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# *Cardiac Responses to Imipramine and Pancuronium during Anesthesia with Halothane or Enflurane*

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**The possibility that acute or chronic imipramine administration predisposes to development of cardiac arrhythmias from pancuronium during anesthesia with halothane or enflurane was explored. Acute administration of imipramine, 0.5, 1, 2, or 3 mg/kg, or pancuronium, 10, 40, or 80 μg/kg, caused dose-dependent tachycardia in dogs anesthetized with halothane (n = 5) or enflurane (n = 5) except for the 3 mg/kg dose of imipramine, which decreased heart rate by 11 ± 1 beats/min ($P < 0.01$). Simultaneous administration of pancuronium and imipramine caused tachycardia in an additive manner in doses of pancuronium to 80 μg/kg and imipramine to 2 mg/kg; at higher doses, the tachycardia became less than additive. Forty additional dogs were given imipramine, 8 (n = 20) or 16 mg/day (n = 20), for 15 days, and then anesthetized with either halothane or enflurane. Pancuronium did not cause cardiac arrhythmias in the dogs anesthetized with enflurane. Although pancuronium, 10 and 40 μg/kg, did not produce arrhythmias in the halothane-anesthetized dogs, the 80 μg/kg dose produced premature ventricular contractions and ventricular tachycardia, which rapidly progressed to ventricular fibrillation and cardiac arrest in two of ten dogs given imipramine, 8 mg/kg/day, and in four of ten dogs given imipramine, 16 mg/kg/day. Although only the dogs that had severe ventricular arrhythmias had significantly increased blood norepinephrine concentrations, the norepinephrine concentrations increased before the appearance of ventricular arrhythmias. The authors conclude that severe ventricular arrhythmias may occur as a result of administration of pancuronium in dogs anesthetized with halothane and receiving imipramine chronically. These results suggest that pancuronium should be given with caution to a patient receiving chronic tricyclic antidepressant therapy who is anesthetized with halothane. (Key words: Anesthetics, volatile: enflurane; halothane. Heart: arrhythmia, tachycardia. Interactions, drug: tricyclic antidepressants. Neuromuscular relaxants: pancuronium. Sympathetic nervous system: catecholamines, norepinephrine.)**

We recently observed two cases in which marked tachyarrhythmias followed pancuronium administration in patients anesthetized with halothane. Both patients had been taking the tricyclic antidepressant drug, imipramine, for prolonged periods, and neither had known cardiovascular disease. Both therapeutic doses[1–3] and overdoses[4–6] of imipramine have caused tachycardia, T-wave or S-T segment changes, prolongation of the Q-T interval, conduction disturbances, ventricular and supraventricular arrhythmias, and cardiac arrest. Pancuronium also causes tachycardia by a vagolytic[7,8] or sympathomimetic effect.[9,10] We explored the possibility that acute or chronic imipramine administration may predispose to the development of arrhythmias from pancuronium during anesthesia. We also investigated the importance of the background anesthetic (*i.e.*, enflurane versus halothane) on the development of arrhythmias.

## Methods

The effects of acute imipramine administration were studied in ten dogs, each weighing 17–35 kg, divided randomly into two groups. Five dogs were anesthetized with halothane and five with enflurane, each on two different occasions. After intubation of the trachea, ventilation was controlled to maintain $Pa_{CO_2}$ at 35 ± 3 torr. End-tidal halothane or enflurane concentration was measured by infrared analysis. The electrocardiogram was continuously recorded. A catheter was inserted into a femoral artery, from which pulse and blood pressure were recorded.

During the first anesthetic administration, heart rate responses to various doses of pancuronium and imipramine were determined as follows. After measurement of the minimum alveolar concentration (MAC)[11] of halothane or enflurane, the alveolar concentrations were maintained at 1.3 per cent halothane or 3.5 per cent enflurane. Thirty minutes later a single bolus of pancuronium, 10, 40, or 80 μg/kg, iv, was given. When heart rate had returned to normal, and not within 60 min of the previous injection of pancuronium, a different dose of pancuronium was given. Two hours after the last dose of pancuronium, imipramine, 0.5, 1, 2, or 3 mg/kg, was administered. The dose order of imipramine and pancuronium was randomized. Ninety minutes after each injection a subsequent dose of imipramine was given, until all four doses were injected. Thirty minutes after completion of the imipramine injections, MAC was redetermined. At least seven days later the dogs were reanesthetized with the same anesthetic to determine whether the cardiac responses to imipramine and pancuronium were additive. The following

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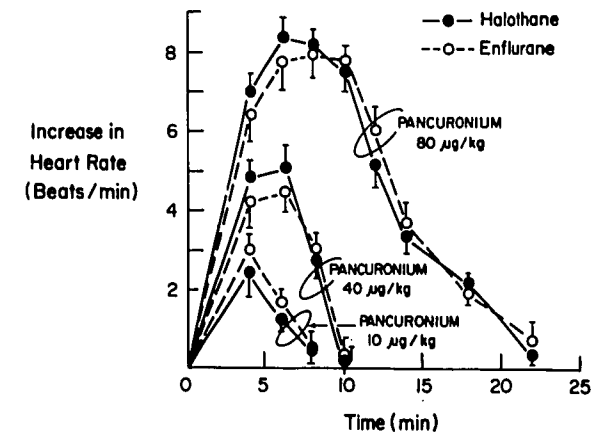


FIG. 1. The effect of pancuronium on heart rate during halothane or enflurane anesthesia. The dots and brackets represent means ± 1 SE.

combinations of doses were given:

Imipramine, 0.5 mg/kg, and pancuronium, 40 μg/kg
Imipramine, 1 mg/kg, and pancuronium, 80 μg/kg
Imipramine, 2 mg/kg, and pancuronium, 80 μg/kg

The effects of chronic imipramine administration were studied in 40 dogs, half of which were given imipramine, 8 mg/kg/day, and the other half, 16 mg/kg/day, iv, for 15 days. Half the dogs from each group, randomly selected, were anesthetized with halothane, and the remainder with enflurane, using the technique described for the acute studies. MAC was determined and the response of the heart rate to pancuronium established as described previously. End-tidal halothane was maintained at 1.3 per cent, and end-tidal enflurane at 3.5 per cent. At the beginning of each study, venous blood was obtained for analysis of imipramine.[12] In addition, blood samples were obtained before and 5 and 15 min after the largest dose of pancuronium was given for determination of norepinephrine concentration.[13]

Statistical analysis was by analysis of variance.

## Results

Heart rates before administration of pancuronium were 91 ± 3 and 87 ± 2 beats/min during halothane and enflurane anesthesia, respectively. Systolic blood pressures before pancuronium were 90 ± 2 and 89 ± 2 torr during halothane and enflurane anesthesia, respectively. Pancuronium increased heart rate in a dose-dependent manner during both halothane and enflurane anesthesia (fig. 1). The time needed for heart rate to return to baseline values after injection of pancuronium also increased with increasing pancuronium dose. Heart rate increases after pancuronium during halothane were not significantly different from those increases during enflurane anesthesia (fig. 1). Cardiac arrhythmias other than sinus tachycardia did not occur.

Heart rates before administration of imipramine were 93 ± 3 and 88 ± 3 beats/min during halothane and enflurane anesthesia, respectively. Systolic blood pressures were 92 ± 2 and 91 ± 2 torr during halothane and enflurane anesthesia, respectively. Acute imipramine administration caused a dose-dependent increase in heart rate, with all but the largest dose, during both halothane and enflurane anesthesia (fig. 2). The largest dose given, 3 mg/kg, caused a decrease in heart rate ($P < 0.01$). Cardiac arrhythmias other than sinus tachycardia or bradycardia did not occur.

Two of the three dose combinations of pancuronium and imipramine increased heart rate in an additive manner (fig. 3). The largest dose combination (pancuronium, 80 μg/kg, and imipramine, 2 mg/kg) increased

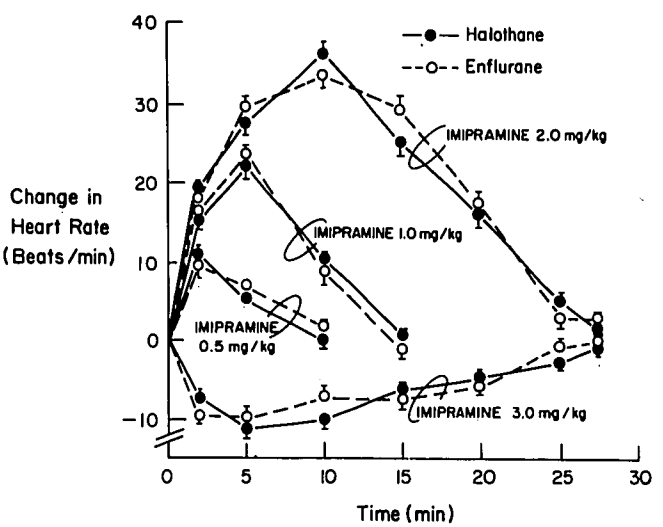


FIG. 2. The effect of acute administration of imipramine on heart rate during halothane or enflurane anesthesia. The dots and brackets represent the mean ± 1 SE.

heart rate in a less-than-additive fashion; that is, the increase in heart rate was less than the sum of the increases resulting from the same doses of the two drugs administered separately. Results were similar regardless of whether halothane or enflurane was used.

Halothane and enflurane MAC values (0.86 ± 0.3 per cent and 2.34 ± 0.4 per cent, respectively, prior to administration of imipramine or pancuronium) were unchanged by any acute drug administration. Halothane and enflurane MAC values after pancuronium were 0.88 ± 0.3 and 2.3 ± 0.3 per cent; after imipramine and pancuronium given together, they were 0.87 ± 0.2 and 2.3 ± 0.3 per cent, respectively.

Heart rates were 96 ± 3, 108 ± 2, and 121 ± 3 beats/min, and systemic blood pressures 91 ± 2, 82 ± 2, and 76 ± 2 torr in dogs anesthetized with halothane alone and with halothane with imipramine, 8 and 16 mg/kg/day, respectively. Heart rates were 89 ± 2, 102 ± 3, and 125 ± 3 beats/min, and systemic blood pressures 87 ± 2, 80 ± 2, and 65 ± 2 torr in dogs anesthetized with enflurane alone and with enflurane with imipramine, 8 and 16 mg/kg/day, respectively. There was no significant difference between the cardiovascular effects of enflurane and halothane. Chronic imipramine administration altered the heart rate response to only pancuronium, 80 μg/kg, during halothane. The response was altered differently for halothane and enflurane. Heart rate increased less than 12 beats/min with pancuronium, 10 or 40 μg/kg (fig. 4). At 80 μg/kg an insignificant change in heart rate occurred when enflurane was the anesthetic and a large increase occurred when halothane was the anesthetic ($P < 0.01$) (fig. 4).

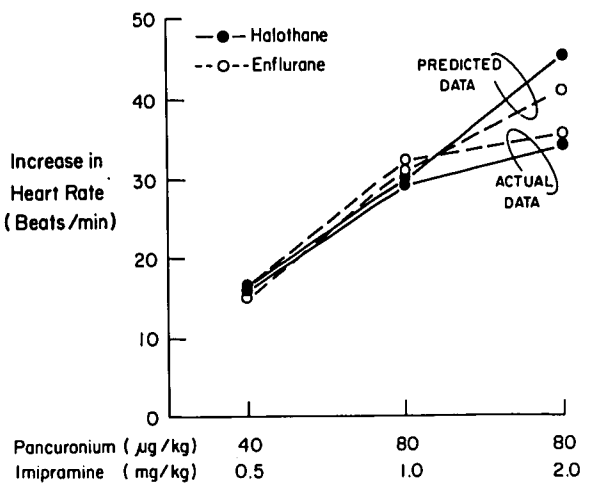


FIG. 3. Correlation between simultaneous acute administration of pancuronium and imipramine and peak change in heart rate during halothane or enflurane anesthesia. Actual data are correlated with the sum of the effects of pancuronium and imipramine given alone (predicted data). If actual data were the same as the predicted data, then the interaction between pancuronium and imipramine would be defined as additive.

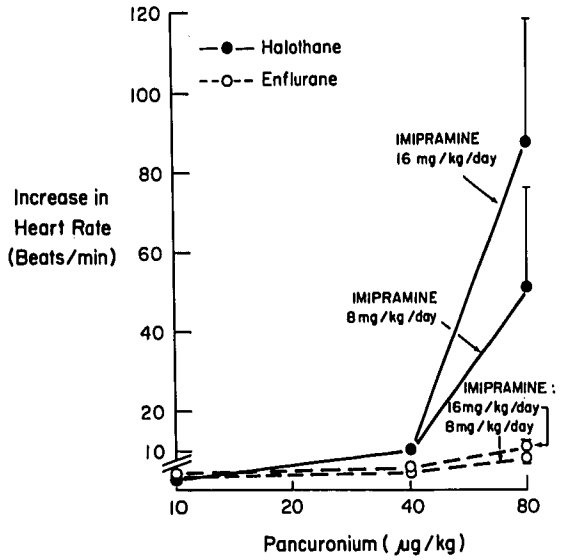


FIG. 4. Correlation between pancuronium and maximum increase in heart rate during halothane or enflurane anesthesia. Dogs were pretreated with imipramine, 8 or 16 mg/kg/day, for 15 days.

Excluding sinus tachycardia, pancuronium, 10 or 40 μg/kg, did not produce cardiac arrhythmias in dogs anesthetized with enflurane or halothane. During halothane anesthesia, two of ten dogs treated with imipramine, 8 mg/kg/day, and four of ten treated with imipramine, 16 mg/kg/day, experienced premature ventricular contractions and ventricular tachycardia (heart rates of more than 170 beats/min) 6–8 min after receiving pancuronium, 80 μg/kg. Ventricular fibrillation and cardiac arrest then developed in these dogs. The remaining eight dogs receiving imipramine, 8 mg/kg/day, and six dogs given 16 mg/kg/day had increases in heart rate of less than 40 beats/min after administration of pancuronium, 80 μg/kg, which accounts for the large standard errors in the values found for these dogs (fig. 4). Ventricular arrhythmias did not appear in the enflurane-anesthetized dogs.

After imipramine, 8 mg/kg/day, blood norepinephrine level was 370 ± 18 $10^{-9}$ g/ml, and after 16 mg/kg/day, the level was 379 ± 20 $10^{-9}$ g/ml, in those dogs anesthetized with halothane. Significant increases in blood norepinephrine concentrations after pancuronium only appeared in those dogs which subsequently experienced severe ventricular arrhythmias and died. In these dogs, blood norepinephrine concentrations increased prior to development of severe ventricular arrhythmias ($P < 0.01$) (fig. 5). Blood norepinephrine levels did not increase significantly as a result of administration of pancuronium during enflurane

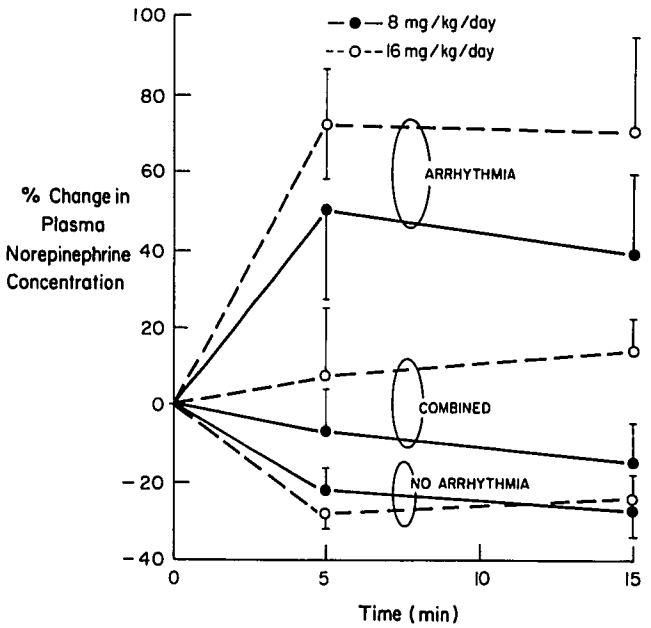


FIG. 5. The effect of pancuronium on blood norepinephrine concentrations in dogs anesthetized with halothane. The dogs were pretreated with either 8 or 16 mg/kg/day for 15 days. Dogs with increased norepinephrine concentrations also experienced ventricular arrhythmias and cardiac arrest.

anesthesia. Blood norepinephrine levels were 395 ± 12 $10^{-9}$ g/ml following imipramine, 8 mg/kg/day, and 425 ± 26 $10^{-9}$ g/ml after 16 mg/kg/day.

Chronic administration of imipramine, 8 mg/kg/day, produced blood imipramine concentrations ranging from 0.25 to 0.43 μg/ml; the 16-mg/kg/day dose produced blood levels ranging from 0.51 to 0.72 μg/ml. Chronic imipramine administration caused small, but significant, decreases in MAC ($P < 0.05$). In dogs anesthetized with halothane, MACs were 0.86 ± 0.3, 0.70 ± 0.2, and 0.71 ± 0.1 per cent with halothane alone and in combination with imipramine, 8 and 16 mg/kg/day, respectively. In dogs anesthetized with enflurane, MACs were 2.34 ± 0.4, 1.86 ± 0.3, and 1.80 ± 0.2 per cent with enflurane alone and in combination with imipramine, 8 and 16 mg/kg/day, respectively.

## Discussion

Tachycardia and other cardiac arrhythmias seen in patients receiving tricyclic antidepressant therapy[14] have been attributed to blockade of norepinephrine reuptake and the resultant high concentrations of norepinephrine in cardiac tissue.[14–16] Larger doses of imipramine may cause hypotension and bradycardia due to direct myocardial depression.[4–7] Tachycardia following pancuronium administration has been attributed primarily to a vagolytic effect.[7,8] However, recently, pancuronium has been shown to have a positive inotropic effect on the myocardium,[17] which was attributed to inhibition of norepinephrine uptake by adrenergic nerve endings.[9,10] Since both chronic tricyclic antidepressant administration and pancuronium block norepinephrine uptake by adrenergic nerve endings, it is not surprising that cardiac arrhythmias are more likely when the two drugs are added to each other.

Our finding of increased blood levels of norepinephrine in dogs experiencing severe cardiac arrhythmias supports the possibility that inhibition of norepinephrine uptake is the mechanism for these arrhythmias. We cannot explain why arrhythmias did not occur and blood norepinephrine levels did not increase in the remaining dogs anesthetized with halothane. The increased blood norepinephrine concentrations were not a result of cardiac arrest because the increases occurred before premature ventricular contractions and ventricular fibrillation occurred. These findings do not rule out the possibility that the vagolytic effect of imipramine also may explain in part our results.

Arrhythmias are more likely to occur during halothane anesthesia. Halothane predisposes the myocardium to arrhythmias following epinephrine[18,19] or atropine[20] administration. Johnston *et al.*[19] found the $ED_{50}$ of epinephrine (dose that causes three or more premature ventricular contractions following epinephrine) to be 2.1 μg/kg during halothane anesthesia and 10.9 μg/kg during enflurane anesthesia. Occasionally ventricular extrasystoles or atrioventricular dissociation occur following pancuronium administration in patients anesthetized with halothane.[21] These observations support our suspicion that the tachycardia observed in the two clinical cases resulted from an interaction between halothane, pancuronium and chronic imipramine therapy. These results and our finding of no cardiac arrhythmia (except sinus tachycardia) during enflurane anesthesia suggest that halothane in combination with chronic imipramine therapy and pancuronium increases the likelihood of cardiac arrhythmias.

That the therapeutic effect of imipramine is not realized until the drug has been given for two weeks[14,22] agrees with our finding of dangerous cardiac arrhythmias seen only in chronically treated dogs. Acute administration of pancuronium and imipramine increased heart rate in either an additive or a less-than-additive manner. To determine whether this interaction is really less than additive is difficult because of the biphasic response to imipramine alone. We can conclude, however, that imipramine acutely administered probably does not increase the tendency for dangerous

arrhythmias to occur following pancuronium, as does chronic imipramine therapy.

Imipramine blocks the reuptake of both norepinephrine and serotonin centrally.[14-16] It is possible that decreases in central catecholamines could account for the small decrease in MAC seen in this study. Other drugs that decrease catecholamine levels centrally also decrease MAC.[23]

Although the arrhythmias that occurred in dogs subjected to chronic imipramine therapy were more severe, they were similar to those observed in the two patients. This is consonant with the fact that the doses of imipramine administered to the dogs produced blood concentrations well within the therapeutic range observed in man.[24,25] On the basis of these clinical cases and this study, we believe pancuronium should be given with caution to patients receiving imipramine therapy who are anesthetized with halothane. Although we studied only imipramine, this conclusion may apply to other tricyclic antidepressants. Like pancuronium, gallamine has a vagolytic and sympathomimetic effect,[26,27] and therefore probably should also be avoided. Although this possibility was not studied, we predict that *d*-tubocurarine would be an acceptable alternative, since it lacks a vagolytic or sympathetic stimulating effect.[28] Last, although the number of dogs studied was small, our results showed no contraindication to giving pancuronium to a patient who is receiving tricyclic antidepressant therapy and is anesthetized with enflurane.

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