy or irregular ventricular arrhythmia with the abnormal beats occurring at least once in three beats.

TABLE 1. Effect of Dehydrobenzperidol on Arrhythmic Threshold, Arterial Blood Pressure, and Cyclopropane Concentration at Threshold

(No.) Age, Weight	Dehydrobenzperidol (mg.)	Threshold μg. Epinephrine/Minute		Arterial Blood Pressure in Mm. Hg at Threshold		Cyclopropane Concentration Volumes %		Remarks
		Control	After Dehydrobenzperidol	Control	After Dehydrobenzperidol	Control	After Dehydrobenzperidol	
(1) 39, 160	10	10.8	18.4	220/120	200/130	22	24	No Premature Ventricular Contractions (P.V.C.) at 13 μg./min. after dehydrobenzperidol
(3) 36, 140	10	10.8	18.4	210/150	195/145	21	26	No P.V.C.'s at 15 μg./min. after dehydrobenzperidol.
(6) 29, 120	11	6.2	18.6	150/100	140/90	20	19	No P.V.C.'s at 12.4 μg./min. after dehydrobenzperidol.
(11) 40, 204	18	8.6	12.9	160/120	160/100	20	20	Few P.V.C.'s at 8.6 μg./min. Fresh epinephrine mixed for threshold after dehydrobenzperidol given.
(12) 36, 118	11	3.8	8.6	170/110	160/110	32	34	Ascorbic acid used to stabilize epinephrine. Few P.V.C.'s at 5.7 μg./min. Fresh epinephrine mixed for threshold, after dehydrobenzperidol.
(13) 51, 126	11	16.1	241	165/95	150/90	19	19	Occasional P.V.C. at 16.1 after droperidol. Ascorbic acid used for stabilization. New solution mixed for threshold for dehydrobenzperidol.
Means	0.18 mg./K; range 0.15–0.20	9.38	16.8	179.2/115.8	167.5/110.8	22.3	23.7	
Probability			$P<0.01$		$P<0.01$/ P Insignificant		P Insignificant	

TABLE 2. Comparison of Change in Heart Rate and Blood Pressure Caused by Equal Infusion Rates of Epinephrine Before and After Dehydrobenzperidol

Subject	Change in MABP (mm. Hg)						Change in Heart Rate (beats/min.)						Epinephrine Dose Rate (μg./min.)
	Before Dehydrobenzperidol			After Dehydrobenzperidol			Before Dehydrobenzperidol			After Dehydrobenzperidol			
	From	To	Δ	From	To	Δ	From	To	Δ	From	To	Δ	
1	152	160	+ 8	108	117	+ 9	87	100	13	70	78	+ 8	10.8
3	145	168	+23	125	158	+33	58	80	+22	58	96	+36	10.8
6	110	120	+10	92	107	+15	66	90	+24	88	75	−13	6.2
11	113	138	+25	110	128	+ 8	76	90	+14	72	76	+ 4	8.6
12	148	157	+9	120	133	+13	120	135	+15	115	120	+ 5	3.8
13	95	122	+27	82	110	+28	75	86	+11	80	85	+ 5	16.1
Means	127.2	144.2	17.0	106.2	125.5	19.3	80.3	96.8	16.5	80.5	88.0	7.5	9.4
Sig.*			None						None				

* Significance of difference owing to treatment.
MABP = mean arterial blood pressure in mm. of mercury.

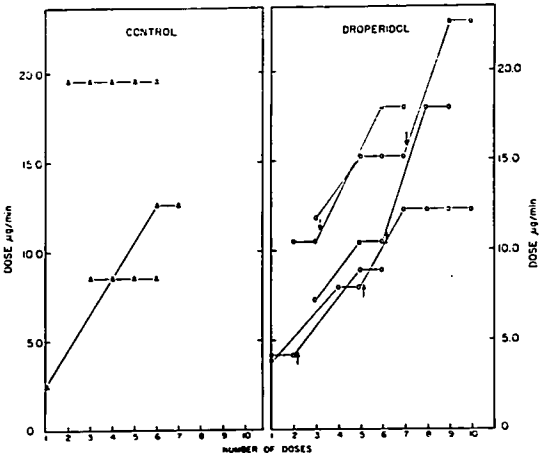

FIG. 1. Effect of repeated testing and of dehydrobenzperidol on arrhythmic threshold. *Abscissa* = total number of infusions, whether arrhythmia produced or not. Sub-threshold infusions are counted on the abscissa but not indicated on the ordinate. *Ordinate* = dose of epinephrine in μg./minute just adequate to produce a ventricular arrhythmia. Arrows indicate administration of dehydrobenzperidol.

epinephrine, was added in order to prevent any oxidation of epinephrine.

Arterial blood pressure was measured at frequent intervals by the Riva Rocci method, and cardiac rate was counted either from the electrocardiographic tracing or by palpation of the pulse.

The significance of changes was assessed by Students' *t* test.[9]

Results

The results are shown in table 1. In summary, DBP in doses averaging 0.18 mg./kg. reduced the systolic arterial pressure, the diastolic arterial pressure, and the mean arterial pressure while increasing the mean threshold for epinephrine arrhythmias from 9.4 to 16.8 μg./minute. The ventricular arrhythmias tended to occur at the same arterial pressure both in the presence and absence of DBP. The increase in arterial pressure occurring at equal rates of injection of epinephrine (shown in table 2) was not altered by the drug. The response of cardiac rate to epinephrine was likewise unaltered by DBP.

Tachyphylaxis was noted on several occasion but did not account *in toto* or even in large part for the results, as seen in figure 1, in which observations made before and after the administration of DBP are graphically shown. In general, the threshold once established tended to remain constant although in some cases the speed of onset and frequency of the abnormal beats declined with repeated doses.

Discussion

DBP is the tranquilizer, or neuroleptic component of Innovar, the neuroleptanalgesic mixture which also contains fentanyl. By itself the drug is a useful antiemetic and sedative with the disadvantage common to all butyrophenone and phenothiazine derivatives of being able to cause delayed extrapyramidal reactions. Its presence in Innovar has been used to explain the clinical impression that patients receiving Innovar appear to tolerate epinephrine injection without the development of ventricular arrhythmias better than when such general anesthetics as halothane and cyclopropane are given.

Our results demonstrate that DBP is active in the prevention of arrhythmias precipitated by infusion of epinephrine in the human heart sensitized by cyclopropane. Yelnosky and associates[6] showed that DBP had an antiarrhythmic action in dogs anesthetized with cyclopropane and infused with epinephrine, although their results indicated that chlorpromazine had a more pronounced effect. They suggested that DBP exerted predominantly an α-blocking anti-epinephrine effect. Since it is generally thought that capacity of drugs to protect hearts from induced arrhythmias correlates with β-blocking ability, the observed protection is difficult to explain. However, as Moe *et al.*[10] demonstrated, and Katz[11] has recently reaffirmed, the level of arterial blood pressure is also important. DBP did not demonstrate any β-blocking properties as evidenced by the response of heart rate during epinephrine infusion, but it did decrease the arterial blood pressure. The blood pressure at the arrhythmic threshold was similar with or without droperidol. Since the increase in mean arterial pressure caused by a standard dose of epinephrine was unaltered by DBP, the results suggest that its action was mainly due to the hypotension which it caused, and that in clinical dosage the drug has neither α or β blocking actions.

In this and previous studies[12] the variability of the threshold of ventricular arrhythmias during anesthesia was marked; in the present series it ranged from 3.8 μg. to 16.1 μg. epinephrine per minute. Arrhythmias are more likely to occur with elevated cyclopropane and carbon dioxide levels and probably also as a result of surgical stimulation. Therefore, in clinical practice the effective threshold may vary widely. The protection afforded by DBP may be insufficient to make it reliable for the prevention of arrhythmias in clinical practice, although some protective action is undoubtedly present. Our demonstration of this action under the described clinical circumstances is attributed to the precision of the method employed.

Summary

The anti-arrhythmic action of DBP was studied by a new method in 6 patients anesthetized with cyclopropane.

The drug raised the threshold infusion rate of epinephrine from a mean of 9.4 to 16.8 μg./minute. The difference was statistically significant at the 1 per cent level.

DBP appears to mediate its effects by producing arterial hypotension. No important α or β blocking properties were observed in the dosage range studied.

The experimental method described would seem safe, and useful for the quantitative study of anti-arrhythmic actions of drugs to be used during anesthesia in man.

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Anesthesia

NEUROLEPTANALGESIA In poor risk patients Innovar 1 ml./10 pounds body weight (fentanyl 0.02 mg., droperidol 1 mg. in a fixed ratio of 50 to 1) was found sufficient to induce and maintain neuroleptanalgesia for several hours. This general dosage schedule was increased or decreased according to anesthetic risk. Besides apnea or marked respiratory depression accompanied by chest wall rigidity, other complications included transient hypotension (82 of 510 cases), extrapyramidal muscular twitching (5 cases), postoperative emesis (4 cases) and six patients with high systolic and diastolic blood pressure upon completion of cardiopulmonary bypass (a distressing side effect that the abstractor has also noted). No deaths were directly connected to anesthesia. The advantages of safety, simplicity, nonexplosiveness, profound analgesia, *relative absence of cardiovascular impairment*, antiemetic and alpha-adrenergic blocking actions, and amnesia are compared to the above mentioned side effects. On considering all factors neuroleptanalgesia is particularly useful and effective in the anesthetic management of the poor risk patient. *(Corssen, G.: Neuroleptanalgesia and Anesthesia: Its Usefulness in Poor-Risk Surgical Cases, South. Med. J. 59: 801 (July) 1966.)*