Cardiovascular effects of nondepolarizing relaxants employed for pretreatment prior to succinylcholine

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A pregnant woman with severe pre-eclampsia experienced a hypertensive crisis following a pretreatment dose (20 mg) of gallamine. That episode initiated a study to determine the cardiovascular effects of non-depolarizing muscle relaxants in 58 nonobese, ASA physical status I and II adults. Subjects were assigned randomly to one of five treatment groups as follows: gallamine (0.29 mg·kg⁻¹), d-tubocurarine (0.04 mg·kg⁻¹), metocurine (0.014 mg·kg⁻¹), pancuronium (0.007 mg·kg⁻¹), or normal saline (control). Baseline measurements of systolic, diastolic, mean arterial pressure, heart rate (HR) and rate pressure product (calculated RPP) were recorded at one-minute intervals while electrocardiogram, lead II, was recorded continuously. Statistically significant increases occurred in HR at minutes 2, 3 and 4; RPP at minutes 3 and 4; and per cent change in HR at minutes 2, 3 and 4 following gallamine pretreatment. The rise in RPP was predominately due to the elevation in HR. These results suggest that even modest doses of gallamine should be avoided in clinical situations where lability of cardiovascular dynamics can be anticipated.

Key words

NEUROMUSCULAR BLOCKING DRUGS: d-tubocurarine, gallamine, metocurine, pancuronium, succinylcholine.

Subparalyzing, pretreatment doses of nondepolarizing muscle relaxants are widely employed in the induction period to limit the adverse effects of succinylcholine. These modest doses of nondepolarizing muscle relaxants can limit changes in intragastric^{1,2} and intraocular pressures,³ serum potassium,⁴ creatine kinase,⁵ the incidence of postoperative myalgias,⁶ and the bradycardia associated with a repeat dose of succinylcholine.^{7,8} Although controversial and recently challenged,⁹ "pretreatment" has become an accepted part of the rapid induction-intubation sequence for general anaesthesia, particularly for the patient with a full stomach.¹⁰

Case Summary

A 38-year-old primagravida at 30 weeks' gestation required emergency Cesarean section for severe pre-eclampsia complicated by progressive reduction in platelet count. There was no history of previous anaesthetics, major illnesses, or adverse reactions to medications. The patient had been taking alpha-methyl dopa and hydrochlorothiazide for blood pressure control. Physical examination revealed: weight, 66 kg; blood pressure, 220/110 torr; pulse, 84 beats/minute; temperature, 37.0°C orally; respiration, 16 per minute. The upper airway and the cardiopulmonary system were judged normal. Pitting edema (2+/4+) of the lower extremities and sustained ankle clonus were demonstrated. Laboratory results were: haemoglobin 15.6 gm/dl, serum potassium 4.1 mEq/L, blood urea nitrogen 28 mg/dl, serum creatinine 1.3 mg/dl, and a normal coagulation profile with the single exception of a

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platelet count of $17,000/\text{mm}^3$. No urine was obtainable for analysis.

The patient was placed in a quiet room with subdued lighting. Using local anaesthesia, a peripheral intravenous cannula was inserted, a loading dose of magnesium sulfate (4 Gm) administered and a continuous infusion initiated. Using local anaesthesia, a teflon 20 gauge $1\frac{1}{2}$ " cannula was inserted into the left radial artery at the wrist and attached to a pressure transducer. Using the same technique, a central venous cannula was inserted via the left antecubital vein. Initial readings were a blood pressure of 220/110 torr and central venous pressure (CVP) of -5 torr. Rapid hydration was begun until the CVP approached normal levels. The patient was taken to the operating room where her blood pressure was controlled (160/80 torr) with sodium nitroprusside ($1\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$). Subsequently anaesthetic induction was begun. After the patient received oxygen by mask for five minutes, gallamine (20 mg) was given into the peripheral intravenous infusion. The pulse rate immediately increased from 90 to 130 and the blood pressure increased from 160/95 to 230/115. This hypertensive response was unchanged by increasing the nitroprusside infusion to approximately $4\text{ }\mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Anaesthetic induction proceeded with sodium thiopentone (200 mg) while skeletal muscle relaxation was accomplished with succinylcholine (100 mg). When the larynx was lost following thiopental, cricoid pressure was applied and the larynx was intubated with a cuffed endotracheal tube. Following induction and intubation, the blood pressure decreased to 200/90. Six minutes after induction of anaesthesia a viable infant was delivered, the placenta manually removed, and the nitroprusside infusion discontinued. The BP slowly decreased to 100/60. The remainder of the case was uneventful. The mother and child were followed for 48 hours and no sequelae were observed.

Comment

The cardiovascular and autonomic side effects of paralyzing doses of nondepolarizing neuromuscular blockers have been extensively examined. For example, in anaesthetized patients, paralyzing doses of gallamine result in increases in heart rate and cardiac output secondary to the muscarinic blocking, chronotropic actions of the drug.¹¹ The cardiovascular effects of these drugs in pretreat-

ment doses have been presumed to be innocuous. However, their effects have not been examined within a controlled experimental (control group, randomization, double blinded) design. The importance of considering the cardiovascular effects of these small doses was the subject of a recent editorial.¹² To evaluate this question we performed a prospective, randomized, blinded clinical trial.

Methods

Following protocol approval by the institutional Human Subjects Committee, verbal and written consent was obtained from 58 subjects on the evening prior to operation. ASA physical status I and II patients scheduled for elective surgical procedures under general anaesthesia were chosen for study. Subjects excluded from the clinical trial were those who were obese (body mass index $> 30\text{ kg/m}^2$),¹³ allergic to iodine or bromide, or receiving adrenergic blocking drugs. All patients were fasted after midnight and no patient received overnight intravenous hydration. Both preoperative medications and preoxygenation were withheld. Patients were assigned, using a table of random numbers, to one of five pretreatment groups as follows: gallamine ($0.29\text{ mg}\cdot\text{kg}^{-1}$), d-tubocurarine ($0.04\text{ mg}\cdot\text{kg}^{-1}$), metocurine ($0.014\text{ mg}\cdot\text{kg}^{-1}$), pancuronium ($0.007\text{ mg}\cdot\text{kg}^{-1}$), or normal saline (control). The total volume of the pretreatment agent was adjusted to one ml prior to injection.

Upon arrival in the operating room holding area, an intravenous cannula was placed and the patient transported to the operating suite where blood pressure (BP), electrocardiogram (EKG), and chest stethoscope monitors were applied. An automated oscillometric technique (Sentry) was employed to measure systolic (SBP), diastolic (DBP), and heart rate (HR) as well as calculate mean arterial pressure (MAP). Subsequent calculations included rate pressure product (HR times SBP) and per cent change from baseline of HR and RPP. Lead II of the EKG was recorded continuously.

All cardiovascular measurements were recorded by a knowledgeable, blinded clinical investigator (MSV). The same anaesthesiologist (RWV) administered all pretreatment drugs and induction agents. The other investigator (BPK), blinded to patient variables and assigned pretreatment group, evaluated all EKG recordings for presence and timing of dysrhythmias.

TABLE I Descriptive characteristics of the sample by treatment group* (mean $\pm$ SE)

	Gallamine [†]	DTC	MTC	PCB	NS
Number of patients	10	13	12	12	11
Age (yrs)	39 $\pm$ 5	32 $\pm$ 3	41 $\pm$ 5	38 $\pm$ 4	45 $\pm$ 5
Weight (kg)	71 $\pm$ 8	59 $\pm$ 3	63 $\pm$ 3	69 $\pm$ 3	68 $\pm$ 5
Height (cm)	167 $\pm$ 5	162 $\pm$ 2	165 $\pm$ 2	168 $\pm$ 2	166 $\pm$ 3

* $p > 0.05$ among groups.[†]Abbreviations: DTC = d-tubocurarine, MTC = metocurine, PCB = pancuronium, NS = normal saline. FIGURE 1 Systolic and diastolic blood pressure in pretreatment groups and control. No significant difference occurred among groups at any time interval ($p > 0.05$).

Once baseline measurements of cardiovascular variables (SBP, DBP, MAP, HR, continuous EKG recording) were completed, pretreatment drug or control (normal saline) was administered. Cardiovascular measurements were recorded at one minute intervals for six minutes. At 3.5 minutes after pretreatment, induction commenced with sodium thiopentone ($4 \text{ mg} \cdot \text{kg}^{-1}$) and succinylcholine ($1.5 \text{ mg} \cdot \text{kg}^{-1}$) injected intravenously over a 20- to 30-second interval. At minute five, ventilation was controlled by mask with 100 per cent oxygen. Following oxygenation, patients requiring an endotracheal tube were intubated while airway management for other patients was by mask without

laryngoscopy. Measurement of cardiovascular variables at minute six concluded the study.

Results were analyzed using a one-way analysis of variance and the Tukey-B multiple range test for interpretation of differences among groups. In addition, Chi-square analysis was used to test differences among groups for incidence of dysrhythmias. Statistical significance was set at $p \leq 0.05$.

Results

Fifty-eight adult subjects, 12 males and 46 females, were studied. Descriptive characteristics for the total sample included (mean $\pm$ SE (range)): age, 39 ± 2 years (19–84); weight, $66 \pm 2 \text{ kg}$ (41–127); and height, $165 \pm 1.3 \text{ cm}$ (147–201). There was no difference among the pretreatment groups with respect to age, weight, height (Table I), medication history, allergies, or smoking history. Of the 35 patients requiring intubation, eight were intubated just prior to minute six and 27 were intubated after the study concluded. No significant difference occurred among the treatment groups with respect to those intubated between minutes five and six. Medication history revealed that 51 subjects received no medication while seven were intermittently taking sedatives (3), diuretics (2), or chemotherapeutic drugs (2). No significant differences among groups in baseline cardiovascular variables were present. In addition, neither SBP nor DBP differed significantly among groups at any time interval (Figure 1). In contrast, the group given gallamine pretreatment developed a significant increase in HR at minutes two, three, and four (Figure 2). Subsequent mask ventilation during light nitrous oxide-barbiturate anaesthesia resulted in persistent increases in HR during the study period. In addition, calculated RPP also was significantly elevated in the gallamine group when compared with the

FIGURE 2 Heart rate (mean $\pm$ SE) in pretreatment groups and control. A significant increase in rate occurred in the gallamine group at minutes two, three, and four ($p < 0.05$).

FIGURE 3 Rate pressure product (mean $\pm$ SE) in pretreatment groups and control. A significant elevation occurred in the gallamine group at minutes three and four ($p < 0.05$).

other groups at minutes three and four following pretreatment nondepolarizer (Figure 3). When change in HR following pretreatment drugs was calculated as percent of baseline, patients receiving gallamine demonstrated a maximum change of 20 per cent that was significantly greater than all other groups at minutes two, three and four (Figure 4). Other treatment groups were not significantly different from each other with respect to SBP, DBP, MAP, RPP or HR.

Dysrhythmias, after succinylcholine but prior to intubation, occurred in seven of 58 subjects (12.1 per cent: (Table II)). Rhythm disturbances were characterized as nodal ($n = 1$), premature atrial contractions greater than five per minute ($n = 4$), premature ventricular contractions greater than five per minute ($n = 2$), and atrial bigeminy ($n = 1$). One patient experienced both premature atrial and ventricular contractions. Five subjects experienced dysrhythmias prior to laryngoscopy, one after, and one dysrhythmia occurred at minute six in a nonintubated subject. There was significant difference in EKG changes between patient groups.

Discussion

Undesirable tachycardia and arterial hypertension can occur in the operative patient following neuromuscular paralyzing doses of nondepolarizing skeletal muscle relaxants.^{14,15} Animal studies suggest that the effects of tachycardia after administration of gallamine result in part from release of norepinephrine from cardiac adrenergic postganglionic nerve endings.¹⁶ Although other investigators conclude that heart rate and arterial pressure changes in cats given $1.2 \text{ mg} \cdot \text{kg}^{-1}$ and $1.5 \text{ mg} \cdot \text{kg}^{-1}$ doses of gallamine are minimal, neuromuscular blocking agents which cause vagal blockade do not produce such a marked degree of tachycardia in cats, dogs, and monkeys as they do in man. It appears that normal vagal tone is less in these animal species.¹⁷ Descriptive studies in man further suggest partial blockade of muscarinic receptors in vagally innervated cardiac muscle.¹¹ As tachycardia develops, cardiac output and blood pressure increase concomitant with mild decrease in systemic peripheral vascular resistance (SVR).¹⁵ Hy-

TABLE II Dysrhythmias - 7/58 = 12.5% (Type: Nodal = 1, PACs = 4, PVCs = 2)

	Groups				
	Gallamine	DTC*	MTC	PCB	NS
Cardiac rhythm†					
Abnormal	1‡	3	0	0	3
Normal	9	10	12	12	8

*Abbreviations: DTC = d-tubocurarine, MTC = metocurine, PCB = pancuronium, NS = normal saline.

† $p > 0.05$ among groups.

‡Number of dysrhythmias.

pertension following gallamine relaxation may be related to increased endogenous cardiac stores of norepinephrine or failure of the moderating decrease in SVR.

Several studies have described tachycardia in operative patients after gallamine dosages of 0.5–1.0 mg·kg⁻¹ and 0.3 mg·kg⁻¹.^{15,18} However, study design limitations do not allow cause-effect determinations. For example, Viby-Mogensen *et al.* in a comparative study in adults described the effect of a second dose of suxamethonium after preinduction (three minutes before induction) administration of atropine, gallamine or an intravenous combination.¹⁸ All patients in the four treatment groups received premedication with diazepam (0.1 mg·kg⁻¹) one hour before induction. A control group (i.e., no treatment) was absent. A cause (gallamine) – effect (tachycardia) relationship could not be established. Factors further limiting interpretation of results included potential interaction of preanaesthetic medications with muscle relaxants, unblinded observations, and potential confounding variables (i.e., patient anxiety, face mask preoxygenation, manipulation of upper airway). Diazepam serves to illustrate the latter problem with confounding variables and the necessity to control each. For example, it is well accepted that diazepam absorption following an intramuscular dose is dependent on site of injection, the patient's body habitus, per cent body fat, and kinetics of drugs distribution. Uniform absorption, distribution, and biotransformation cannot be assumed. Our study design was experimental and prospective in nature utilizing random assignment with a random numbers table. Extraneous variables such as preoperative medication and preoxygena-

FIGURE 4 Per cent change in heart rate (mean $\pm$ SE) in pretreatment groups and control. A significantly greater per cent change occurred in the gallamine group at minutes two, three, and four ($p < 0.05$).

tion were eliminated to avoid confounding the recorded cardiovascular effects after pretreatment drug administration. Further, treatment groups were compared to control (normal saline) while employing double blinded observers strengthened

the research design. A cause-effect relationship can now be concluded and clinical care altered.

Dysrhythmias (Table II) were evident in a certain per cent of study patients. EKG changes occurred after pretreatment and succinylcholine administration but before laryngoscopy and intubation. No patient experienced serious or continuous nodal changes, premature atrial contractions, or premature ventricular contractions requiring therapy.

No significant increase in systolic or diastolic blood pressures occurred among study groups. This contrasts with the hypertensive crisis experienced by our case study patient. However, that patient manifested pre-eclampsia with apparent constricted blood volume and concomitant labile cardiovascular dynamics. Patients in the research groups were not pre-eclamptic hypertensives, and met the criteria for ASA I or II classification.

Finally, significant changes occurring after minute 3.5 in our study are undoubtedly due to interactive effects of sodium thiopentone and succinylcholine. The effects of nondepolarizing relaxants would likely be masked at minute four by such confounding, interactive effects. In conclusion, our controlled, clinical trial demonstrated a statistically significant increase in heart rate and RPP following even a small pretreatment dose ($0.29 \text{ mg} \cdot \text{kg}^{-1}$) of gallamine when contrasted to other nondepolarizing relaxants and control. The cardiovascular effects of gallamine appear to occur even in these minimal doses, suggesting that the drug is unsuitable for use in patients with an increased or fixed SVR, such as an individual with pre-eclampsia.

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Résumé

Une femme enceinte souffrant de pré-éclampsie sévère a présenté une crise hypertensive à la suite d'un pré-traitement à la galamine (20 mg). Cet incident est à la source de ce travail qui a étudié les effets cardio-vasculaires des myo-résolutifs non dépolarisants employés pour prévenir les douleurs causées par la succinylcholine. Nous avons étudié 58 adultes non-obèses, d'état physique 1 et 2 de l'A.S.A.

Chaque sujet a été assigné au hasard à un de cinq groupes différents: galamine $0.29 \text{ mg} \cdot \text{kg}^{-1}$, détubocurarine $0.04 \text{ mg} \cdot \text{kg}^{-1}$, méthocurine $0.014 \text{ mg} \cdot \text{kg}^{-1}$, pancuronium $0.007 \text{ mg} \cdot \text{kg}^{-1}$ et solutés salins pour une groupe contrôle.

Les mesures de contrôle: pression systolique, diastolique et moyenne, la fréquence cardiaque et produit fréquence/pression ont été enregistrés à une minute d'intervalle alors que l'électrocardiogramme en dérivation était inscrit de façon continue. Dans le groupe recevant de la galamine, on a observé des augmentations statistiquement significatives de la fréquence cardiaque à deux, trois et quatre minutes, du RTP à trois et quatre minutes; de même le changement de la fréquence cardiaque demeurait statistiquement significatif lorsqu'exprimé en pourcentage de changement aux minutes deux, trois et quatre. L'élévation du RPT était en partie due à l'augmentation de la fréquence.

Ces résultats suggèrent que l'on devrait s'abstenir de la galamine même à dose modeste dans les situations cliniques où on soupçonne une instabilité cardio-vasculaire.