

# Prolonged Apnea Following Succinylcholine in Cancer Patients Receiving AB-132

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In our hospital many patients are receiving new cancer chemotherapeutic drugs preoperatively. A potential hazard of unexpected complications exists in anesthetization of such patients. In this paper two cases of prolonged apnea resulting from the use of succinylcholine in patients receiving a cancer chemotherapeutic drug, AB-132 or ethyl-N-(bis[2,2-dimethylenimido]phosphoro)carbamate, are described. The inhibitory effects of AB-132 on blood cholinesterase levels are presented.

## Case Reports

*Case 1.* A 52 year old man with inoperable squamous cell carcinoma of the left lung was treated with a cancer chemotherapeutic drug, AB-132, at an intravenous dosage of one gram daily for ten consecutive days. During the course of chemotherapy he experienced occasional episodes of nausea, vomiting, dizziness and tiredness. Physical examination and laboratory findings were otherwise not remarkable. Bronchoscopy was scheduled to evaluate the effect of chemotherapy. Preanesthetic medications were 50 mg. of meperidine hydrochloride and 0.2 mg. of scopolamine hydrochloride, intramuscularly. Induction of anesthesia was carried out with intravenous thiopental sodium (125 mg.). After 80 mg. of succinylcholine intravenously (about 1.0 mg./kg.) and hyperventilation with oxygen, bronchoscopy was performed during apnea. Following bronchoscopy the patient failed to resume spontaneous breathing. To rule out hyperventilation as the cause of apnea, intermittent periods of hypoventilation (500 ml. at four times a minute with oxygen) were tried but found ineffective to initiate respiration. Two separate doses of 2.5 mg. of n-allylnormorphine were administered intravenously

without return of spontaneous respiration. The trachea was then intubated and the lungs ventilated with 40 per cent oxygen in air with a Bennett intermittent positive-pressure machine for a subsequent four and one-half hours. Not until seven hours after administration of succinylcholine did he start to move his arms and legs, open his eyes, and show adequate spontaneous respiration. It should be pointed out that following extubation the patient acknowledged complete awareness of the preceding events. In the following 30 hours he had several episodes of hypoventilation, bradycardia, and hypotension. In spite of successful resuscitation and supportive measures, he expired on the second postoperative day. Autopsy revealed squamous cell carcinoma of the left lung with metastasis to the mediastinum and the presence of bronchopneumonia.

*Case 2* was a 74 year old man with a diagnosis of papillary carcinoma of the urinary bladder with regional metastases. As radical surgery was thought contraindicated, he was treated with AB-132 at an intravenous dosage of one gram daily for four days. He was then scheduled for cystoscopic examination. Preanesthetic medications were 4 mg. of morphine sulfate and 0.2 mg. of scopolamine hydrochloride, intramuscularly. Induction of anesthesia was carried out with 25 mg. of meperidine hydrochloride and 500 mg. of thiopental sodium intravenously in divided doses. Anesthesia was maintained with N<sub>2</sub>O and O<sub>2</sub> mixture. At the end of the cystoscopy 20 mg. of succinylcholine (about 0.3 mg./kg.) was administered to facilitate bimanual abdominorectal examination. Spontaneous respiration failed to return for over an hour after the administration of succinylcholine. Fortunately, this patient's subsequent postoperative recovery was uneventful.

## Discussion

Prolonged apnea after succinylcholine has been discussed in detail by Foldes *et al.*<sup>1</sup> The

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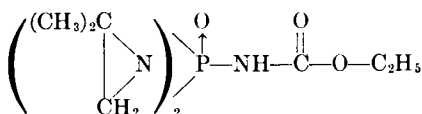


FIG. 1. The molecular structural formula of AB-132 or ethyl-N-(bis(2,2-dimethylenimido)-phosphoro) carbamate.

two general causes for prolonged apnea after succinylcholine are a low plasma pseudocholinesterase level and an altered sensitivity of the myoneural junction.<sup>2</sup>

It has become apparent that a sharp clinical distinction between the two forms of neuromuscular block, depolarizing and the non-depolarizing, may not be possible. Various investigators have suggested that many cases of prolonged apnea after succinylcholine are due to the development of a dual block in which reversal of the apnea by neostigmine or edrophonium is accomplished.<sup>3,4</sup> However, the administration of neostigmine to patients with a low esterase level will not shorten the duration of apnea due to succinylcholine, and may well intensify it.

In the present two cases the probable cause for prolonged apnea was believed to be a

low blood cholinesterase level. Since both patients had normal liver function tests, any reduction of cholinesterase activity was the likely result of AB-132 received prior to operation.

AB-132 or ethyl-N-(bis[2,2-dimethylenimido]phosphoro)carbamate (fig. 1) is one of the antitumor agents currently being investigated in patients with solid tumors.<sup>5,6</sup> However, the drug is toxic, and its administration may cause many undesirable side effects.<sup>7</sup>

In order to evaluate the effects of AB-132 on blood cholinesterase levels, various amounts of the compound were added *in vitro* to equal aliquots of a plasma sample from each of four healthy blood donors. A typical dose-related effect can be seen in figure 2 in which, when the concentration of AB-132 was increased from 0 to 0.2 per cent, the cholinesterase activities in terms of  $\Delta pH/\text{hour}$  measured by the electrometric method of Michel<sup>8</sup> were found to decrease from 1.044 to 0.136.

To establish the *in vivo* inhibitory effect of AB-132, the cholinesterase levels in plasma and red blood cells of four other cancer patients were measured before, during and after

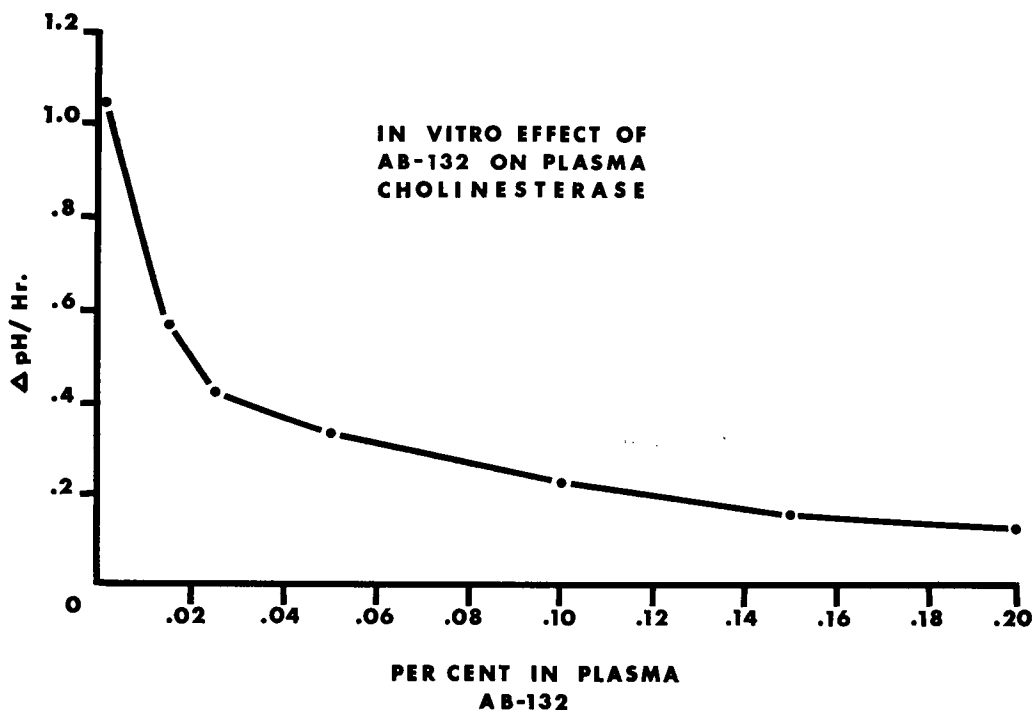


FIG. 2. The *in vitro* inhibitory effect of AB-132 on the plasma cholinesterase activities of a healthy blood donor.

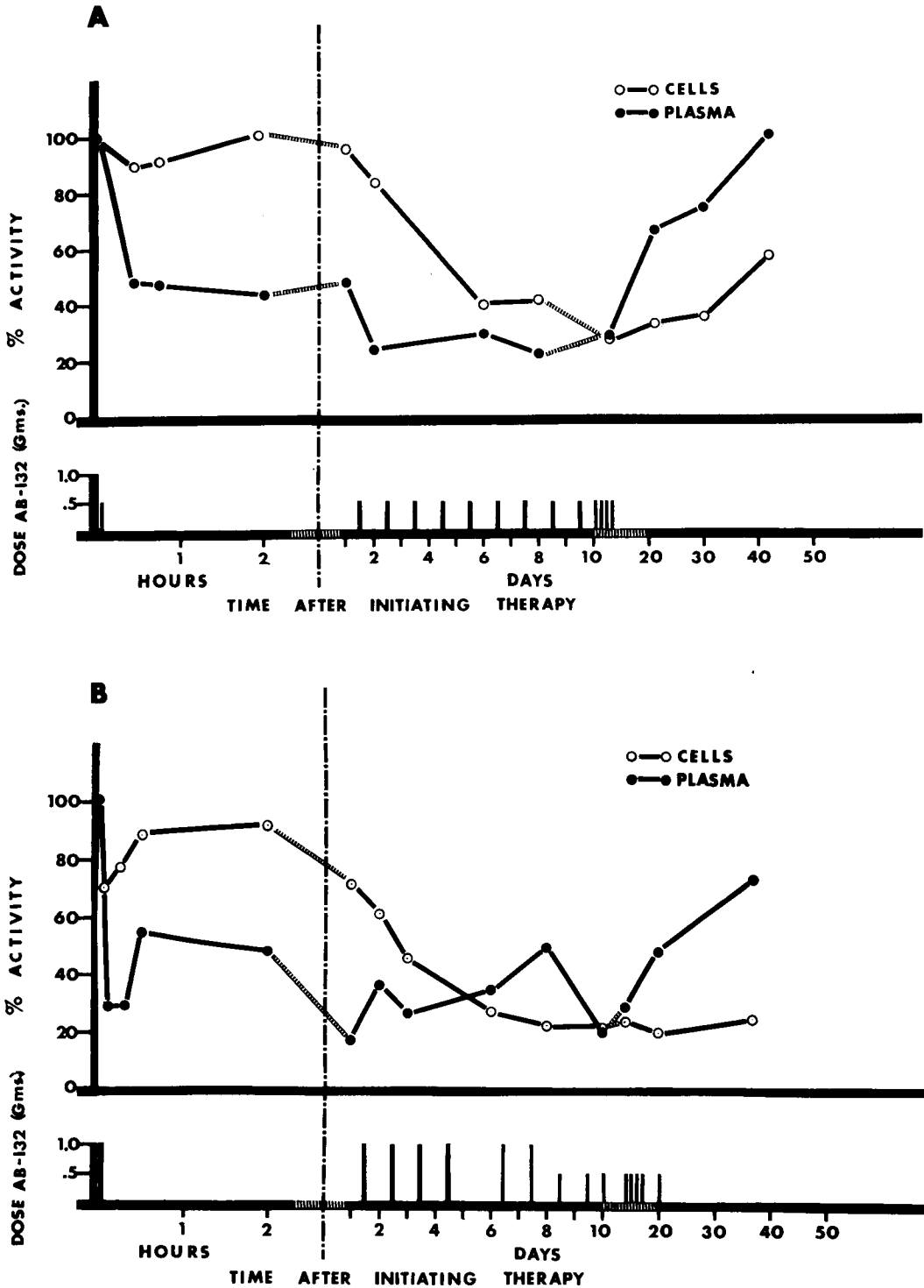


FIG. 3. The *in vivo* inhibitory effect of AB-132 on the cholinesterase levels in plasma and red blood cells of two cancer patients, A and B, receiving AB-132 therapy.

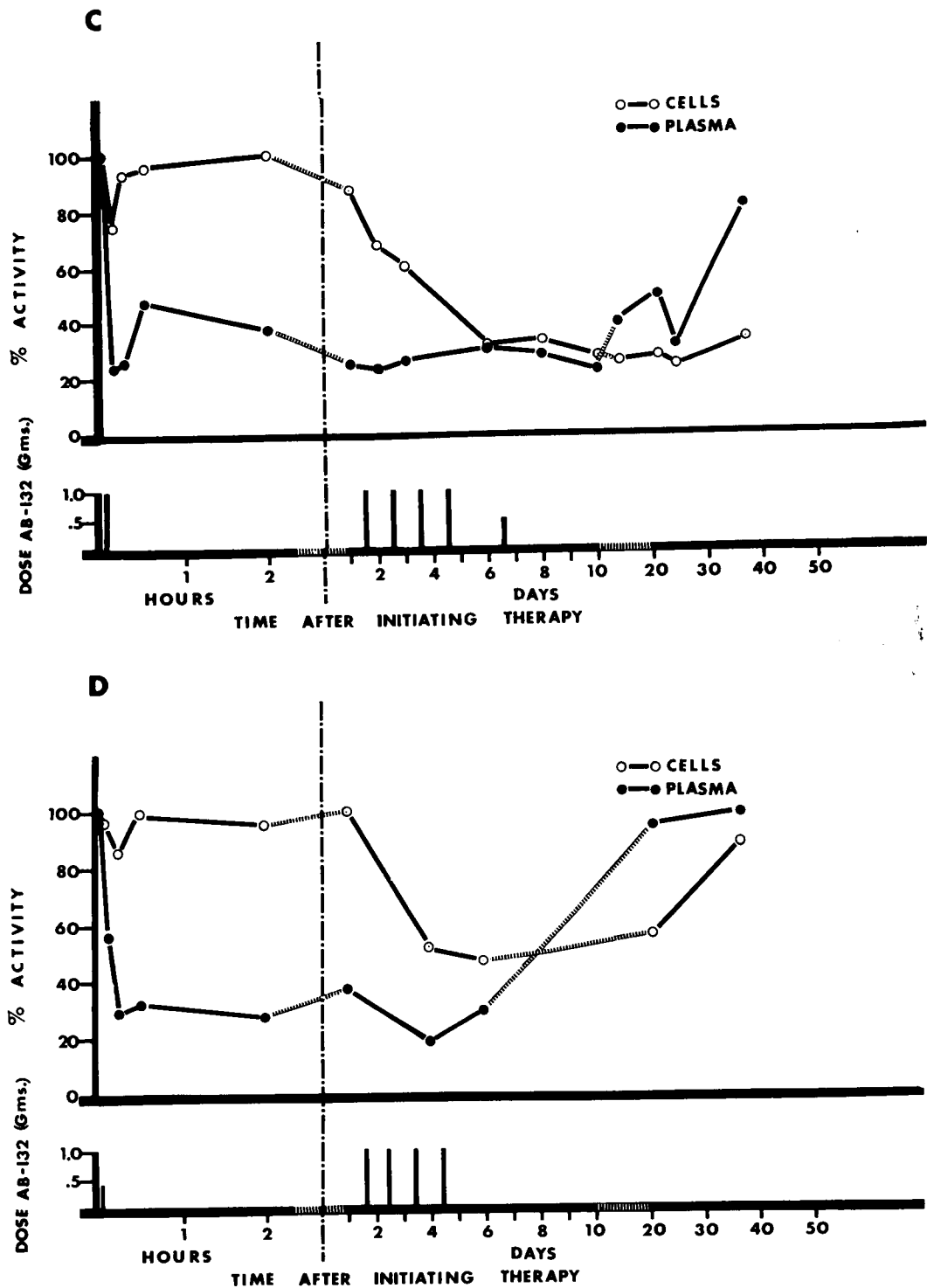


FIG. 4. *In vivo* inhibitory effect of AB-132 on the cholinesterase levels in plasma and red blood cells of two cancer patients, C and D, receiving AB-132 therapy.

a course of AB-132 therapy. It was found that following the intravenous administration of a single dose of 0.5 or 1.0 g. of AB-132 the plasma pseudocholinesterase levels dropped markedly without significant decreases in true cholinesterase activity (figs. 3 and 4). On repeated daily administration of the drug both the true and pseudocholinesterase activities decreased to as little as 20 per cent of the initial levels. Thus, AB-132 is a potent inhibitor of cholinesterase. The exact mechanism of inhibition of cholinesterase is not known. Since the cholinesterase activities failed to return to normal until 30 to 40 days after the cessation of AB-132 therapy, it resembles the long acting inhibition of di-isopropylfluorophosphate. In a separate study<sup>9</sup> it was found that on the basis of molar concentration, the degree of inhibition of cholinesterase by AB-132 is much greater than the combined inhibitory effects of nitrogen mustard and urethane. Thus, it seems that the organic phosphorous group in the molecular structure of AB-132 may also have inhibitory effect on cholinesterase.

From these studies, it is concluded that succinylcholine should not be given during anesthesia to patients receiving this cancer chemotherapeutic agent, AB-132. Determination of blood cholinesterase levels in these patients before operation should be encouraged. With the availability of a simple test-strip method of determining serum or plasma cholinesterase,<sup>10</sup> the effect of new drugs on the cholinesterase activity can be determined preoperatively. In the absence of a cholinesterase determination the possibility of prolonged postanesthetic apnea following the administration of depolarizing relaxants to patients receiving new drugs must be kept in mind.

### Summary

Two cases of postanesthetic prolonged apnea were presented. One patient failed to resume spontaneous breathing until seven hours after the intravenous administration of 80 mg. of succinylcholine and expired on the second postoperative day. Another patient had apnea of one hour following the intravenous administration of 20 mg. of succinylcholine. Prolonged apnea was attributable to the inhibition

of the plasma and red blood cell cholinesterases by a antitumor agent, AB-132, which was given to the patients prior to operation. The marked inhibitory effects of AB-132 on blood cholinesterase were demonstrated both *in vitro* and in four other cancer patients on AB-132 therapy. It is concluded that succinylcholine should not be given during anesthesia to patients receiving this cancer chemotherapeutic agent.

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