ORIGINAL ARTICLES

Systemic hormonal, electrolyte, and substrate changes after non-thermal limb injury in children

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Abstract

Relatively little is known regarding the hormonal changes after injury in children. Adult protocols are often applied to children, although the latter often have different physiological responses to trauma. Twenty children with an angulated displaced fracture of the radius and/or ulna (injury severity score 9) were studied prospectively for changes in adrenaline, noradrenaline, cortisol, angiotensin II, arginine vasopressin, urea, electrolytes, and glucose. Two blood samples were taken: one on arrival at the accident and emergency department and one preoperatively several hours later. There were marked increases in adrenaline, noradrenaline, cortisol, and arginine vasopressin above the normal range. Five (25%) cases demonstrated greater early increases in adrenaline than those reported for adult injuries of similar severity. Early hypokalaemia in four cases had corrected towards normal within a few hours without potassium supplementation.

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Much is known about the neurohumoral stress response to injury from adult studies and animal experimentation. The early involvement of the sympathoadrenal system is well established. Plasma catecholamine concentrations rise early after injury[1] and in proportion to the degree of injury.[2–4] Fear, haemorrhage, pain, and tissue damage are individually associated with rises in catecholamine concentrations.[5] Increases in serum cortisol also occur after injury but these are less marked in severe than moderate trauma.[6 7]

Relatively little is known regarding the hormonal changes after injury in children. Regulation of fluid and electrolyte balance after thermal injury in children has been described,[8] and relationships between circulating vasopressor hormones and blood pressure have been reported.[9] After such injury, there is also a disruption of the secretion profile of thyroid hormones[10] and of glucose metabolism.[11]

Frequent assumptions are made that paediatric responses mimic those of adults and consequently adult protocols are used in the treatment of their smaller and younger counterparts. However, children are less able to withstand some forms of trauma than adults[12] and their physiological responses may be different.[11 13]

This study describes the early phase stress response in a small number of children with a given severity of injury with a view to identifying further avenues of research.

Methods

STUDY DESIGN

This prospective study was conducted in the accident and emergency (A&E) department of the Royal Hospital for Sick Children, Edinburgh. Approval was obtained from the Paediatric/Reproductive Medicine Ethics Board of the Medical Research Subcommittee of Lothian Health Board for the removal of two aliquots of blood from each patient. The first was to be taken on admission and the second several hours later. Informed verbal consent was obtained from the parent or accompanying adult person in every case.

PATIENT CHARACTERISTICS

Patients were considered eligible for this study if they had sustained an angulated displaced fracture of the radius and/or ulna, required intravenous access for the administration of analgesia, and would be referred to the admitting orthopaedic team for manipulation of the deformity under general anaesthetic.

METHODS OF SAMPLING

The first blood samples was taken just after the patient was admitted to the A&E department. Morphine (0.2 mg/kg) was then administered intravenously according to departmental protocol. The limb was splinted, usually

Table 1 Patient characteristics

Characteristic	*Data*
No of subjects	20
Age (years)*	8.5 (7, 12) 5–14
No (%) male sex	17 (85)
Time interval from accident to:	
First blood sample (min)*	55 (32, 79) 5–186
Second blood sample (min)*	198 (168, 265) 145–350

*Median (interquartile range) range.

Table 2 Hormones, electrolytes, and glucose concentrations from the first and second blood samples. Values are median (interquartile range) and range

	Normal range	*First sample*	*No outside normal range*	*Second sample*	*No outside normal range*	*p Value**
Adrenaline (nmol/l)	0.3–0.8	0.88 (0.57, 4.77) 0.09–62.8	12	0.64 (0.41, 1.64) 0.02–61.8	6	0.03
Noradrenaline (nmol/l)	1.0–2.0	2.27 (1.62, 3.06) 0.42–4.32	10	2.35 (1.65, 2.89) 0.82–3.41	12	0.72
Cortisol (nmol/l)	160–565	636 (515, 761) 127–906	13	425 (231, 656) 125–863	6	0.03
Arginine vasopressin (pmol/l)	<4	6.5 (2.15, 15.1) 0–29.2	12	3.0 (2.1, 4.8) 1.0–19.2	5	0.10
Angiotensin II (pmol/l)	5–35	26.1 (12.8, 35.8) 9.9–56.5	5	22.4 (11.5, 27.1) 6.5–48.9	3	0.13
Potassium (mmol/l)	3.3–4.7	3.5 (3.2, 3.75) 2.2–4.1	4	3.8 (3.7, 4.1) 3.1–4.2	1	< 0.02
Sodium (mmol/l)	132–142	139 (139, 141) 133–145	1	139 (138, 140) 134–140	0	<0.01
Osmolality (mosmol/kg)	275–295	287 (283, 290) 279–300	2	283 (281, 285) 266–293	0	0.051
Urea (mmol/l)	2.5–6.6	4.4 (3.6, 5.3) 1.7–6.1	0	3.9 (3.6, 3.9) 3.0–5.8	0	0.35
Glucose (mmol/l)	3.3–6.4	6.1 (5.3, 7.8) 4.8–13.1	5	6.4 (5.9, 6.7) 4.6–7.2	4	0.46

*Wilcoxon signed rank test for the difference in pairs between the first and second groups.

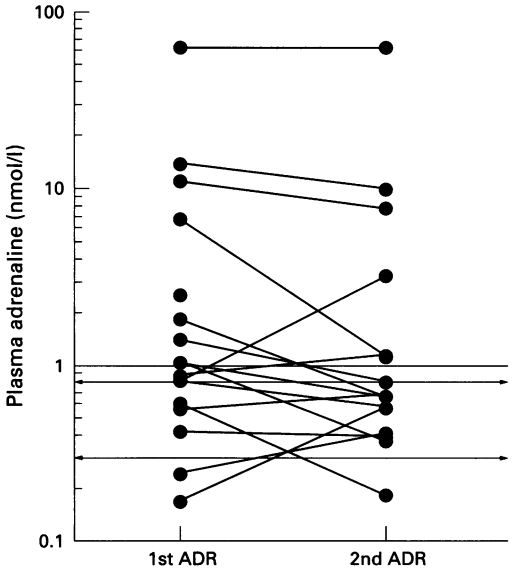

Figure 1 Plasma adrenaline samples taken on admission to the A&E department (1st ADR) and before operation (2nd ADR). The normal range (between arrowed lines) is 0.3–0.8 nmol/l. The y axis is presented as a logarithmic scale.

with a temporary plaster cast, before radiography. The patient was then admitted to a ward. No patient received intravenous fluid, potassium supplementation, or a general anaesthetic before the withdrawal of the second blood sample. The timing of the second sample was dependent upon the time of operation and was taken before anaesthesia on each occasion.

COLLECTION, PREPARATION, STORAGE, AND MEASUREMENTS

Blood was collected into a plain glass tube for serum cortisol, an EDTA/sodium metabisulphite medium for adrenaline and noradrenaline, EDTA/aprotonin medium for angiotensin II, and arginine vasopressin. All samples were then centrifuged at 13 000 *g* for two minutes and serum and plasma stored at −70°C pending analysis. All samples were analysed within three months. Adrenaline and noradrenaline concentrations were measured using high performance liquid chromatography, and arginine vasopressin, angiotensin II, and cortisol by radioimmunoassay.

DEFINITIONS

The injury severity score (ISS) was that first described by Baker and subsequently modified.[14] We used the 1990 revision of the abbreviated injury score (AIS) to score the patients' anatomical injuries.[15] All closed angulated, displaced, or compound fractures of the radius/ulna have an AIS of 3. The ISS is the sum of the square of AIS from three separate body regions. Therefore our patients would all have an ISS of $3^2 = 9$.

STATISTICAL ANALYSES

Statistical analyses were performed on a Sigma Pentium PC using the Statview statistical package version 4.5 marketed by Abacus Concepts. Following descriptive summary statistics it was evident that not all the data satisfied a normal distribution. Therefore results are presented as medians, interquartile ranges, and

Table 3 Relationships between hormones, electrolytes, and glucose concentrations from the first and second blood samples

	First sample			*Second sample*		
	No	*Rho**	*r***	*No*	*Rho**	*r***
Adrenaline *v* noradrenaline	16	0.18	−0.15	16	0.09	0.04
Adrenaline *v* cortisol	16	−0.08	**−0.74§**	16	0.05	0.10
Adrenaline *v* arginine vasopressin	16	0.07	−0.17	15	0.20	−0.34
Adrenaline *v* glucose	12	0.42	−0.03	12	−0.02	−0.24
Adrenaline *v* sodium	12	0.28	−0.47	11	0.09	**−0.78§**
Noradrenaline *v* cortisol	19	0.02	0.20	17	0.44	0.66
Noradrenaline *v* arginine vasopressin	18	0.35	0.60	15	0.14	0.54
Noradrenaline *v* glucose	14	0.43	0.25	12	0.19	0.15
Cortisol *v* angiotensin II	20	−0.24	**−0.75§**	17	0.18	0.12
Cortisol *v* arginine vasopressin	19	0.05	0.34	17	0.14	0.24
Cortisol *v* sodium	15	0.46	**0.60†**	17	0.44	0.26
Arginine vasopressin *v* potassium	15	**−0.65‡**	−0.40	12	0.27	0.19
Angiotensin II *v* sodium	15	**−0.55†**	−0.54	11	−0.45	−0.41
Glucose *v* potassium	15	−0.52	**−0.86§**	13	−0.11	−0.10

*Rho is the Spearman rank correlation coefficient. No is the number of observations used to compute rho.
**r is the Fisher's correlation coefficient. Eleven observations were used for computing the r value.
†p<0.05; ‡p<0.02; §p<0.01.

ranges. The Wilcoxon rank sum test was used to compare the differences in pairs between results from the first and second groups. Correlations between hormones, electrolytes, and substrates were analysed using Spearman's rank correlation coefficient and Fisher's correlation coefficient.

Results

Twenty children were enrolled into the study. Patient characteristics and time intervals from injury to blood sampling are presented in table 1. All patients arrived at hospital between 9 am and 8 pm.

Table 2 shows the normal reference ranges for our laboratory and the distribution of hormones, glucose, urea, and electrolytes taken just after admission (first sample) and later before receiving a general anaesthetic (second sample). The normal range includes 95% values derived from healthy subjects. Therefore in a study population of 20 patients no more than one should fall outside the normal range. Over half of our children had increases in adrenaline, noradrenaline, cortisol, and arginine vasopressin above the normal range at the time of arrival at the A&E department. Five patients demonstrated increases in angiotensin II and glucose above the normal range. Plasma adrenaline values exceeded 5 nmol/l in five (25%) patients (fig 1). One patient had values exceeding 60 nmol/l.

Four children were hypokalaemic on admission, one with markedly depressed concentrations. All apart from one were within the normal range by the time that the second sample was taken. There was a significant difference in plasma sodium between early and later samples ($p<0.01$), although the median and ranges do not differ greatly (table 2).

No correlation was found between hormones and glucose in either the first or second groups of samples. Correlation coefficients between hormones, substrate, and electrolytes are shown in table 3.

Discussion

It is well recognised from adult studies and animal experiments that a "stress" response follows injury. The sympathoadrenal system responds almost immediately with increases in adrenaline and noradrenaline, and these increases are proportional to the degree of injury severity. This study on children compares well with previous adult studies.[1-4 6] We found that after non-thermal limb injury in children there is a marked stress response predominately involving increases in catecholamines, cortisol, vasopressin, and glucose. However while the increase in noradrenaline in our study was comparable with that found in adults for an equivalent injury severity score,[2 3] the increase in adrenaline in an important proportion (25%) of our patients was much greater than that found in adults on arrival at hospital. Adrenaline concentrations in adult studies, although increased, was less than 4 nmol/l in those with an ISS <11.[2 3] After thermal injury in children a marked sympathoadrenal response has also been noted,[8 9] but this was not as great as in some individuals who had sustained mechanical limb injury.

Children appear to vary in the degree and time course of their adrenaline responses to stress and those with very high catecholamine concentrations may merely represent the extremity of the usual response to stress. However, some patients demonstrated very high admission concentrations of plasma adrenaline that tended to persist for several hours despite the administration of analgesia. It is possible that we are observing two different types of stress response in children—one group with moderate responses that subside towards the normal range quickly, and another group with more extreme responses that persist. The number of subjects in this preliminary study was small and we cannot exclude the possibility that a more powerful study would not minimise these differences.

As some children generate a much greater adrenaline response than adults this suggests that they either suffer a greater degree of psychological stress for a comparable degree of injury, or that they have a much lower pain threshold. Some of the highest concentrations of systemic adrenaline known in man have been found in the umbilical cord blood of neonates after delivery.[16] It is possible that the higher values in the first sample after admission are partially a result of intravenous cannulation. This alone might increase catecholamine concentrations. However, one very high initial value remained high when the second sample was taken 160 minutes later when blood was withdrawn through the originally placed cannula. The half life of catecholamines in the circulation is about three minutes,[17 18] so establishing venous access probably had a minimal effect when compared with the injury itself.

Little is known about the role of arginine vasopressin after trauma in adults, although increases are well documented in association with hypertension after injury after thermal trauma.[8 9] We found increases on admission, though not as great as those after thermal injury.

In this study hyperglycaemia was evident in 25% patients within the first few hours after limb injury. Previous studies on children sustaining burn injury have also established that there are increases in blood glucose in the first 24 hours after injury.[11] The increase in blood glucose was most marked in those sustaining head injury, but alterations also occur after thermal injury. It is possible that some subjects had just eaten before their injury, which might itself result in raised blood glucose concentrations. However, several "stress" hormones may also affect circulating glucose concentrations.[3] Insulin is responsible for the cellular uptake of glucose and potassium. After injury, there is catecholamine induced suppression of the secretion of insulin resulting in reduced plasma insulin concentrations. Catecholamines also stimulate glycogen breakdown, while glucocorticoids stimulate hepatic gluconeogenesis and inhibit glycolysis.

Although there were significant correlations between some stress hormones and serum

electrolytes, the relationships between "stress" hormones and glucose were not as marked as in other studies.[1-4 6 7] This may partly be due to the power of this study and partly because the study population involves a narrow and precisely defined group with a specific injury. Previous studies demonstrating correlations between catecholamines and glucose have included subjects with a wider range of injury severity and also in some circumstances included control samples. Consequently the much wider distribution of data results in more clearly defined relationships. However this study clearly shows a stress response, although the relationships are not as clearly defined.

The hormonal values in our second sample all showed a tendency to fall towards the normal reference range when compared with the first sample. These changes in hormonal concentrations followed analgesia and appropriate limb splintage. We are not able from our study design to assess the role of analgesia when compared with time alone in resolving our hormonal changes but this may be worth further study.

While the majority of our potassium results fell within the normal range, four (20%) were low and one was very low (2.2 mmol/l). In adults, hypokalaemia is well recognised after stress states and is due to a combination of the effect of adrenaline and insulin.[19] Adrenaline stimulates β receptors on skeletal muscle with consequent uptake of potassium from the circulation. It is probable that total body potassium is not reduced. Although no patient received any potassium supplement during this study, we found that all serum potassium results returned towards normal within a few hours and only one was just below the normal range at the time of the second sample. As normal reference ranges, by definition, include 95% recorded data from healthy individuals it is to be expected that one data point may lie outside the normal range. No child appeared to suffer any ill effects from this early episode of hypokalaemia.

The statistically significant difference between early and late plasma sodium concentrations needs to be interpreted with caution. In most patients there was either no change in plasma concentrations or a small fall. As a rise in plasma sodium was not evident in any patient the statistical test generated interpreted the result as significant. However, clinically this is of little relevance as the changes were negligible. As no patient received intravenous fluid there is no associated dilutional effect. There may be a small association between the changes in plasma sodium and circulating arginine vasopressin. The changes in arginine vasopressin were more dramatic than sodium but much less consistent. In some patients a rise in arginine vasopressin was evident, while in others there was a fall. Thus the difference between the two groups was not significant clinically.

Conclusions

This was a preliminary study and its power is small. It investigates the physiological stress response after mechanical injury in children. Children sustain a physiological stress response that in many ways is comparable with that reported in adults. However concentrations of plasma adrenaline in some children are much greater than that found in adults. This area needs further study to correlate physiological changes with validated pain severity scores, to assess the effect of analgesia, to correlate changes with a range of injury severity, and to separate the relative contributions of anxiety and pain after injury. Finally, hypokalaemia in an otherwise normal child appears to correct itself and probably does not require potassium supplementation.

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Conflict of interest: none.

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