ACID-BASE CHANGES FOLLOWING EXCHANGE TRANSFUSION WITH CITRATED BLOOD

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The acid-citrate-dextrose (ACD) solution used to preserve blood consists in effect of 2 parts trisodium citrate to 1 part citric acid. It forms a buffer solution such that the pH of bank blood less than 5 days old is, in our experience, 6.6 ± 0.2 . It can be predicted, therefore, that infusion of ACD blood must lead to an initial *acidosis*, and that this will in due course be replaced by a metabolic *alkalosis* as citrate is metabolized to form 3 moles of sodium bicarbonate for each mole of trisodium citrate retained. In the individual subject, the rates at which these two effects operate will determine the severity of the initial acidosis, and the stage at which the later alkalosis develops.

Material and Methods

The babies studied received exchange transfusion for Rh or ABO haemolytic disease, or, in one case, for unexplained hyperbilirubinaemia. Their ages varied between 3 hours and 7 days. Two blood volumes (i.e. 180 ml./kg.) were exchanged in the course of 2 hours. In about half the cases both umbilical artery and vein were utilized for the transfusion, the baby's blood being allowed to drip from a catheter placed in an umbilical artery, while being replaced by donor blood dripped into a catheter placed in the umbilical vein. In the remaining cases the conventional intermittent method was used, with 20 ml. aliquots taken and given via the umbilical vein. Calcium gluconate 0.1 g. was given with every 100 ml. transfused.

Donor blood was less than 5 days old. The ACD routinely used in this area has the composition shown in Table 1. This provides rather more citrate than the formula commonly used which has 2 g. disodium citrate.

The donor blood was usually concentrated by the removal of about 150 ml. supernatant plasma. The final analysis varied somewhat on account of the variable haematocrit of the donor's blood, but from analyses of 24 bottles (8 analyses for citrate) the average composition of bank blood after concentration was as given in Table 2 (values for a normal baby are quoted for comparison).

Blood samples were obtained during the course of transfusion either from the aorta via umbilical artery catheter, or from the umbilical vein when the artery had not been catheterized. In practice there was little difference between the analyses of samples from the two sources, as blood from the region of the portal vein is almost arterial in character. Furthermore, plasma bicarbonate, with which we were chiefly concerned, is substantially the same in venous and arterial blood (Gandy, Grann, Cunningham, Adamsons, and James, 1964). After the end of transfusion, samples of 'arterialized' blood were obtained by skin-prick of the well-warmed foot. Samples were analysed without delay by the Astrup technique for pH, P_{CO_2} , and bicarbonate; the latter has been expressed throughout this paper in terms of *standard bicarbonate* (Astrup, Jørgensen, Siggaard Andersen, and Engel, 1960), as this provides a convenient measure of metabolic acidosis and alkalosis. Chloride was measured by electrometric titration. Citrate was measured by the method of McArdle (1955).

TABLE 1
COMPOSITION OF ACID-CITRATE-DEXTROSE

Disodium citrate ($Na_2H.C_6H_5O_7.1\frac{1}{2}H_2O$)	2.85 g. (12 mm.)
Glucose	3.27 g.
Water	120 ml.
Blood	420 ml.

TABLE 2
AVERAGE COMPOSITION OF BANK BLOOD AFTER CONCENTRATION

	Donor Blood	Blood of Normal Baby (1st week)
Plasma Na (mEq/l.)	160	134
Plasma K (mEq/l.)	6.8	4.0
Plasma Cl (mEq/l.)	63	104
Plasma bicarbonate (mEq/l.)	6	23
Plasma citrate (mg./100 ml.)	620	<4
(mM/l.)	32.3	<0.2
Plasma protein (g./100 ml.)	6.7	6.2
Blood Hb (g./100 ml.)	13	19
Blood haematocrit (%)	42	57
Blood pH	6.6	7.4

FIG. 1.—Plasma bicarbonate during exchange transfusion on 1st day of life in 14 babies (normal level 23 mEq/l. indicated).

FIG. 2.—Plasma bicarbonate during exchange transfusion in 7 babies 3-7 days old.

Results

Plasma Bicarbonate During Exchange Transfusion. 21 babies were studied, of between 37 and 40 weeks' gestation. They fell into two groups: (a) 14 babies transfused on the first day of life; many of these babies were anaemic, the Hb varying from 5.4 to 13.8, mean 10.5 g./100 ml.; (b) 7 babies transfused at 3-7 days old; the Hb level was higher in this group, ranging from 12.5 to 16.5, mean 14.6 g./100 ml.

Fig. 1 shows the change in plasma bicarbonate in the 14 babies transfused on day 1. The pre-exchange value ranged from 17 to 23 mEq/l. During the first half of the 2-hour exchange transfusion the bicarbonate fell in 12 of the 14 cases. During the second half it continued to fall in some and rose in others, but with one exception the final value was less than 21.5 mEq/l.

Fig. 2 shows comparable results for the 7 babies transfused when 3-7 days old. In 3 babies there was an initial fall in bicarbonate, but in 6 of the 7 the bicarbonate rose during the second half of the transfusion so that the final value was, with a single exception, higher than the pre-exchange value, and more than 23 mEq/l.

Plasma Citrate During Exchange Transfusion. This was followed in 8 cases (Table 3). Despite the fact that the plasma citrate in the donor blood was

about 620 mg./100 ml., the highest level recorded during transfusion was 96 mg./100 ml.

TABLE 3
PLASMA CITRATE LEVELS IN 8 BABIES RECEIVING EXCHANGE TRANSFUSION

Case	Age (days)	Plasma Citrate Level: mg./100 ml. (and mM/L)	
		Mid-exchange (1 hour)	End-exchange (2 hours)
1	1	—	59.5 (3.1)
2	1	44 (2.3)	96 (5.0)
3	1	36 (1.9)	51 (2.7)
4	1	96 (5.0)	39 (2.0)
5	3	13 (0.65)	27 (1.4)
6	4	58 (3.0)	77 (4.0)
7	4	48 (2.5)	78 (4.1)
8	6	—	57 (3.0)

Plasma Chloride During Exchange Transfusion. Plasma chloride levels before and after transfusion were measured in 10 cases. Before transfusion the mean value was 104 mEq/l. (range 97-107), after transfusion it was 95 mEq/l. (range 81-101). In every case there was a fall in chloride, which averaged 9 mEq/l.

It is useful to calculate the approximate amount of chloride removed from the body as a result of exchange transfusion. The mean concentration of

FIG. 3.— PCO_2 , pH, and bicarbonate of plasma in a premature baby who became ill towards the end of exchange transfusion. Note development of severe acidosis during transfusion, rapid correction after transfusion terminated, followed by development of alkalosis.

chloride in the effluent (10 cases) was 98 mEq/l., and in the donor blood 63 mEq/l. Since 180 ml./kg. of blood was exchanged, and assuming a haematocrit of 42% for both donor and recipient blood, the net loss of chloride was $(98-63) \times 180/1000 \times (100-42)/100 = 3.7$ mEq. per kg. body weight.

Blood pH and PCO_2 During Exchange Transfusion.

Values for pH and PCO_2 were obtained at the same time as those for bicarbonate in the 21 cases shown in Figs. 1 and 2, but have not been detailed here as they would have added little of importance. With few exceptions PCO_2 remained near normal and within the range 37–46 mm.Hg, so that changes in pH ran parallel with changes in bicarbonate. The pH seldom fell below 7.2 and never below 7.1.

A different pattern was recorded, however, in a baby not included in the above series because it was premature, 36 weeks' gestation, 2.4 kg. (Fig. 3). Haemolytic disease was of moderate severity, the Hb being 10 g./100 ml.; exchange transfusion was carried out at 3 hours. During the first 1½ hours of the transfusion a mild metabolic acidosis developed, HCO_3^- falling from 22.5 to 18.5 mEq/l., but the clinical state occasioned no anxiety until 1¾ hours, when the baby's breathing became laboured and his colour pale. This abrupt clinical deterioration coincided with the development of a severe respiratory acidosis superimposed on a sharply increased metabolic acidosis, the PCO_2 rising to 65 mm.Hg, and HCO_3^- falling to 13 mEq/l. and pH to 7.03. The trans-

FIG. 4.—Plasma bicarbonate following exchange transfusion in 5 babies receiving one transfusion (—), and in one baby (—) receiving a second transfusion 36 hours after a transfusion on day 1. At 60 hours bicarbonate is still raised.

fusion was stopped and the baby's condition thereafter improved rapidly, as did both the respiratory and metabolic acidosis (Fig. 3).

Plasma Sodium and Potassium During Exchange Transfusion. These remained within the normal range in 13 cases investigated. In no case did potassium reach 5 mEq/l.

Plasma Bicarbonate Following Exchange Transfusion. This was determined in 5 cases after a single exchange transfusion, and in 1 case after a second exchange transfusion carried out 36 hours after an initial exchange at 4 hours old (Fig. 4).

The plasma bicarbonate rose rapidly after transfusion in all cases, so that the acidosis that was often present at the end of transfusion was replaced by an alkalosis within an hour or so (see also Fig. 3). During the first 24 hours after transfusion the bicarbonate in the 5 single-transfusion cases rose to between 27 and 33 mEq/l., and to 35 mEq/l. in the case receiving a second transfusion. The maximum pH in the same period was between 7.48 and 7.53 in 5 of these 6 cases, and was 7.43 in the remaining case.

Thereafter the bicarbonate level slowly fell, a period of more than 72 hours elapsing before a normal level of 23 mEq/l. was reached.

It was pointed out to us by Dr. John Davies that the rate at which post-transfusion alkalosis was corrected might be limited by the amount of chloride

Fig. 5.—Plasma bicarbonate following exchange transfusion in 5 babies, to whom a supplement of NaCl (6-10 mEq/kg.) was given. At 60 hours the mean plasma bicarbonate is almost normal.

available to the baby, since the chloride content of milk, both human (12 mEq/l.) and cows' (29 mEq/l.), is low. To test this idea we gave a supplement of NaCl, 6-10 mEq/kg., to a series of 5 babies. The salt was given during the period 6-30 hours after transfusion, along with the ordinary feed. The 5 babies who received NaCl were comparable with the 5 who did not, 4 babies in each group having been transfused on the first day and 1 in each group on the fourth day of life.

Results are shown in Fig. 5. The babies receiving NaCl corrected the post-transfusion alkalosis somewhat more quickly. Comparing the two groups of babies at 60 hours after transfusion (Figs. 4, 5), in 4 out of the 5 babies receiving NaCl the bicarbonate level had by this time fallen below 24, while in 4 of the 5 controls the level was still above 27 mEq/l. At 60 hours the mean bicarbonate level was 23.3 mEq/l. (SD 1.62) for the babies receiving NaCl, and 26.6 mEq/l. (SD 0.85) for the controls. The difference between the two means is highly significant ($p < 0.001$).

An alternative and more logical way of correcting a hypochloreaemic alkalosis is to give NH_4Cl rather than NaCl, and the former was, therefore, given to a further 4 babies after transfusion. In 3 babies the dosage and timing of the NH_4Cl administration was essentially similar to that of the group receiving NaCl, 5-8 mEq/kg. being given along with the baby's milk feeds between 12 and 21 hours after transfusion

Fig. 6.—Plasma bicarbonate following exchange transfusion in 3 babies (A_1 , A_2 , A_3) given NH_4Cl 5-8 mEq/kg., and in 1 baby (B) given NH_4Cl 15 mEq/kg. within the periods of time indicated. The shaded area includes the values for the 5 babies receiving NaCl as shown in Fig. 5.

(Fig. 6, Cases A_1 , A_2 , A_3). Comparing the rate at which the bicarbonate level of these babies fell to normal with the results for the NaCl-treated group (shaded area in Fig. 6), it is seen that in one case (A_1) the rate of fall was similar and in two cases (A_2 , A_3) it was faster. A fourth case received a dose of NH_4Cl which was both much larger (15 mEq/l.) and was given early, within 10 hours of the transfusion. This resulted (Case B, Fig. 6) in the post-transfusion alkalosis being rapidly overcorrected, the bicarbonate falling to 20 mEq/l.

Discussion

Acid-base Changes During Exchange Transfusion. The acidosis occurring during exchange transfusion with citrated blood has been recorded by Povey (1964), who measured the pH of blood withdrawn from the umbilical vein. In 3 of his 6 cases the pH fell below 7.1, which contrasts with the fact that in none of our 21 cases of more than 37 weeks' gestation did the pH fall below 7.1; indeed values below 7.2 were exceptional. His paper contains no description of the age, gestational age, or degree of anaemia of the cases, but one factor probably explaining the lower pH values occurring during transfusion in his series is that transfusions were usually completed in 50 to 90 minutes, as against the 120 minutes of our series.

Plasma citrate levels during exchange transfusion have been recorded by several authors, with divergent

results. In our cases the highest citrate level recorded was 96 mg./100 ml., and comparable values were found by Wexler, Pincus, Natelson, and Lugovoy (1949) and by Anderson, Marks, Tomlinson, and Walker (1963). The latter authors in an earlier study (Anderson, Smith, and Walker, 1961) had found much higher levels up to 350 mg./100 ml., with the highest levels tending to occur in premature babies; the different results in the two studies were attributed to the fact that in the earlier study the rate of transfusion was faster (J. Anderson, personal communication). In Farquhar and Smith's (1958) series, levels of 100-200 mg./100 ml. were common, and in one case with a severe haemolytic disease the level rose to 346 mg./100 ml.

Since for every 3 moles of citrate in ACD transfused (and retained) 2 moles when metabolized reappear as bicarbonate, the rate at which citrate is metabolized can conveniently be measured in terms of plasma bicarbonate. So measured, our results show that this rate is a function of a baby's age and/or its clinical status, since first-day babies, who in this series tended also to be moderately anaemic, metabolized citrate a good deal less rapidly than 3-7-day-old babies who were not anaemic (Figs. 1, 2). Thus at the end of transfusion, first-day babies showed a metabolic acidosis, while a metabolic alkalosis had usually already developed by the end of transfusion in the babies of 3-7 days old.

These facts can best be explained in terms of the functional efficiency of the liver, infused citrate being mainly metabolized in the liver. In our series, the younger group of babies was also the more severely affected by haemolytic disease (in terms of anaemia), so that we have been unable to separate two factors that may influence hepatic function—the age of the baby, and liver damage resulting from haemolytic disease. As regards the age factor, there is evidence that certain aspects of hepatic function (activity of glucuronyl transferase, bromsulphalein excretion) improve during the first few days after birth (see Smith, 1959), and it seems not unlikely that the capacity to metabolize citrate may behave similarly. That liver damage impairs the ability to metabolize citrate has been concluded both from observations on adult patients and from experiments on animals (Bunker, Stetson, Coe, Grillo, and Murphy, 1955; Sjöström, 1937).

In summary of this section: our own data, taken in conjunction with those of other workers quoted, are consistent with a conclusion that the severity of the acidosis developing during exchange transfusion is inversely related to the rate at which citrate is metabolized, and that this rate is probably slower in the premature than in the mature baby, in the anaemic

or otherwise sick baby than in the well baby, and in the baby a few hours old than in the baby of a few days.

Acid-base Changes After Exchange Transfusion. Two components of the alkalosis developing after transfusion can be distinguished. One is the depletion of body chloride resulting from the use of donor blood with a chloride concentration only two-thirds that of plasma: this was reflected in a lowering of plasma chloride by an average of 8 mEq/l. by the end of transfusion. The other is the build-up of plasma bicarbonate as citrate is metabolized. The combined effect is to produce a hypochloreaemic alkalosis, pH in our series rising to 7.5 or more, with plasma bicarbonate levels of up to 35 mEq/l. In due course the alkalosis is corrected by the kidneys excreting HCO_3^- and retaining Cl⁻ in its place, and the rate at which this takes place is limited by the supply of chloride.

The amount of chloride removed as a result of exchange transfusion has been assessed at about 3.7 mEq/kg. body weight, representing about 7% of the total body chloride, which is 50 mEq/kg. at birth (Forbes, Reid, Bondurant, and Etheridge, 1956). The depletion of chloride for a 3.5 kg. baby must thus amount to 13 mEq, requiring for its replacement the ingestion by the baby of about 1 litre of human milk, or $\frac{1}{2}$ litre of cows' milk. These figures make it clear that the relatively small amount of chloride ingested by a baby in the first few days of life, particularly when taking breast milk, necessarily limits the rate at which the post-transfusion alkalosis can be corrected. Supplying additional chloride as NaCl, or better as NH_4Cl , is shown to hasten correction of the alkalosis (Figs. 5, 6).

Practical Implications. The wisdom of employing a slow rate of transfusion is underlined, particularly in first-day babies and those with anaemia. Slow transfusion gives time for the initial acidosis to be offset by the alkalizing effect of metabolized citrate. A slower rate of transfusion would probably have prevented the severe acidosis and clinical deterioration which developed in the case shown in Fig. 3.

There is some evidence to suggest that acidosis favours the passage of bilirubin from plasma, where it is largely bound to albumin, into cells, alkalosis favouring the reverse trend. Martin (1949), for instance, provides data showing that albumin binds 30% more bilirubin at pH 7.6 than at 7.4. Odell (1964) studied the partition of bilirubin *in vitro* between mitochondria and a solution of albumin, and concluded that 'any reduction in extracellular pH or addition of organic anions would favour

intracellular diffusion of bilirubin displaced from albumin'. These facts imply that in any hyperbilirubinaemic situation it is particularly important to avoid acidosis developing during exchange transfusion. For the same reason, the post-transfusion alkalosis may be a positive advantage in hyperbilirubinaemia.

In the light of these facts, the pros and cons of concentrating citrated blood by removal of some plasma are worth considering.

The effects of concentrating donor blood are four:

- (1) The baby will be left with a higher haematocrit and Hb level at the end of transfusion, which may obviate the need for a later top-up transfusion for anaemia.
- (2) To the extent that the haematocrit at the end of transfusion is higher, the total circulating plasma protein is lower, and hence its binding capacity for bilirubin is lower.
- (3) The amount of citrate administered will be less, hence the acidosis developing during transfusion will be lessened.
- (4) The post-transfusion alkalosis will be diminished, which may perhaps be disadvantageous if there is hyperbilirubinaemia.

The first and third of these effects are advantageous and will usually be considered to outweigh the more marginal disadvantages of the second and fourth effects.

With the idea of offsetting the metabolic acidosis developing during exchange transfusion (Fig. 1). Boda, Tóth, Eck, and Murányi (1965) have advised giving an intravenous dose of sodium lactate to babies before transfusion, especially if an acidosis is already present. Povey (1964) suggested adding NaHCO_3 or tris-buffer (THAM) to the donor blood. These approaches seem logical, particularly so if the baby is premature or affected by a severe degree of haemolytic disease. However, such procedures might well cause an exaggeration of the post-transfusion alkalosis, similar to that observed in the baby receiving a second exchange transfusion (Fig. 4). Although we have not discerned any clinical disorder resulting from the alkalosis (pH up to 7.53) after transfusion with ACD blood, it would be unwise to assume that more severe degrees of alkalosis would be harmless.

Summary

Acid-base changes have been followed in 21 babies during exchange transfusion with citrated blood.

During exchange transfusion a metabolic acidosis developed initially. In the babies transfused on the first day of life, many of whom were also anaemic, the acidosis persisted throughout the course of a 2-hour transfusion. In older babies, 3-7 days of age, the initial acidosis was corrected by the end of transfusion.

Following exchange transfusion a hypochloraemic alkalosis developed and was not corrected until about the fourth day after transfusion.

Correction of post-transfusion alkalosis was accelerated by providing supplementary chloride, either as NaCl or NH_4Cl , because the amount of chloride available to the milk-fed baby is small relative to the depletion of chloride caused by exchange transfusion.

Certain practical implications of these findings are discussed.

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