CARDIOVASCULAR REACTIONS TO GAMMA HYDROXYBUTYRATE IN MAN*

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OUR PRELIMINARY EXPERIENCE with gamma hydroxybutyrate¹ has shown it to be a relatively non-toxic useful hypnotic agent which permits subjects to breathe spontaneously and to maintain adequate blood pressure. It therefore seemed desirable to investigate the cardiovascular effects of the drug in non-operated subjects to obtain data unaltered by surgical procedures.

METHOD

Eight fasting, healthy volunteer subjects ranging from 22 to 29 years of age, weighing from 52 to 100 kg, were given atropine 0.4 mg. and secobarbital 100 mg. each per 70 kg. body weight. A short length of polyethylene 160 tubing was introduced into the brachial artery by the Seldinger² technique. A polyethylene 60 tube was introduced into the antecubital vein either percutaneously or via a 16-gauge thin-walled needle. Control blood pressures were recorded via a P_{23ab} transducer. Arterial blood samples were withdrawn for determination of pH, lactic acid dehydrogenase,³ serumglutamic oxalotransaminase,⁴ serum glutamic puruvic transaminase,⁴ leucine amino peptidase,⁵ isocitric dehydrogenase,⁶ aldolase,⁷ glucose,⁸ and urea nitrogen.⁹ Several measurements were made of tidal volume and respiratory rate, until a minimum steady state had been reached. Control tidal volume, respiratory rate, and exhaled air samples were then taken. Cardiac output was measured, the Cardiogreen dye being injected simultaneously with the taking of the air sample. Gamma hydroxybutyrate was administered intravenously over a period of four minutes in a dose of 65 mg./kg. Beginning five minutes after completion of injection, ventilation and cardiac output measurements were repeated. These measurements were determined at approximately five-minute intervals for 30 minutes. Atropine was injected at varying intervals into five of the eight subjects, with measurements of ventilation and cardiac output being made five minutes after each administration of atropine. Arterial blood was withdrawn just before the termination of each anaesthetic for the same determinations that had been made preanaesthetically.

RESULTS

After administration of gamma hydroxybutyrate, adequate spontaneous ventilation was maintained with little change in control rate or volume (Table I).

*Supported by a grant from the Wyeth Company.

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TABLE I
CIRCULATORY AND RESPIRATORY MEASUREMENTS IN HUMAN SUBJECTS RECEIVING GAMMA HYDROXYBUTYRATE, 65 mg./kg.

	Control	15 min. post-injection	30 min. post-injection	45 min. post-injection	5 min. after atropine
Cardiac output (L./min.)	7.78±.73* I	7.10±.88 II	5.08±.45 III	5.80±.79 IV	7.33±.84 V
Cardiac index (L./min.)	4.03±.26 VI	3.68±.38 VII	2.57±.20 VIII	3.16±.53 IX	3.94±.45 X
Stroke volume (ml.)	104±10.1 XI	96.9±17.0 XII	100.4±9.2 XIII	87.8±7.1 XIV	79.6±7.2 XV
Systolic B.P. (mm. Hg)	126.6±7.5 XVI	127.8±6.1 XVII	115.6±2.7 XVIII	117.2±11.3 XIX	134.0±6.9 XX
Diastolic B.P. (mm. Hg)	71.9±2.2 XXI	80.4±4.7 XXII	78.1±4.0 XXIII	76.2±19.2 XXIV	95.2±2.9 XXV
Venous pressure (mm. Hg)	6.86±.89 XXVI	7.38±.70 XXVII	7.50±.82 XXVIII	6.75±1.00 XXIX	5.2±.75 XXX
Pulse	76.1±5.9 XXXI	68.8±8.5 XXXII	57.4±2.2 XXXIII	67.0±11.5 XXXIV	94.6±9.1 XXXV
Minute volume (L./min.)	6.38±.37 XXXVI	6.19±.53 XXXVII	6.33±.54 XXXVIII	6.65±.44 XXXIX	6.80±.30 XL
pH	7.418±.012 XLI			7.407±.005 XLII	
*S.E. mean	Significant	II-III III-V	XVIII-XX	XXVII-XXX XXVIII-XXX	XXXII-XXXV
	Highly Significant	VII-VIII VIII-X VI-VIII	XIII-XV	XXII-XXV	XXXI-XXXIII
	Very Highly Significant	I-III		XXI-XXV XXIII-XXV XXIV-XXV	XXXIII-XXXV

TABLE II
AVERAGE VALUES (8 SUBJECTS) FOR GLUCOSE, UREA NITROGEN, AND ENZYME STUDIES USING GAMMA HYDROXYBUTYRATE

	Glucose (mg. %)	Urea nitrogen (mg. %)	All enzyme values are expressed in units					Leucine amino peptidase
			Lactic acid dehydrogenase	SGOT	SGPT	SGOT/SGPT	Aldolase	
Control	130	19.5	339	3.3	3	1.1	4	186
After anesthesia	138	18.4	376	6.4	5	1.3	4.5	217
Control values in our laboratory	75 to 130	Below 20	100 to 350	0 to 25	0 to 35	More than 1	3 to 8	70 to 230

No significant differences.

Systemic and central venous blood pressures were stable. pH was essentially unchanged. The heart rate generally slowed somewhat, and the cardiac output diminished in seven of the eight subjects, reaching a minimum in about 30 minutes. The reduced cardiac output was concomitant with decreased rate in three subjects, and concomitant with a decrease in both rate and stroke volume in four. In two of the five subjects receiving atropine after the pulse had slowed there was an increase of heart rate and a corresponding increase in cardiac output. In the other three subjects both heart rate and stroke volume increased with atropine. Administration of atropine in all cases was followed by an increased arterial pressure and a decreased venous pressure.

Gamma hydroxybutyrate in the doses used did not produce a deep sleep. The lid reflexes disappeared, but there was little analgesia. The E.E.G. showed disappearance of the awake pattern, and appearance of slower waves of higher voltage. Induction was pleasant. When the subjects awakened they were immediately alert, their state contrasting with the drowsy feeling experienced after the commonly used intravenous agent, thiopental. Three subjects who attempted to move about as soon as they had wakened were nauseated for a few minutes. Duration of sleep was about two hours after the administration of the drug, and ranged from 65 to 250 minutes. Post-anaesthesia enzyme, glucose, and urea nitrogen figures were essentially identical with control data (Table II).

DISCUSSION

Gamma hydroxybutyrate appears to be a basal sedative agent which permits the subject to breathe well spontaneously. Since it has little analgesic property, any noxious stimulus is likely to produce a sympathomimetic response (vasoconstriction). Without such stimulus the heart rate diminishes, but will increase upon administration of atropine. Our previous experiences¹ with surgical patients, in contrast to these subjects who received the drug without stimuli, indicated that operative stimulus was quite adequate to engender responses that maintain or even increased blood pressure. In the absence of surgical stimulus, present results indicate that atropine permitted circulatory values to resume control levels. Laryngeal reflexes were depressed, for endotracheal intubation was easily performed, and bucking on the tube was slight unless stimuli were present. The drug seems to have potential for such procedures as bronchoscopy and other situations with the patient asleep where spontaneous respiration is desirable.

SUMMARY

Eight volunteer subjects were put to sleep with 65 mg./kg. of gamma hydroxybutyrate. Respiratory function and cardiac output were determined. Cardiac output diminished, related to a reduction of either cardiac rate or stroke volume or both, and increased again to control levels on administration of atropine. Spontaneous respiration was well maintained. Once the subject had recovered, he rapidly became alert without residual depression.

Several serum enzyme activities, blood glucose, and blood urea nitrogen values remained at control levels throughout the anaesthetic period.

RÉSUMÉ

Huit volontaires ont été endormis au "gamma hydroxybutyrate" à la dose de 65 milligrammes par kilo. On a étudié la fonction respiratoire et le débit cardiaque. Le débit cardiaque fut diminué, en rapport avec une diminution du rythme cardiaque ou du débit systolique ou des deux, puis augmenté par l'administration d'atropine. La respiration spontanée s'est maintenue. Après le réveil, le sujet est devenu rapidement actif sans trace de dépression.

Plusieurs activités enzymatiques du sérum, le glucose sanguin et l'urée sanguine sont demeurés dans les limites de la normale au cours de l'anesthésie.

ACKNOWLEDGMENT

The authors wish to thank Daniel Cooley for his aid in the technical determinations of cardiac output and his assistance with the calculations.

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