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Dear Etta,

It was good to talk to you on Friday and thank you for your understanding. I feel frustrated and want to get the report out and am happy to defend it! However I understand the position.

I enclose some stuff on hyponatraemia. Malcolm Holliday (who is 80 yrs old now) knows more about it than anyone I know. The article is a draft which he has submitted for publication and he responded to the Lancet article on their website. Let me know if I can help. I hope the weekend brought cheerful thoughts!

V. best

Cyril

DHSSPS

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A CRITIQUE OF SHORT TERM FLUID THERAPY IN HOSPITALIZED CHILDREN: AVOIDING HYPONATREMIA AS A TREATMENT RISK

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ABSTRACT

Objective: To review the settings in which hospital induced hyponatremia occurred in children given short term fluid therapy because of admission for acute illness, diarrheal dehydration, or surgery. To determine the frequency of mild hypovolemia in this group and the frequency of excess maintenance fluid therapy as factors contributing to the cause of this hyponatremia. To review protocols for rehydrating/restoring ECF with isotonic saline or with oral rehydration and those for estimating maintenance therapy including the method for indexing maintenance therapy to metabolic rate.

Methodology: We reviewed articles over the last twenty years in which hyponatremia was reported in children given short term fluid therapy. We used elevated ADH levels with normal or low plasma sodium as evidence of hypovolemia, reinforced by history of restricted intake, diarrhea, or dislocation of ECF. We noted where excess maintenance therapy was given. We cited the effectiveness of giving extra ECF to restore circulation and control of salt and water balance in burn shock. We redefined fluid therapy protocols.

Results: A preponderance of children with hospital induced hyponatremia met our criteria for hypovolemia; rehydration/restoration of circulation prevented or reversed it. Maintenance therapy often was given in excess of need and protocol.

Conclusions: Rapidly correcting hypovolemia with isotonic saline and providing maintenance therapy in accordance with protocol reduces the risk for hospital induced hyponatremia and its complications.

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Introduction: Hyponatremia is a frequent complication of short term fluid therapy given to children admitted to hospital for acute illnesses[1,2] or surgery[3]. It sometimes causes water intoxication, convulsions, brain injury or death[4]. A review of the literature describing hyponatremia in this setting has led us to conclude that it is commonly caused by unrecognized hypovolemia which elevates plasma levels of antidiuretic hormone [ADH] irrespective of plasma sodium. When hypotonic maintenance solutions are given intravenously the elevated plasma ADH inhibits excretion of the free water leading to hyponatremia. Less commonly it is caused by giving miscalculated maintenance fluids that exceed renal capacity for excreting free water even with ADH suppressed.

The purpose of this article is to review the nature of maintenance therapy as originally described; to cite the clinical findings supporting the case that hypovolemia or giving excess free water are primary causes of hyponatremia. Further we describe protocols for correcting hypovolemia and the method for calculating maintenance fluid. Advantages of using oral rehydration therapy in treating diarrheal dehydration are noted.

Maintenance therapy: Maintenance therapy as originally described[5] was to replace ongoing physiological losses of water when oral intake is suspended. The average vary as metabolic rate[a] and are net insensible water loss [~35 ml] and urinary water loss [~65 ml] per 100 kcals/da. Maintenance allowance for water therefore should be indexed to

[a] Infant: 3-10 kg, 100 kcals/kg
Preschool: 10-20 kgs, 1000 + 100 kcals for each 2 kg > 10.
Older: 20-70 kgs, 1500 +100 kcals for each 5 kg > 20.

metabolic rate [see footnote a and Table], not body weight [BW]. Average maintenance allowance for water is 100 ml/100 kcal/da usually met by giving hypotonic [between 0.45 and 0.18 %[b]] saline. Exceptions to the average figures for net insensible losses are uncommon in the modern hospital setting except with mechanical ventilation; exceptions for urinary losses are uncommon but can be inferred from clinical findings; maintenance therapy should be adjusted accordingly. For example, when hyponatremia is present and there is no evidence for hypovolemia, the syndrome of inappropriate ADH [SIADH] may be suggested and its cause sought; in that case maintenance therapy should be reduced to half average [not "half maintenance"] or 50 ml/100 kcal/da [see Table], because renal loss is reduced to a minimum. Using isotonic saline for all maintenance therapy, as recently recommended[6], incurs needless additional risks[7].

The case for hypovolemia: Hypovolemia stimulates release of ADH even though plasma sodium is normal or low[8]. This release inhibits normal renal free water excretion so that giving hypotonic solutions intravenously in this setting leads to free water retention and hyponatremia. The hypovolemia seen in these children is of two types[9]: 1) dehydration due to the loss of extracellular fluid [ECF] as seen with diarrhea or loss of other body fluids, 2) plasma volume displacement seen post surgery or with infectious disease due to inflammation or to pooling of blood into dependent areas, as occurs with bed rest[10]. Hypovolemia responds to giving normal saline which restores circulation, venous return and renal regulation of salt and water balance, and depresses ADH.

[b] The term normal saline, though widely used, is not permitted in labeling by FDA because it is not a chemically defined Normal solution. Isotonic saline is 0.9% saline (154 meq/L Na). Hypotonic saline solutions vary between 0.45 and 0.18% saline (77 and 30 meq/L Na) and deliver between half and 4/5 of their volume as free water.

The evidence for hypovolemia is taken from several reports. In one[11] 25 of 27 acutely ill patients with hyponatremia had elevated plasma ADH levels. In another ADH levels were elevated in children with hyponatremia due to gastroenteritis and dehydration[12]. In a prospective study, children with meningitis and elevated ADH levels who were given "maintenance plus replacement" fluids lowered ADH levels, whereas children given maintenance fluids alone did not[13]. In another prospective study, children who were given isotonic saline during surgery had lower plasma levels of ADH postoperatively than those given no fluids although plasma sodium was the same for both groups[14]. When children with diarrheal dehydration and elevated ADH levels were given 0.45% saline [77 meq/L] as therapy for dehydration, many became hyponatremic; when they received isotonic saline [154 meq/L], plasma sodium generally remained normal[15].

In each instance cited, the children were hypovolemic and vulnerable to hyponatremia when given just maintenance therapy. When ECF was expanded before giving maintenance therapy plasma ADH decreased and hyponatremia was avoided.

The case for excess water: Maintenance therapy is often given well in excess of that recommended[5]. In one report[2] physicians gave >150% recommended maintenance fluid to 16 of 23 patients. Commonly, orders are written for "one and a half" maintenance without evidence that physiologic losses are increased. More may not be better! In other instances maintenance fluids are indexed to BW at a rate of 100 ml/kg/da [not per 100 kcals] increasing the intake by as much as three times recommended [see Table]. Giving maintenance fluid in excess of recommended will rarely exceed the patient's capacity to excrete free water, so long as plasma ADH is not elevated, because that capacity is generous. But sometimes it is a cause of hyponatremia. Occasionally egregious amounts of free water are given as hypotonic saline and death has resulted[4].

The Nature of Water intoxication: When hyponatremia develops due to free water retention, regardless of cause, solutes of both extracellular and intracellular fluid are diluted because water rapidly equilibrates across cell membranes and solutes do so only slowly. Cell and extracellular volumes increase. Given the unique anatomic and physiologic features of the brain, this causes brain swelling and increased intracranial pressure. If of sufficient magnitude, brain ischemia follows which is the physiological basis of water intoxication. With time brain solutes are lost and brain volume returns to normal. In the interim convulsions and brain injury may have occurred.

Expanding ECF to suppress ADH: Further evidence that isotonic saline infusion suppresses plasma ADH and prevents hyponatremia is noted in management of severe hypovolemia as seen in burn or septic shock. For example, a 40% skin surface area burn, releases vasoactive agents that effect a huge transfer of plasma and albumin into both the burn site and normal interstitium. Circulation and renal perfusion are severely compromised; the stimulus to ADH secretion is intense. Current treatment is to give 80 ml/kg [2 ml/% skin surface burn] of isotonic saline or Ringers solution in the first four hours[16]. That dose or more is repeated in the next 12-16 hours until blood pressure and pulse are stable, urine output and organ perfusion normal and the patient, as defined by Moyers[17] "is alert, able to converse and drink fluids". Hyponatremia seldom develops[18]. Managing the hypovolemia of burn shock by generous expansion of ECF with isotonic saline restores circulation and suppresses ADH with no change in plasma sodium[19]. Renal regulation of salt and water balance are restored to normal. As inflammation subsides, the "extra" ECF is recovered into plasma and excreted as urine. Septic shock is an example of extreme vasodilatation and dislocation hypovolemia that dramatically raises ADH levels[20]. A critical component of treatment is massive isotonic saline infusion given quickly to restore circulation and renal regulation of salt and water balance[21]. Once vasomotor tone is restored, ADH decreases, and the "extra" ECF is excreted.

The shock that comes with experimental "quiet standing" illustrates the capacity of gravity to cause blood pooling and dislocation even in normal subjects that is sufficient to result in shock. Normal young men, when standing with muscles fully relaxed, develop tachycardia, hypotension, and syncope within 15 minutes. These develop from blood gravitating to the capacitance vessels in the lower limbs and plasma sequestering in the dependent interstitium; venous return to the heart is compromised. Plasma ADH dramatically rises. All is reversed when the subjects lie down[22]. Bed rest or "quiet lying" as occurs in acute illness or following surgery has a comparable effect often abetted by inflammation; ECF expansion with isotonic saline maintains/restores circulation.

Steps in planning short term fluid therapy: The first priority in planning short term fluid therapy is to determine if hypovolemia, as described, is likely. If so, rehydration/restoration therapy is indicated. If it is marginal to moderate, giving 20-40 ml/kg of isotonic saline or Ringers solution quickly, should suffice. With more severe dehydration or shock, 40-80 ml/kg or even more may be needed. Note that this therapy is indexed to BW, not metabolic rate, because blood and ECF volumes vary as a function of BW. Some pre-op patients may have hypovolemia from being without fluids and from "quiet lying"; surgical trauma will sequester ECF. These patients will benefit from 20-40 ml/kg of isotonic saline. For patients needing only a 'keep-open" line going into surgery, isotonic saline offers the safest solution for ready use in case of unanticipated events.

The special case of oral rehydration therapy in diarrheal dehydration: In the case of diarrheal dehydration, the protocol, prior to introduction of oral rehydration therapy [ORT], was to infuse isotonic saline [20-40 ml/kg] to partially restore ECF volume and then plan intravenous deficit and maintenance therapy. Acute ECF expansion is still the recommendation if oral fluids aren't tolerated. But oral rehydration solution [60- 90 meq/L Na], given aggressively [60-100 ml/kg in 4-6 hrs], restores ECF volume, replaces continued diarrheal losses and normalizes plasma sodium[23]. It is the treatment recommended by the American Academy of Pediatrics[24]. As noted above[14] giving 0.45% saline [77 meq/L Na] intravenously increases the risk for hyponatremia. This apparent paradox may be explained by the different endocrine response to an intravenous versus an oral salt load of 30 ml/kg of isotonic saline given in one hour to normal subjects on a very low salt diet[25]. The intravenous load increased plasma atrial natriuretic peptide [ANP] more than the oral; plasma volume and initial salt excretion also more[c]. These findings may explain why giving 0.45% saline [77 meq/L Na] intravenously induces hyponatremia whereas giving oral rehydration solution [60- 90 meq/L Na] does not.

Summary: Those prescribing short term fluid therapy for children admitted for acute disease or elective surgery often fail to identify subtle hypovolemia, or they use incorrect estimates of maintenance therapy or both. These practices follow from the common tendency to compress principles of management into readily remembered rules. The results sometimes lead to serious complications. Hypovolemia initiates ADH release

[c] The responses of plasma levels of aldosterone and renin between the intravenous and oral sodium loads were not significantly different

which limits free water clearance. When hypotonic saline is used for maintenance therapy, without first correcting hypovolemia, water is retained causing hyponatremia, sometimes sufficient to induce water intoxication. Occasionally maintenance allowance is so miscalculated or is indexed to BW not metabolic rate and exceeds renal excretory capacity causing hyponatremia and water intoxication in the absence of ADH. These are the commonest causes of hospital induced hyponatremia and the attendant risk for water intoxication in children given short term intravenous fluid therapy. The risk is greatly reduced 1) by initially giving to children with acute illnesses or admitted for surgery who are at risk to hypovolemia, 20- 40 ml/kg of isotonic saline and 2) by correctly calculating maintenance allowance- usually 100 ml/100 kcal/da. Isotonic saline, not hypotonic maintenance fluids, should be used for rehydration/restoration therapy. Moderate diarrheal dehydration is preferably treated by oral rehydration therapy, not intravenous fluid therapy, because it has a lower risk for causing hyponatremia.

TABLE.

RELATING BW TO METABOLIC RATE [see footnote a] AND
TO AVERAGE AND HALF AVERAGE MAINTENANCE ALLOWANCES
FOR DAILY AND HOURLY PERIODS

BW	METAB RATE	MAINTENANCE ALLOWANCE			
		ML/DA		ML/HR	
KG	KCALS	AVER	1/2 AVER	AVER	1/2 AVER
3	300	300	150	12	6
5	500	500	250	20	10
7	700	700	350	24	12
10	1000	1000	500	40	20
12	1100	1100	550	45	22
16	1300	1300	650	50	25
20	1500	1500	750	60	30
30	1700	1700	850	70	35
45	2000	2000	1000	80	40
70	2500	2500	1250	100	50

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