The Effect of CT 1341, a New Steroid Anesthetic, on the Isolated Heart Muscle

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IWATSUKI, N. *The Effect of CT 1341, a New Steroid Anesthetic, on the Isolated Heart Muscle.* Tohoku J. exp. Med., 1973, 109 (1), 69-75 — A direct inotropic effect of CT 1341, a new steroid intravenous anesthetic, upon the myocardium was studied in isolated heart muscles of dogs by measurements of force-velocity relation. CT 1341 at the concentrations over 0.139 ml/100 ml caused a dose-dependent leftward shift of the force-velocity curve. The maximum velocity of muscle shortening at zero load (V_{max}) was decreased progressively with increasing concentration of CT 1341. The values of V_{max} at the concentrations of 0.139 ml/100 ml, 0.279 mg/100 ml and 0.556 ml/100 ml were 94.2%, 86.5% and 67.9% of the control, respectively. Peak force, maximum rate of force development and time to peak force during isometric contraction also showed a dose-dependent decrease. Isotonic net shortening, power and work on the heart muscle were decreased dose-dependently at any given load levels. These results suggest that CT 1341 exerts a direct negative inotropic effect on the myocardium. However, the values of V_{max} were 98.6% and 94.2% of the control at the concentrations of 0.056 ml/100 ml and 0.139 ml/100 ml, which were considered approximately to be the range of blood concentration at the clinically recommended induction doses (0.04-0.1 ml/kg). Therefore, the negative inotropic effect of CT 1341 upon the myocardium seems to be minor when it is used within the range of these doses. — CT 1341; steroid anesthetic; isolated heart muscle; force-velocity relation; inotropism

CT 1341 is a new intravenous anesthetic agent which is a mixture of two steroids dissolved in cremophore EL. The injection is formulated as follows:

Steroid I	
3 α -hydroxy-5 α -pregnane-11,20-dione.....	0.9% w/v
Steroid II	
21-acetoxy-3 α -hydroxy-5 α -pregnane-11,20-dione	0.3% w/v
Cremophor EL	20.0% v/v
Sodium chloride AR	0.25% w/v
Water for injection BP	to 100%

Steroid I
3 α -hydroxy-5 α -pregnane-11,20-dione

Steroid II
21-acetoxy-3 α -hydroxy-5 α -pregnane-11,20-dione

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Preliminary studies have indicated that CT 1341 is a promising intravenous anesthetic agent characterized by immediate induction of anesthesia of short duration, and rapid and uncomplicated recovery from anesthesia (Child *et al.* 1971; Campbell *et al.* 1971; Clarke *et al.* 1971; Savege *et al.* 1971; Swerdlow *et al.* 1971). In regard to cardiovascular effects, Campbell *et al.* (1971) reported a slight fall in blood pressure and stroke volume and a significant rise in heart rate with minimal changes in cardiac output. Savege *et al.* (1971) also reported a well-sustained cardiac output associated with a considerable fall in systolic blood pressure and increase in heart rate. An investigation of a direct effect of this agent on the contractility of the myocardium is considered to be significant to evaluate its effect on cardiac function.

A hyperbolic relation between the velocity of shortening and the force development of cardiac muscle has been described to provide a precise means for quantifying the mechanical behavior of the myocardium (Sonnenblick 1962). The present study is, therefore, undertaken to evaluate the effect of CT 1341 on the contractility of the myocardium by measurements of the force-velocity relation in isolated heart muscles.

MATERIALS AND METHODS

Trabeculae were excised rapidly from the right ventricles of dogs anesthetized with intravenous pentobarbital sodium (25 mg/kg). The muscle was suspended in Krebs-Henseleit solution kept at 27°C by a surrounded thermo-bath. The composition of this solution was as follows: NaCl 118, KCl 4.7, CaCl₂ 2.5, MgSO₄ 1.2, NaHCO₃ 21, KH₂PO₄ 1.2 and glucose 5.6 mM/liter. The muscle was oxygenated by bubbling a 95%O₂-5%CO₂ gas mixture in the bathing solution. Electrical stimulation was applied by means of mass electrodes placed parallel to the muscle at a frequency of 18/min. The voltage was maintained 15-20% above threshold (Nihon Kohden MSE-3). One end of the muscle was connected to a force transducer (Nihon Kohden SB-IT) and the other end was attached to the tip of a longer side of the isotonic lever system by a steel wire. A displacement transducer (Sanborn Model 7DCDT-050) was arranged on a shorter side of the lever (Fig. 1). A load to the muscle was applied by hanging a weight on a shorter side of the lever. The initial muscle length was determined by applying a small load (0.4 g-preload). The muscle was then fixed at this length by a micrometer arranged at the tip of a longer side of the lever, so that the muscle was not elongated by adding loads (after-loads) during force-velocity measurements. The force-velocity relation was obtained by measuring peak velocity of muscle shortening when the after-loads were increased progressively from zero to isometric force. The velocity of shortening was computed by a RC-differentiator (time constant: 0.6 msec). The initial muscle length was measured with a telescope (Pika PPM-2) placed in front of the muscle bath.

The concentrations of CT 1341 used in the experiments were 0.056 ml, 0.139 ml, 0.278 ml and 0.556 ml per 100 ml, and the measurement at each concentration was done 15 minutes after the administration of the agent directly to the bathing solution (180 ml).

Recordings of shortening, velocity of shortening, force as well as stimuli were made with a direct-writing recorder (Nihon Kohden WI-260-M). The maximum velocity of shortening at zero load (V_{max}) was obtained by extrapolating the force-velocity curve to the vertical axis. The maximum rate of isometric force development (max dF/dt) was obtained from a tangent line on the isometric force-time curve. Each heart muscle served as its own control. Values were expressed as mean±SE and analyzed statistically by Fisher's t-test for paired data.

Fig. 1. A schematic diagram of setup for the study.

A: isotonic lever. B: thermo-bath. C: platinum mass electrode.

RESULTS

Four experiments were performed in each series. Muscle length, blotted weight and cross-sectional area of four trabeculae were 6.30 ± 0.25 mm, 17.1 ± 1.5 mg and 2.72 ± 0.24 mm² (mean $\pm$ SE), respectively.

Force-velocity curves were shifted to the left in all four experiments when the heart muscles were exposed to CT 1341 at the concentrations over 0.139 ml/100 ml. The degree of leftward shift was dose-dependent (Fig. 2). Consequently, the maximum velocity of shortening at zero load (V_{max}) and the isometric peak force (F) also showed a dose-dependent decrease (Fig. 3). The percentage values to the control at the concentrations of 0.056, 0.139 and 0.278 ml/100 ml were 98.6 ± 1.0 ($0.3 > p > 0.2$), 94.2 ± 2.4 ($0.05 > p > 0.01$) and 86.5 ± 0.7 ($0.001 > p$) in V_{max} and 95.0 ± 1.6 ($0.1 > p > 0.05$), 79.8 ± 2.0 ($0.01 > p > 0.001$) and 62.8 ± 3.7 ($0.001 > p$) in F , respectively. In one experiment performed at a concentration of 0.556 ml/100 ml, the percent value of V_{max} was 67.9 and that of F was 34.8 of the control. There were concomitant decreases in shortening, power and work at any given load levels under the influence of CT 1341 in all four experiments (Fig. 4). The maximum rate of force development (max dF/dt) was also decreased progressively with increasing the concentration. The percentage values of max dF/dt to the control at the concentrations of 0.056, 0.139, 0.278 and 0.556 ml/100 ml of CT 1341 were 92.2 ± 4.3 ($0.2 > p > 0.1$), 71.6 ± 2.9 ($0.01 > p > 0.001$), 52.7 ± 3.6 ($0.001 > p$) and 27.5 (one experiment), respectively (Fig. 5). The time to peak force from the onset of force development (TPF) were shortened by increasing the concentration of CT 1341 (Fig. 5).

Fig. 2. Force-velocity curves under various concentrations of CT 1341. Abscissa: force (load) in g. Ordinate: velocity of shortening (dl/dt) in mm/sec. Curves are extended to the velocity axis to show the maximum velocity of shortening at zero load ($V_{\max}$). Initial muscle length 5.85 mm, cross-sectional area 2.58 mm². ●—● Control, ○—○ 0.056 ml%, ×—× 0.139 ml%, △—△ 0.278 ml%, ▲—▲ 0.556 ml% of CT 1341.

Fig. 3. Dose-response relations of the maximum velocity of shortening ($V_{\max}$) and isometric peak force (F). Abscissa: concentrations of CT 1341 in ml per 100 ml of Krebs-Henseleit solution. Ordinate: mean per cent values $\pm$ SE to the control in $V_{\max}$ (upper) and in F (lower).

Fig. 4. The effects of CT 1341 on shortening, work and power. Data are derived from the experiment shown in Fig. 2. Note: dose-dependent decreases are seen in shortening, work and power at any given load levels during the administration of CT 1341. •—• Control, ○—○ 0.056 ml%, ×—× 0.139 ml%, △—△ 0.278 ml%, ▲—▲ 0.556 ml% of CT 1341.

Fig. 5. Relations of the concentrations of CT 1341 in ml/100 ml (abscissa) to the changes in maximum rate of force development ($\max dF/dt$) and time to peak force (TPF) in percentage to the control (ordinate).

DISCUSSION

The force-velocity relations of cardiac muscle have been reported to provide a quantitative means of describing the mechanical performance of the myocardium and $V_{\max}$ is particularly sensitive as an index of contractile state of the myocardium (Sonnenblick 1962). A leftward shift of the force-velocity curve and a decrease in $V_{\max}$ produced by CT 1341 in the present study, therefore, clearly indicate that CT 1341 exerts a direct negative inotropic effect on the contractile state of cardiac muscle. A depressed contractile state was also evidenced by a decreased ability of cardiac muscle to shorten and to develop work and power at any given loading conditions. Another interesting finding in the present study is that a reduction of isometric force (F) was accompanied by both decreases in the maximum rate of force development ($\max dF/dt$) and the time to peak force (TPF). Sonnenblick (1967) has suggested that the changes in $\max dF/dt$ reflect the intensity of the active state which is related to the rate of chemical processes, and the changes in TPF are proportional to the duration of the active state which indicates how long the chemical processes persist during muscle contraction. Therefore, the present study suggests that CT 1341 may cause changes in both the rate and the duration of chemical processes within the contractile site.

As the active substances of CT 1341 are dissolved in cremophore EL, there is a possibility that the solvent may play a part in the negative inotropic effect of the agent. In the present study, however, the administration of cremophore EL did not cause any changes in the force-velocity curve (Fig. 6). Therefore, the effect of CT 1341 on the cardiac muscle is considered to be due to the active substances themselves, but not due to the solvent.

The optimum doses of CT 1341 for the induction of anesthesia in man have been reported to be 0.04–0.1 ml per kilogram of body weight (Clarke *et al.* 1971).

Fig. 6. The effect of cremophore EL on force-velocity curve. Note: The force-velocity curve under the influence of cremophore EL does not differ from that of the control. The concentrations of cremophore EL are the same as those used in the study of CT 1341. Initial muscle length 7.22 mm, and cross-sectional area 1.13 mm². •—• Control, △—△ 0.139 ml%, ×—× 0.278 ml%, of cremophore EL.

The blood concentrations at these doses are calculated to be 0.056 and 0.139 ml/100 ml when blood volume is estimated to be 75 ml per kilogram of body weight. Since $V_{\max}$ was unchanged by 0.056 ml/100 ml and slightly decreased by 0.139 ml/100 ml in the present study, it may be reasonable to state that a direct depressive effect of CT 1341 on the myocardium is minor when it is used within the range of these doses. However, as depressions in F and dF/dt during isometric contraction were greater than that in $V_{\max}$ during isotonic contraction, the depressive effect of CT 1341 on the myocardium may become more prominent in patients with the higher after-loaded heart such as arteriosclerosis.

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