CHANGES IN THE BLOOD CONCENTRATION OF GLUCOSE, α -OXOGLUTARATE, PYRUVATE AND CITRATE DURING EXCHANGE TRANSFUSION IN HAEMOLYTIC DISEASE OF THE NEWBORN

BY

JOHN ANDERSON, VINCENT MARKS, ROBERT W. S. TOMLINSON
and WILLIAM WALKER

*From the Departments of Medicine and Chemical Pathology, King's College Hospital Medical School, London,
and the Department of Child Health, Durham University Medical School, King's College, Newcastle upon Tyne*

(RECEIVED FOR PUBLICATION APRIL 17, 1963)

In a previous study by Anderson, Smith and Walker (1961), it was observed that in four out of 100 infants undergoing exchange transfusion for haemolytic disease of the newborn, a rise of blood pyruvate occurred during the procedure. It was suggested that the rise of blood pyruvate might be due either to the metabolic action of citrate or glucose, and that this biochemical change might be related to the clinical deterioration of some infants during exchange transfusion.

Since the previous study was completed, newer enzyme methods for the determination of organic acids have become available. It was decided to make further observations in infants undergoing exchange transfusion to confirm the previous findings and to determine whether the citrate or the dextrose in the acid citrate dextrose (ACD) solution used for preserving the blood was responsible for these changes.

Materials and Methods

Observations were made during 23 exchange transfusions. The umbilical vein route was used in all cases. In most infants 80 ml. blood per lb. body weight was exchanged and the procedure took approximately one hour. Thus the rate varied in different infants in relation to body weight, being more rapid in the large infants and intentionally slower in the small babies. In the majority of babies the standard rate of blood exchange was 10 ml. per minute.

Seventeen transfusions were carried out using bank blood collected in ACD (420 ml. blood in 120 ml. ACD) not more than four days old and from which 190 ml. supernatant plasma citrate mixture had been removed immediately before use. Two transfusions were carried out with 500 ml. units of blood collected into plastic bags containing 30 ml. isotonic saline and 2,000 U.S.P.

units of heparin as the anticoagulant. Two transfusions were carried out with similar blood to which 10 ml. 20% w/v dextrose had been added. The other two transfusions were carried out with blood collected into trisodium citrate without the addition of dextrose. For these latter six transfusions donors were bled approximately two hours before the transfusions. In all cases blood for exchange transfusion was warmed by standing in water at 37° C. for 20-30 minutes before use.

In two infants, who received more than one transfusion, heparinized blood was used for the first and ACD for the second transfusion.

Samples of blood were withdrawn through the umbilical vein catheter at the start of the transfusion, and at the completion of 40 ml., 60 ml. and 80 ml. of blood per lb. body weight exchanged. A final sample was taken 30 minutes after the completion of transfusion. Care was taken to prevent admixture with donor blood. 10 ml. blood were placed in a tube containing 10 ml. 7% perchloric acid and a similar volume into a tube containing dry heparin. The former was used for the estimation of pyruvate and oxoglutarate by an enzymatic method (Marks, 1961) and glucose using a standard glucose oxidase method. The heparin sample was used to determine the haemoglobin concentration, packed cell volume, bilirubin and the citrate concentration (Taylor, 1953).

Results

The birth weights of the infants varied from 4 lb. 9 oz. (2,069 g.) to 9 lb. 7 oz. (4,280 g.) (mean = 6 lb. 14 oz. (3,117 g.)), four having birth weights of 5.5 lb. (2,493 g.) or less. The cord haemoglobin concentration varied from 8.17-8% (mean 14.4 g./100 ml.), and the plasma bilirubin concentration from 3.2-7.1 mg./100 ml. (mean 4.4 mg./100 ml.).

Exchange transfusion was carried out within 1 hour of birth in one infant, between 1 and 9 hours

FIGURE.—Mean changes in blood organic acids and glucose with volume of ACD blood exchanged in 17 babies.

in nine, between 9 and 24 hours in six and after the first day in the remaining seven.

In no instance did the condition of the infant deteriorate during the procedure.

The mean blood pyruvate, oxoglutarate, glucose and plasma citrate concentrations are shown in the Figure. The rise in blood pyruvate concentration during the exchange of 60 ml. blood per 1 lb. body weight is highly significant ($p > 0.001$), the standard

deviation for each point being about ± 130 $\mu\text{g./100 ml.}$ Thereafter there was a fall in the blood pyruvate, but this was not statistically significant. Two infants showed no significant rise of blood pyruvate, but no explanation for this could be found. There was no significant change in the blood oxoglutarate concentration, although in several infants the actual concentration fell during the course of the transfusion. Significant rises in plasma citrate and glucose concentrations occurred during transfusion, the rise in citrate being thirtyfold. Neither plasma citrate nor blood glucose concentrations had returned to normal within half an hour after the completion of transfusion. No infant showed evidence of tetany or other disturbance.

Heparinized blood was used in two transfusions and the results are shown in Table 1. No significant alteration of the plasma citrate or blood glucose occurred in these cases. However, the blood oxoglutarate concentration increased during these exchange transfusions but fell immediately after completion. The blood pyruvate concentration on the other hand fell during the procedure and was still low half an hour afterwards.

Two infants were treated with heparinized blood to which dextrose had been added. The following mean values were found on this blood before transfusion: citrate 3.2 mg./100 ml.; oxoglutarate 162 $\mu\text{g./100 ml.}$; pyruvate 261 $\mu\text{g./100 ml.}$ and glucose 518 mg./100 ml. During the transfusion the citrate concentration did not change. There was some variation of the concentration of blood oxoglutarate (Table 2). There was a rise of blood glucose and a significant rise of blood pyruvate, the latter persisting after the end of the procedure.

Citrated blood alone was used in two transfusions and the results are shown in Table 3. There was a rise of plasma citrate to the usual high value, but the plasma glucose concentration did not significantly change. The blood oxoglutarate concentration was variable, but there was a definite rise of plasma pyruvate which continued to rise after the end of the exchange.

TABLE 1
MEAN CHANGES IN BLOOD ORGANIC ACIDS AND GLUCOSE DURING EXCHANGE TRANSFUSION WITH HEPARINIZED BLOOD IN TWO INFANTS

Time and Volume of Blood Exchanged	Plasma Citrate (mg./100 ml.)	Blood Oxoglutarate ($\mu\text{g./100 ml.}$)	Blood Pyruvate ($\mu\text{g./100 ml.}$)	Blood Glucose (mg./100 ml.)
Start	3.6	562	1,160	71
40 ml./lb.	5.1	1,058	232	78
60 ml./lb.	4.5	1,249	48	84
80 ml./lb.	4.4	1,120	100	82
Half an hour after end of exchange	4.6	870	94	78

TABLE 2

MEAN CHANGES IN BLOOD ORGANIC ACIDS AND GLUCOSE DURING EXCHANGE TRANSFUSION
WITH HEPARINIZED DEXTROSE BLOOD IN TWO INFANTS

Time and Volume of Blood Exchanged	Plasma Citrate (mg./100 ml.)	Blood Oxoglutarate (μ g./100 ml.)	Blood Pyruvate (μ g./100 ml.)	Blood Glucose (mg./100 ml.)
Start	3.2	495	689	58
40 ml./lb.	2.7	315	716	116
60 ml./lb.	3.2	627	600	148
80 ml./lb.	2.9	365	705	155
Half an hour after end of exchange ..	2.6	230	851	100

TABLE 3

MEAN CHANGES IN BLOOD ORGANIC ACIDS AND GLUCOSE DURING EXCHANGE TRANSFUSION
WITH CITRATED BLOOD IN TWO INFANTS

Time and Volume of Blood Exchanged	Plasma Citrate (mg./100 ml.)	Blood Oxoglutarate (μ g./100 ml.)	Blood Pyruvate (μ g./100 ml.)	Blood Glucose (mg./100 ml.)
Start	2.3	594	497	50
40 ml./lb.	32.4	385	588	62
60 ml./lb.	43.4	397	625	55
80 ml./lb.	52.0	410	843	56
Half an hour after end of exchange ..	15.4	455	988	68

Comment

Anderson *et al.* (1961) suggested that in some infants citrate given during exchange transfusion could produce metabolic effects in the liver and other organs, giving rise to an increase in the concentration of pyruvate in the plasma. The present study of exchange transfusions with ACD blood in 17 infants indicates that a rise of blood pyruvate is common but not inevitable under the conditions of exchange transfusion prevailing in this series. The rise did not appear to be related to the clinical condition of the infants either before or during transfusion. However, the lower the citrate load and the slower the transfusion, the less the risk that these changes would be pronounced.

Increase in blood pyruvate may be due either to the effect of dextrose or citrate used in the anti-coagulant. In six instances exchange transfusion was performed with blood collected in different anticoagulants: two heparin, two heparin and dextrose and two citrate alone. The results of these experiments showed that both the dextrose and citrate contributed to the rise of blood pyruvate.

No significant change in the blood oxoglutarate was observed, but it was variable and in some infants there was a considerable fall. As there was no significant alteration of the concentration of oxoglutarate in the blood, it is probable that the intermediates of the tricarboxylic acid cycle are present in normal concentration in cells. It seems most likely that citrate blocks the entry of pyruvate

into this cycle and this is exaggerated if glucose is also given.

High plasma citrate concentrations always occur when blood collected in ACD is used and the more rapidly the transfusion is performed the more rapid is the rise of plasma citrate. However, in the present study, in spite of the high concentrations of citrate there was never any evidence of tetany or other complication. This may be because acidosis accompanies exchange transfusion performed with ACD blood, and this would tend to mask tetany even if present.

The use of citrate in exchange transfusion, however, does produce a metabolic abnormality of organic acids which persists for some time after the transfusion is completed. Both glucose and citrate contribute to these changes.

In the previous study (Anderson *et al.*, 1961) similar changes were recognized in infants upset or even dying during exchange transfusion, and it was observed that in prolonged or repeated transfusion these changes in organic acids were more pronounced. However, in the present study no associated clinical deterioration was recognized. Further studies on the changes in organs are required before the full implications are known, but in the meanwhile there seems to be no contra-indication to the use of ACD blood provided certain simple precautions are taken.

Summary

Exchange transfusion has been performed in

23 infants suffering from haemolytic disease of the newborn. Seventeen exchange transfusions used ACD 'Bank' blood, two were heparinized blood, two were heparinized blood to which dextrose had been added and two were with blood collected in trisodium citrate alone.

Significant rises in plasma pyruvate, citrate and glucose were observed when ACD blood was given.

Both glucose and citrate contribute to the high pyruvate concentration.

No deterioration in the clinical condition of the infants occurred despite marked biochemical changes.

REFERENCES

- Anderson, J., Smith, B. M. and Walker, W. (1961). Certain biochemical changes during exchange transfusion. *Vox Sang. (Basel)*, n.s., 6, 525.
- Marks, V. (1961). A combined enzymatic method for measuring α -oxoglutarate and pyruvate in blood and urine. *Clin. chim. Acta*, 6, 724.
- Taylor, T. G. (1953). A modified procedure for the micro-determination of citric acid. *Biochem. J.*, 54, 48.