Bull. Tokyo Med. Dent. Univ., 32: 91–96, 1985

EFFECT OF THIAMYLAL AND DIAZEPAM ON RELEASE OF MYOGLOBIN AND CREATINE PHOSPHOKINASE BY SUCCINYLCHOLINE CHLORIDE DURING HALOTHANE ANESTHESIA

BY

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ABSTRACT

The effects of thiamylal and diazepam on the release of myoglobin and creatine phosphokinase following the administration of succinylcholine chloride during halothane anesthesia were studied. Thirty patients receiving halothane anesthesia were divided into three groups. In Group I, 1.5–2 mg/kg of thiamylal were given intravenously as pretreatment before the injection of succinylcholine chloride. In Group II, 0.3 mg/kg of diazepam were given and, in Group III, only succinylcholine chloride was injected.

A significant increase in the serum myoglobin and creatine phosphokinase levels was observed in all groups. However, the values in Group I were significantly lower than those in Groups II and III and a significant difference was not detected between Group II and III. Our results indicate that thiamylal has a considerable inhibitory effect on the release of myoglobin and creatine phosphokinase from the muscle following the administration of succinylcholine chloride.

Key words: Thiamylal, Diazepam, Succinylcholine chloride, Myoglobin, Creatine phosphokinase.

INTRODUCTION

Intravenous administration of the depolarizing muscle relaxant succinylcholine chloride (S.C.C.) is often associated with adverse effects, including myoglobinuria (Bennike and Jarnum [1]), elevated serum potassium and creatine phosphokinase (CPK) (Tammisto and Airaksinen [2]; Tammisto *et al.* [3]).

Muscle damage induced by fasciculation following the S.S.C. administration has been proposed as a possible cause of these adverse effects (Tammisto and Airaksinen [2]). Nevertheless, it has been previously observed that anesthetic agents, especially halothane, enhance the release of CPK, potassium and myoglobin (Mb) from the muscle by S.C.C. (Tammisto *et al.* [3]; List [4]; Bali *et al.* [5]; Inagaki *et al.* [6]; Shinohara *et al.* [7]).

We also demonstrated previously that the serum Mb and CPK levels were remarkably elevated following the administration of S.C.C. in halothane anesthesia but not in modified anesthesia using diazepam, thiamylal or pentazocine (Umino *et al.* [8]). The present study was, there-

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Received for publication, June 1, 1985.

fore, undertaken to determine the effects of pretreatment with diazepam or thiamylal on the release of Mb and CPK following the S.C.C. administration in halothane anesthesia.

Material and Method

The subjects were 30 patients (21 males, 9 females) without any muscle disease ranging from 15 to 66 years of age undergoing sinusotomy. All patients had been informed as to the nature of the study and their consent was obtained. We already documented that the Mb and CPK levels in the serum were unchanged in the procedures for sinusotomy (Umino *et al.* [8]).

The patients were premedicated with 10 mg of diazepam orally and with 35–50 mg of pethidine and 0.5 mg of atropine intramuscularly. All patients were induced with nitrous oxide (66%), oxygen (33%) and halothane (1.5–2.5%). After sleep, 1 mg/kg of S.C.C. was administered to facilitate the endotracheal intubation. The patients were divided into three groups according to the mode of pretreatment before the injection of S.C.C.

Group I: Twelve patients (8 males, 4 females, mean age 48 years); 1.5–2 mg/kg of thiamylal were given intravenously five minutes prior to the injection of S.C.C. as pretreatment.

Group II: Eight patients (6 males, 2 females, mean age 37 years); 0.3 mg/kg of diazepam was given intravenously five minutes prior to the injection of S.C.C.

Group III: Ten patients (7 males, 3 females, mean age 35 years); no pretreatment was given and only S.C.C. was injected.

In all three groups, anesthesia was maintained with nitrous oxide (50%), oxygen (50%) and halothane (1–1.5%) under manually controlled ventilation. For blood sampling an intravenous catheter was placed in the antecubital vein. Four m*l* of blood samples for serum Mb and CPK estimation were obtained respectively seven times (before the induction and at 15, 30, 45, 60, 120 and 240 minutes after the injection of S.C.C.). All samples were centrifuged. The serum was separated. The serum samples were stored at −20°C until measurement. Mb was measured by the radioimmunological assay using myoglobin kits (Eiken Immunochemical Laboratory, Tokyo) according to the method of Rasano [9]. Serum CPK activity was estimated by a modification (Rosalki [10]) of the method by Oliver [11] using an automatic enzyme analyzer 705 (Hitachi LTD, Tokyo). The normal range of the CPK activity in our laboratory is 56 to 193 IU/*l*. Student's t-test was used for statistical comparison and the level of $p<0.05$ was considered to be significant.

Results

The three groups were similar in duration of surgery and anesthesia, blood loss and volume of fluid transfusion (Table 1). Table 2 shows that there was a significant increase in the serum Mb level in all three groups. There was a much smaller rise in Group I than that in Groups II and III. In Group I, the maximum rise in the serum Mb was 153.1±27.5 ng/m*l* at 120 minutes after the administration of S.C.C. In Groups II and III, the serum Mb levels rose rapidly after the administration of S.C.C., reaching the maximum values of 747.5±248.9 ng/m*l* and 894.2±269.8 ng/m*l*, respectively, at 60 minutes after the administration of S.C.C. Subsequently, they fell slowly in both groups. By statistical analysis the serum Mb levels in Group I were found to be significantly lower in comparison with those in Groups II and III (Table 3).

Table 1. Duration of Surgery and Anesthesia, Blood loss and Volume of Fluid Transfusion

Group	Duration of surgery (min)	Duration of anesthesia (min)	Blood loss (m*l*)	Volume of fluid transfusion (m*l*)
I	95(9)	140(9)	212(38)	896(86)
II	91(7)	151(15)	297(82)	994(69)
III	84(7)	128(9)	158(30)	867(77)

All values are mean (SE).

Table 2. Comparison of Myoglobin Levels in Serum Following S.C.C. Administration

Group	Before induction	15 min after S.C.C.	30 min after S.C.C.	45 min after S.C.C.	60 min after S.C.C.	120 min after S.C.C.	240 min after S.C.C.
I (ng/m*l*)	27.8 (4.0)	104.6* (13.2)	126.0* (20.4)	143.0* (22.3)	138.0* (21.0)	153.1* (27.5)	130.4* (21.2)
II (ng/m*l*)	37.8 (6.6)	613.8* (206.0)	673.8* (218.5)	694.4* (234.0)	747.5* (248.9)	708.8* (220.4)	445.6* (174.4)
III (ng/m*l*)	29.3 (7.9)	541.5* (175.2)	653.3* (186.7)	772.1* (231.0)	894.2* (269.8)	879.6* (259.8)	723.6* (235.2)

All values are mean (SE).
* $P<0.05$ versus before induction.

Table 3. The Statistical Difference Between Three Groups With Change in Serum Myoglobin and Creatine Phosphokinase Levels Following S.C.C. Administration

		Before induction	15 min after S.C.C.	30 min after S.C.C.	45 min after S.C.C.	60 min after S.C.C.	120 min after S.C.C.	240 min after S.C.C.
Between I and II	Mb	NS	S	S	S	S	S	NS
	CPK	NS	S	S	S	S	S	S
Between I and III	Mb	NS	S	S	S	S	S	NS
	CPK	NS	NS	S	S	S	S	S
Between II and III	Mb	NS	NS	NS	NS	NS	NS	NS
	CPK	NS	NS	NS	NS	NS	NS	NS

S Significant ($p<0.05$).
NS Not significant.

However, there were no significant differences between Groups II and III. Serum CPK activities continuously increased up to 240 minutes after the administration of S.C.C. in all groups (Table 4). In each group, a significant increase in the CPK activities over the baseline value was observed. However, the increase of the enzyme in Group I was significantly smaller than that in the other two groups (Table 3). There were no significant differences between Groups II and III.

Table 4. Comparison of Creatine Phosphokinase Levels in Serum Following S.C.C. Administration

Group	Before induction	15 min after S.C.C.	30 min after S.C.C	45 min after S.C.C.	60 min after S.C.C	120 min after S.C.C.	240 min after S.C.C
I (IU/L)	61.5 (7.0)	62.4 (6.7)	64.6 (5.0)	71.6* (6.4)	77.7* (7.6)	113.3* (12.2)	157.7* (20.7)
II (IU/L)	78.5 (7.8)	139.5* (25.4)	222.4* (59.7)	308.5* (91.8)	453.4* (138.3)	872.0* (318.5)	1136.1* (420.0)
III (IU/L)	89.7 (9.8)	180.8 (54.4)	235.8* (62.9)	373.8* (123.6)	571.8* (204.4)	1044.3* (342.2)	1714.3* (526.9)

All values are mean (SE).
* $P<0.05$ versus before induction.

Discussion

In the present study, a marked rise of Mb and CPK in the serum was observed following the administration of S.C.C. in halothane anesthesia but, in the thiamylal-pretreatment group, the rise of Mb and CPK was significantly lower than that in the non-pretreated group or diazepam-pretreatment group. These results demonstrate that thiamylal has a considerable inhibitory effect on the release of Mb and CPK from the muscle damage induced by fasciculation following the S.C.C. administration.

It is already well known that anesthetic agents exert an action on the release of Mb, CPK and potassium from the muscles induced by S.C.C. (Tammisto *et al.* [3]; List [4]; Bali *et al.* [5]; Inagaki *et al.* [6]). In particular, halothane potentiates the effect of S.C.C. on the release of Mb (Ryan *et al.* [12]), CPK (Innes and strømme [13]) and potassium (Bali *et al.* [5]) Our study also revealed that the release of Mb and CPK induced by S.C.C. was accelerated in non-pretreated halothane anesthesia. On the contrary, it has been indicated that barbiturates reduced not only the release of Mb (Inagaki *et al.* [6]), CPK (Tammisto and Airaksinen [2]) and potassium (List [4]) but also the incidence of myalgia (Craig [14]; Manani *et al.* [15]) and fasciculation after the injection of S.C.C. These previous reports suggest that barbiturates have a protective effect on the muscle damage induced by fasciculation by S.C.C. Our result that thiamylal pretreatment in halothane anesthesia was able to suppress the rise of Mb and CPK supports the previous suggestion. This mechanism of suppressive action on the release of Mb and CPK by thiamylal is not necessarily well elucidated. Torda [16] and Kraunak [17] *et al.* demonstrated that barbiturates depress the neuromuscular transmission in vitro. From their results, it is deduced that thiamylal possibly plays a role in the neuromuscular junction.

On the other hand, pretreatment with diazepam could not prevent the rise of Mb and CPK in the serum in the present study. These findings indicate that diazepam does not have a protective effect on the muscle damage caused by S.C.C., at least in halothane anesthesia.

Originally, as diazepam has a muscle-relaxing action and an anticonvulsant effect, it has been used for the treatment of tetanic and epileptic convulsions. In the field of anesthesia, diazepam-pretreatment has been attempted to decrease the fasciculation or to prevent the

development of myalgia induced by S.C.C. (Verma *et al.* [18]). Eisenberg *et al.* [19] indicated that diazepam-pretreatment was effective in preventing the S.C.C.-induced myalgia, fasciculation and increase of serum potassium but not effective against the rise of CPK. It has already been reported that there was not necessarily a correlation between the muscle pain and CPK elevation (Tammisto *et al.* [3]). Furthermore, Erkola *et al.* [20] failed to prevent either the fasciculation or rise of potassium with diazepam-pretreatment. From these early reports and our results, we do not believe that diazepam inhibits the action of S.C.C. at the neuromuscular junction and depresses the release of Mb and CPK from the muscles. Since the muscle-relaxing action of diazepam is produced centrally via the inhibition of polysynaptic reflex activity, enhancement of presynaptic inhibition and depression of motor neuron activity at the spinal and brainstem levels (Martin [21]), it would be reasonable to consider that diazepam has peripherally a small muscle-relaxing action at the neuromuscular junction (Martin [21]; Bradshaw and Maddison [22]). Fahmy *et al.* [23] found that diazepam-pretreatment prevented the increase in the serum potassium and CPK levels. Our results are not consistent with their findings. However, we were unable to compare our results with theirs because in their study thiopental instead of halothane was used as the induction agent before treatment with diazepam and the serum CPK following the administration of S.C.C. was estimated only at 24 hours postoperatively.

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