METHAEMOGLOBINAEMIA IN MOTHER AND FOETUS FOLLOWING CONTINUOUS EPIDURAL ANALGESIA WITH PRILOCAINE

Clinical and Experimental Data

BY

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SUMMARY

The methaemoglobinaemia induced by prilocaine administered as a continuous epidural analgesic to women in labour has been examined. At delivery the level of methaemoglobin present in both the maternal and foetal blood was found to be similar in most of the ten cases examined. The decline in methaemoglobinaemia after birth of two infants born with high methaemoglobin levels (14.2 and 16 per cent) was examined. In both cases the level fell to very low values within 24 hours (2 and 3.7 per cent respectively). A parallel study was carried out on cats in labour when it was found that administration of prilocaine to the mother produced virtually no methaemoglobin in the foetus, illustrating the species difference of this response. Cats were chosen because they are particularly sensitive to the methaemoglobin formation induced by aromatic amines and amides.

It has been reported (Daly, Davenport and Newland, 1964; Scott, Owen and Richmond, 1964) that the local anaesthetic agent prilocaine (Citanest) can cause methaemoglobinaemia in some patients when administered in large doses. Women in labour receiving analgesia by means of a continuous lumbar or sacral epidural block, when the total dose of prilocaine may exceed 1 g, are likely to be affected.

Methaemoglobin does not take part in the transport of oxygen, and its dark colour produces a cyanotic appearance of the skin and mucous membranes. Cyanosis becomes apparent at a much lower concentration of methaemoglobin (1.5 g/100 ml) than of reduced haemoglobin (5 g/100 ml) and therefore cyanosis may be quite obvious clinically at a level of methaemoglobinemia which results in a relatively small loss of the oxygen-carrying capacity of the blood (Geddes, 1965). However, even a small decline in the oxygen content of the blood may be of vital importance to some foetuses during labour and immediately after delivery.

The reported methaemoglobin levels in maternal blood are not high but there is little information available about effects on the foetus when large doses of prilocaine are given to the mother. The only quantitative report which has been published (Hjelm, 1965) refers to a series of patients undergoing hysterotomy for the termination of pregnancy in the 16th to 20th weeks. The women were given an epidural block with a single injection of 600 mg of prilocaine with adrenaline 1/250,000. One hour later the foetal blood was found to contain no more than 1 per cent methaemoglobin.

Following the introduction of prilocaine into the labour ward in 1965, clinical observation suggested that many women developed methaemoglobinaemia and some otherwise healthy newborn infants were cyanosed for many hours. The object of the present investigation was to determine the levels of methaemoglobin in maternal and foetal blood following the use of prilocaine for continuous epidural analgesia during labour. Observations were made on ten patients and their infants. A parallel study was carried out on cats following the intravenous administration of prilo-
caine, to investigate possible species differences in this response. Cats were chosen because they are known to be particularly sensitive to methaemoglobin formation induced by aromatic amines (Lester, 1943).

METHODS

Subjects.
The obstetric department frequently requests a continuous epidural block for a woman in labour when systemic narcotics and inhalation analgesia provide inadequate relief. For inclusion in this series the following conditions were observed:

1. The woman was at full term with a normal sized healthy foetus.
2. There was no indication of placental insufficiency.
3. It was anticipated that delivery would not take place for at least 5 hours.

Anaesthetic technique.
The epidural catheter was introduced at the interspace between the third and fourth lumbar vertebrae and passed caudally 2-3 cm. In nine cases prilocaine 1 per cent with adrenaline 1/500,000 was injected to provide skin analgesia to the tenth thoracic dermatome and repeat doses were injected at hourly intervals until delivery. The doses used varied from 10 to 15 ml (100-150 mg). In this series the duration of epidural block was from 5 to 8 hours and the total dose of prilocaine ranged from 500 mg to 1,050 mg. In one case (case 3), 1,450 mg of plain prilocaine 1 per cent was used during the first 7 hours. Lignocaine was then substituted.

Methaemoglobin estimation.
Samples of venous blood were taken from the mother prior to administration of prilocaine and at intervals afterwards until delivery, when a sample of cord blood was obtained. The blood samples were placed in a refrigerator immediately after withdrawal and methaemoglobin estimations carried out as quickly as possible, always within 1 hour. The cord blood was invariably examined within a few minutes of being taken. Methaemoglobin estimations were made in duplicate on each blood sample using the cyanomethaemoglobin method of Evelyn and Malloy (1938). All solutions of haem pigments in phosphate buffer were centrifuged at 3,800 r.p.m. for 5 minutes to remove

<table>
<thead>
<tr>
<th>TABLE I</th>
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<tbody>
<tr>
<td>Methaemoglobin induced by continuous epidural administration of prilocaine</td>
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<tr>
<td>-----------------------------------------------</td>
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<tr>
<td>Methaemoglobin per cent and dose of prilocaine (mg) administered</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Time after commencement of administration of prilocaine (hour)</th>
<th>Cord blood (C)</th>
<th>M-C</th>
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<tbody>
<tr>
<td>1</td>
<td>23</td>
<td>58</td>
<td>1 6.6</td>
<td>12.3</td>
<td>12.7</td>
</tr>
<tr>
<td>2</td>
<td>40</td>
<td>68</td>
<td>1/2 3.7</td>
<td>700</td>
<td>0</td>
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<tr>
<td>*3</td>
<td>29</td>
<td>76</td>
<td>3 7.5</td>
<td>12.5</td>
<td>15.9</td>
</tr>
<tr>
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<td>23</td>
<td>63</td>
<td>2 7.5</td>
<td>12.5</td>
<td>18.2</td>
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<tr>
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<td>25</td>
<td>45</td>
<td>3 7.5</td>
<td>12.5</td>
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<tr>
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<td>22</td>
<td>108</td>
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</tr>
<tr>
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<td>20</td>
<td>91</td>
<td>5 0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>60</td>
<td>6 0</td>
<td>0</td>
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</tr>
<tr>
<td>9</td>
<td>27</td>
<td>71</td>
<td>7 0</td>
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</tr>
<tr>
<td>10</td>
<td>30</td>
<td>71</td>
<td>8 0</td>
<td>0</td>
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</tr>
</tbody>
</table>

*Case 3. Prilocaine replaced with lignocaine at 7 hours. Delivery was at 11 hours when methaemoglobin level was 19.7 per cent.
red cell stromata and other particulate matter which was found to cause errors due to light scattering in the spectrophotometric measurements.

In two cases (cases 8 and 10) the decline in methaemoglobin level was followed in the infants. Blood was taken directly into two 0.1-ml pipettes from a heel puncture and diluted immediately for methaemoglobin estimation.

RESULTS
The results obtained are given in tables I and II. In table I the results obtained from ten patients are summarized. The percentage methaemoglobin found in the mother is given together with the dose of prilocaine administered and the time after the commencement of prilocaine administration. The last maternal value given for each case is the methaemoglobin percentage present in the mother at delivery, except for case 3. Two points emerge from these results. The first is that in every case except one (case 5) the methaemoglobin level in the mother rises as the dose of prilocaine administered rises. The second is that there is a considerable variation among the patients in their sensitivity towards methaemoglobin formation induced by prilocaine. In the penultimate column the percentage of methaemoglobin found in the cord blood of each patient is recorded and in the last column the difference between the value in the mother at delivery and in the cord is shown. A negative value indicates that there was a higher methaemoglobin percentage in the cord and a positive value indicates the opposite. It can be seen that there is no obvious correlation between the maternal delivery values and cord values and that except for two cases (cases 3 and 10) the two values are similar. No suggestion can be offered to explain why case 3 in particular is so different from the other cases.

In table II the fall in methaemoglobin level with time in two of the neonates (cases 8 and 10) is given. It can be seen that in both cases the methaemoglobin percentage is down to a low level after 24 hours.

DISCUSSION
Maternal methaemoglobin levels.
As has been observed by other workers (Hjelm and Holmdahl, 1965) little methaemoglobin appeared in the mother's blood until the total dose of prilocaine reached 500 mg. The rate and extent of the rise in methaemoglobin level are governed by a number of factors, causing a variable methaemoglobin response even to a single injection of prilocaine into the epidural space (Hjelm and Holmdahl, 1965). There is also considerable variation in the time of the maximum methaemoglobin response (4-8 hours after injection). A further complicating factor in the present study is that prilocaine was administered at different rates to different patients. The methaemoglobin levels reported here are, however, of the same order as those of Hjelm and Holmdahl (1965) who detected methaemoglobininaemia ranging from 3 per cent to 19 per cent 6 hours after 900 mg of prilocaine had been administered to fifteen patients.

Effect of storage of blood samples.
It is noticeable that in some reports on methaemoglobin formation following the administration of prilocaine the values are considerably lower than in this study (e.g., Lund and Cwik, 1965). A possible explanation for this difference is the time and method of storage of blood samples before the methaemoglobin estimations were carried out. Glycolysis continues in the red cell after blood has been withdrawn and any methaemoglobin present would be gradually reduced back to haemoglobin (Stolk and Smith, 1966). Storage in the cold retards this process and the lysis of the red cells which occurs when blood is diluted in phosphate buffer renders the solutions of haem pigments stable for several hours (Onji and Tyuma, 1965).

A sample of maternal blood known to contain 6.6 per cent methaemoglobin was allowed to stand at room temperature for 3 hours, by which
time the methaemoglobin level had fallen to zero. A number of samples of both cord and maternal blood which contained up to 14 per cent methaemoglobin were incubated at 37°C and in all cases no methaemoglobin could be detected after 5 hours.

In this series all maternal blood samples were examined within an hour and all cord blood samples within a few minutes of being taken.

Biochemical considerations.

Aromatic amides such as prilocaine do not form methaemoglobin in vitro (Scott, Owen and Richmond, 1964). These compounds have to be metabolized before they can cause the formation of methaemoglobin. With prilocaine there are at least two steps involved. One is hydrolysis of the amide link to produce o-toluidine and the second is a further metabolism of o-toluidine to a compound which exerts its action on haemoglobin. Kiese (1965) considers that the second metabolic reaction is N-hydroxylation and he has shown that N-hydroxy derivatives of aromatic amines are potent formers of methaemoglobin in vitro.

Cord blood when incubated with phenylhydroxylamine and other N-hydroxy aromatic amines forms methaemoglobin faster than maternal venous blood (Stoffler, Thauer and Uehleke, 1966). It has also been shown (Ross and Desforges, 1959) that infants have a temporary deficiency of the methaemoglobin reductase co-enzyme diphosphopyridine nucleotide which is normally generated by glycolysis within the red cell, which presumably explains why foetal blood is more sensitive to methaemoglobin formation than normal adult blood.

The mechanism by which methaemoglobin is formed in the foetal blood following administration of prilocaine to the mothers is not known. A number of possibilities exist. The first is that prilocaine passes from the mother to the foetus and is metabolized as described above. However, it is known that liver microsomal enzymes which catalyze these reactions are poorly developed in the neonate (Conney and Burns, 1962). Thus, the metabolism of drugs in neonates is not necessarily the same as in adults. The second possibility is that the methaemoglobin-forming metabolite of o-toluidine from the mother passes the placenta and exerts its effect on the particularly sensitive foetal haemoglobin. Clearly, both mechanisms could be operating simultaneously.

Further oxidation of haemoglobin to irreversible degradation products, including sulphaemoglobin and Heinz bodies, has been observed with aromatic amines (Allen and Jandl, 1961) including prilocaine (Onji and Tyuma, 1965). In three cases (7, 8 and 9) both maternal and cord blood were examined for Heinz bodies by staining one drop of heparinized blood with two drops of an aqueous solution containing 0.5 per cent methyl violet and 0.85 per cent sodium chloride (Harley and Robin, personal communication 1965). None were found.

Effect on the neonate.

Apart from cyanosis, none of the infants in this series was clinically affected by the temporary deprivation of some of the oxygen-carrying capacity of their blood. They were observed closely but no treatment such as methylene blue or ascorbic acid was employed.

On two of the more seriously affected infants follow-up estimations on heel-prick blood samples showed a steady fall in methaemoglobin levels over the first 24 hours (table II). No information is available from this study on the effect of methaemoglobinemia on premature or sickly infants. If a child is struggling to survive in the face of adverse intra-uterine conditions it is difficult to justify the use of any drug which is known to reduce significantly the oxygen content of its blood. Moreover, it is known that agents which cause methaemoglobinemia are less well tolerated in early life than later (Kübler, 1965).

The results of this study indicate that if prilocaine is employed to produce obstetrical analgesia in a dose sufficient to cause methaemoglobinemia in the mother, it is probable that the foetus will also be affected and to a similar degree.

EXPERIMENTS WITH CATS

Method.

Two cats in labour, each of which had given birth to one kitten, which served as a control, were given prilocaine intravenously at a dose level of 0.1 mM/kg. This dose would be expected, from previous experiments in non-pregnant cats, to produce in the order of 60 per cent methaemoglobin within 2 hours after administration. The intravenous route of administration was used to
eliminate the problems of diffusion of prilocaine from the injection site since it was not being used as a local analgesic in these experiments but simply as an agent to induce the formation of methaemoglobin.

The methaemoglobin level in the maternal blood was determined 2 hours after administration of prilocaine. The cats were then anaesthetized with ether, the uterus opened and blood samples taken from the cord and the jugular vein of each kitten. Methaemoglobin estimations were carried out on each of these blood samples. Two cats were examined in this manner and in both cases the course of labour ceased after the administration of prilocaine.

In contrast to the results obtained with humans, those obtained with cats (table III) indicate that in this species prilocaine administered to the mother in labour does not produce a significant methaemoglobin response in the foetus.

<table>
<thead>
<tr>
<th>TIME AFTER PRIOLOCAINE (HR)</th>
<th>MATERNAL BLOOD</th>
<th>KITTEN 1</th>
<th>KITTEN 2</th>
<th>KITTEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
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</tr>
<tr>
<td>2</td>
<td>48.3</td>
<td>3.5</td>
<td>3.5</td>
<td>1.8</td>
</tr>
<tr>
<td>70</td>
<td>0</td>
<td>0</td>
<td>0</td>
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**ACKNOWLEDGEMENTS**

We are grateful to the obstetricians and paediatricians of the Royal Hospital for Women for their interest and co-operation. Astra Pharmaceuticals (Aust.) Pty. Ltd. generously provided the prilocaine for the investigation. This study was supported in part by the New South Wales Pharmacy Research Trust.

**REFERENCES**


BOOK REVIEW


This book is designed, as its subtitle indicates, for medical students and house officers and it could be read with benefit by those just starting a fulltime career in anaesthesia who want to orientate themselves to earth and practical, and every page provides evidence that the authors have been concerned in the teaching of medical students and will know what points to emphasize. Thus one reads that "one of the dangers of general anaesthesia given in the text.

There are twelve chapters dealing with general anaesthesia (including preparation of the patient and postoperative complications), local and spinal anaesthesia, and a final short chapter on the clinical anaesthetist. There are no discrete sections dealing with special types of anaesthesia, for example for obstetric or dental operations, but though these are perhaps the anaesthetics most commonly given in general practice it would be undesirable to give details of these techniques and have to exclude, for reasons of space, some of the lucid explanations of the general principles of anaesthesia given in the text.

Though historically a "minor specialty" the increasing number of anaesthetists in the hospital service has made anaesthesia one of the largest specialties in the hospital service in the United Kingdom. The possible adverse effect on recruitment of removal of anaesthesia as an undergraduate subject should make the medical educators think twice before embarking on such a step. Recruitment, too, requires interest and for this reason perhaps future undergraduate textbooks might give a rather fuller outline of the anaesthetist's contributions to intensive therapy.

In recent years there has been in the U.S.A., and lately in this country, an increasing desire to teach the man in the street the elements of resuscitation. The medical student is in danger of coming to know less about the subject than the man who drives the ambulance. It is difficult to see where the undergraduate will gain this knowledge if it is not in a course of instruction in anaesthesia, and it is knowledge which he may well have to apply on his first night on duty as a houseman. For this reason it might be suggested that resuscitation receive a special place in the course of elementary instruction in anaesthesia and that, for instance, an illustration of the correct position for mouth-to-mouth respiration and of the correct position for external cardiac massage might be of more value than pictures of the Clausen and Connell harness.

These, however, are minor and admittedly contentious criticisms of a very good little book.

J. E. Utting