This is a second witness statement by

Dr Malcolm Coulthard

in relation to the inquiry into the death of

Adam Strain

04/12/2010

Introduction

I wrote a report on 04/08/2010 giving my professional opinion about the cause of death of Adam Strain. I have since been asked to clarify some of my answers, and to answer additional questions. These are the subject of this second report.

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CORRECTIONS

The word 'osmolality' on page 16, line 17 of my first report should have read 'osmosis'.

POINTS OF CLARIFICATION

The definition of hyponatraemia

The normal range of plasma sodium concentrations in children is widely agreed to be 135-145 mmol/l. This is not controversial; there does not appear to be any disagreement about this by any of the experts. It is a definition which would be quoted in a wide range of standard paediatric and laboratory textbooks. What this means is that if the plasma concentration of sodium was measured in a healthy child it would be expected to fall within that range of concentrations.

Given that definition of normal, then it follows that any concentration outside of these values must be defined as abnormal, that is as being hyponatraemic if it was 134 or less, or hypernatraemic if it was 146 or more.

However, in children that are unwell it is common to see plasma sodium concentrations that are a little higher or lower than absolutely normal for a wide variety of reasons. Minor perturbations of that sort do not usually cause any medical complications of themselves, and typically correct as a consequence of the general management of the child's underlying illness, without the need for any particular measures actively directed specifically at altering the plasma sodium concentration.

Thus, a plasma sodium concentration measured in the range of 130 to 133 might fall into the category of being unlikely to be of great clinical concern, if

a) it made sense in that clinical context (for example, if the child was generally unwell), and
b) it was judged as a single reading.

However, obviously a single marginally abnormal value could not be taken as reassuring if there were other plasma sodium concentration measurements known about that were taken earlier or later which indicated that the sodium concentration in that child was unstable. Similarly, it could not be taken as reassuring or unimportant if it was measured in a child who was otherwise completely well, in whom there was therefore no potential explanation for it. Obviously, paediatricians do not often perform blood tests on children who are completely well, but it is sometimes done, for example in the context of routine tests following a previous illness, when a range of screening tests are taken at the same time.

On page 15 of my first report I made the point that the further away from the normal range any particular sodium concentration falls, the more concern it will cause to paediatricians because it is increasingly likely to be harmful to the child's health in itself, and because it is increasingly likely to indicate an extreme imbalance or the presence of an underlying serious medical condition. For this reason, some paediatricians choose arbitrary concentrations of plasma sodium to define as clinically important hyponatraemia, below which great attention must be given to managing this abnormality.

Perhaps the best way to explain this is to make an analogy with motorists breaking the speed limit. The only speed permissible in a 30 mph speed limit zone is 30 mph or less, and strictly speaking a motorist travelling at 31 mph is speeding. However, few ordinary people would take much notice of a car travelling along a high street at 31 mph, or refer to it as a speeding vehicle, and few would be concerned that it was likely to be harmful to other people or an indication that there was a problem with the driver, such as being drunk or psychopathic. On the other hand, almost everyone would agree that a car travelling down the same street at 90 mph was speeding, and would be concerned that it might cause harm to others, and might consider that there was something not quite right about its driver. However, pedestrians in such a street might find it difficult to reach a consensus about defining cut-offs for when minor speeding became more concerning, or a major problem.

My interpretation of the nursing record statement of 25th November 1991 that Adam "*looked puffy and has gained weight*" and of his mother's observation on 27th November 1995 that he appeared *"bloated".*

In my first report I stated that the fact that the nursing record said that Adam "*looked puffy and has gained weight*" on 25th November 1991 contributed to the sum of evidence that he had gained weight by retaining water and thereby suffered from dilutional hyponatraemia. I do consider this nursing observation to be an important one, but it must be seen alongside the other strands of evidence, as I clarified in my first report.

I give this observation important status in the light of my many years of experience in diagnosing whether babies and children are fluid overloaded or not, and of ...

a) witnessing nurses and junior doctors diagnosing fluid retention
b) being able to establish the diagnosis precisely in retrospect, after dialysis and ultrafiltration; that is with a precise yardstick.

I will clarify. It is relatively common for young children with kidney failure to retain fluid, simply by drinking more water than their kidneys are able to excrete. Despite their best efforts, parents are frequently unable to maintain tight fluid restriction. It is a common consequence of this for children's kidney doctors and nurses to admit such children to hospital and give extra dialysis treatment to remove that fluid and to bring them back to their normal fluid status. This is usually referred to clinically as bringing them back to their "dry weight", as weight measurements provide the best way to plan the amount of dialysis required and to monitor progress. The fact that they have reached their dry weight is easy to confirm clinically because if extra fluid is removed after this, it produces clear clinical signs and symptoms.

I have therefore seen many children admitted with fluid retention, and have witnessed them being corrected to their normal or dry weights. What is very striking is that the clinical appearances of looking puffy or bloated do not occur until children have retained very large volumes of fluid proportional to their body weight. In my experience, neither I nor experienced children's kidney nurses that are trained to detect fluid overload can detect any visual impact of extra fluid in the tissues until children have gained a considerable amount of extra water.

Thus, when a nursing record refers to a child as looking puffy, I consider that it could indicate a significant degree of fluid overload, and give it credence.

Estimates of daily sodium intake

In the case notes and all of Prof Savage's letters, the name of the milk formula was given as Nutrizone, so I assumed that this was the product used. I was not familiar with it, but the Nutrizone website indicated that this is a milk substitute type of nutritional product, and hence my use of that sodium concentration.

However, I have since been informed that the product used was Nutrison, also a form of milk formula. When writing my first report, I did consider whether the entry should have read Nutrison, but did not pursue this further once I discovered that Nutrizone is also a milk substitute. This was partly because Adam had been on Nutrison for some time before reaching the body weight at which it is commonly used (over 20 kg), the same company making Nutrini for children weighing between 8 and 20 kg.

Now that I have been given the correct information, I have made the following adjustments to the calculations.

It is not possible to be completely precise about exactly how much of what constituents Adam actually did receive because of ambiguities in the records. The reason for this is that the daily quantity of feed that the dietician instructed Adam's mum to make up daily (1,700 ml, constituted

from 1,200 ml Nutrison, 400 ml water, 100 ml saline) is 400 ml less than the volume which Prof Savage states she was actually giving to him (2,100 ml, given as 1,500 ml overnight, plus 600 ml during the day). It is not possible to be sure how Adam's mother made up that difference, but I will outline the most likely possibilities below. Throughout, I will assume that Adam's mother made up at least for the overnight feed exactly as instructed by the dietician in June 1995, as there is no reason not doubt this.

1) It may be that the 1,700 ml of feed was made up in the ratios instructed by the dietician and that 1,500 ml was given overnight, and the rest of this mixture discarded, and that she gave 600 ml of standard Nutrison feed during the day. This would give the following sodium intakes:

a) Nutrison overnight	= 43 mmol x 1.2 litres x 1.5/1.7	= 45.5 mmol/day
b) Added NS overnight	= 150 mmol/l x 100ml x 1.5/1.7	= 13.2 mmol/day
c) Nutrison in day	= 43 mmol x 0.6 litres	= 25.8 mmol/day
d) Sodium bicarbonate, 15 mmol, 4-times daily		= 60 mmol/day
Total		= 144.5 mmol/day
Expressed per kg		= 7.2 mmol/kg/day

2) It may be that the 1,700 ml of feed was made up in the ratios instructed by the dietician and 1,500 ml of it given overnight, and the rest of this mixture given during the day, with the balance of the other 400 ml of during the day being given as standard Nutrison. This would give the following sodium intakes:

a) Nutrison overnight and in day	= 43 mmol x 1.6 litres	= 68.8 mmol/day
b) Added NS = 150 mmol/l x 100ml		= 15 mmol/day
c) Sodium bicarbonate, 15 mmol, 4-times daily		= 60 mmol/day
Total		= 143.8 mmol/day
Expressed per kg		= 7.1 mmol/kg/day

3) It may be that the full volume of feed was made up using the ratios used to make 1,700 ml of feed, but with a bigger bulk made (eg, an extra quarter again of each ingredient), to provide at least 2,100 ml of milk each day. This would give the following sodium intakes:

a) Nutrison overnight and in day	= 43 mmol x 1.55 litres	= 66.7 mmol/day
b) Added NS = 150 mmol/l x 124ml		= 18.6 mmol/day
c) Sodium bicarbonate, 15 mmol, 4-times daily		= 60 mmol/day
Total		= 145.3 mmol/day
Expressed per kg		= 7.2 mmol/kg/day

It is clear that these possible variations in the way that the full 2.1 litres of feed was made up give very similar values for the total sodium intake. It is reasonable to use the single figure of 7.2 mmol/kg/day to examine how this alters the subsequent calculations.

Estimate of daily urinary volumes

On page 21 of my report, I state that "*the likely quantity of urine or dialysis losses he would have produced is about 300 ml less than his milk feed volume per day, or about 1.8 litres/day.*" In addition, "*it is likely that his actual urine output was fixed at about 1.5 litres per day, but perhaps as low as 1.3 or as high as 1.7 litres per day. I note that Prof Savage assumes that Adam voids about 1.5 litres per day.*"

I made my statement that "I note Prof Savage assumes that Adam voids about 1.5 litres per day" on the basis of his statements, as follows:

- In his statement in Tab 4a, he says that "*he continued to pass in excess of 1 litre of urine each day.*" on page 2, and goes on to clarify this on page 3 where he says "*I estimate that his*

urine output each day was 1200 – 1500 ml." Since the latter estimate is in excess of 1 litre per day, these 2 statements are mutually compatible.

- In his letter on 7th June 1996 (059-003-005), Prof Savage goes through a process of deduction to estimate Adam's urine output, and reaches the conclusion that *"then his urine output per hour is likely to have been around 75 mls."* This hourly volume equates to 1800 ml per day.

Thus, to complete the comparison of our estimates, Prof Savage's lowest volume was 1200 ml and his highest was 1800 ml, with a mid-point of 1500, while my lowest estimate was 1300 ml and highest was 1700 ml, also with a mid-point of 1500.

You will note that these estimates are therefore in broad agreement. Prof Savage's range could be described as 1500 ml, plus or minus 300 ml, and mine as 1500 ml, plus or minus 200 ml. This is why I put in my report *"that Prof Savage assumes that Adam voids about 1.5 litres per day."*

The likely urinary sodium concentration of Adam's urine when he was admitted for a kidney transplant, and why this is likely to have been different to values 2 years or more earlier.

When the kidney function declines, the concentration of sodium in the urine usually changes. Adam's intrinsic kidney function declined between December 1993 and his death, which is why he had to start dialysis. His plasma creatinine concentration measurements in November 1993 and January 1994 (that is, either side of December 1993) were 480 and 500 µmol/litre. These levels were very high compared to normal, indicating very poor renal function. However, by the time of his death, Adam's creatinine concentrations were much higher than this at about 700 µmol/litre. This indicates that the clearance provided by his peritoneal dialysis combined with the contribution made by his kidneys amounted to less than his kidneys alone were contributing about 2 years earlier.

My estimates of Adam's likely urine sodium concentrations prior to his transplant operation were based on my estimates of his likely urine volume (which, as discussed above, I have assumed to be about 1.5 litres per day) and my estimates of his likely urinary sodium losses. It is now clear that he was on a different feed from the one I assumed when I wrote my original report, as Prof Savage misspelt the name of the milk. I have now revised his urinary sodium losses up to about 144 mmol per day. This would produce a prediction of a urinary sodium concentration of 96 mmol/litre. This is a relatively high value, but within the ranges sometimes seen in end-stage kidney failure.

One problem with making assessments of this nature in a child like Adam is that it is difficult to know how much sodium he was losing via his peritoneal dialysis. If this was a high amount, it would mean that the concentration in the urine would be lower than the 96 estimated without that knowledge. It is because of these uncertainties that we in Newcastle routinely measure the urine sodium concentrations of children facing surgery, including transplantation.

The urinary sodium concentration which kidneys can generate gradually becomes fixed within relatively high ranges as children's kidneys fail; this is part of the pathophysiology of abnormal kidneys. If a child's kidneys were able to produce a lower concentration at an earlier stage, while the kidneys retained their ability to flexibly respond to the child's needs, then that concentration will inevitably rise as the kidneys lose that capacity.

The implications of this change of estimated urinary sodium losses in the overall calculation of the impact of Adam's management on his change in plasma sodium concentration during the early period of his anaesthesia, when I believe that those changes resulted in him developing cerebral oedema are small. In my estimation of the events that occurred then, I interpret the case notes as indicating that Adam voided a total of 49 ml of urine during that time.

- In my report, I assume that that volume of urine had a concentration of sodium of 60 mmol/l. I then expressed this volume of urine as losses to his body which were equivalent to losing virtual volumes of 20 ml of saline and 29 ml of water (page 30, paragraph 4).
- If I had assumed that the urinary sodium concentration had been 96 mmol/l, this would alter these virtual volumes to losses of the equivalent of 31 ml of saline and 18 ml of water.
- These differences mean that my new estimate, based on the correct feed formula, is that Adam's losses of sodium were a little higher, equivalent to 11 ml more saline rather than water lost. This would further exaggerate the inappropriateness of him being given a replacement fluid with a low sodium concentration, and would have been responsible for a slightly greater impact of this therapy on his final low plasma sodium concentration. In other words, using the estimate of 96 mmol/l instead of 60 mmol/l would have made my estimate of the impact of him receiving N/5 saline slightly worse. However, in the context of the much larger volumes of fluid that he was administered, this difference is of trivial proportion, and makes no impact on any importance.

Using the Schwartz formula to estimate Adam's GFR

The Schwartz formula is used to estimate a child's kidney function, the glomerular filtration rate or GFR, from measurements of their height and their plasma creatinine concentration. I have already given a full explanation of what GFR is and how it relates to the plasma creatinine concentration in the last 2 paragraphs of page 8 of my first report, and how the Schwartz formula is used to calculate an estimated value for GFR in the first paragraph of page 9 of my first report.

In summary, the normal plasma creatinine concentration varies directly with the child's height, so a healthy young child would be expected to have a much smaller level than a healthy older child. This is why the child's height appears in the Schwartz formula, to compensate for this fact. In addition, as the GFR halves, the creatinine doubles, which is why the constant and height are divided by the plasma creatinine concentration in the formula. This is the most widely used formula to estimate GFR from the plasma creatinine concentration that there is.

Using Boyd's equation to estimate Adam's body surface area

There are a number of formulae used by paediatricians to estimate the body surface area of children from other measurements. Many use height and weight. The Boyd equation only uses weight. It is the most extensively researched formula in existence, and was compared by Edith Boyd to other highly sophisticated self-adjusting power equations which did incorporate both height and weight, and was chosen because it correlated best with empirical measurements.

It is a standard formula used by many UK paediatricians, especially since I published a letter in the Archives of Diseases in Childhood (the main UK paediatric journal) in 1994 which argued that Boyd's equation should replace the other equations.[1]

A specialist group of paediatricians in the UK whose drug dosage calculations are critical, and mostly depend on a knowledge of the body surface area are the paediatric oncologists, or children's cancer specialists because under-dosage risks failure to treat effectively, and over-dosage carries particularly high toxicity risks. Since I published my letter recommending the Boyd equation, the UK Children's Cancer group have adopted it, and now use it to the exclusion of all other formulae.

Children's ability to excrete water

In a normal child with healthy kidneys, approximately 80% of the water filtered by the kidneys (the GFR) is reabsorbed by the proximal tubules, leaving 20% to be delivered distally. The proportion of this 20% which is then reabsorbed and the proportion that is then excreted in the urine can be varied by the kidneys according to the needs of the body.

The kidneys excrete the correct amount of water to keep the body in neutral balance. This means that if a child drinks a certain volume of water in a day, and after losing some water through perspiration, in their breath, and in stools (grouped together as insensible losses), they have to excrete the rest as urine to avoid becoming either dehydrated or overloaded with water.

Given normal children's fluid intakes, and their normal values for GFR and for insensible losses, the FEwater required to excrete the rest of the water would typically be between about 0.5% and about 2%, but might range occasionally up to approximately 3% or so.

During shock or dehydration, when the body conserves water avidly, the FEwater will always fall to under 1%, and usually to a small fraction of that.

In conditions of extremely high water intakes, it is theoretically possible for the entire 20% of the GFR which is delivered distally to appear as urine. This would be a fractional excretion rate of water (FEwater) of 20%. It would be exceptionally rare for this to ever happen in reality. In 30 years of experience as a paediatric nephrologist I have never seen it rise above about 6% in healthy children due to a high fluid intake alone. It can reach as high as the 20% ceiling if the kidneys are being driven to excrete large quantities of other substances, such as glucose in diabetes that is out of control, or sodium in children that have been administered this in excess (salt poisoning).

A worked example helps to understand why in practice the FEwater never reaches near to the 20% maximum which is theoretically possible in healthy children. For a 30 kg child with a surface area of 1 m^2 and a GFR of 100 ml/minute/1.73 m^2 to produce 20% of their GFR as urine by drinking a large amount of water, they would need to drink approximately 700 ml/hour, a rate of drinking of nearly 17 litres or about 2 full buckets full of water per day! Children could not tolerate drinking so much so quickly, so this limit is not seen in normal children whose intake is voluntary drinking.

In kidney failure, as the GFR falls to a small volume, a bigger proportion of it must be excreted as urine to maintain balance. For example, if a child needs to void 1 litre of urine to keep in balance, but only filters 3 litres of GFR fluid per day, they have to excrete a third of it (that is, have a FEwater of 33%) to maintain balance. Children with renal dysplasia therefore do have a much higher than usual FEwater than normal children as they reach end-stage renal failure. I have seen such children with FEwater values ranging from about 20% to over 50%.

The lack of necessity to repeat the measurement of Adam's plasma sodium concentration pre-operatively

Clinical protocols are often written to cover "all possibilities" and to some extent to ensure that procedures are carried out more "automatically" than might otherwise occur. An inevitable consequence of writing guidelines for clinical practice is that some procedures are included as routine practices which are often sensible in general, but which are unnecessary in certain particular circumstances. I believe that this applies to the question of whether Adam's blood tests should have been repeated on the morning of his transplant, prior to him going to theatre.

There will be a number of circumstances when it would be sensible to recheck the biochemistry immediately pre-operatively of a child admitted earlier for a transplant operation. For example, if the blood tests on admission were unsatisfactory and measures were taken to improve them, it would be sensible to check that the hoped for improvement had happened. I imagine that it was

circumstances such as that which would have led to the inclusion of a repeat pre-operative measurement in a guideline or check list.

Our Newcastle guidelines do not include a mandatory repeat of the biochemistry tests immediately pre-operatively. This is because our policy includes checking them on the child's admission, and discussing all of the results with a consultant. We would use this process to generate a decision on whether to repeat the blood test again pre-operatively, rather than assume an automatic retesting approach.

Thus, in my opinion, in the circumstances of a child being admitted with blood tests that were satisfactory, and who was to receive dialysis overnight which in any case tends to correct imbalances in biochemistry, it would be unnecessary to undertake a repeat in the morning. Again, other aspects of clinical judgement come into the decision. If the child had had a central line in place which would have allowed bloods to be accessed without any trauma to the child, that would weigh in favour of taking an extra sample for marginal clinical indications, whereas I would be much more strongly opposed to obtaining a sample if that meant inflicting pain and trauma onto that child, as was the case with Adam.

It follows that it was not necessary for anyone to obtain a blood sample for testing once Adam was asleep and a line was inserted. Clearly, however, if there were any clinical concerns thereafter on the part of the paediatric nephrologists, the anaesthetists or the surgeons, a sample could have been obtained without delay or trauma to him.

It has been pointed out to me that Mr Koffman, a transplant surgeon, has stated a different opinion on this matter in his report, as follows: "*The sodium and potassium should have been repeated prior to start of surgery. The polyuric patient with poor renal function would pass large quantities of dilute urine and may have difficulty controlling the concentration of sodium and potassium in the blood.*" (094-007-032). Clearly, Mr Koffman is entitled to his opinion on this issue. However, in my experience, managing the biochemistry of a child such as Adam in the situation of preparing him for a transplant is generally predominantly the remit of the paediatric nephrologists and the paediatric anaesthetists within the team, rather than of the transplant surgeon.

Would my opinion on this be different if his plasma sodium on admission had been 134 rather than 139?

It has been put to me that there is some uncertainty whether Adam's plasma sodium concentration on admission was 139, as Dr Taylor states in his deposition (011-015-109), or whether it was 134 as written in a biochemistry result list (057-007-008), and that the handwritten medical notes are unclear (058-035-144) whether the number is 134 or 139, and because no printed report is available.

A plasma sodium value of 134 mmol/l is very near to the normal range of 135 to 145, and as stated in clarification about the definition of hyponatraemia above, would not generate any anxiety in me as a paediatric nephrologist. This is particularly the case in Adam's situation because he was subsequently dialysed overnight, a process which tends to correct the sodium concentration towards that in the dialysis fluid, of about 140 mmol/l.

I would certainly not request a repeat of the plasma sodium measurement pre-operatively in a child whose plasma sodium was 134 on the previous night, especially if they were going to receive dialysis in the interim. My opinion would not be different whether the value had been 134 or 139.

It can be very confidently assumed that Adam's plasma sodium at the start of surgery was at least as high as it was the night before, and probably even nearer to normal. The low plasma sodium concentration recorded 2½ hours after surgery must therefore have been caused by events that occurred between the start of the anaesthetic and that point in time.

Obviously, if the starting plasma sodium concentration was different from the value of 139 which I used in my calculations to look at the impact of him receiving a large volume of hypotonic saline, the precise conclusions would differ in slight detail. However, these differences would be insignificant. The changes in the plasma sodium concentration that occurred were huge compared to the differences between a starting sodium which may have been nearer to 134 or to 139 mmol/l.

The fluid known as N/5 saline, or 0.18% sodium chloride solution: clarification of what it is, and about the figures "20% and 18%" which may cause confusion.

The fluid known as "one-fifth-normal saline" may be referred to by more than one name. Sometimes it is called "fifth-normal saline", or "0.18% sodium chloride" or "fluid 18", and it is often written as "N/5" saline.

It contains 0.18% sodium chloride by weight, or 0.18 grams of sodium chloride per 100 ml of solution. That is where the 0.18% figure comes from – it is not "18%". Verbally, it is often referred to as "point one eight percent saline", but never as "eighteen percent". The molecular weight of sodium chloride is 58.5 daltons, which means that a solution containing 0.18 grams of sodium chloride per 100 ml, or 1.8 grams per litre, contains 30 mmol of sodium per litre.

Normal saline is a solution containing sodium chloride at a concentration of 150 mmol per litre. It is approximately isotonic, that it has about the same strength of ionised chemicals in solution as plasma does. In plasma the cations (positively charged components of these ionised chemicals) are made up mostly of sodium, with a small amount of other chemicals including potassium and calcium. This is why the sodium concentration of normal or physiological saline is a little higher than that in plasma.

A solution of 0.18% saline, or 30 mmol/l of sodium obviously has one-fifth of the concentration of sodium as does normal saline. This is why it is referred to as N/5 saline, as it is 20% of physiological strength with respect to sodium.

The concentration of glucose that is provided in bags of N/5 saline is usually 4%, or 40 grams per litre. Since the molecular weight of glucose is 180 daltons, this is the equivalent of 222 mmol/l of glucose in N/5 saline. This brings the overall strength of the solution to 282 mosmol/kg, made up of 222 mosmol/kg as glucose, and 30 mosmol/kg each from sodium and chloride ions. This means that as the solution is infused into the blood stream it is of a very similar strength to the blood plasma, and therefore that it does not provoke an osmotic challenge to the red blood cells as it immediately mixes with the blood on first contact, which would otherwise have the potential to damage them.

It should be remembered that once the N/5 saline has been diluted into the blood stream, the extra glucose content it provides is rapidly dissipated. This occurs by the glucose either being immediately metabolised (burnt for energy), or by it being converted into a storage molecule (such as being deposited in the liver as a polymer called glycogen). Thus, almost instantly, the contribution of adding N/5 saline to the plasma in terms of altering its salt and water balance is the equivalent of having added 4 volumes of water and 1 volume of normal saline to the blood. This is why I conclude that the infusion of *"about 1,167 ml of N/5 saline"* into Adam was the *"equivalent to administering 234 ml of normal saline and 933 ml of water."*

The terms 'zero mixing' and 'complete mixing'

On page 31 of my first report, I used the terms 'zero mixing' and 'complete mixing' without sufficient explanation. I apologise that I did not make this clearer. I attempt to do so below:

In the section immediately prior to this section (that is section **"b) The effects on the plasma sodium concentration"** on page 30), I explain that the concentration which results from infusing N/5 saline into a patient depends on whether it is distributed just into the plasma, or if it is also

distributed into the total body water volume. It is in this context that I went on to talk about zero or complete mixing. I will explain below.

The blood circulates very rapidly through the body. A person's entire blood volume is pumped out of the heart and round the body in less than 2 minutes; for example an average adult has about 8 litres of blood in their body, and their heart pumps it out at about 5 litres per minute. The plasma is the water component of blood (the red blood cells being the 'solid' bits). Because the plasma circulates so quickly, if fluid is added to it through an intravenous infusion it mixes very rapidly indeed, and becomes distributed evenly throughout it extremely fast. Colloquially, I used the term 'zero mixing' to refer to the N/5 saline being added to the plasma and being mixed throughout it so fast that it can be considered to have been distributed instantaneously, or in zero time.

The sums for zero mixing therefore refer to the concentration that would theoretically be achieved if the N/5 saline was mixed evenly into the plasma water, but that none of it was redistributed from there into the rest of the water in the body.

The term 'complete mixing' refers to the theoretical situation where all of the sodium and water infused as N/5 saline is completely mixed with the body's entire fluid volume.

The redistribution of sodium and water from the plasma into the entire body fluid volume takes time, probably a few minutes in healthy individuals. In a complex real life situation such as Adam receiving N/5 at varying rates over a period of 2½ hours, the degree of mixing between the 2 extremes of it all being in the plasma and it all being distributed throughout the total body water volume cannot be precisely known. However, it can be assumed that all of the N/5 saline infused during the early part of that period will have had time to fully mix, that most of the next period of infusion will have dissipated, and so on. Clearly it cannot all have been fully redistributed from the plasma as some of it had only been infused for a few minutes, or a few seconds.

I went on to calculate how much redistribution from the plasma into the rest of the body water would have needed to occur to produce the plasma concentration of 123 mmol/litre which was recorded at 2½ hours, and this answer was 87.5%. As I state in my first report (page 30, penultimate paragraph), this is a physiologically plausible result. By this, I mean that if I had been asked to guess a value by approximate modelling, it would have been close to this. If it is of interest to the court, I have measured the redistribution times of kidney marker substances in babies in a previous publication (which formed part of my PhD studies), and discuss some of the modelling issues that are covered here by using the mathematics of a single-exponential approach and half-life measurements.[2]

NEW QUESTIONS POSED TO ME

Should Dr Taylor or the operating surgeon or his assistant have inserted a bladder catheter soon after the induction of anaesthesia? If so, which of them should have done so?

This question should be addressed to paediatric anaesthetists and/or paediatric transplant surgeons. It has generally been the practice that I have witnessed for polyuric patients that have been transplanted in Newcastle and during my training in London for them to be catheterised, at least in part to monitor the urine output, but I am not the right person to provide a powerfully reasoned argument about this.

Should Adam's plasma sodium concentration reading of 123, measured on a blood gas analyser at 9:32am on 27th November 1995, have been repeated in the laboratory?

I am not an expert on measuring sodium using the method incorporated into the blood gas analyser. However, under clinical governance arrangements in the UK mainland, hospital

laboratory managers have responsibility for the quality control of peripheral or satellite laboratory tests. A blood gas analyser with a sodium electrode would definitely come within the remit of such a service, and would be routinely tested and maintained by the central laboratory. It would only be allowed to be used if it provided results that agreed satisfactorily with control samples. If these questions were asked of me about a mainland UK hospital in 1995, I would therefore be confident that such a measurement could be relied upon. However, I am not sure if these considerations can be applied to Northern Ireland in 1995.

Clearly, if a clinician had serious doubts about the value of any particular near-patient test, such as a plasma sodium measurements made on the blood gas machine, it would appear illogical to measure it since routine laboratory facilities are available. I am not familiar with the specific laboratory arrangements in the hospitals in Belfast. However, any hospital designated for paediatric kidney transplantation should be able to produce an urgent plasma sodium concentration result within a maximum of an hour, including the time to take the sample, transport it to the laboratory, phone the lab staff to request an urgent service, and inform the operating theatre staff of the result.

However, sometimes clinicians use near-patient tests as relatively imprecise screening tools to decide whether to request formal laboratory test analyses. For example, bedside blood glucose testing is widely undertaken in paediatrics, using a single drop of blood, often from a finger prick. The results are not precise, but give the range that the blood glucose is likely to be in. If the results are clearly normal, then no other glucose measurements are used, but if the result suggests that the value is particularly low or extremely high, then the staff use that information to initiate taking a venepuncture and measuring a true blood glucose in the laboratory.

This could have been a reasonable use of a near-patient sodium analyser if it was perceived to be less than absolutely precise. However, it was clearly not used in this way in Adam's case, otherwise the obviously abnormal result recorded would have initiated an immediate and urgent true blood sodium measurement in the hospital laboratory, which could have been used as a basis to confidently alter his management.

An obvious and important question following from this issue is whether or not a confirmatory plasma sodium concentration measurement made in a laboratory would have altered the clinical outcome for Adam. This would depend on whether his brain had already been irreversibly damaged by cerebral oedema by that time, and this is impossible for us to determine now. If it had been, then clearly it would not have been possible to have altered the final outcome. If, however, the permanent brain damage had not occurred by that stage, it may have been possible to gradually and carefully correct the plasma sodium concentration by judicious fluid and electrolyte management, and prevent any damage from occurring. Unfortunately this did not happen, so the potential for his recovery at that stage can never be known.

Did Dr Taylor's note of his administration of fluids (see below) alter my calculations about how much sodium and water was administered between 7am and 9:32am on the day of Adam's transplant?

I have been asked whether paragraph 4 of a note from Dr Taylor to Mr Brangham solicitor (059-004-007) has any impact on my calculations of the amounts of fluid administered to Adam. The paragraph reads: "*500 mls were given in the first 30 minutes to replace this deficit and provide maintenance in preparation for the impending transplanted kidney"* and at the bottom states that *"following the blood test at 09:32 I drastically slowed the rate of 0.18 NaCl and commenced Hartmanns. I cannot exactly remember but I was perhaps attempting to correct the low sodium at that time."*

My calculations of the amounts of sodium and water Adam received took into account all of the details of the fluids administered, including the statements quoted above, so it does not alter my conclusions at all.

The effects of anaemia on Adam's kidney function

Adam was anaemic, but this would not have made any significant difference to the calculations or conclusions reached about his kidney function or sodium or water handling.

What is the role of paediatric transplant guidelines, and how would the Belfast 1990 or 1996 guidelines have influenced Adam's management?

The 1990 guidelines were complied with pre-operatively in Adam's case. Particular points to note are that the guideline did not include the need for his urinary sodium concentration to be measured on admission, nor for his blood biochemistry (referred to here as U & E) to be automatically checked immediately pre-operatively.

The 1990 guidelines were **not** complied with regarding the use of intra-operative fluids. They stated the following:

- Blood, PPF or N/2 Saline may be required before unclamping the artery to ensure a good intravascular volume.
- This is determined by reference to BP and CVP levels.

Instead, N/5 saline was administered (that is, a much more dilute solution in relation to its sodium content), and it was continued at a high rate despite the fact that the CVP indicated a high pressure, consistent with too much fluid having already been given.

The 1996 guidelines differ from the 1990 guidelines in relation to the pre-operative and intra-operative blood testing and fluid management details.

The 1996 pre-operative guidance would not have been met in Adam's case if it had been operative at the time because it asks for a urine sample to be sent for measurement of the urea, electrolytes and creatinine concentrations ("U/E and creatinine"), which was not done.

The 1996 pre-operative guidance would have requested for Adam to have his electrolytes (sodium and potassium concentrations) to be measured 2-hourly throughout his operation. This was not a requirement in 1990, and was not done. It is unlikely that this aspect is present in many other units' guidelines, and appears to be a direct (and understandable) response by the Belfast to having experienced Adam's problems. It would, however, not be needed if the fluid administration advice was adhered to.

Adam's intra-operative fluid management fell outwith the 1996 guidance in essentially the same way that it fell outside the 1990 recommendations. In 1996, the list of fluids suggested for volume expansion had replaced N/2 saline with normal saline, which was an appropriate change. Thus, Adam's management would have been different from them both.

The guidance in the 1996 document is much more specific about the CVP target than the 1990 one. However, the record of Adam's anaesthetic indicates that fluid was administered at high rate despite the pressure reading being far higher than physiological values, and thus far higher than any reasonable guideline would ever recommend.

The 1996 guidelines represent a significant improvement on the 1990 version:

- The addition of the measurement of the urine creatinine and electrolytes on admission is an improvement.
- The addition of the advice to discuss the results of the initial investigations with the consultant if the initial sodium is <133 is also an improvement.

The statement about repeating the biochemistry pre-operatively is not quite clear to me, as I am not certain if this applies only if the sodium is <133, or automatically. In any case, it is not necessary because the preceding instruction to discuss the presence of a low sodium with the consultant covers this situation. The purpose of the discussion would obviously be to plan a

strategy of managing the low sodium, and this would definitely include whether and when to repeat testing. If the sodium was not low, there would not be any need to repeat the test for that indication.

The advice about intra-operative management is a definite improvement on the 1990 version. Hypotonic fluids are no longer recommended for volume replacement, the only options now being blood, a plasma product or saline, and the desired target range to maintain the CVP at is stated.

There are far more robust systems in place in 2010 to keep guidelines up to date than there were in the 1990s. No further suggestions are needed from me.

Does pulmonary oedema normally occur during a renal transplant or is it unusual?

The word oedema refers to excess accumulation of fluid within tissues. There are different mechanisms by which this may occur, and the fluid may be distributed quite differently within different tissues. Sometimes different types of oedema can occur in different organs of the same patient for different reasons. It is vital to distinguish each of these clearly.

The 3 main types of oedema are cerebral oedema (in the brain), pulmonary oedema (in the lungs) and oedema in the rest of the body.

I have already explained the pathophysiology and mechanisms of development of **cerebral oedema** in detail in my first report. In summary, it is not due to the accumulation of fluid in the interstitium or intercellular spaces (the spaces between the cells) as it is in the other types of oedema, but it is the accumulation of extra fluid inside the cells (intracellular fluid). It occurs because of a change in the balance between the strength (osmolality) of the fluids inside and outside the cells which causes water to shift into the cells. Sodium is the main cation (positively charged chemical) in solution in the fluid outside the cells, so rapid changes in its concentration in the blood can cause fluid to shift in or out of cells. Although these shifts affect all the cells of the body, they are only of clinical importance in the brain because it is housed in a rigid box and does not have room to expand as water enters the cells and increases their volume. Instead, the pressure increases inside the skull, forcing brain tissue out of any available holes (such as down into the top of the spinal column), and reducing or stopping blood from entering the brain.

Pulmonary oedema is the accumulation of fluid within the air sacs (alveoli) of the lungs due to excessive amounts of circulating water within the blood vessels which leads to an increase in the pressure of blood within the veins and the small blood vessels (capillaries). The water is then squeezed out of the capillaries into the surrounding tissue spaces. In the case of the lungs, this includes the air spaces in the air sacs where oxygen and carbon-dioxide are exchanged between the air and the blood. It may occur in children if the chambers in the right side of the heart fail to pump adequately, and in any situation which results in the excessive administration of fluid.

One of the general principles of paediatric renal transplantation is that hypovolaemia (a shortage of fluid inside the blood vessels) carries a risk of damaging a newly transplanted kidney by limiting the blood supply available to it, and great emphasis is put on ensuring that the fluid intake is maintained relatively high to prevent this. As a result, children often have a mild and controlled degree of deliberate fluid overload. Occasionally, this is extensive enough to result in pulmonary oedema, but this is rare, and because it is anticipated it is typically dealt with promptly and does not cause clinical problems. I personally have seen 2 children with overt pulmonary oedema following renal transplantation in my career of over 25 years, both of whom were treated easily and did not suffer any consequences of this, and both had successful longterm kidney transplants.

Adam had both of the above processes occurring during his transplant operation. His plasma sodium concentrations changed rapidly during it leading to cerebral oedema, and he was administered a total fluid overload which increased the pressure within his veins (measured as the central venous pressure, or CVP). He was therefore at risk of suffering from both of these types of oedema.

To complete the description of the 3 types of oedema, fluid can accumulate in the interstitium of **other parts of the body**. Clinically, it is usually most obvious in the extremities, where it is referred to as peripheral oedema. This is usually defined and detected clinically as 'pitting oedema' because the application of gentle sustained pressure by the fingers to the skin results in the fluid being shifted away to the surrounding tissues, and leaves a depression or pit which stays for some time. Although pitting peripheral oedema can occur as the result of extreme fluid overload, this is usually a very late sign, and simple fluid overload usually merely produces a distortion of the tissues, such as puffiness of the hands and feet and a bloated appearance to the face, especially around the eyes. Gross pitting oedema is usually only obvious in children who have a low concentration of plasma proteins, especially of the protein albumin.

Albumin is normally present at high concentrations in the plasma, but much lower concentrations in the rest of the interstitial fluid, and this difference in its concentrations across the walls of the small blood vessels exerts a pressure (the oncotic pressure) which retains water inside the blood vessels. If the albumin concentration falls, water leaks out from the plasma to the spaces between the cells in the tissues where it causes pitting oedema. This is then markedly exaggerated if more fluid is drunk or administered.

The commonest causes of a low albumin in the UK is a kidney condition called nephrotic syndrome. Worldwide, the commonest cause is malnutrition (kwashiorkor). Adam did not have a low plasma albumin, nor was there any record in his notes of him having had pitting oedema.

REFERENCES

1. Coulthard MG. Surface area is best estimated from weight alone: pocket calculators and nomograms are unnecessary. *Archives of Disease in Childhood* 1994;71:281.
2. Coulthard MG. A comparison of methods of measuring renal function in preterm babies using inulin. *Journal of Pediatrics* 1983;102:923-30.

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