Current Comment

S. G. HERSHEY, M.D., *Editor*

Propitocaine (Citanest) and Methemoglobinemia

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Propitocaine (Citanest) is a new local anesthetic chemically related to lidocaine.[1] A number of clinical studies indicate that this agent is similar in potency to lidocaine, but has a significantly greater margin of safety because of lower systemic toxicity.[2-5] Studies in our department indicate that propitocaine is an effective local anesthetic agent which can be administered in single doses of 900 to 1,000 mg. without serious toxic effects. However, following such large doses, various investigators report the occurrence of a cyanotic-like state in some patients.[4, 6] This observation was also made during our clinical studies. This cyanotic-like state, which does not respond to the administration of oxygen, is not accompanied by dyspnea, tachycardia or hypotension. Spectroscopic examination of the blood of these patients reveals the presence of methemoglobin. This study was initiated to determine the relationship between various dosages of Citanest and the incidence and degree of methemoglobinemia.

METHODS

Methemoglobin determinations were carried out in 95 patients who received propitocaine in doses varying from 400–1,200 mg. In each instance the total amount of propitocaine was administered as a single injection. In the majority of patients propitocaine was administered peridurally, but in some cases other types of regional blocks were performed. It became apparent that the dose of propitocaine administered, rather than the type of block performed, determined the incidence as well as the degree of methemoglobinemia. Therefore grouping of data was determined by the total dose of propitocaine regardless of the route of administration. Methemoglobin levels were determined by the neutralized cyanide method according to Evelyn and Malloy.[7] Blood samples were taken prior to and at 30-minute intervals following the administration of propitocaine. Blood sampling was discontinued 90 minutes following administration of the local anesthetic if no methemoglobin was detected in the blood. In those cases in which methemoglobin was found, samples were taken at 30-minute intervals until the methemoglobin level began to regress. In a second series of patients, methemoglobin levels were determined prior to and at 30-minute intervals following the administration of lidocaine administered in doses of 400–600 mg.

RESULTS

The incidence of methemoglobinemia following the administration of various dosages of propitocaine or lidocaine is presented in table 1. Only one patient of the 20 who re-

TABLE 1. Incidence of Methemoglobinemia Following the Administration of Various Doses of Propitocaine and Lidocaine

Agent	Dose	Patients	Patients with Detectable Methemoglobinemia
Propitocaine	400	29	1 (3.4%)
Propitocaine	600	45	13 (28.8%)
Propitocaine	900	16	11 (68.7%)
Propitocaine	1,200	5	5 (100%)
Lidocaine	400	3	0
Lidocaine	600	25	0

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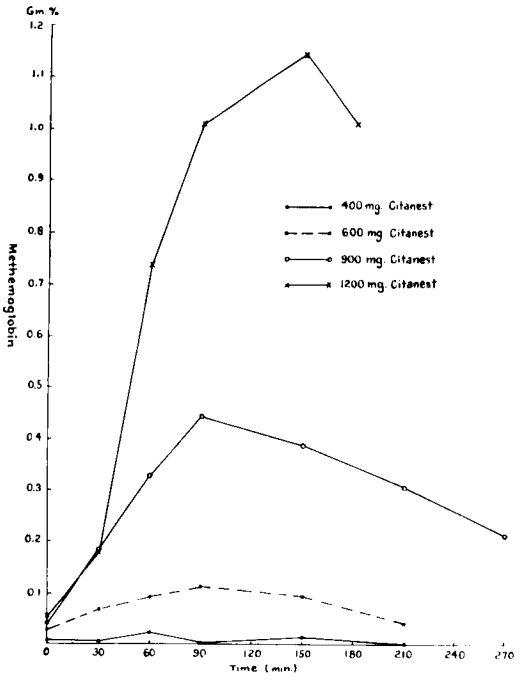

FIG. 1. Methemoglobin blood levels (g./100 ml.) at various time intervals following the administration of various doses of propitocaine (Citanest). The 400-mg. line represents the average of 29 patients. The 600-mg. line represents the average of 45 patients. The 900-mg. line represents the average of 16 patients. The 1,200-mg. line represents the average of 5 patients.

ceived 400 mg. of propitocaine showed chemically detectable methemoglobinemia. The incidence of methemoglobinemia increased as the dose of propitocaine was increased. At a dose of 900 mg., 11 of 16 patients showed some degree of methemoglobinemia, and at a dose of 1,200 mg. all 5 patients were found to have methemoglobin in their blood. On the other hand, no methemoglobin was found in any of the patients receiving 400–600 mg. of lidocaine. Figure 1 shows the degree of methemoglobinemia in g./100 ml. at various time intervals following the administration of 600–1,200 mg. of propitocaine. As can be seen, the degree of methemoglobinemia increases as the dose is increased. At doses of 500–1,200 mg., the methemoglobin level reaches a peak at 90–150 minutes and then begins to recede at 180 minutes.

DISCUSSION

Propitocaine has been found to be a local anesthetic of considerable efficacy and to possess a safety margin apparently greater than that of the more commonly used local anesthetics. At dose levels in the order of 900 mg. or higher a cyanotic-like state, not reversed by O_2 administration was frequently noted. Recently Sadove *et al.*,[4] and Scott [5] have reported that this cyanotic-like appearance was related to the production of methemoglobinemia.

Methemoglobin is a form of hemoglobin in which the iron of the heme complex has been oxidized to the ferric form by electron transfer to oxygen and so cannot be disassociated by changes in oxygen tension and thus participate in respiration. Normally, methemoglobin is continually being formed in the body, but is promptly reduced by the enzyme reductase(s) so that the concentration of methemoglobin in blood under physiological conditions rarely exceeds 1 per cent of the total hemoglobin. Abnormal methemoglobin levels can occur as a result of the genetic absence of the enzyme reductase(s) or by chemical agents which enhance the oxidation of hemoglobin to methemoglobin. Propitocaine most likely falls into the latter category, that is, this agent or a metabolite of this agent acts to increase the oxidation of hemoglobin to methemoglobin just as is the case with other chemical compounds, such as aniline, sulfonamides, acetanilid, the nitrites and nitrates, etc. Since the addition of propitocaine to blood *in vitro* does not produce methemoglobin, Scott [6] postulates that the methemoglobinemia produced *in vivo* by propitocaine is related to a metabolite of this local anesthetic.

The clinical consequences of methemoglobinemia produced by propitocaine must be weighed against the greater safety margin of this agent with respect to potential systemic toxicity. Our studies indicate that a relation exists between the total amount of propitocaine administered and the amount of methemoglobin formed. At dose levels of 600 mg. or less, the maximum amount of methemoglobin observed in our study was 0.9 g./100 ml. observed in one patient. It would appear that in the normally effective dosage range of this agent

(200–600 mg.), methemoglobin levels of 1 g./100 ml. or greater would rarely be achieved. Thus, under usual clinical conditions, it is unlikely that the methemoglobinemia produced as a result of the injection of propitocaine would be of significance. However, in patients with anemia, or with cardiac failure in whom the availability of oxygen has already been decreased, the potential disadvantage of further hypoxic embarrassment due to the use of large doses of this agent must be carefully considered. For example, in doses of 900 mg. or greater, we observed a methemoglobin value of 2.7 g./100 ml., and Scott reported a methemoglobin value of 3.4 g./100 ml. Despite the occurrence of such high levels of methemoglobinemia, neither Scott [6] nor ourselves observed clinical symptoms of hypoxia. Except for the cyanotic-like appearance of the patients, these individuals did not demonstrate change in blood pressure, heart rate, or respiration. It would appear that in normal individuals, even the use of excessive amounts of propitocaine would be well tolerated. Drug-induced methemoglobinemia is readily reversible. Our data revealed that methemoglobin levels began to regress spontaneously 2–3 hours following the administration of propitocaine. In addition, Scott has shown that propitocaine-induced methemoglobinemia can be quickly reversed by the administration of methylene blue.[6] It is apparent from our studies as well as those of others, at the present time, that clinically significant methemoglobinemia does not occur except following excessive doses of propitocaine. Therefore, the production of methemoglobin should not be considered as a serious contraindication to the use of propitocaine as a conduction anesthesia agent.

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Amitriptyline (Elavil) as an Agent for Premedication

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Amitriptyline possesses tranquilizing, antidepressant and anticholinergic properties.[1] The hypnotic effects of this drug were confirmed by Dobkin and associates,[2] who also demonstrated that in the adult dose range of 20 mg., given intravenously, little hypotension resulted from its administration. It was therefore decided to investigate the properties of amitriptyline when used for premedication.

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A preliminary study indicated that the average optimum preoperative sedative dose of amitriptyline for adult patients was 10 mg. intramuscularly one hour before operation. Of 155 patients studied initially, 55 were given amitriptyline 10 mg., 52 meperidine 50 mg. and 48 received pentobarbital 50 mg. as premedication. Analysis of the results indicated that amitriptyline relieved anxiety and apprehension without producing hypotension or hypnosis.

A double-blind study was then instituted to compare amitriptyline 10 mg., pentobarbital