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Neuromuscular Effects of Subcutaneous Administration of Pancuronium

HIROSHI IWASAKI, M.D.,* AKIYOSHI NAMIKI, M.D., PH.D.,† TETSUO OMOTE, M.D.,‡ KEIICHI OMOTE, M.D.,‡

Clinically, nondepolarizing neuromuscular blocking agents are nearly always administered intravenously. Recently, we encountered a patient who demonstrated prolonged neuromuscular blockade following accidental subcutaneous administration of pancuronium bromide. To our knowledge, there have been no reports of the effects of subcutaneous administration of pancuronium during general anesthesia. Therefore, we investigated the neuromuscular blocking effect of subcutaneously injected pancuronium in anesthetized patients.

CASE REPORT

The patient was a 67-yr-old man who weighed 54 kg and underwent surgery for removal of a brain tumor under enflurane anesthesia. The patient had no hepatic, renal, or neuromuscular disorders in the laboratory screening tests. He was not receiving any drugs known to interfere with neuromuscular transmission, and neurologic testing at the bedside revealed no evidence of muscle weakness in the extremities.

Atropine 0.5 mg and hydroxyzine 100 mg were given intramuscularly 1 h before induction of anesthesia. After an 18-G Teflon catheter was inserted into a vein on the left hand for infusion of lactated Ringer's solution and administration of intravenous anesthetic drugs, anesthesia was induced by intravenous administration of 300 mg thiamylal and 50 mg succinylcholine *via* the catheter. The trachea was intubated, and anesthesia was maintained with 60% nitrous oxide in oxygen and an inspired enflurane concentration of 0.7–1.2%. Ventilation was controlled to maintain normocapnia.

We then inserted another 18-G Teflon catheter into a peripheral vein on the ankle. A 6-mg bolus dose of pancuronium was administered through this catheter, but shortly after the administration of pancuronium a swelling was noticed around the site of the venous catheter. An accidental subcutaneous injection of pancuronium was assumed. Immediately thereafter, the adduction force of the thumb following train-of-four stimulation of the ulnar nerve was measured every 12 s *via* the transducer and was recorded (Myograph 2000, Biometer, Denmark).

Initially there was no fade following train-of-four stimulation. A decrease in the train-of-four response appeared approximately 10 min after subcutaneous administration of pancuronium. The inspired enflurane concentration of 0.7–1.2% was used to keep the blood pressure in the normal range without additional neuromuscular blocking agents during the surgery. About 40 min after the administration of pancuronium, no response to peripheral nerve stimulation was demonstrated.

The patient regained the fourth twitch response upon train-of-four stimulation about 3 h and 30 min after the administration of pancuronium. At the end of surgery, 5 h and 30 min after the administration of pancuronium, the train-of-four value was 0.46. During the surgery, vital signs had remained stable, and rectal temperature varied between 36.4 and 36.7° C. The patient was not given any antibiotics perioperatively. Administered fluids totaled 2,200 ml crystalloid, and urine output was 600 ml during surgery. After the administration of neostigmine 2.5 mg and atropine 1.0 mg, the train-of-four value increased to greater than 0.90 within 10 min, and the enflurane and nitrous oxide was discontinued. The trachea was extubated 6 h after pancuronium had been given, and the patient was able to open his eyes and move all extremities. Neuromuscular function was monitored continuously by the peripheral nerve stimulator in the recovery room for the next 2 h, and no sign of residual neuromuscular blockade was present during the recovery period.

MATERIALS AND METHODS

Fifteen male, ASA physical status 1 and 2, patients aged 28–67 yr (mean 48.3 yr, SD 6.2), weighing 50–59 kg (mean 54.3 kg, SD 2.6), and scheduled for neurosurgical operations lasting more than 6 h were included in the study. None of the patients had neuromuscular disease or were receiving any drugs known to affect neuromuscular function. Patients with paresis, hepatic, or renal disorders also were excluded. The study was approved by the institution's Ethics Committee, and informed consent was obtained from all patients. All patients received atropine 0.5 mg and hydroxyzine 100 mg intramuscularly 1 h before induction of anesthesia. Anesthesia was induced with thiamylal 4–5 mg/kg, and the trachea was intubated with the aid of succinylcholine 1.0 mg/kg. Anesthesia was maintained with 60% nitrous oxide in oxygen and an inspired enflurane concentration of 1.0–1.2% during the study. At least 20 min after the induction of anesthesia, patients were assigned to one of three treatment groups (n = 5 in each group). Groups 1 and 2 received a dose of pancuronium 6 mg subcutaneously in the ankle and the hand, respectively. Group 3 was given an intravenous bolus of pancuronium 6 mg. Ventilation was maintained at Pa_{CO_2} 34.4 ± 0.52 mmHg during the study.

As described in the present case report, neuromuscular train-of-four responses were evaluated every 12 s by mea-

* Assistant Professor.
† Chairman and Professor.
‡ Research Fellow.

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Address reprint requests to Dr. Iwasaki: Department of Anesthesiology, Sapporo Medical College and Hospital, South-1, West-16, Chuoku, Sapporo, Japan 060.

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suring the force-of-thumb-adduction produced in response to supramaximal stimulation of the ulnar nerve at the wrist. The force-of-thumb-adduction was recorded *via* a force displacement transducer on paper. The resting tension applied to the thumb was adjusted to 200 g. The train-of-four (T_4/T_1) ratio, defined as the ratio of the height of the fourth evoked response to the height of the first response (T_1) in the same train, was measured. These measurements were made until at least 60% recovery of the train-of-four ratio was reached. Also the time from injection to fade in train-of-four responses, the time to maximum T_1 blockade, and the recovery time from 20% to 50% in the train-of-four ratios were measured.

Data were analyzed statistically by the Mann-Whitney U test after Kruskal-Wallis one-way analysis of variance. $P < 0.05$ was considered significant. Data were expressed as mean ± standard deviation.

Results

The three groups of patients did not differ significantly in weight, height, age, or enflurane anesthetic time before the administration of pancuronium among the groups. In the study groups, the onset and the recovery after pancuronium are shown in table 1.. The onset of fade in train-of-four responses was significantly more rapid in group 3 (intravenous administration) than in patients in groups 1 and 2 (subcutaneous administration) ($P < 0.01$). With the pancuronium dose of 6 mg administered intravenously and subcutaneously in the hand, complete depression of twitch responses occurred in all patients studied. However, the same dose of pancuronium produced complete blockade in only one of five patients who received the drug subcutaneously in the ankle. Times to maximum T_1 depression from pancuronium in groups 1, 2, and 3 averaged 106.2, 11.6, and 3.1 min, respectively. Patients administered pancuronium subcutaneously in the ankle took more time to produce maximum T_1 depression ($P < 0.01$). Recovery time of the train-of-four responses in group 1 was significantly longer than those in groups 2 and 3 (fig.1). No significant differences in the recovery times were demonstrated between groups 2 and 3.

TABLE 1. Onset and Recovery Times Following Subcutaneous or Intravenous Pancuronium

Group	Time to Onset of Fade in T_4/T_1 (min)	Time to Maximal T_1 Blockade (min)	Recovery Time of T_4/T_1 from 0.2 to 0.5 (min)
1	9.3 ± 2.1*	106.2 ± 11.8*	112.5 ± 13.3*
2	4.2 ± 1.3†	11.6 ± 5.2†	46.3 ± 5.1
3	1.1 ± 0.2	3.1 ± 0.8	45.2 ± 3.8

All data represent mean ± SD. Group 1: subcutaneous ankle injection; group 2: subcutaneous hand injection; group 3: intravenous injection.

* $P < 0.01$ compared with groups 2 and 3.

† $P < 0.05$ compared with group 3.

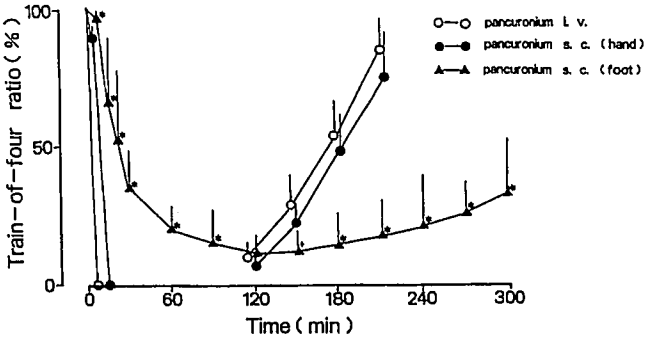

FIG. 1. Time courses of decay and recovery of the train-of-four ratios after intravenous (i.v., group 3) and subcutaneous (s.c.) administration of pancuronium in the foot (group 1) and hand (group 2) during enflurane anesthesia. All data points represent mean ± SD. *$P < 0.01$ compared with group 2 and 3. †$P < 0.05$ compared with group 3.

Discussion

The patient described in this report demonstrated delayed onset and markedly prolonged duration of neuromuscular blockade after unintentional subcutaneous administration of pancuronium during enflurane anesthesia.

To further characterize the neuromuscular blocking effects of subcutaneous administration of pancuronium, male patients of a similar size as the patient were given the same dose of pancuronium intravenously or *via* one of two different subcutaneous sites (hand *versus* ankle).

The results demonstrate that the onset of neuromuscular blockade occurred more slowly in the subcutaneous groups than in the intravenous group and that the peak effects of blockade differed in the routes of the administration of pancuronium. Following intravenous administration of pancuronium, a direct relationship was demonstrated between the concentration of the drug in plasma and the magnitude of neuromuscular blockade in anesthetized patients.[1,2] In patients receiving pancuronium subcutaneously, the rate of drug absorption from the subcutaneous injection site to capillary blood is probably the determining factor for the onset of neuromuscular blockade. The speed of absorption of pancuronium determines the time course of plasma concentration of the drug. The cause of delayed onset of paralysis observed in the patient receiving pancuronium subcutaneously may be the result of slow systemic absorption of the drug from the subcutaneous injection site to the plasma.

In addition to delayed onset of effect, recovery from neuromuscular blockade was substantially prolonged in the group receiving pancuronium subcutaneously in the

ankle. In a study on the regional differences of the skin blood flow at various sites of the body, a tendency was observed for the skin blood flow to decrease gradually from the upper part of the body to the lower part of the body; the skin blood flow at the dorsum of the foot was significantly lower by about 25% than that of the hand.[3] After an intravenous injection of a neuromuscular agent, the plasma concentration of the drug increases rapidly and then decreases as a result of redistribution and binding to both active and nonactive receptor sites. The rate at which the drug is removed from the receptor sites is dependent on the binding of drug to the receptor and a suitable concentration gradient between the receptor and the plasma, which allow it to diffuse away from the site of activity. The rate of recovery from neuromuscular blockade is governed largely by the rate of decline of the plasma concentration.[4,5]

We speculate that the prolonged recovery from neuromuscular blockade in the group receiving pancuronium subcutaneously in the ankle is caused by the continued absorption of the drug over a prolonged period of time from the subcutaneous tissue in the ankle, and that the subcutaneous source served as a reservoir for the drug. However, it should be noted that the actual skin blood flow will depend on the vascular architecture as well as the distribution of the flow during various physiologic conditions such as age and anesthesia and the degree of arteriosclerosis. It seems, therefore, that one cannot accurately predict the duration of paralysis following subcutaneous administration of pancuronium. We confirm that delayed onset and prolonged recovery from neuromuscular blockade in the present case were produced by subcutaneous administration of pancuronium.

In summary, we describe a patient with a markedly prolonged neuromuscular blockade after inadvertent subcutaneous administration of pancuronium. When nondepolarizing relaxants are administered subcutaneously, special attention should be paid to the delayed onset and prolongation of neuromuscular blockade.

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Flumazenil Counteracts Intrathecal Baclofen-induced Central Nervous System Depression in Tetanus

J. M. SAISSY, M.D.,* M. VITRIS, M.D.,† J. DEMAZIÈRE, M.D.,
M. SECK, M.D.,‡ L. MARCOUX, M.D., M. GAYE, M.D.‡

Tetanus, provoked by an infection due to *Clostridium tetani* (a gram-positive bacillus), is characterized by severe muscular contractures and convulsions. Death can occur through respiratory muscle contracture. These symptoms are due to the action of tetanospasmin, a neurotoxin produced by the bacterium. At the level of γ-aminobutyric acid (GABA) and glycine synapses, the toxin acts through a presynaptic blockade of motoneuron inhibition by Renshaw cells and Ia fibers of reciprocal innervation.[1] Tetanus has become rare in industrialized societies[2] but is still frequent in Third-world countries.[3] And despite the availability of artificial ventilation, benzodiazepines, and neuromuscular relaxants, the disease is often lethal.[2]

Baclofen (β-[4-chlorphenyl] γ-aminobutyric acid) inhibits polysynaptic nociceptive reflexes through an action on $GABA_B$ medullary interneurons.[4] Although baclofen can cross the blood–brain barrier and can exert its antispasticity effect by a systemic route, the dose required to manage severe spasticity may result in significant side effects, such as somnolence and respiratory depression. To diminish these side effects and to obtain high concentra-

* Professor.
† Assistant Professor.
‡ Assistant.

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Address reprint requests to Dr. Saissy: Service d'Anesthésie-Réanimation, Hôpital Principal de Dakar, Boite Postale 3006, Dakar, Sénégal.

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