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Effects of Dantrolen sod. on the Circulatory System and Others

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The effects of Dantrolen on body temperature, circulatory system and others have been studied in healthy adult dogs.

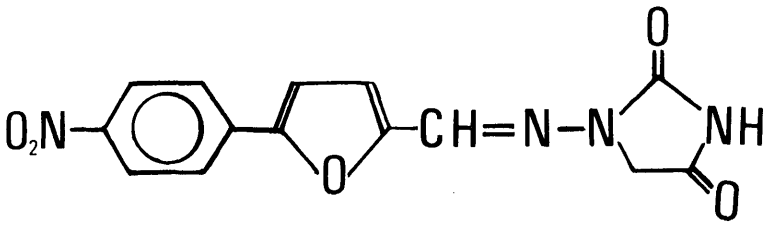
The infusion of Dantrolen produced changes which esophagial temperature was lowered, but no markred change of circulatory system.

These results are discussed.

INTRODUCTION

Malignant hyperthermia, a serious complication under general anesthesia, has not yet been clarified for its etiology, Thus, neither preanesthetic diagnosis nor criterion on early finding have been established yet.

On the other hand, however, Dantrolen[21], which is considered to be its only



Dantrolene

1-{[5-(p-nitro phenyl)furfurylidene] amino}hydantoin

Fig. 1, Dantrolen sodium

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specific remedy, is drawing much attention recently, Harrison[14] in 1975 reported using swine susceptible to malignant hyperthermia that Dantrolen is a most effective therapeutic agent. Furthermore, Anderson et al.[1] and Gronert et al.[11] reported experimental results showing its positive efficacy. Since Dantrolen is a preparation which has a muscle relaxant properties by direct intramuscular action, it is assumed that the same activity may be shown on cardiac muscle and smooth muscle. There is also a report of endorsing the fact that upon administration to pigs it invited cardiac standstill[5].

Therefore, for the purpose of studying effects upon intravenous administration of Dantrolen sod., the following experiment was done.

METHODS

Using 15 hybrid adult dogs, after an induction with 30 mg/kg of pentrobarbital, groin was incised and cannulation was made to measure arterial and central venous pressures. At the same time ECG was continously recorded using RM-150 manufactured by Nihon Koden, while blood flow at the origin of aorta was observed using an electromagnetic flowmeter F-M 25. On the other hand, in addition to measuring esophageal temperatures with time using MGA-Ⅲ manufactured by Nihon Koden, arterial and venous blood were drawn and blood gas, serum electrolytes and serum enzymes were determined.

Serum electrolytes were measured by the automatic flame photometer 343 manufactured by I. L., and for measurement of serum enzymes "Eskalab" spectrophotometer of Eiken was used.

Next, since this preparation is dissolved in polyethylene glycol, that adjusted with mannitol, NaOH, etc., was used according to Castellion's formulation.

RESULTS

1) Esophageal temperature

When Dantrolen was dosed at 10 mg/kg, esophageal temperature started to fall immediately after administration. About 100 minutes later a fall of 3.3°C was noted, which gradually restored. On the other hand, when polyethylene glycol, used as solvent for this preparation, was dosed in the same manner, about 1°C of fall was noted 30 minutes after administration, which however restored in about 60 minutes.

Such change of esophageal temperature, a fall of mean 2.47°C with Dantrolen and 0.87°C with solvent, showed a significant difference.

Table. 1. Effects of Dantrolen sod and polyethlen glycol on esophageal temperature.

	△T(°C)
Dantrolen sod. (F-440)	−2.47±0.96
Polyethylen glycol	−0.87±0.12

2) Effects on the circulatory system

Upon administration of Dantrolen

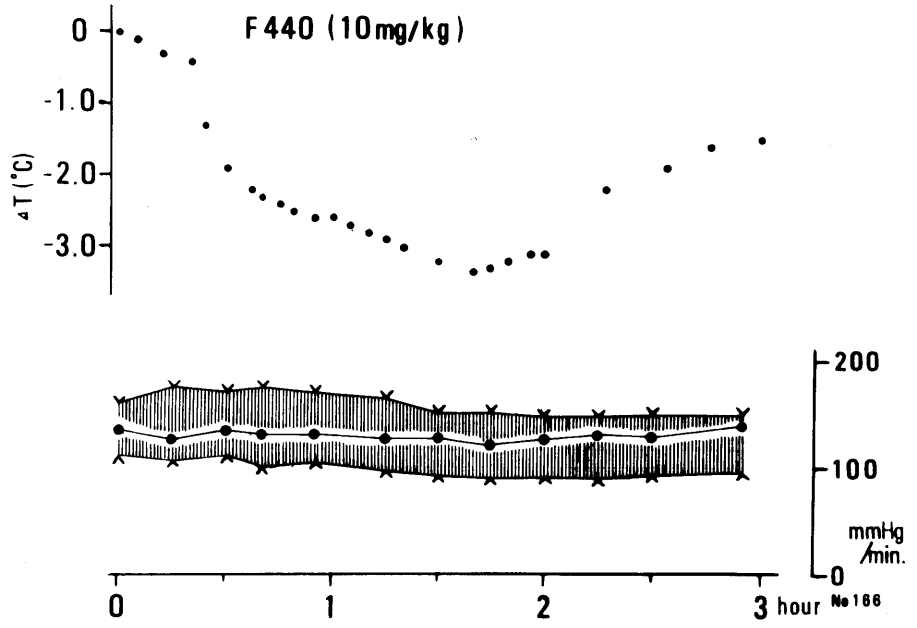

Fig. 2, Effects of Dantrolen sod. (F-440) on esophageal temperature (upper panel) and, arterial pressure and heart rate (lower panel).

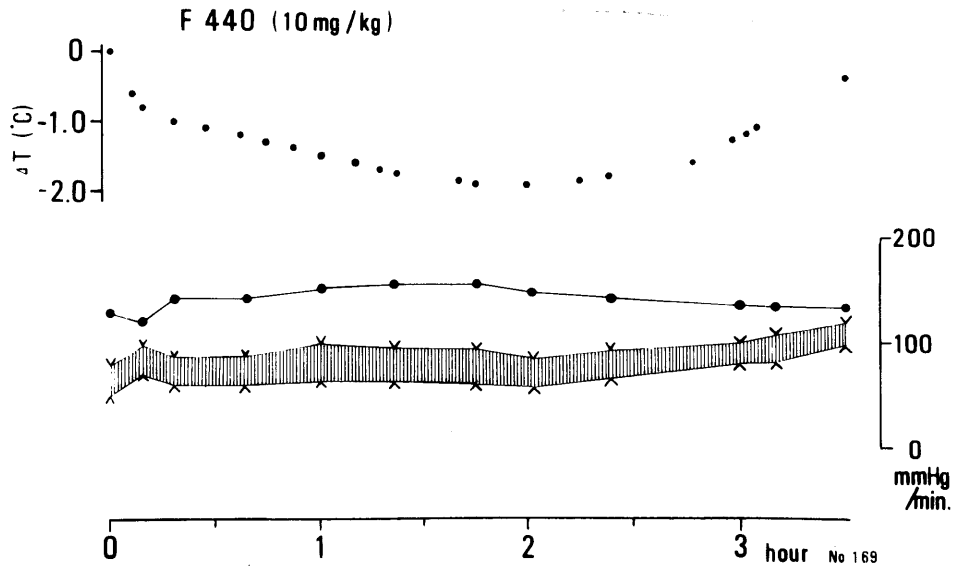

Fig. 3, Effects Dantrolen sod. (F-440) on esophageal temperature (upper panel) and, arterial pressure and heart rate (lower panel).

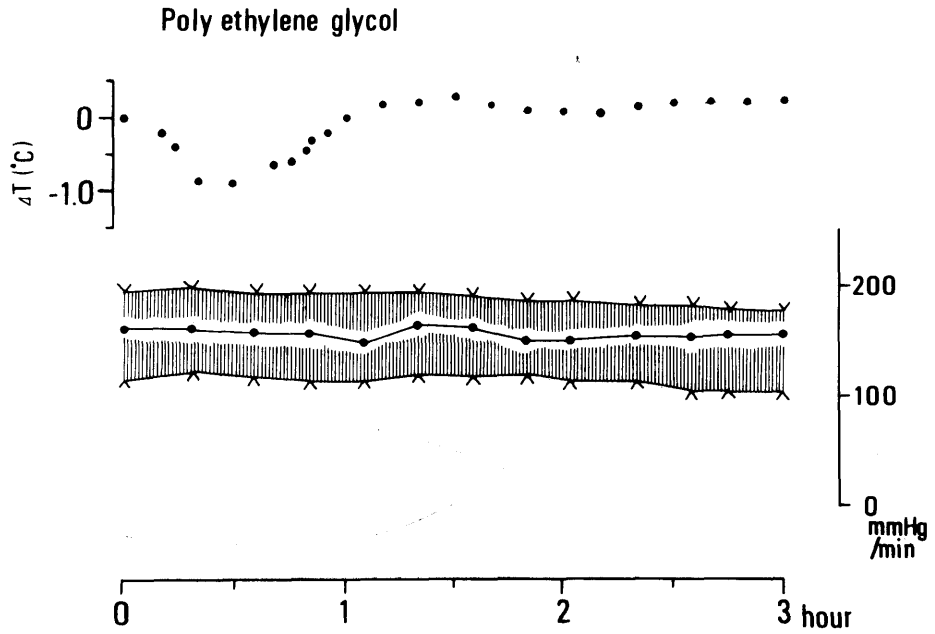

Fig. 4, Effects of polyethylene glycol on esaphageal temperature (upper panel) and, arterial pressure and heart rate (lower panel).

at 10mg/kg arterial pressure first somewhat rose in systolic pressure, which gradually restored to the level before administration showing no marked change. Little change was observed on heart rate. The same applied to ECG and blood flow showing no marked change.

When solvent polyethylene glycol was dosed, either of blood pressure, heart rate, ECG or blood flow showed no marked change at all.

3) Electrolytes

Out of serum electrolytes no fixed trend was observed as to K ion and Ca ion, while Na ion decreased 5-13 mEq/L in 30 minutes after dosing Dantrolen, which was not observed with the solvent.

4) Serum enzyme - CPK

As to change of CPK an increasing trend was observed with either Dantrolen or its solvent, the latter increased much resulting in a significant difference after 90 minutes.

5) Effects on induced hyperthermia

First, when esophageal temperature began to decrease upon administration of Dantrolen at 10 mg/kg, 5 mg/kg of 2, 4-dinitrophenol (DNP) was dosed, however, esophageal temperature began to rise immediately up to 40.3°C, whereat the animal died. Rate of rising temperature was nearly same as that of DNP in single dose, thus, it is considered to have no inhibitory effect on DNP induced hyperthermia. Furthermore, dosis of Dantrolen after DNP administration showed no effect either.

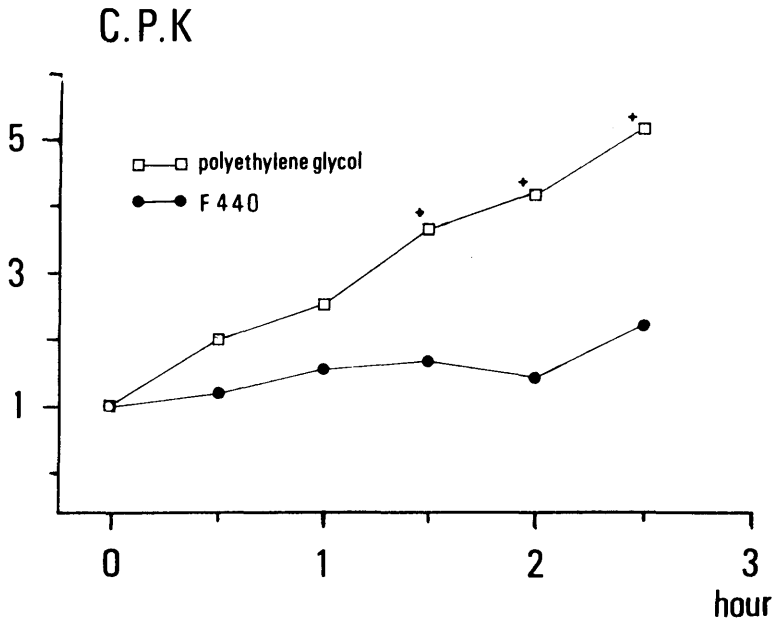

Fig. 5, Effects of Dantrolen sod. (F-440) and polyethylen glycol on CPK.
+: Significant difference from values at F-440

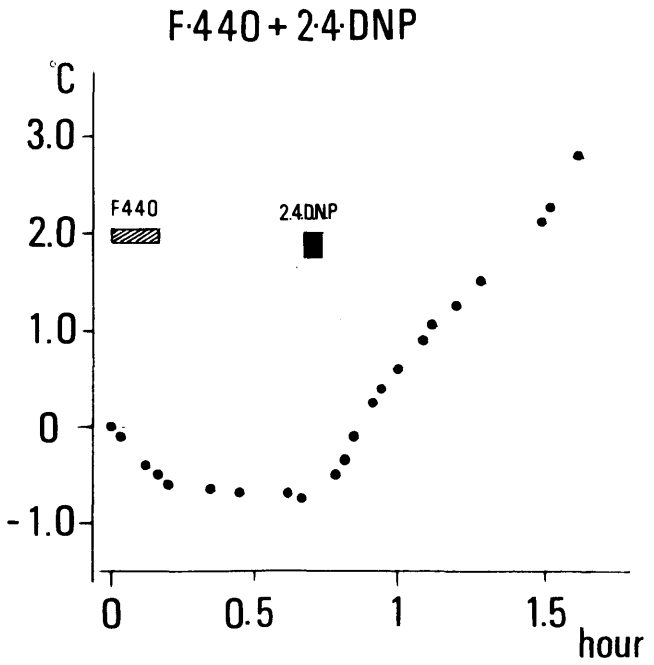

Fig. 6-1, Body temperature responses on DNP induced hyperthermia
▒ : Dantrolen sod. was given during this time
■ : 2, 4-DNP was given during this time

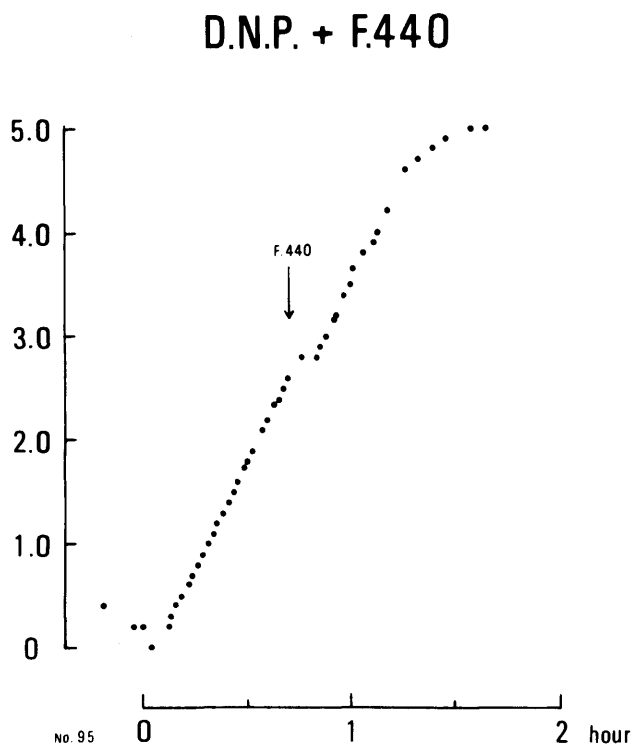

Fig. 6-2, Body temperature responses of DNP induced hyperthermia. Arrow denotes Dantrolen sod administration.

DISCUSSION

This preparation, one of the muscle relaxants consisting of Hydantoin derivatives developed by Snyder et al.,[21] is called Dantrolen generally. It is soluble in polyethylene glycol with molecular weight of 400, but insoluble in water. Dantrolen does not act to central nervous system, etc., but directly to E-C coupling of skeletal muscle and impair the release of Ca ion. As a result it is said to cause muscle relaxation, and reported to show an exellent effect on lesion of spinal cord, cerebral parlysis and other spastic paralysis, generally being dosed orally.

According to the results obtained by the authors, body temperature itself indicates a decreasing trend by this preparation, but no abnormality is observed on arterial pressure, heart rate, blood flow, and ECG, thus it is considered that its effect on the circulatory system is quite a bit and accordingly no effect is extended to cardiac muscle, smooth muscle of blood vessel, etc. The same results have been reported by Ellis et al.[6], Takagi[23], Bailey et al.[2] and Gollan et al.[9].

However, the result in vitro is not always the same. Takagi[23] reported that with the arterial specimen little effect was found on systole, but spontaneous movement of uterus was inhibited; Mayler et al. [17] recognized a systolic reduction 75% less than the

control as to isolated rat heart; Graves[10] stated that there was an inhibitory effect on reaction of vas deferens and ileum; and J.J. Salata et al. [19] observed a significant decrease in action potential on cardiac Purkinje's fibers of dog, and since it was completely restored with Ca^{++}, Dantrolen might have an effect on slow inward current.

Thus, it cannot simply be decided that Dantrolen does not work on cardiac muscle and smooth muscle at all. According to Britt et al.[3] more than 1/3 of the patienst susceptible to malignant hyperthermia with muscle biopsy positive for MH had abnormal findings on ECG, while in addition abnormal findings are pointed out upon myocardial scanning[16]. Accordingly when some abnormal findings are observed on cardiac and smooth muscles, it cannot be determined that no effect of Dantrolen is concerned, therefore, special care must be taken upon use of this preparation intravenously.

Fall of temperature by Dantrolen has not generally been reported, but since usually heat production on living body is said to be quantitatively depending mostly on skeletal muscles, it can be assumed that by muscle relaxation with Dantrolen, body temperature is lowered.

Furthermore, CPK is said to be increased by motion and labor, thus when relaxation is obtained by this preparation naturally it shows lowere values than the control.

Next, when effect of this preparation was studied with DNP, either case did not show effect, but while Dantrolen interfered at E-C coupling and DNP did generally at mitochondria, thus, it seems that such difference on site of action resulted in ineffectiveness.

Since, in a number of case reports, Dantrolen was reported to be effective in the treatment of malignant hyperthermia referring to human[4][8] and swine[7][12][13][15], it is considered to be true that this is effective on malignant hyperthermia with rigidity as stated by Britt, but as it is stated that in case of non rigid type, it might be due to uncoupling action of anesthesics[22], some malignant hyperthermia exists, on which Dantrolen is not effective, but this has not been clarified yet.

Meanwhile, as to Dantrolen, hepatites[20] and other[18] complications are also reported, therefore, it is considered that coution should be employed during and after administration.

CONCLUSION

Dantrolen, a muscle relaxant of hydantoin derivative, directly acts on skeletal muscle and brings muscle relaxation. For the purpose of studying effect of this preparation on cardiac muscle and smooth muscle of blood vessel, 10 mg/kg of this preparation was dosed to adult dogs intravenously, and obtained the following results:

1) Esophageal temprature was lowered by 2.47°C in one or one hour and half, and then restored.

2) No marked change was observed on arterial pressure, heart rate, ECG, blood flow, thus little effect on the circulatory system is considered.

3) As to electrolytes no fixed trend was observed with K ion and Ca ion, while

5-13 mEq/L of decrease was observed with Na ion.

4) Serum CPK showed a lowere increases rate than that of the control with significant difference.

5) Dantrolen was not effect on DNP induced hyperthermia.

Dantrolen is said to be effective on human or swine malignant hyperthermia with rigidity, but on account of the report stating on cardiac standstill of pig, care must be taken to dose intravenously, although less effect is expected on the circulatory system.

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