A HAEMORHEOLOGICAL STUDY OF LIGNOCaine

J. E. ORR, G. D. O. LOWE, W. S. NIMMO, R. WATSON AND C. D. FORBES

Significant differences in whole blood viscosity and red cell deformability between two matched groups of patients undergoing subarachnoid or general anaesthesia have been reported (Drummond et al., 1980): subarachnoid anaesthesia resulted in an increase in red cell deformability. Lignocaine itself has been shown to alter erythrocyte morphology in vitro, although in therapeutic concentrations it had no effect on the rheological behaviour of erythrocyte suspensions in vitro (Chen, Lee and Chien, 1979). In vitro haemorheological studies may be misleading as drugs may have in vitro effects on red cell deformability which are not substantiated by in vivo studies, and as dilutional effects may be introduced (Orr et al., 1982). Ex vivo studies are, therefore, more appropriate when investigating haemorheology, particularly when a drug has active metabolites, or when the pharmacodynamic effects of a drug may contribute to its haemorheological effects (Kaltenrieder, Meneely and Allen, 1942; Aronson, Magora and London, 1970). After the subarachnoid administration of lignocaine 75 mg and 100 mg, venous plasma lignocaine concentrations of 0.3 µg ml⁻¹ have been reported (Giasi, D'Agostino and Covino, 1979; Axelsson and Hidman, 1981). Similar plasma lignocaine concentrations have been observed after i.m. injection of the drug with peak concentrations between 30 and 60 min (Jebson, 1971).

The ex vivo haemorheological findings in eight volunteers who received lignocaine i.m. are reported.

SUBJECTS AND METHODS

Eight healthy unpaid volunteers (ASA grade I; five male; mean age 28.5 yr) gave informed consent for the study. Heart rate, arterial pressure, respiratory rate and a standard lead II ECG were monitored throughout. Venous blood samples (30 ml) were withdrawn with minimal venostasis from a vein in the antecubital fossa. After the withdrawal of a control blood sample, lignocaine 75 mg (1.5 ml of 5% solution) was administered by i.m. injection to the lateral aspect of the thigh. Three further blood samples were withdrawn at 30, 60 and 90 min. Haemorheological studies and lignocaine analysis were performed on all samples.

Blood for the haemorheological studies was anticoagulated with solid dipotassium EDTA 1.5 mg ml⁻¹ in plastic tubes (Steyne Laboratories) and analysed within 90 min of venepuncture. Haematocrit was measured in a Hawksley microhaematocrit centrifuge (13 000 g for 5 min). Plasma viscosity was measured at 25 °C in a Coulter-
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Harkness capillary viscometer. Whole blood viscosity was measured at high (94 s\(^{-1}\)) and low (0.94 s\(^{-1}\)) shear rates in a Contraves Low Shear 30 rotational viscometer at 37 °C and corrected to a standard hematocrit of 45% using regression equations derived from 200 subjects. For the measurement of red cell deformability, EDTA-blood was depleted of contaminating leukocytes and proteins by prefiltration through treated cotton wool (Kenny, Meakin and Stuart, 1983). The absence of leukocytes was confirmed by examination of the filtrate in an improved Neubauer counting chamber. Red cells were resuspended at 5% hematocrit in phosphate-buffered saline (pH 7.4, 290 mosmol kg\(^{-1}\)) and filtered for 6 min through special quality Nuclepore filters (pore size 5 μm) (Leiper et al., 1984). Red cell deformability was assessed by the ratio of the pressure generated by the cell suspension to the pressure generated by buffer alone (\(P_b\)). Two indices were calculated, \(P_i/P_b\) and \(P_f/P_b\) where \(P_i\) is the initial pressure generated by cells reaching the filter face, and \(P_f\) is the final pressure generated by cells after 6 min filtration. \(P_f\) is greater than \(P_i\) as a result of progressive pore plugging by rigid red cells.

Samples for the measurement of lignocaine concentration were anticoagulated in lithium-heparin tubes and centrifuged to separate the plasma which was stored at −20 °C. Plasma samples were analysed for lignocaine by an adaptation of the method used by Zylber-Katz, Granit and Levy (1978) and described previously by this laboratory for the determination of bupivacaine (Dutton et al., 1984; Neill and Watson, 1984). A Pye Unicam 204 series gas chromatograph, fitted with a flame ionization detector was used. Samples and standards were spiked with bupivacaine before extraction and this was used as an internal standard for the assay procedure. Separation was effected on a 2 m × 2 mm i.d. glass column packed with 3% SP 2250 on 100/120 mesh Supelcoport. Carrier gas was oxygen-free nitrogen at a flow rate of 20 ml min\(^{-1}\) and the column oven was maintained at 250 °C with the injection port and detector set at 275 °C and 300 °C, respectively.

The results were analysed using the paired t test and linear regression analysis of the percentage change in plasma viscosity, high shear blood viscosity and low shear blood viscosity relative to lignocaine concentration. A probability of < 0.05 was taken as significant.

RESULTS

Maximum venous plasma lignocaine concentrations ranging from 0.31 to 1.86 μg ml\(^{-1}\) (mean 0.80 μg ml\(^{-1}\)) were attained 30 min after i.m. injection of lignocaine 75 mg. These concentrations were greater than those expected after subarachnoid anaesthesia with lignocaine.

Haematocrit was unchanged after the administration of lignocaine (table I). Small but statistically significant decreases in plasma viscosity were observed at 30 min (P < 0.01) and 60 min (P < 0.05). High shear rate blood viscosity was significantly reduced at 30 min (P < 0.05). Low shear rate blood viscosity showed a mean decrease of 11% and significant reductions were attained 30 min (P < 0.01) and 60 min (P < 0.01) after the administration of lignocaine. Linear regression

| Table I. Means of values (± SD) for lignocaine concentration, haematocrit, plasma and whole blood viscosities and red cell deformability in eight volunteers at 0, 30, 60 and 90 min. * P < 0.05, paired t test. ND = Not detected |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| Time (min)      | 0               | 30              | 60              | 90              |
| Plasma lignocaine concn (μg ml\(^{-1}\)) | ND | 0.80 (±0.50) | 0.50 (±0.31) | 0.34 (±0.20) |
| Haematocrit (%) | 44.00 (±3.12) | 43.75 (±3.41) | 43.88 (±3.60) | 43.75 (±3.69) |
| Plasma viscosity (mPas) | 1.601 (±0.070) | 1.565 (±0.090)* | 1.566 (±0.098)* | 1.576 (±0.095) |
| Blood viscosity (mPas) | | | | |
| Shear rate 94 s\(^{-1}\) | 5.58 (±0.37) | 5.36 (±0.28)* | 5.43 (±0.36) | 5.49 (±0.34) |
| 0.94 s\(^{-1}\) | 18.75 (±2.89) | 16.68 (±2.81)* | 16.79 (±3.02)* | 17.35 (±3.36) |
| Red cell deformability index | | | | |
| \(P_i/P_b\) | 1.07 (±0.11) | 1.05 (±0.2) | 1.16 (±0.21) | 1.12 (±0.17) |
| \(P_f/P_b\) | 1.07 (±0.46) | 2.34 (±0.69) | 3.07 (±0.95) | 3.20 (±1.11) |
analysis of the percentage change in viscosities relative to lignocaine concentration failed to show any significant association — for plasma viscosity, $P = 0.067$; for high shear blood viscosity, $P = 0.053$; for low shear viscosity, $P = 0.20$. Red cell deformability was not significantly changed after the administration of lignocaine. There was an initial trend to improved filtrability and then a trend to decreased filtrability. No morphological changes in the red cells were observed on microscopy following the administration of the lignocaine.

**DISCUSSION**

The small decrease in plasma viscosity reported here is difficult to explain. The central sedative action of lignocaine could lead to vasodilatation and, hence, decreases in haematocrit and plasma viscosity (Aronson, Magora and London, 1970; Orr et al., 1982). However, no significant reduction in haematocrit was observed, so this explanation is unlikely. As lignocaine is 64% bound to plasma protein at therapeutic concentrations (Tucker, 1983) a change in the plasma proteins, which are the main determinants of plasma viscosity (Harkness, 1971), may be a possible explanation.

The observed reduction in high shear rate blood viscosity may be a reflection of the decrease in plasma viscosity. The 11% decrease in low shear rate blood viscosity requires further explanation, as haematocrit, plasma viscosity and red cell deformability underwent little or no change. Low shear blood viscosity is greatly influenced by red cell aggregation. Lignocaine may decrease red cell aggregation, either by altering aggregating plasma proteins or the red cell membrane, and this may explain the decrease in blood viscosity at low shear rate.

Amide-type local anaesthetics have been shown to reduce platelet adheresiveness (O'Brien, 1961) and, also, to decrease leucocyte adherence and migration (Giddon and Lindhe, 1972; Stewart, Ritchie and Lynch, 1974). These effects have been attributed to a membrane-stabilizing effect of the amide-type local anaesthetics, and a similar effect on red cells might result in decreased red cell aggregation.

Previous reports suggested that local anaesthetics may improve red cell deformability (Drummond et al., 1980; Thorburn, personal communication). However, the method used to determine red cell deformability in these earlier studies did not remove the white cells before analysis. In the present study, removal of the white cells by pre-filtration ensured that only the red cells were included in the determinations of red cell deformability. No change in red cell deformability was observed. Previous reports of altered red cell deformability after local anaesthetic administration could, therefore, have been the result of effects on white cells.

In conclusion, this communication does not support the view that local anaesthetics improve red cell deformability. The statistically significant decreases in plasma viscosity and whole blood viscosity which followed the administration of lignocaine may result from alterations in plasma proteins and from a reduction in red cell aggregation.

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**REFERENCES**


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