

Methemoglobin Formation and Oxygen Transport Following Intravenous Regional Anesthesia Using Prilocaine

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Methemoglobin levels, changes in oxygen content of blood, and appearance of cyanosis were studied in 58 subjects following induction of regional anesthesia with 5 mg./kg. of prilocaine intravenously. The average maximum rise in methemoglobin was 1.02 Gm./100 ml. blood, 155 minutes after release of the tourniquet. Cyanosis was not detected. A significant shift in the hemoglobin dissociation curve occurred at P_{O_2} levels below 30 mm. Hg. When methemoglobin levels were above 0.8 Gm./100 ml. blood and the P_{O_2} levels were below 30 mm. Hg, this shift resulted in a mean increase in oxygen content of 2.64 ± 3.40 ml. O_2 /100 ml. blood above the calculated normal. Assuming constant flow, less oxygen would be available to the tissues under these conditions. The use of prilocaine by this technique at this dose level in patients with circulatory compromise of heart or brain cannot be recommended until the physiologic importance of these changes is determined. In healthy patients the rise in methemoglobin levels and decrease in oxygen availability are probably within acceptable limits.

THE EFFICACY of regional anesthesia produced by intravenous injection of a local anesthetic into an extremity isolated from the systemic circulation has been confirmed.¹⁻⁶ Not only is

prilocaine (Citanest)^{*} effective,^{2,3,7,8} but it may have a lower toxicity than lidocaine (Xylocaine).⁹⁻¹² Cyanosis secondary to methemoglobin formation has been reported following the use of prilocaine by other routes.¹³⁻¹⁷ In the present study, rates of appearance and disappearance of methemoglobin, its influence on the hemoglobin dissociation curve of blood, and occurrence of cyanosis following intravenous regional anesthesia with prilocaine have been examined in a series of 58 subjects.

Ischemia of the limb prior to injection of the drug has been shown to enhance production of anesthesia.^{4,5} Since methemoglobin is thought to be induced by a metabolic product of prilocaine,¹⁸ the metabolic changes resulting from ischemia could play a role in the rate of degradation of prilocaine and in formation of methemoglobinemia. Therefore, the effect of ischemia prior to injection of the drug was studied in relation to methemoglobin production.

Methods

The 58 fasting, unpremedicated adult volunteers ranged in age from 20 to 56 years (mean, \pm S.D. = 29.6 ± 7.6 years). The forearm was exsanguinated by means of an Esmarch bandage and isolated from the systemic circulation by an upper arm tourniquet inflated to 200 mm. Hg. Next, prilocaine, 5 mg./Kg., was injected into a forearm vein.

Twenty-six subjects underwent a 15-minute period of ischemia of the limb prior to injection of prilocaine. Injection was made without prior ischemia in 32. The tourniquet was released ten minutes after injection, whether or

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TABLE 1. PO₂ vs. O₂ Content Calculated-O₂ Content Measured (ml/100 ml)

N	PO ₂ Range	Mean	S.D.	S.E.	t	P
78	0-29	-1.64	±3.05	±0.35	4.74	0.001
291	30-59	-0.15	±2.10	±0.12	1.25	N.S.*
84	60-90	+0.05	±1.91	±0.21	0.246	N.S.

* Not significant.

$$\text{Correlated } t \text{ test: } \sqrt{\frac{\sum d/N}{N(N-1)}}$$

where d = difference between calculated and measured values.

not anesthesia was complete, to standardize the time of release of prilocaine into the circulation.

The experiments were carried out in an operating room with a staff anesthetist (D. C.) present and with resuscitative equipment at hand. Each volunteer was carefully appraised of the nature of the experiment and was permitted to withdraw from it if he had reservations.

Venous blood samples were drawn from the opposite limb prior to and at frequent intervals during the five-hour period following injection of the drug. Blood was allowed to flow freely through an indwelling plastic catheter without a venous tourniquet. Blood was collected in heparinized tubes, iced immediately, and analyzed within 30 minutes for methemoglobin by the method of Evelyn and Malloy.¹⁹ In our laboratory duplicate samples agreed within 0.1 Gm. methemoglobin per 100 ml. blood. Total hemoglobin was determined colorimetrically after conversion to cyanmethemoglobin. O₂ content was determined in 0.05 ml. samples of blood with an oxygen electrode.²⁰ P_{O₂}, P_{CO₂}, and pH were read by means of appropriate blood gas electrodes maintained at 38° C. Changes in oxygen content were assessed as follows: O₂ saturation of a particular sample was read from the Severinghaus Blood Gas Calculator²¹ at BE = 0 for the determined hemoglobin, pH and P_{O₂}. The O₂ content of the blood was calculated according to the formula:

$$\begin{aligned} \text{O}_2 \text{ content (ml./100 ml.)} = \\ S_{O_2} \times 1.35 (\text{total hemoglobin} \\ - \text{methemoglobin}) + (0.0031 \times P_{V_{O_2}}) \end{aligned}$$

where P_{V_{O₂}} = oxygen tension (mm. Hg) of blood obtained from a peripheral vein and S_{O₂} = oxyhemoglobin saturation from the blood gas calculator.²¹ The calculated value was compared with the measured O₂ content.

Results

The distribution of venous methemoglobin levels prior to injection of prilocaine is shown in figure 1. Figure 2 shows mean venous methemoglobin levels for the whole group plus the standard deviation, plotted against time following injection. The peak mean value, 1.02 ± 0.33 Gm. methemoglobin/100 ml. blood, was reached 155 minutes after the release of the tourniquet.* The highest value obtained was 1.98 Gm. methemoglobin/100 ml. blood. A progressive fall in methemoglobin level occurred after 155 minutes. No correlation was found between peak methemoglobin level and hemoglobin level or between rise in methemoglobin and hemoglobin level. Subjects with higher pre-injection methemoglobin levels tended to have the highest peak values, but change in methemoglobin levels did not correlate with pre-injection values. Comparison of the maximum change in methemoglobinemia of subjects with pre-injection ischemia and those without disclosed no increase in the ischemia group. The average peak percentage of total hemoglobin as methemoglobin was 7.6 per cent at 155 minutes (maximum: 12 per cent).

* The peak methemoglobin levels were obtained 165 minutes after intravenous injection of the drug, or 155 minutes after release of the upper arm tourniquet.

The difference between calculated and measured O_2 content considered against the corresponding P_{O_2} is shown in table 1. There was a highly significant (P less than 0.001) shift of the curve of O_2 content versus P_{O_2} to the left at low P_{O_2} values (i.e., 0 to 29 mm. Hg). No significant difference was found in hemoglobin dissociation at P_{O_2} values above 30 mm. Hg. Table 2 shows the difference between the calculated and measured O_2 content considered against corresponding methemoglobin values. A slight (0.8 to 1.1 ml. O_2 /100 ml. blood) shift to the left was significant for methemoglobin levels above 0.80 Gm./100 ml. blood.

Combination of data for all subjects with methemoglobin levels above 0.80 mg./100 ml. blood at P_{O_2} values below 30 mm. Hg ($N = 39$), revealed a mean difference of -2.64 ± 3.40 ml. O_2 /100 ml. blood (P less than 0.01) between O_2 content calculated and measured.

Although the marked subjective element in assessing visible cyanosis is freely admitted, clinically evident cyanosis was not present in any subject at any time during the course of the experiment.

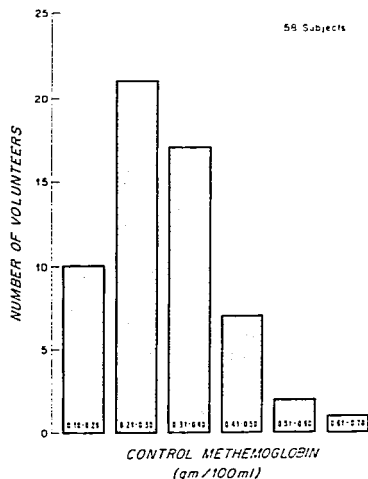


FIG. 1. Histogram showing the distribution of control methemoglobin values.

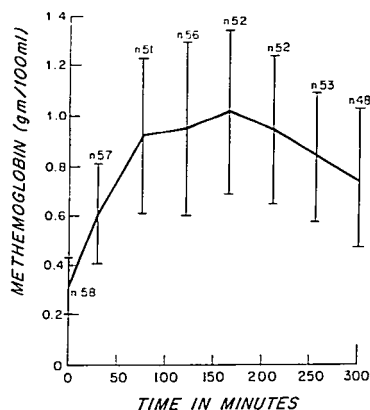


FIG. 2. Mean methemoglobin value and standard deviation plotted against time following injection of prilocaine. The peak value of 1.02 ± 0.33 Gm./100 ml. occurred at 165 minutes following injection of the drug and 155 minutes following release of the tourniquet.

Discussion

The cyanosis and rise in serum methemoglobin following injection of prilocaine by other routes usually has occurred after doses in excess of 600 mg.¹³⁻¹⁷ Although the dose required for effective intravenous regional anesthesia is less than 600 mg.,²² it is not beyond the dosage range which occasionally has been associated with methemoglobinemia. For example, Duly *et al.*²³ reported cyanosis after 400 mg. of prilocaine had been given for a continuous lumbar epidural block.

The experimental dose of 5 mg./Kg. of prilocaine was chosen because it exceeds the dose required for satisfactory anesthesia.⁵ Even at this dosage, the levels of methemoglobin produced, with or without a 15-minute period of ischemia, produced only small changes in O_2 content.

Only the peak values of the methemoglobin levels produced by 5 mg./Kg. intravenous prilocaine had significant effects on *in vivo* O_2 transport characteristics of whole blood; these effects averaged from 0.8 to 1.1 ml. O_2 /100 ml. blood. With a P_{O_2} of less than 30 mm. Hg and methemoglobin levels greater than 0.8

TABLE 2. Methemoglobin vs. O₂ Content Calculated-O₂ Content Measured (ml./100 ml.)

N	Methemoglobin Range (Gm./100 ml.)	Mean	S.D.	S.E.	t	P
64	0-0.39	+0.41	±2.47	±0.31	1.333	N.S.*
179	0.4-0.79	+0.07	±1.78	±0.13	1.003	N.S.
146	0.8-1.19	-0.82	±2.40	±0.20	4.211	<0.001
55	1.20-1.59	-1.11	±2.69	±0.36	3.083	0.01-0.001
6	1.60-1.99	-0.83	±1.11	±0.45	18.430	<0.001

* Not significant.

mg./100 ml. blood, the mean effect was 2.6 ml. O₂/100 ml. blood. Darling and Rough-ton²⁴ demonstrated the effect of methemoglobin on the hemoglobin dissociation curve, showing a significant shift to the left *in vitro* using lysed human red blood cells suspended in phosphate buffer at methemoglobin levels presumably 14 per cent of total hemoglobin. In the present study a significant change in O₂ transport occurred when the mean peak methemoglobin concentration was 7.6 per cent of total hemoglobin.

Two facts stand out: 1. there is no discrepancy between calculated normal and measured O₂ content above the venous P_{O₂} value of 30 mm. Hg; and 2. a significant alteration in oxygen content of venous blood was present in the absence of cyanosis.

The significant shift of the oxygen dissociation curve to the left at methemoglobin levels above 0.80 Gm./100 ml. blood is small and is unlikely to be of physiologic significance in normal patients. Since no significant difference occurred even at peak methemoglobin levels when the P_{O₂} exceeded 30 mm. Hg, only those vital organs with a venous P_{O₂} below 30 mm. Hg require special consideration. The range of venous P_{O₂} of the coronary and cerebral circulation is about 25-30 mm. Hg.^{25,26} Compromise of oxygen transport to the brain and heart, though transient, is possible following the use of prilocaine at this dose level and given by this route, especially if the oxygen transport is already compromised by anemia, arterial disease, cyanotic states, etc. The total decrease in O₂ available to the tissue would be the result of both a reduction in total available hemoglobin and a shift in the dissociation curve to the left. It is important to realize that the changes in

O₂ transport demonstrated in this study can exist without gross cyanosis.

The effect of change in the arteriovenous difference to these organs could be offset by an increase in blood flow. However, in patients with borderline coronary or cerebral circulation, decrease in O₂ transport due to the methemoglobin might exceed the ability for circulatory compensation. Therefore it would appear unwise to use this drug in this dose and by this route in patients with evidence of reduced cerebral or cardiac blood flow until the physiologic importance of these changes can be established.

Summary

In a study of 58 patients, the average rise of methemoglobin following the production of regional anesthesia using 5 mg. per Kg. of prilocaine intravenously was from 0.33 ± 0.11 Gm./100 mg. to 1.02 ± 0.33 Gm./100 mg. Gross cyanosis was not observed in any subject. A 15-minute period of ischemia of the limb prior to injection of the drug did not increase the amount of methemoglobin formed. When venous P_{O₂} was below 30 mm. Hg or methemoglobin level exceeded 0.80 Gm./100 ml. blood, a statistically significant increase in oxygen content occurred. If both conditions existed simultaneously, the shift amounted to 2.64 ± 3.40 ml. O₂/100 ml. blood. When venous P_{O₂} exceeded 30 mm. Hg no significant difference existed between calculated normal and measured oxygen content of the blood. The magnitude of these changes does not contraindicate the use of prilocaine for intravenous regional anesthesia in normal subjects, but might be important if coronary or cerebral oxygen transport were already compromised.

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