Modification by Halogenated Anaesthetics of Chronotropic Response During Reversal of Neuromuscular Blockade

Satwant K. Samra MD, Uma A. Pandit MD, Sujit K. Pandit MD, Sarla P. Kothary MD

The effect of halothane and enflurane on changes in heart rate during reversal of neuromuscular block was compared in 48 adult patients. Premedication and anaesthetic technique were standardized. Either halothane or enflurane was the primary anaesthetic while pancuronium was used in all patients to achieve muscle relaxation. Ventilation was mechanically controlled and PaCO₂ was between 30–40 mmHg. The neuromuscular block was reversed by an intravenous injection of atropine 1.2 mg and neostigmine 2.5 mg, given either separately or simultaneously, in different patient subgroups. Heart rate changes were significantly different between the halothane and enflurane groups. In general, reversal of neuromuscular block was accompanied by less fluctuations in heart rate after enflurane as compared to halothane anaesthesia. Simultaneous injection of atropine and neostigmine modified the tachycardiac response in the halothane sub-group only. Our observations suggest that use of enflurane offers an advantage over halothane in those patients in whom rapid fluctuations in heart rate during reversal of neuromuscular block may be dangerous.

Key Words

ANTAGONISTS, NEUROMUSCULAR RELAXANTS: neostigmine; HEART: pulse rate; ANAESTHETICS, VOLATILE: halothane, enflurane.

From the Department of Anesthesiology, University of Michigan Medical Center, Ann Arbor.

Address correspondence to: Satwant K. Samra MD, Department of Anesthesiology, Box 43, University of Michigan Medical Center, Ann Arbor, MI 48109.

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Since the early reports of deaths associated with administration of anticholinergic and anticholinesterase drugs,^{1,2} methods of administration of these agents have been the subject of much clinical interest and investigation. Several studies^{3–5} in recent years have attempted to compare the changes in heart rate and rhythm following injection of anticholinergic and anticholinesterase drugs given either simultaneously or separately. All studies, however, have totally ignored any influence that volatile anaesthetic agents used might have had on these changes. In children, modification of the chronotropic response to anticholinergic drugs by halothane has recently been reported.⁶ It is conceivable that the various inhalation anaesthetics used during surgery could have different modifying effects on the changes in heart rate and rhythm which occur during reversal of neuromuscular blockade. We designed this clinical investigation to compare the influence of the two commonly used volatile anaesthetics on changes in heart rate and rhythm during reversal of neuromuscular blockade.

Methods

The protocol for this study was approved by the Committee to Review Grants for Clinical Research and Investigations Involving Human Beings at our institution. Forty eight adult patients (ASA Class I or II) between 20 to 69 years of age undergoing elective surgery requiring the use of non-depolarizing muscle relaxants were studied. All patients were premedicated with diazepam 10 mg given orally approximately one hour prior to induction of anaesthesia. After induction with thiopental, anaesthesia was maintained either with halothane (Group H,

FIGURE 1 Heart rate in beats/minute (mean $\pm$ S.E.M.) during study period. HA = Atropine preceded neostigmine after halothane anaesthesia. HAN = Atropine and neostigmine given simultaneously after halothane anaesthesia. EA = Atropine preceded neostigmine after enflurane anaesthesia. EAN = Atropine and neostigmine given simultaneously after enflurane anaesthesia.

$n = 24$) or enflurane (Group E, $n = 24$) in a mixture of nitrous oxide 60 per cent and oxygen 40 per cent. Ventilation was controlled. Pancuronium was used to provide muscle relaxation. Duration of anaesthesia varied between one to five hours. Each group of patients was divided into 2 sub-groups of 12 each depending upon the mode of reversal of the neuromuscular block. Twelve patients in each group were given atropine 1.2 mg followed five minutes later by neostigmine 2.5 mg (sub-groups HA and EA). In the remaining 24 patients a mixture of atropine 1.2 mg and neostigmine 2.5 mg given as a rapid intravenous injection was used for reversal of the neuromuscular block (sub-groups HAN and EAN). Continuous EKG recording was obtained during the reversal and blood pressure was recorded once every minute for ten minutes after initial injection of atropine or the atropine-neostigmine mixture. Administration of halogenated anaesthetic was continued during the reversal process and other

non-surgical stimulation, such as suction of oropharyngeal secretions was avoided during the period when changes in heart rate and blood pressure were being recorded. Mechanical ventilation was maintained until the end of the study to maintain PaCO_2 between 30–40 torr (confirmed by arterial blood gas analysis). EKG strips were studied for changes in heart rate and rhythm during the reversal process. In each patient the heart rate prior to injection of medications is referred to as the baseline heart rate, while the maximum increase from this rate during the study period is referred to as peak tachycardia. The difference between the peak tachycardia and the minimum heart rate recorded after neostigmine is labelled peak bradycardia.

Baseline heart rates and maximum changes in heart rates (peak tachycardia and peak bradycardia) from each sub-group were compared with all other sub-groups using one-way analysis of variance to determine statistical significance.

Results

Table 1 shows the baseline heart rate (mean $\pm$ SEM beats/minute) and the maximum increase and decrease during the reversal of neuromuscular blockade in the 48 patients studied. The actual changes in the heart rates are presented in Figure 1. Mean baseline heart rate varied between 75 to 87 beats/min. Differences between the groups were not statistically significant.

Peak Tachycardia

The maximum increase in heart rate was seen two minutes after injection of atropine in all patients, both when injection of atropine preceded neostigmine and when the two drugs were given simultaneously.

The patients who received halothane developed marked tachycardia soon after the injection of atropine (sub-group HA). The rise in pulse rate after atropine in patients receiving enflurane (sub-group EA) was much less marked and the difference in the peak tachycardia between these two groups (HA vs EA) was statistically significant ($p < 0.001$).

When atropine was injected in a mixture with neostigmine, the initial tachycardia was significantly different only between the two halothane sub-groups (HA vs HAN). There was no statistical

TABLE I Changes in Heart Rate During Reversal of Neuromuscular Block (mean $\pm$ S.E.M.)
Beats/Minute

Sub-group	N	Baseline Heart Rate	Changes in Heart Rate	
			Peak Tachycardia	Peak Bradycardia
HA	12	76 $\pm$ 2.5	33 $\pm$ 3.7	50 $\pm$ 14.5
EA	12	78 $\pm$ 3.5	14 $\pm$ 3.2	26 $\pm$ 7.5
HAN	12	75 $\pm$ 3.8	19 $\pm$ 3.6	36 $\pm$ 10.4
EAN	12	87 $\pm$ 3.7	12 $\pm$ 2.0	22 $\pm$ 6.4

Statistical Analysis: No significant difference in baseline heart rates.

Peak Tachycardia:

HA vs EA - $p < 0.001$
HAN vs EAN - $p = 0.46$
HA vs HAN - $p < 0.01$
EA vs EAN - $p = 0.23$

Peak Bradycardia:

HA vs EA - $p < 0.001$
HAN vs EAN - $p < 0.002$
HA vs HAN - $p < 0.001$
EA vs EAN - $p = 0.35$

difference in the peak heart rates between the enflurane sub-groups (EA vs EAN).

Thus, when the patients were receiving enflurane the initial tachycardia was modest and it did not make any difference whether atropine was given separately or mixed with neostigmine. The difference was significant when halothane was the volatile anaesthetic.

Peak Bradycardia

As expected the heart rates dropped after neostigmine, given either separately or combined with atropine. However, the fall in the heart rate (peak bradycardia) was especially marked in patients who received halothane as the primary anaesthetic (groups HA and HAN). Statistically significant difference was observed between the groups who received halothane compared to those given enflurane, irrespective of the mode of administration of neostigmine (sub-group HA vs EA and HAN vs EAN). Statistical significance was also observed between the two halothane sub-groups (HA vs HAN). However, there was no statistically significant difference between the two enflurane sub-groups (EA vs EAN). Thus, when the patients received enflurane rather than halothane, the drop in the heart rate was not significant irrespective of the mode of administration of neostigmine (separately or combined with atropine).

Final heart rate at the end of the study was less than 60 beats/min in ten patients (out of 48) and their distribution in sub-groups was HA = 6, HAN = 3 and EA = 1. In none of the patients was heart rate less than 50.

Cardiac Rhythm

Cardiac dysrhythmias were very rare in all the groups. In no case did the dysrhythmia produce significant haemodynamic effects.

Discussion

The purpose of this investigation was to compare the changes in cardiac rate and rhythm during reversal of neuromuscular blockade in patients anaesthetized with either halothane or enflurane. Significant differences between halothane and enflurane were noted in both initial tachycardia and final bradycardia, irrespective of whether atropine and neostigmine were administered separately or together. Significantly, more fluctuations in heart rates (tachycardia and bradycardia) were observed in patients who received halothane rather than enflurane.

Volatile anaesthetics are known to modify chronotropic effects of anticholinergic agents. Samra and Cohen⁶ recently found that children who received halothane anaesthesia developed more tachycardia after intravenous injection of either atropine or glycopyrrolate compared to children who were anaesthetized with enflurane. Munchow and Denson⁷ have reported that patients anaesthetized with either halothane or cyclopropane showed increased sensitivity of the heart to the positive chronotropic effects of atropine as compared to adult awake volunteers. In the present study we confirmed that the increased sensitivity during halothane anaesthesia is not only true for positive chronotropic effects of atropine but also for the negative chronotropic effects of neostigmine. En-

flurane does not seem to increase the sensitization in either direction and appears to produce a relatively stable heart rate during the use of atropine and neostigmine.

The mechanism of these effects is not known; however, some volatile anaesthetics are known to affect cardiac rate by themselves. Krishna and Paradise⁸ compared the chronotropic effects of volatile anaesthetics in isolated rat atrial preparations. They showed that anaesthetic ethers elicited dose dependent positive chronotropic effects while halothane had a slight negative chronotropic effect and that the mechanism of this anaesthetic effect did not seem to involve stimulation of beta-adrenergic or cholinergic receptors. In an earlier study comparing the inotropic and chronotropic effects of halothane in normal and chronically denervated dogs, Morrow and co-workers⁹ concluded that the negative chronotropic effect of halothane in the dog is a direct cardiac effect and not of vagal origin. To what extent this information gained in animal studies is applicable to intact human beings in the present clinical setting is uncertain. In clinical studies, halothane and enflurane are shown to have different effects on cardiac rate and rhythm.^{10,11} Difference in response to exogenous catecholamines given during halothane and enflurane anaesthesia are well documented.¹² Therefore it is not surprising to find a difference in the chronotropic response during reversal of neuromuscular drugs in patients anaesthetized with halothane and enflurane. The mechanism of this difference probably represents a complex interaction of anaesthetics, anticholinergics and anticholinesterases both acting directly and mediated via autonomic nervous system.

In a previous study, Rosner and co-workers⁵ reported that simultaneous administration of neostigmine reduced the degree of tachycardia that followed administration of atropine during reversal of non-depolarizing muscle relaxants. However, they did not standardize the anaesthetic technique used in different groups. In our study it was noticed that this mode of administration of atropine and neostigmine made a difference only when patients were anaesthetized with halothane and not enflurane. In patients who received enflurane as the primary anaesthetic, there was no difference in heart rates between sub-groups EA vs EAN, while in halothane sub-groups the initial tachycardiac

response could be restricted to a great extent by administering atropine and neostigmine simultaneously (HA vs HAN).

The negative chronotropic effect of neostigmine seems to be exaggerated in the presence of halothane, but not in the presence of enflurane. We emphasize that we have been referring to *fluctuations* in heart rates (baseline vs peak tachycardia and peak tachycardia vs peak bradycardia) and not the difference between initial (baseline) versus the final heart rates. Comparison of the later two values does not show statistical significance. However, great fluctuations in the heart rate during reversal may have deleterious effects in some patients.

In conclusion, volatile anaesthetics have a significant effect on the alterations in heart rate during reversal of neuromuscular blockade. When injection of atropine precedes neostigmine, patients receiving halothane anaesthesia develop significantly greater tachycardia than those receiving enflurane. Bradycardia following use of neostigmine is also more marked after halothane anaesthesia. The initial tachycardia can be minimized by administering atropine in a mixture rather than before neostigmine. Patients receiving enflurane as the primary anaesthetic have more stable heart rates, irrespective of the mode of administration of atropine and neostigmine. Thus, we recommend that halothane should probably be avoided in cases where great fluctuations in the heart rate during the reversal of the neuromuscular block may be critical to the patient's myocardial oxygen supply and demand ratio.

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Résumé

Les effets de l'halotane et de l'enflurane sur la fréquence cardiaque pendant l'inversion du bloc neuromusculaire ont été comparés chez 48 patients adultes. La prémédication et la technique anesthésique ont été normalisées. L'halotane ou l'enflurane sont administrés en premier, tandis que le pancuronium a été administré chez tous les patients comme mesure de relaxation. La ventilation a été contrôlée mécaniquement et le PaCO₂ était entre 30 et 40 mmHg. Le bloc neuromusculaire a été inversé par une injection intraveineuse d'atropine 1.2 mg et de néostigmine 2.5 mg, administrés soit séparément, soit en même temps chez différents sous-groupes de patients. On observa une différence de fréquence cardiaque significative entre les patients recevant l'halotane et l'enflurane. En général, l'inversion du bloc neuromusculaire est accompagné de moins de fluctuations de la fréquence cardiaque après injection d'enflurane comparé à l'anesthésie avec l'halotane. Des injections simultanées d'atropine et de néostigmine ont modifié la réponse en tachycardie chez les sous-groupes seulement. Nos observations suggèrent que l'usage de l'enflurane offre plus d'avantages que l'halothane chez les patients chez qui la fréquence cardiaque rapide pendant l'inversion neuromusculaire peut devenir dangereuse.