Review

Clinical review: The meaning of acid–base abnormalities in the intensive care unit – effects of fluid administration

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Abstract

Stewart's quantitative physical chemical approach enables us to understand the acid–base properties of intravenous fluids. In Stewart's analysis, the three independent acid–base variables are partial CO_2 tension, the total concentration of nonvolatile weak acid (A_{TOT}), and the strong ion difference (SID). Raising and lowering A_{TOT} while holding SID constant cause metabolic acidosis and alkalosis, respectively. Lowering and raising plasma SID while clamping A_{TOT} cause metabolic acidosis and alkalosis, respectively. Fluid infusion causes acid–base effects by forcing extracellular SID and A_{TOT} toward the SID and A_{TOT} of the administered fluid. Thus, fluids with vastly differing pH can have the same acid–base effects. The stimulus is strongest when large volumes are administered, as in correction of hypovolaemia, acute normovolaemic haemodilution, and cardiopulmonary bypass. Zero SID crystalloids such as saline cause a 'dilutional' acidosis by lowering extracellular SID enough to overwhelm the metabolic alkalosis of A_{TOT} dilution. A balanced crystalloid must reduce extracellular SID at a rate that precisely counteracts the A_{TOT} dilutional alkalosis. Experimentally, the crystalloid SID required is 24 mEq/l. When organic anions such as L-lactate are added to fluids they can be regarded as weak ions that do not contribute to fluid SID, provided they are metabolized on infusion. With colloids the presence of A_{TOT} is an additional consideration. Albumin and gelatin preparations contain A_{TOT}, whereas starch preparations do not. Hextend is a hetastarch preparation balanced with L-lactate. It reduces or eliminates infusion related metabolic acidosis, may improve gastric mucosal blood flow, and increases survival in experimental endotoxaemia. Stored whole blood has a very high effective SID because of the added preservative. Large volume transfusion thus causes metabolic alkalosis after metabolism of contained citrate, a tendency that is reduced but not eliminated with packed red cells. Thus, Stewart's approach not only explains fluid induced acid–base phenomena but also provides a framework for the design of fluids for specific acid–base effects.

Introduction

There is a persistent misconception among critical care personnel that the systemic acid–base properties of a fluid are dictated by its pH. Some even advocate 'pH-balanced' fluids, particularly when priming cardiopulmonary bypass pumps [1]. This is not to deny the merit of avoiding very high or very low pH in fluids intended for rapid administration. Extremes of pH can cause thrombophlebitis, and on extravasation tissue necrosis, and rapid administration is a hemolysis risk (specific data on this topic are sparse). However, these effects occur before equilibration. What must be understood is that fluids with widely disparate pH values can have exactly the same systemic acid–base effects. To illustrate, the acid–base properties of 'pure' 0.9% saline (pH 7.0 at 25°C) are identical to those of 0.9% saline equilibrated with atmospheric CO_2 (pH 5.6 at 25°C).

Until recently, the challenge was to find a logical basis for predicting the acid–base properties of intravenous fluids. In this review important concepts of quantitative physical chemistry are presented, concepts originally set out by the late Peter Stewart [2–5]. They provide the key to understanding fluid induced acid–base phenomena and allow a more informed approach to fluid design. On this background we consider the effects of intravenous fluids on acid–base balance.

The Stewart approach in brief

There are just three independent variables that, when imposed on the physical chemical milieu of body fluids, dictate their acid–base status. They are strong ion difference (SID), the total weak acid concentration (A_{TOT}), and partial CO_2 tension (P_{CO_2}). The interplay between SID, A_{TOT}, and PCO_2 is the sole determinant of pH, as well as of other dependent variables such as [HCO_3^-]. All acid–base interventions, including fluid administration, act through SID, A_{TOT} and PCO_2, alone or in combination. The single exception is the addition of weak base (e.g. tris-hydroxymethyl aminomethane) [6], which is normally absent from body fluids.

A_{TOT} = total concentration of weak acid; CO_{2TOT} = total concentration of CO_2; Pa_{CO_2} = arterial CO_2 tension; P_{CO_2} = partial CO_2 tension; SBE = standard base excess; SID = strong ion difference.

Strong ion difference

Elements such as Na^+, K^+, Ca^{2+}, Mg^{2+}, and Cl^- exist in body fluids as completely ionized entities. At physiologic pH this can also be said of anions with pKa values of 4 or less, for example sulphate, lactate, and β-hydroxybutyrate. Stewart described all such compounds as 'strong ions'. In body fluids there is a surfeit of strong cations, quantified by SID. In other words, SID = [strong cations] – [strong anions]. Being a 'charge' space, SID is expressed in mEq/l. SID calculated from measured strong ion concentrations in normal plasma is 42 mEq/l.

Partial CO_2 tension

Arterial P_{CO_2} (Pa_{CO_2}) is an equilibrium value determined by the balance between CO_2 production (15,000 mmol/day) and CO_2 elimination via the lungs. In areas where P_{CO_2} is less directly controlled by alveolar ventilation (e.g. venous blood and interstitial fluid during low flow states), the total CO_2 concentration (CO_{2TOT}) becomes the independent variable.

Total concentration of weak acid (A_{TOT})

Body fluid compartments have varying concentrations of nonvolatile (i.e. non-CO_2) weak acids. In plasma these consist of albumin and inorganic phosphate. The same applies to interstitial fluid, although total concentrations here are very small. In red cells the predominant source is haemoglobin.

Nonvolatile weak acids dissociate in body fluids as follows:

$$HA \leftrightarrow H^+ + A^-$$

The group of ions summarized as A^- are weak anions (pKa approximately 6.8). Unlike strong ions, weak ions in body fluids vary their concentrations with pH by dissociation/association of their respective parent molecules. The total concentration of nonvolatile weak acid in any compartment is termed A_{TOT}, where $A_{TOT} = [HA] + [A^-]$. Although $[A^-]$ varies with pH, A_{TOT} does not, and as such it is an independent variable.

Weak ions

The SID space is filled by weak ions, one of which is A^-. The only other quantitatively important weak ion is HCO_3^-, but there are also minute concentrations of CO_3^{2-}, OH^-, and H^+. To preserve electrical neutrality, their net charge must always equal the SID.

Stewart's equations

Stewart set out six simultaneous equations primarily describing the behaviour of weak ions occupying the SID space (Table 1). They are applications of the Law of Mass Action to the dissociation of water, H_2CO_3, HCO_3^-, and nonvolatile weak acids, coupled with the expression for A_{TOT} and a statement of electrical neutrality. If P_{CO_2}, SID and A_{TOT} are known, then the equations in Table 1 can be solved for the remaining six unknowns – $[A^-]$, $[HCO_3^-]$, $[OH^-]$, $[CO_3^{2-}]$, [HA] and, most importantly, $[H^+]$.

Table 1

Stewart's six simultaneous equations

$[H^+] \times [OH^-] = K'w$
$[H^+] \times [A^-] = Ka \times HA$
$[HA] + [A^-] = A_{TOT}$
$[H^+] \times [HCO_3^-] = Kc \times P_{CO_2}$
$[H^+] \times [CO_3^{2-}] = Kd \times [HCO_3^-]$
$SID + [H^+] - [HCO_3^-] - [CO_3^{2-}] - [A^-] - [OH^-] = 0$

All K values are known dissociation constants. P_{CO_2}, partial CO_2 tension; SID, strong ion difference.

Isolated abnormalities in strong ion difference and total concentration of weak acid (A_{TOT})

From Stewart's equations, four simple rules can be derived concerning isolated abnormalities in SID and A_{TOT} (Table 2). These can be verified by *in vitro* experimentation [7].

Standard base excess

The rules in Table 2 illustrate an important Stewart principle. Metabolic acid–base disturbances arise from abnormalities in SID and A_{TOT}, either or both. However, to quantify metabolic acid–base status at the bedside, neither SID nor A_{TOT} needs individual measurement. For this the standard base excess (SBE) is sufficient. The SBE concept was developed by Siggaard-Andersen and the Copenhagen group [8,9]. It is calculated from buffer base offsets by assuming a mean extracellular haemoglobin concentration of 50 g/l. A useful formula is as follows (with SBE and $[HCO_3^-]$ values expressed in mEq/l):

$$SBE = 0.93 \times \{[HCO_3^-] + 14.84 \times (pH - 7.4) - 24.4\}$$

SBE supplements the Stewart approach as a practical tool [10–12]. A typical reference range is –3.0 to +3.0 mEq/l. The SBE deviation from zero is the change in extracellular SID needed to normalize metabolic acid–base status without changing A_{TOT}. If the SBE is below –3.0 mEq/l then there is metabolic acidosis, either primary or compensatory. The deviation below zero is the increase in extracellular SID needed to correct the acidosis. Although this value should also equate to the dose (in mmol) of $NaHCO_3$ required per litre of extracellular fluid, in practice more is usually needed – a dose corresponding to an extracellular space of 30% body weight rather than 20%. Similarly, if the SBE is greater than 3.0 mEq/l then there is metabolic alkalosis. The positive offset from zero represents a theoretical dose calculation for HCl rather than for $NaHCO_3$.

Thinking about fluids in Stewart's terms

Fluids are administered into the physiological milieu. Their *in vivo* properties can therefore be described using Stewart's physical chemical language, in other words in terms of their SID, A_{TOT} and CO_{2TOT} [13]. Acid–base effects come about

Table 2

Rules for isolated abnormalities in strong ion difference (SID) and total concentration of weak acid (A_{TOT})

SID/A_{TOT}	Isolated abnormality	Result
SID	Increased	Metabolic alkalosis
SID	Decreased	Metabolic acidosis
A_{TOT}	Increased	Metabolic acidosis
A_{TOT}	Decreased	Metabolic alkalosis

as a fluid with a particular set of physical chemical properties mixes and equilibrates with extracellular fluid (which itself continually equilibrates across cell membranes with intracellular fluid). This alters extracellular SID and A_{TOT}, the final determinants of metabolic acid–base status, toward the SID and A_{TOT} of the infused fluid.

The CO_{2TOT} of infused fluid is worth mentioning separately. First, it has no effect on extracellular SID and A_{TOT}, and therefore it does not influence the final metabolic acid–base status. In other words, it is not the presence of HCO_3^- in bicarbonate preparations that reverses a metabolic acidosis; rather, it is the high SID (1000 mEq/l for 1 mol/l $NaHCO_3^-$) and the absence of A_{TOT}. The same metabolic effect would be achieved if the weak anion were OH^- rather than HCO_3^-, although the resultant high pH (14.0 rather than 7.7) introduces a risk for haemolysis and tissue damage, and mandates extremely slow administration via a central vein.

However, the CO_{2TOT} of administered fluid can be important for other reasons. Rapid infusion of fluids with high CO_{2TOT} can transiently alter CO_2 homeostasis, mainly in areas under less direct control of respiratory servo loops, such as venous blood, the tissues and the intracellular environment [14–18]. The crystalloid and colloid fluids discussed in this review are not in this category.

Crystalloid effects from the Stewart perspective

No crystalloid contains A_{TOT}. Crystalloid loading therefore dilutes plasma A_{TOT}, causing a metabolic alkalosis (Table 2). Simultaneously, plasma and extracellular SID are forced toward the SID of the infused crystalloid, primarily by differential alteration in $[Na^+]$ and $[Cl^-]$. If these changes increase SID then the effects of A_{TOT} dilution are enhanced, and if they decrease SID then they oppose them (Table 2).

'Dilutional' acidosis

It has been reported on many occasions that large-scale saline infusions can cause a metabolic acidosis [19–21]. Although best documented during repletion of extracellular fluid deficits, acute normovolaemic haemodilution [22,23] and cardiopulmonary bypass [23–26] have similar potential. The mechanism is not bicarbonate dilution, as is commonly supposed [27]. Bicarbonate is a dependent variable. The key fact is that the SID of saline is zero, simply because the strong cation concentration ($[Na^+]$) is exactly the same as the strong anion concentration ($[Cl^-]$). Large volumes of saline therefore reduce plasma and extracellular SID. This easily overwhelms the concurrent A_{TOT} dilutional alkalosis. A normal (in fact reduced) anion gap metabolic acidosis is the end result [28,29], albeit less severe than if A_{TOT} had remained constant.

The critical care practitioner should be alert to this possibility when confronted with a patient who has a metabolic acidosis and a normal anion gap. It is wise to check that the corrected anion gap [30,31] and perhaps the strong ion gap [32,33] are also normal. These are thought to be more reliable screening tools for unmeasured anions [34,35]. (For a more detailed discussion of the anion gap, corrected anion gap and strong ion gap, see other reviews in this issue.) A history of recent large volume saline infusion (e.g. >2 l in <24 hours) in such a patient is highly suggestive of infusion related metabolic acidosis. Even if there is an alternative explanation, such as renal tubular acidosis or enteric fluid loss, saline infusions will perpetuate and exacerbate the problem.

The phenomenon is not confined to 0.9% saline, and the resultant metabolic acidosis may or may not be hyperchloraemic. Hypotonic NaCl solutions also have a zero SID. Even fluids with no strong ions at all, such as dextrose solutions, mannitol and water, have a zero SID. Infusion of any of these fluids reduces plasma and extracellular SID by the same equilibration mechanism, irrespective of whether plasma $[Cl^-]$ rises or falls, forcing acid–base in the direction of metabolic acidosis [36]. For a theoretical illustration of dilutional SID effects, imagine adding 1 l of either saline or water to a sealed 3 l mock 'extracellular' compartment with a SID of 40 mEq/l, as illustrated in Table 3. In either case the SID is reduced to 30 mEq/l, but with a fall in $[Cl^-]$ after water dilution.

Interestingly, hypertonicity makes solutions more acidifying [36]. In this case the reduction in extracellular SID is magnified by an added dilution effect, because water is drawn by osmosis from the intracellular space. An unproven corollary is that hypotonic solutions are less acidifying. The important message here is that the intracellular space is a participant in the final equilibrium, and can contribute significantly to fluid induced acid–base effects.

'Saline responsive' metabolic alkalosis

Patients categorized as suffering from 'contraction alkalosis' or 'diminished functional extracellular fluid volume' are said to be 'saline responsive', and complex hormonal and renal tubular mechanisms are often invoked [37–39]. In fact, from the perspective of physical chemistry, any metabolic alkalosis is 'saline responsive', provided sufficient saline (or any zero SID fluid) can be administered. Unfortunately, in the absence

Table 3

Equivalent strong ion difference reductions by adding 1 l water or 1 l of 0.15 mol/l NaCl to a 3 l sample of mock extracellular fluid

	'ECF'	After saline dilution	After water dilution
$[Na^+]$	140	142.5	105
$[Cl^-]$	100	112.5	75
$[A^-] + [HCO_3^-]$	40	30	30
SID	40	30	30

Electrolyte concentrations are given in mEq/l. ECF, extracellular fluid; SID, strong ion difference.

of hypovolaemia the amount of saline required introduces a risk for overload.

Hence, a diagnosis of volume depletion should be established before treating metabolic alkalosis in this way. Signs of extracellular volume depletion include reduced skin turgor, postural hypotension, and systolic pressure variability [40]. There may also be a prerenal plasma biochemical pattern (high urea:creatinine ratio), and if tubular function is preserved then urinary $[Na^-]$ is normally under 20 mmol/l [41].

KCl and metabolic alkalosis

Some types of metabolic alkalosis are associated with hypokalaemia and total body potassium deficits [37,42]. When dealing with these categories, correcting the deficit with KCl is a particularly effective way to reverse the alkalosis. From the Stewart perspective, this practice has similarities to infusing HCl, minus the pH disadvantages of a negative SID. This is because potassium and potassium deficits are predominantly intracellular, and so all but a small fraction of retained potassium ends up within the cells during correction. The net effect of KCl administration is that the retained strong anion (Cl^-) stays extracellullar, whereas most of the retained strong cation disappears into the intracellular space. This is a potent stimulus for reducing plasma and extracellular SID.

To give another rough illustration, imagine the repletion of a 200 mmol total body potassium deficit using KCl. If the extracellular $[K^+]$ is increased by 3 mmol/l during the process, then approximately 50 mmol of K^+ has been retained in the 17 l extracellular space and about 150 mmol has crossed into the cells. This means that 150 mmol Cl^- is left behind in the extracellular space, now unaccompanied by a strong cation. This lowers extracellular SID and thus SBE by about 9 mEq/l.

'Balanced' crystalloids

To avoid crystalloid induced acid–base disturbances, plasma SID must fall just enough during rapid infusion to counteract the progressive A_{TOT} dilutional alkalosis. Balanced crystalloids thus must have a SID lower than plasma SID but higher than zero. Experimentally, this value is 24 mEq/l [23,43]. In other words, saline can be 'balanced' by replacing 24 mEq/l of Cl^- with OH^-, HCO_3^- or CO_3^{2-}. From this perspective, and for now ignoring pH, solutions 1 and 3 in Table 4 are 'balanced'. However, it is noteworthy that, unless stored in glass, solutions 1 and 3 both become solution 2 by gradual equilibration with atmospheric CO_2 (Table 4). Solution 2 is also 'balanced'.

To eliminate the issue of atmospheric equilibration, commercial suppliers have substituted various organic anions such as L-lactate, acetate, gluconate and citrate as weak ion surrogates. Solution 4 (Table 4) is a generic example of this approach (for actual examples, see Table 5). L-lactate is a strong anion, and the *in vitro* SID of solution 4 is zero. However, solution 4 can also be regarded as 'balanced', provided L-lactate is metabolized rapidly after infusion. In fact, in the absence of severe liver dysfunction, L-lactate can be metabolized at rates of 100 mmol/hour or more [44,45], which is equivalent to nearly 4 l/hour of solution 4. The *in vivo* or 'effective' SID of solution 4 can be calculated from the L-lactate component subject to metabolic 'disappearance'. If the plasma [lactate] stays at 2 mmol/l during infusion, then solution 4 has an effective SID of 24 mEq/l.

Hence, despite wide variation in pH, solutions 1–4 in Table 4 have identical effective SID values. They are all 'balanced', with identical systemic acid–base effects. However, other attributes must be considered. Solution 1 (pH 12.38) is too alkaline for peripheral or rapid central administration. The situation for solution 2 is less clear. Atmospheric equilibration has brought the pH to 9.35, which is less than that of sodium thiopentone (pH 10.4) [46] – a drug that is normally free of venous irritation. Similarly Carbicarb, a low CO_{2TOT} alternative to $NaHCO_3$ preparations [47], has a pH of 9.6 [48]. Thus, the pH of solution 2 may not preclude peripheral or more rapid central administration. On the downside, and like Carbicarb, solution 2 contains significant concentrations of carbonate, which precipitates if traces of Ca^{2+} or Mg^{2+} are present. A chelating agent such as sodium edetate may be required.

Choosing a balanced resuscitation crystalloid

Hartmann's solution (Table 5) is the best known commercial 'balanced' preparation. It contains 29 mmol/l of L-lactate. In the absence of severe liver dysfunction, the effective SID is therefore approximately 27 mEq/l. Although this should make it slightly alkalinizing, much as Hartmann originally intended [49], it is close to the ideal from an acid–base perspective. Slight alkalinization is difficult to demonstrate in laboratory and especially in clinical studies, but the available evidence shows that Hartmann's solution reduces or eliminates infusion related metabolic acidosis [50–54].

The acid–base status of a patient before resuscitation is a consideration. If it is normal to start with, then higher SID fluids such as Plasma-Lyte 148 (effective SID 50 mEq/l;

Table 4

Four balanced crystalloids (see text)

	Solution 1	Solution 2	Solution 3	Solution 4
[Na^+]	140	140	140	140
[Cl^-]	116	116	116	114
[HCO_3^-]		19.2	24	
[CO_3^{2-}]		4.8		
[OH^-]	24			
[L-lactate]				26
P_{CO_2} (mmHg)	0	0.3[a]	760	0.3[a]
pH	12.38	9.35	6.04	6.49
Effective SID	24	24	24	24

[a]Atmospheric sea level partial CO_2 tension (P_{CO_2}). Electrolyte concentrations are given in mEq/l. SID, strong ion difference.

Table 5) are likely to cause a progressive metabolic alkalosis from the outset. Again, evidence is limited, but in support of this statement Plasma-Lyte 148 priming cardiopulmonary bypass pumps has been shown to increase arterial base excess by the end of bypass [25]. On the other hand, if there is a pre-existing metabolic acidosis, caused by diabetic ketoacidosis or hypovolaemic shock for example, then fluids with higher effective SID such as Isolyte E or Plasma-Lyte 148 will correct the acidosis more rapidly (provided their organic anions are metabolized with efficiency) while counteracting ongoing generation of acidosis. The problem with high SID fluids is the potential for over-correction and 'break through' metabolic alkalosis, particularly when the cause of the acidosis is accumulation of organic strong anions such as ketoacids and lactate, which disappear as the illness resolves.

Unfortunately, available commercial 'balanced' preparations have unresolved problems. Many contain either calcium or magnesium (or sometimes both; Table 5). Calcium neutralizes the anticoagulant effect of citrate, and both can precipitate in the presence of HCO_3^- and CO_2^{2-}. This restricts their range of *ex vivo* compatibilities (e.g. there are incompatibilities with stored blood and sodium bicarbonate preparations) and makes them poor drug delivery vehicles. Another disadvantage is that they all require an intermediary metabolic step, often at times of severe metabolic stress, to achieve their effective SID.

Hartmann's solution is also hypotonic relative to extracellular fluid. Although a potential disadvantage in traumatic brain injury [55], this was not borne out in a comparison with hypertonic saline given prehospital to hypotensive brain-injured patients [56]. Diabetic ketoacidosis is another scenario that predisposes to brain swelling during fluid loading [57], but here Hartmann's solution and other mildly hypotonic preparations seem safe for a least part of the repletion process [58–61]. If used from the beginning, the slightly alkalinizing Hartmann's SID of 27 mEq/l is probably sufficient to ameliorate or even prevent the late-appearing normal anion gap metabolic acidosis to which these patients are prone [57], although this remains to be demonstrated.

Table 5

Four commercial crystalloids

	Hartmann's	Plasma-Lyte 148	Isolyte S (pH 7.4)	Isolyte E
[Na^+]	129	140	141	140
[Cl^-]	109	98	98	103
[K^+]	5	5	5	10
[Ca^{2+}]	4			5
[Mg^{2+}]		3	3	3
[L-lactate]	29			
[Acetate]		27	27	49
[Gluconate]		23	23	
[Citrate]				8
[Phosphate]			1	
Effective SID	27[a]	50	50	57

[a]Assumes stable plasma lactate concentrations of 2 mmol/l (see text). All concentrations are given in mEq/l.

Overcoming current shortcomings

Given the limitations of commercially available solutions and assuming that infusion-related acidosis causes harm, as seems likely [62], then an argument could be put for new 'balanced' resuscitation solutions. Ideally, these should be normotonic and free of organic anion surrogates and divalent cations. The design could be along the lines of solution 3 in Table 4. However, because solution 3 requires CO_2-impermeable storage, solution 2 might be preferable, provided its higher pH does not preclude rapid peripheral administration. Such a fluid could become the first line crystalloid in all large volume infusion scenarios, including intraoperative fluid replacement, acute normovolaemic haemodilution and cardiopulmonary bypass, as well as resuscitation of hypovolaemic and distributive shock, diabetic ketoacidosis and hyperosmolar nonketotic coma. Refinements would include a selection of [Na^+] and corresponding [Cl^-] values to cater for varying osmolality requirements. The standard SID for neutral acid–base effects would be 24 mEq/l, perhaps with variations above or below to correct pre-existing acid–base disturbances.

Colloids

The SAFE (Saline versus Albumin Fluid Evaluation) study has lifted the cloud hanging over albumin solutions [63], and clinicians should now feel more comfortable using colloid preparations in general. Just as with crystalloids, the

Table 6

Six colloid solutions

	Albumex 4	Haemaccel	Gelofusine	PENTASPAN	HESpan	Hextend
[Albumin][b]	40 g/l					
[Gelatin urea-linked][b]		35 g/l				
[Gelatin succinylated][b]			40 g/l			
[Pentastarch]				100 g/l		
[Hetastarch]					60 g/l	60 g/l
[Na^+]	140	145	154	154	154	143
[K^+]		5.1				3
[Ca^{2+}]		12.5				5
[Mg^{2+}]						0.8
[Cl^-]	128	145	120	154	154	124
[L-lactate]						28
[Glucose]						5.5
[Octanoate]	6.4					
Effective SID	12	17.6	34	0	0	26[a]

[a]Assumes stable plasma lactate concentrations of 2 mmol/L (see text). [b]Weak acid. Electrolyte concentrations are given in mEq/l. SID, strong ion difference.

effective SID of a colloid is a fundamental acid–base property. This is tempered by two other factors. First, lower infusion volumes are normally required for the same haemodynamic effect [63], reducing the forcing function of SID equilibration. Second, the colloid molecule itself may be a weak acid. In other words some colloids contain A_{TOT}, as is the case with albumin and gelatin preparations (Table 6) [64]. A_{TOT} dilutional alkalosis is thus reduced or eliminated when these fluids are infused, at least until the colloid disappears from the extracellular space.

However, the SID values of commercially available weak acid colloids are all significantly greater than zero (Table 6). On infusion, the raised SID will tend to offset the acid–base effects of A_{TOT} infusion. As a result the overall tendency of standard albumin and gelatin based colloids to cause metabolic acidosis is probably similar to that of saline. By contrast, hetastarch and pentastarch are not weak acids, and the SID of standard starch preparations is zero (Table 6). Their acid–base effects are therefore likely to be similar to those of saline and the weak acid colloids [17].

'Balanced' colloids are still at the investigational stage. Hextend (Table 6) is a balanced hetastarch preparation [65]. It contains L-lactate, which, by raising the effective SID to 26 mEq/l, reduces or eliminates infusion related metabolic acidosis, and perhaps improves gastric mucosal blood flow [66]. Experimentally, this appears to offer a survival advantage in endotoxaemia [67].

Blood

At collection, blood is mixed with a preservative, normally CPDA-1 [68], providing approximately 17 mEq trivalent citrate anions per unit, and a small amount of phosphate [69]. The accompanying sodium cation adds about 40 mEq/l to the effective SID of whole blood. For this reason it is not surprising that large volume whole blood transfusion commonly results in a post-transfusion metabolic alkalosis (following citrate metabolism). With packed red cells, the standard red cell preparation in most countries, the preservative load per blood unit is reduced. Nevertheless, large volume replacement with packed red cells still produces metabolic alkalosis [69]. Conversely, if liver dysfunction is severe enough to block or grossly retard citrate metabolism, then the problem becomes ionized hypocalcaemia and metabolic acidosis [70].

Conclusion

The principles laid down by the late Peter Stewart have transformed our ability to understand and predict the acid–base effects of fluids for infusion. As a result, designing fluids for specific acid–base outcomes is now much more a science than an art.

Competing interests

The author declares no competing interests.

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