EFFECTS OF GALLAMINE ON PLASMA CORTISOL AND CATECHOLAMINE LEVELS IN MAN

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THE CARDIAC AND NEUROMUSCULAR BLOCKING EFFECTS of the non-depolarizing muscle relaxant gallamine have been widely studied.[2,3,6,8,23] However, no report is available concerning endocrine responses to the administration of gallamine in man.

The present investigation was undertaken to explore whether or not administration of a clinical dose of gallamine influences adrenocortical and sympathetic nervous function as reflected by plasma cortisol and catecholamine concentrations in peripheral blood during halothane-nitrous oxide-oxygen anaesthesia in man.

MATERIALS AND METHODS

Ten patients were studied, ranging in age from 19 to 52 years with a mean age of 34.5 years. Nine were female and one was male. They were free from hepatic, renal and endocrine disease and had no history of steroid therapy. The surgical procedures and the duration of operation and anaesthesia are listed in Table I.

Pre-anaesthetic medication consisted of 50 mg meperidine and 0.4–0.5 mg atropine sulphate in five patients and 5 to 8 mg morphine, 10 mg diazepam and 0.4 mg atropine sulphate in five patients given intramuscularly one hour prior to the start of anaesthesia.

The patients received halothane – nitrous oxide – oxygen anaesthesia for at least 30 minutes before the start of the operation as described previously.[10,11] No intravenous ultrashort acting barbiturate was used for induction of anaesthesia except in one patient who received 40 mg of intravenous thiamylal. Respiration was manually assisted or controlled for the first 45 minutes. Five minutes after the beginning of anaesthesia 40 mg of gallamine was given intravenously, followed by incremental doses of 40 mg up to total 200 mg every four minutes in all cases except the last three. In these the initial dose was 80 mg and the remaining 120 mg was given as in the other seven cases.

Induction of anaesthesia in all cases was between 9 a.m. and 11 a.m. in consideration of the circadian variation of plasma cortisol levels.[12] Tracheal intubation was easily performed in all cases after blood sampling had been completed.

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TABLE I

PATIENTS AND PROCEDURES STUDIED

Case No.	Age	Sex	Surgery	Duration of Surgery (min)	Duration of Anesthesia (min)
1	31	F	Vaginal Hysterectomy	90	165
2	30	M	Cholecystectomy	135	180
3	44	F	Abdominal Hysterectomy	100	150
4	32	F	D & C	20	50
5	38	F	D & C	25	60
6	27	F	Laparotomy	120	150
7	42	F	D & C, Tubal Ligation (Presacral Neurectomy)	25	60
8	30	F	Abdominal Hysterectomy	60	135
9	19	F	Abdominal Hysterectomy	115	155
10	52	F	Vaginoplasty	220	380
Mean	34.5			91.0	148.5

The arterial blood samples were taken through an indwelling catheter from the brachial artery.

Blood sampling times for determination of plasma cortisol and blood gas analyses were immediately before the induction of anaesthesia and 5, 15, 20 and 30 minutes after the start of anaesthesia. Arterial blood samples for the estimation of plasma catecholamines were also taken at 0, 2, 5 and 10 minutes following the first intravenous injection of gallamine.

Plasma cortisols were determined by Rudd's method[21] and plasma catecholamine concentrations were measured by Vendsalu's method modified by Kelsch.[9] Arterial blood gas analyses were performed by Astrup's micro-method utilizing the Siggard–Anderson nomogram.[1]

RESULTS

1. *Circulatory Changes*

As illustrated in Figure 1, the mean systolic blood pressure remained unchanged during the first 30 minutes after induction of anaesthesia, while the mean diastolic pressure rose significantly at 20 and 30 minutes after the start of anaesthesia ($p < 0.02$). Significantly increased pulse rates over the base line level were observed at 15, 20 and 30 minutes after the beginning of anaesthesia ($p < 0.001$).

2. *Plasma Cortisol Concentrations*

As illustrated in Figure 2, the mean plasma concentration of cortisol was 15.4 $\pm$ 2.4 μg/100 ml ($\pm$SEM) just prior to the induction of anaesthesia, and 15.4 $\pm$ 2.5 μg/100 ml five minutes after the induction at the time when the initial dose of gallamine was given. It remained almost unchanged at 15 and 20 minutes after the start of anaesthesia and after repeated incremental doses of gallamine. At 30 minutes after induction and after the total dose of 200 mg gallamine, it increased significantly ($p = 0.034$). The pattern observed was similar to that observed after succinylcholine and diallyl-nor toxiferine as illustrated in Figure 3. With all three muscle relaxants the increase in cortisol concentration was found

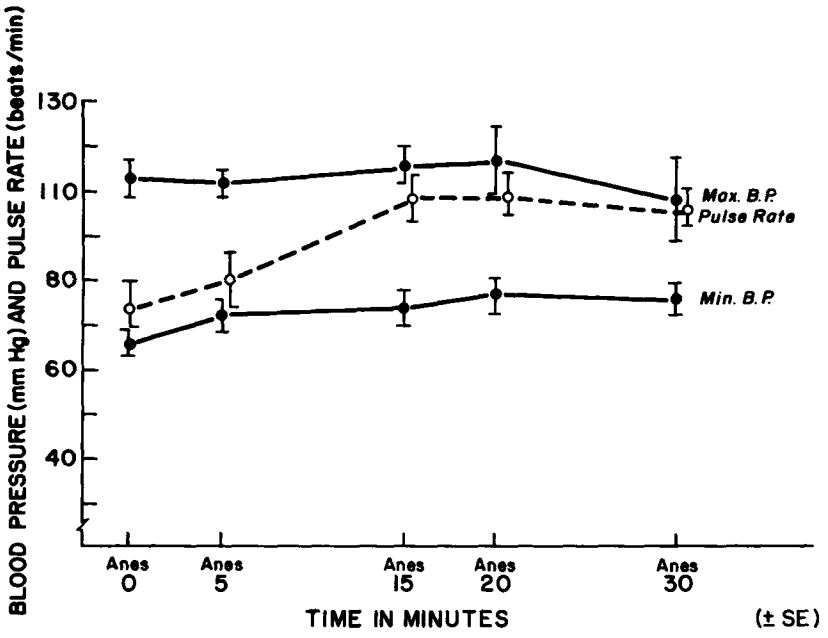

FIGURE 1. Blood pressure and pulse rate changes during induction of anaesthesia and following gallamine administration.

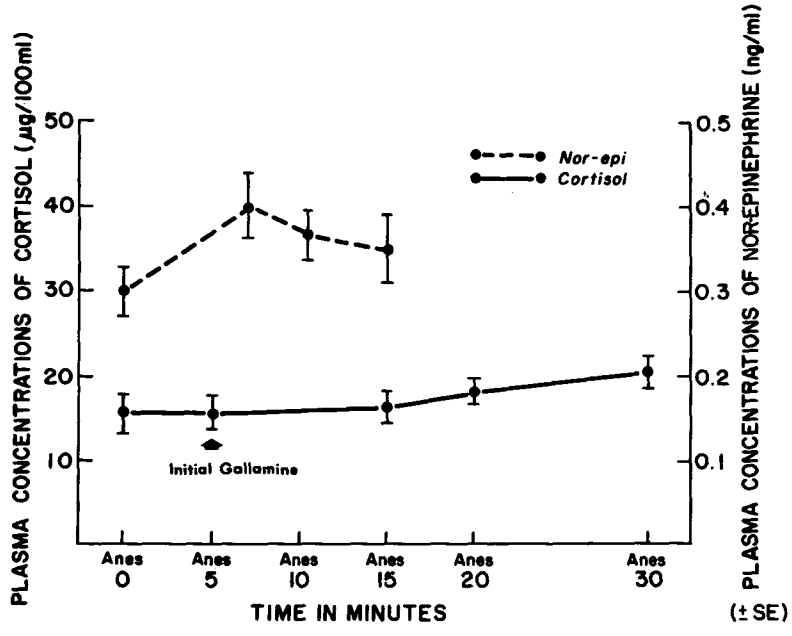

FIGURE 2. Plasma concentrations of cortisol and norepinephrine following intravenous administration of gallamine.

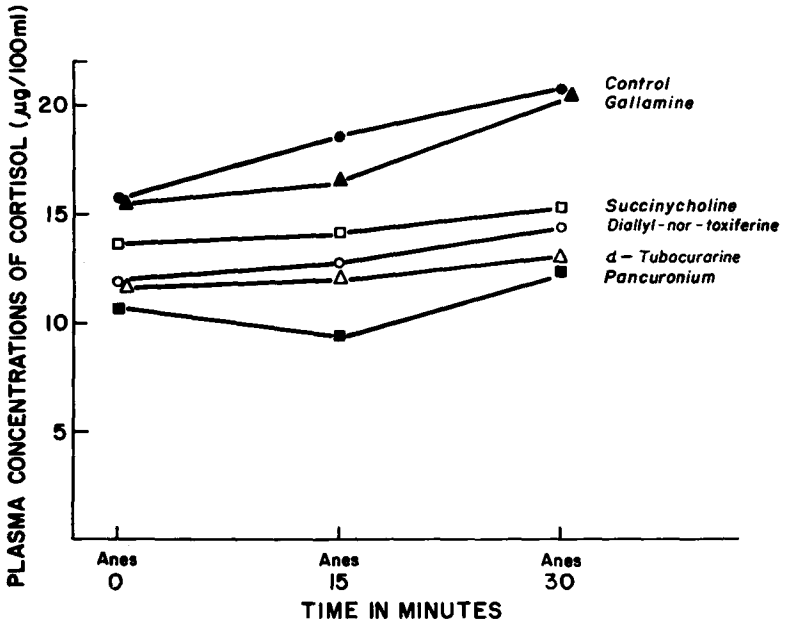

FIGURE 3. Effects of various muscle relaxants on plasma cortisol concentrations.

to be significant ($p < 0.05$) but did not differ from the controls who had received no muscle relaxants ($p < 0.05$); this has been published previously.[10,11]

3. *Plasma Catecholamine Concentrations*

As illustrated in Figure 2, there was a significant elevation in plasma catecholamine concentrations at two minutes ($p < 0.05$) and five minutes ($p < 0.025$) following the first administration of intravenous gallamine. The value at 10 minutes after the gallamine injection was not significantly higher than the base line level ($p > 0.05$).

4. *Arterial Blood Gas Analyses*

Simultaneous analyses of arterial blood gases revealed neither respiratory nor metabolic abnormalities.

DISCUSSION

The sinus tachycardia frequently observed following intravenous administration of gallamine has been considered to be due solely to its vagolytic action.[16,22] Recently, however, Brown and Crout,[3] Smith and Whitcher[22] and Rathbun and Hamilton[19] have demonstrated that gallamine may cause positive inotropic and chronotropic effects in both *in vitro* and *in vivo* animal experiments and also in man. They suggested that the release of catecholamines from cardiac sympathetic nerves was responsible for the observed effect. Although *in vitro* pharmacologic studies by Brown and Crout[2] indirectly indicated the increased release of nor-

epinephrine, no determinations have been carried out on catecholamine concentrations in mammals and in man *in vivo*. Therefore, it seemed appropriate to investigate further the effects of gallamine on adrenal function which in turn is related to the sympathetic nervous system. It was anticipated that the administration of gallamine might result in elevated plasma concentrations of catecholamines and consequently in cortisol concentration. However no significant changes were observed in the plasma levels of cortisol following the administration of gallamine except at 30 minutes after the start of anaesthesia. The pattern was similar to that of the halothane group in the previous study in which no muscle relaxant had been given.[10] The data obtained show that clinical doses of gallamine have no appreciable influence on plasma cortisol levels, since the findings were similar to those obtained with succinylcholine and diallyl-nor-toxiferine.[10]

The authors used a total paralyzing dose of 200 mg of gallamine which was almost equi-potent to the other muscle relaxants employed in the previous study.[10,11] Although a single dose of over 2 mg/kg at rapid rate of injection might have resulted in an elevated cortisol concentration, such a large dose is not usually used in clinical anaesthesia. The plasma cortisol concentration is influenced by various factors: secretion from the adrenal cortex, hepatic metabolism, excretion by the kidneys and utilization in the peripheral tissues. Diethyl ether,[13] halothane[14] and ketamine[15] *per se* cause a significant elevation of the plasma level of cortisol, mediated by ACTH release from the anterior lobe of the pituitary gland, while no appreciable alterations in plasma cortisol concentrations are observed during methoxyflurane anaesthesia[16] and a significant ($p < 0.05$) decrease during thiopentone anaesthesia.[17]

Brunt and Ganong,[4] Castognoli, Goldfine and Ganong[5] reported that the release of ACTH from the hypophysis results in elevated levels of cortisol during acute hypoxia. On the other hand, Done, Ely and Kelly[7] demonstrated that chronic hypoxia is accompanied by decreased concentrations of plasma cortisol in man. The results of blood gas analyses in the present study revealed no abnormalities; therefore, respiratory depression can be eliminated as the cause of the observed changes.

Plasma catecholamine concentrations were determined only in five out of ten patients in the present study. Significant elevation of free norepinephrine was observed at two and five minutes following the initial intravenous dose of 40 to 80 mg of gallamine. No rise in free epinephrine concentration was noted. The increase in norepinephrine concentration, however, was not as great as that observed following intravenous ketamine injection[24] or inhalation of cyclopropane or diethyl ether.[18]

It has been said that gallamine may cause release of catecholamines from sympathetic nerve endings of the heart muscle.[3,19] The results of the present study, though the number of the patients was small, seems to confirm this. Part of the released norepinephrine could escape metabolism, which might result in elevated catecholamine concentrations in the arterial plasma. Further studies with larger doses are in progress to elucidate the exact mechanism of catecholamine release caused by gallamine.

Summary

Effects of gallamine on plasma cortisol and catecholamine concentrations were studied in ten elective surgical patients. A total of 200 mg of gallamine in divided doses was administered intravenously to each patient prior to start of the operation. Maintenance of anaesthesia was with halothane–nitrous oxide–oxygen. Hypoxia and hypercarbia were not allowed to occur, as substantiated by blood gas determinations.

Until 20 minutes after induction, no significant changes from base line were observed in plasma cortisol concentrations. A significant increase was observed at 30 minutes following induction and before the operation had started ($p < 0.05$). This pattern is similar to those observed previously with succinylcholine chloride and dialyl-nor-toxiferine.

Significant elevations of free norepinephrine concentrations were observed at two minutes ($p < 0.05$) and five minutes ($p < 0.025$) following the initial intravenous dose of 40 to 80 mg of gallamine. However, no alteration was found in free plasma epinephrine. It is concluded, therefore, that gallamine is likely to cause the release of free norepinephrine from sympathetic nerve endings.

Résumé

Chez dix candidats à de la chirurgie élective, nous avons étudié les effets de la gallamine sur les concentrations des catecholamines et du cortisol plasmatiques. A chacun des malades, avant le début de l'opération, nous avons donné, par voie endoveineuse, en doses fractionnées, un total de 200 mgs de gallamine. Le maintien de l'anesthésie s'est fait avec de l'halothane, du protoxyde d'azote et de l'oxigène. Nous avons évité l'hypoxie et l'hypercabie comme le prouvent les résultats des gaz artériels.

Jusqu'a vingt minutes après l'induction, nous n'avons pas observé de changement des taux de cortisol plasmatique. Trente minutes après l'induction, avant le début de la chirurgie, nous avons noté une augmentation significative ($p< 0.05$). Cette allure est semblable à celles observées antérieurement avec le chlorure de succinylcholine et le dialyl-nor-toxiferine.

Nous avons trouvé une augmentation importante des concentrations de norephinephrine ibre à deux minutes ($p< 0.05$) à 5 minutes ($p < 0.025$) après une dose initiale par voie endoneineuse de 40 à 80 mgs de gallamine. Toutefois, nous n'avons pas noté de modification du taux d'épinéphrine plasmatique libre. En conséquence, nous concluons que, selon toute vraisemblance, la gallamine provoque la libération de nor-epinephrine libre des terminaisons nerveuses sympathiques.

REFERENCES

1. Astrup, P., Jørgensen, K., Siggard-Anderson, O., & Engel, K. The acid-base metabolism, a new approach. Lancet *1*: 1035–1039 (1960).
2. Brown, B.R. & Crout, J.R. Mechanism of the positive inotropic effect of gallamine on guinea pig heart muscle. Fed. Proc. 25: 472 (1966).
3. Brown, B.R. & Crout, J.R. The sympathomimetic effect of gallamine on the heart. Anesthesiology 29: 179–180 (1968).

4. BRUNT, E.E. & GANONG, W.F. The effects of preanesthetic medication, anesthesia and hypothermia on the endocrine response to injury. Anesthesiology *24*: 500–514 (1963).
5. CASTOGNOLI, JR., N., GOLDFINE, A., & GANONG, W.F. Release of adrenal steroids during asphyxia. Fed. Proc. *20*: 178 (1961).
6. CONDON, H.A. The clinical use of Flaxedil. Anaesthesia *6*: 92–95 (1951).
7. DONE, A.K., ELY, R.S., & KELLY, V.C. Studies of 17-hydroxycorticosteroids. Amer. J. Dis. Child. *96*: 655–665 (1958).
8. EISELE, J.H., MARSA, J.A., & DAVIS, H.S. Quantitative aspects of the chronotropic and neuromuscular effects of gallamine in anesthetized man. Anesthesiology *35*: 630–633 (1971).
9. KELSCH, R.C., LIGHT, G.S., LUCIANO, J.R., & OLIVER, W.J. The effects of Prednisone on plasma norepinephrine concentration and renin activity in salt-depleted man. J. Lab. Clin. Med. *77*: 267–277 (1971).
10. MATSUKI, A., SATO, K., & OYAMA, T. Effects of muscle relaxant on adrenocortical function during halothane anesthesia in man. Agressologie *12*: 149–155 (1970).
11. MATSUKI, A. & OYAMA, T. Adrenocortical function related to administration of muscle relaxants during halothane anesthesia in man. Agressologie *12*: 283–289 (1971).
12. MIGEON, C.J., TYLER, F.H., MAHONEY, J.P., FLORENTINE, A.A., CASTLE, H., BLISS, E.L., & SAMUELS, L.T. The diurnal variation of 17-hydroxycorticosteroids in normal subjects. J. Clin. Endocri. *16*: 622–633 (1956).
13. OYAMA, T., SAITO, T., ISOMATSU, T., SAMEJIMA, N., UEMURA, T., & ARIMURA, A. Plasma levels of ACTH and cortisol in man during ether anesthesia and surgery. Anesthesiology *29*: 559–564 (1968).
14. OYAMA, T., SHIBATA, S., MATSUMOTO, F., TAKIGUCHI, M., & KUDO, T. Effects of halothane anesthesia and surgery on adrenocortical function in man. Canad. Anaes. Soc. J. *15*: 258–266 (1968).
15. OYAMA, T., MATSUMOTO, F., & KUDO, T. Effect of ketamine on adrenocortical function in man. Anes. Analg. *49*: 697–700 (1970).
16. OYAMA, T., SHIBATA, S., MATSUMOTO, F., MATSUKI, A., KIMURA, K., TAKAZAWA, T., & KUDO, T. Adrenocortical function related to methoxyflurane anesthesia and surgery in man. Canad. Anaes. Soc. J. *15*: 362–368 (1968).
17. OYAMA, T., TAKIGUCHI, M., AOKI, N., & KUDO, T. Adrenocortical function related to thiopental–nitrous oxide–oxygen anesthesia and surgery in man. Anes. Analg. *50*: 727–731 (1971).
18. PRICE, H.L., LINDE, H.W., JONES, R.E., BLACK, G.E., & PRICE, M.L. Sympathoadrenal responses to general anesthesia in man and their relation to hemodynamics. Anesthesiology *20*: 563–575 (1959).
19. RATHBUN, F.J. & HAMILTON, J.T. Effects of gallamine on cholinergic receptors. Canad. Anaes. Soc. J. *17*: 574–590 (1970).
20. RIKER, W.F. & WESCOE, W.C. The pharmacology of Flaxedil, with observations on certain analoges. Amer. N.Y. Acad. Sci. *54*: 373–394 (1957).
21. RUDD, B.T., COWPER, J.M. & CRAWFORD, N. The determination of plasma free hydrocortisone and corticosterone by a combined fluorimetric and modified Poter-Silber procedure. Clin. Chem. Acta. *6*: 686–695 (1961).
22. SMITH, N.T. & WHITCHER, C.E. Hemodynamic effects of Gallamine and Tubocurarine administered during halothane anesthesia. J.A.M.A. *199*: 704–708 (1967).
23. WALTON, F.A. Flaxedil: a new curarizing agent. C.M.A.J. *63*: 123–129 (1950).
24. ZSIGMOND, E.K., KELSCH, R.C., & KOTHARY, S.P. Plasma free norepinephrine concentrations during induction with ketamine. Unpublished.