Anaphylaxis gets the adrenaline going

A F T Brown

Adrenaline and now atropine for anaphylactic shock

Anaphylaxis today still generates as much excitement, fear, rhetoric, and ripostes as it must have done for Charles Richet and Paul Portier at the turn of the 19th century. While they were guests on board Prince Albert of Monaco's yacht in the Mediterranean, they reported on their experiments on dogs rechallenge with *Physalia* extracts, and first coined the phrase "anaphylaxis", literally meaning "against protection", when some dogs unexpectedly died. Since then, anaphylaxis has come to symbolise one of medicine's great clinical bedside challenges, demanding rapid recognition without the benefit of an immediate laboratory test, and urgent management to avert a potentially fatal outcome usually in an otherwise healthy, young patient. Its evanescent nature has mitigated against the development of a solid scientific database to guide clinicians, and has generated as spiritedly polarised views on management as any therapeutic topic. No more so than when the use, dose, and delivery of adrenaline (epinephrine) is being argued.

Brown *et al* in this issue contribute reliable clinical evidence supporting the use of carefully titrated intravenous adrenaline with volume resuscitation for treating significant anaphylaxis.¹ In their case this followed jack jumper ant (*Myrmecia pilosula*) sting challenge on 68 healthy volunteers in Tasmania known to have a history of hypersensitivity to this ant. Their original paper in the *Lancet* attested to the efficacy of the ant venom immunotherapy they had developed,² while this paper reporting on the same group of patients describes in detail their management. All received a sting challenge, and in a randomised, double blind protocol they received either venom immunotherapy or placebo, followed by resuscitation in a supervised resuscitation area. The ensuing sometimes dramatic reactions were suffered almost exclusively by the placebo group, and were to an extent ameliorated by the study exclusion criteria that had eliminated volunteers with hypertension, heart disease, poorly controlled lung disease, ACE inhibitor or β blocker therapy, and age less than 17 or over 65 years. None the less, of the 21

systemic reactions from 29 patients in the placebo group, eight were grade IV or severe according to the grading system developed by Müller, with features of hypotension, collapse, loss of consciousness, incontinence of urine or faeces, or cyanosis. Three were grade III reactions manifesting dyspnoea, wheeze or stridor and two or more of dysphagia, dysarthria, hoarseness, weakness, confusion, or a feeling of impending disaster, and the remaining 10 had grade II (three patients) or grade I (seven patients) reactions. There is no question, this really was significant anaphylaxis being studied, enough to make even the most torporous ED physician coming off a long nightshift galvanise back into action!

Brown's results highlight some important features about anaphylaxis of relevance to us all, some of which are already recognised, some merely assumed to be true and some would be less well known, even surprising. Thus, all his patients developed cutaneous features albeit often subtle, such as erythema, itch or urticaria, which highlight an essential diagnostic spectrum that must always be looked for as corroborating evidence of the possibility of anaphylaxis, whether by properly undressing the patient in the resuscitation room; or by the anaesthetist peering under the surgical drapes in theatre, as the patient suddenly loses their blood pressure or develops raised airway pressures.

The hypotensive anaphylactic reactions Brown measured in the most severe group were characterised by an initial fall in diastolic blood pressure from systemic vasodilatation, followed by a drop in systolic pressure too, with mean arterial pressures ranging from zero (unrecordable) to 55 mm Hg (with a median at 45 mm Hg). All these patients were initially tachycardic, but of interest all then developed a relative bradycardia as hypotension ensued, with heart rates from 15–65 per minute (median 32). The mechanism of this bradycardia is consistent with neurocardiogenic syncope as suggested by Brown, although it is not possible to exclude direct ant venom mediator effects on the heart.

Neurocardiogenic syncope, vasodepressor or vasovagal syncope, is notable for its variable afferent limb and threshold, with triggers ranging from posture, pain, fear, and psychological stress to the use of vasodilators, inferior myocardial ischaemia (Bezold-Jarisch reflex), and severe haemorrhage. However, the efferent response is uniform with a vagally mediated bradycardia, and paradoxical vasodilatation with the concurrent interruption of sympathetic vasoconstriction.³ Thus sensory input from arterial baroreceptors as well as cardiac mechanoreceptors appear to modulate the balance of the parasympathetic and sympathetic nervous systems. A neurocardiogenic mechanism was further supported by a dramatic response to intravenous atropine 600 μ g in two of Brown's most parlous patients in virtual cardiac arrest. Rather than ascribing this to near terminal hypoxia, the successful use of atropine in these situations to counter vagal tone deserves further study.

Neurocardiogenic syncope may also explain Pumphrey's personal observations on 214 anaphylactic fatalities, where some deaths clearly followed a change in the victim's posture to a more upright position, either sitting or standing.⁴ He exhorts us to keep victims of anaphylaxis lying down, even those self administering adrenaline, and to support or raise their legs to maintain vena caval filling at all costs.

What Brown did show unequivocally was the efficacy of intravenous adrenaline and fluid to successfully treat all his subjects with anaphylactic shock, without the use of any antihistamines or corticosteroids in the acute phase. The adrenaline was given cautiously at a dilution of 1:100 000 (that is, 10 μ g/ml), starting at 5–15 μ g/min to a total dose of around 5–20 μ g/kg, with more adrenaline being required the more severe the hypotension. This approach gratifyingly supports the hereto intuitive (non-evidence based) recommendations of several authors including this editorial's writer.⁵ It also supports the perennial warning of others to always administer adrenaline for significant anaphylaxis with care, suitably diluted, given slowly and titrated against response in an adequately monitored patient.⁶

The limitations of Brown's paper are to be aware that certain patients were excluded from the study as mentioned previously, and that as there were few life threatening respiratory complications, extrapolating the universal success of intravenous adrenaline to all forms of severe anaphylaxis, although highly likely to be efficacious, still effectively remains an eminence based recommendation. Likewise, there

seemed to be no clear answer as to how much fluid should be being given at the same time for hypotension, with Brown's dose comparatively small at one litre of normal saline (with only one patient receiving a total of three litres). Also, as Brown mentions, the early use of intramuscular adrenaline, particularly prehospital or in the unmonitored patient, still warrants direct comparison with intravenous adrenaline to quantify their relative efficacy compared with complication rates.

The other paper on suspected allergy in this issue is a far more sanguine reminder that "all is not gold that glitters". Goodyear *et al* describe a case of orbital cellulitis in a 14 year old boy that was initially diagnosed and treated as an allergic reaction on the strength of unilateral periorbital oedema and a history of known dog hair allergy.⁷ Two days later, despite a high temperature of 39.3°C the condition was still considered to be allergic, delaying the final referral to an ophthalmology

specialist until day 4 when the serious, true infective diagnosis was rapidly made. As the authors pointed out, a delay in diagnosing orbital cellulitis contributes to a higher rate of serious complications such as blindness or even death from cavernous venous thrombosis. A useful table highlighting the differences expected between an infective or allergic presentation of periorbital swelling is given, and the authors emphasise the pivotal role of the CT scan in investigating suspected orbital cellulitis.

Anaphylaxis naturally has a potentially vast differential diagnosis, although the rapid onset, accompanying cutaneous features, and direct relation to a potential trigger or particular iatrogenic precipitant suggest the diagnosis in most cases. In this instance, the authors did emphasise that unilateral orbital swelling is more likely to be attributable to infection than allergy. I agree with this, and unfortunately on this occasion I am unable to blame a dog for this unfortunate boy's illness!

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War

Personal view: a day in the life of an emergency physician at war

T J Hodgetts

The reality of emergency medicine in the war arena

I would not regard myself as superstitious, but 13 April 2003 was not what I would call a lucky day. It was the 22nd day of the ground war in Iraq and I was the officer in command of the emergency department of 34 Field Hospital. Seventeen days previously this had moved into Iraq in support of the 1st (UK) Armoured Division and had begun treating battle casualties on 27 March. Unusually the hospital was co-located far forward with the infantry and armour units on a disused military airfield close to the city of Al Basrah. By this time in the war the explosions around the perimeter had become less frequent, and the hostile incoming mortar and artillery fire had stopped. Challenger II tanks of the Scots Dragoon Guards and 2 Royal Tank Regiment could no longer be seen racing across the desert and engaging targets; and the nightly firework display of tracer from heavy artillery lobbing rounds across our accommodation tents had also

ceased (an event that would wake even the heaviest sleeper, and cover the tent in gunpowder).

The day had started inspiringly at 0700 hours with a medley of marching music from the attached military band practising outside A&E, poignantly interspersed with the *Last Post* from a cornet player raised on a flat bed truck against a sky darkened by oil pit fires. An hour later the first routine of the day was the heads of department attending the Commanding Officer's briefing ("Orders Group"). Serious business in hand, the Regimental Sergeant Major had stated that the stethoscope was not an article of uniform, and was not to be worn around a doctor's neck outside clinical areas. Predictably this was to precipitate a flurry of fluorescent and improvised striped tubes worn defiantly by the senior clinicians. In turn I briefed A&E clinical staff with the latest intelligence and assigned daily tasks, then flicked through the week old newspapers

in the department. Later I reflected in my journal on the impact of the plethora of personal tributes in the tabloids to our soldiers killed in action. Dealing with death regularly in A&E, I considered, was often by dissociation and reliance on the fact that there is little opportunity to form any substantial relationship with a patient or their family. But I could not mentally dismiss those soldiers on whom I had pronounced death and placed in our temporary mortuary (a refrigerated ISO container, or "reefer", known as the Grim Reefer) and whose images repeatedly appeared in print.

Since 2001 I had spent five months in the deserts of Oman, Afghanistan, and Kuwait where the weather could change in an instant, and today was to be a striking example. Imperceptibly to those working in the dim artificial light inside the green tented hospital complex a storm had rapidly closed in and was heralded by a "dust devil" (a euphemism for a small tornado). This proceeded with divine direction through the senior officers' accommodation tents, most of which were unoccupied, miraculously sparing the near capacity 200 bed hospital. A young female soldier in the shower tent was witnessed to be lifted and transported spinning in canvas, Dorothy-like, some 50 metres sustaining serious chest injuries on landing. My own tent was forcibly moved, pulling free the securing bolts drilled in the runway, with the contents churned in an action akin to a giant

washing machine. The same evening mother nature gave a second impressive demonstration, this time of sheet lightning: two soldiers on the airbase were struck, and one died of his wounds.

In the build up to war I had been deployed with the first medical elements to establish the A&E department in 22 Field Hospital in Kuwait. Attendance here had peaked at 80 per day, which although a fraction of a standard NHS department's activity the manning was only one consultant and one SHO. Furthermore, the clinical routine was regularly interrupted by ballistic missile warnings for incoming SCUDs, or chemical attack alarms (one second on, one second off a vehicle horn). So reactive was the system that a reversing lorry could have the whole camp masked up in seconds (the same ripple effect was memorably produced by some chump running in his respirator to increase his cardiovascular workout). At two hours notice I had been transferred to 34 Field Hospital as it moved into Iraq to establish itself as the main medical effort to receive battle casualties. I had crossed the border at night in the back of a battlefield ambulance with one of my registrars, having been "sanitised" of all personal effects. We were to join the main body of personnel at the airbase. In satirical contrast with the convoys of armoured vehicles, they had moved forward on a blue coach bearing the inscription "Happy Journey". A small department was established in 24 hours to support a 25 bed rapidly deployable hospital. Over the next week the 200 bed hospital was built alongside, using the necessary engineering expertise to supply running water, improved sanitation, and power. The department's manning was then boosted to three consultants, four specialist registrars, and four SHOs, with two of the consultants resident at any time during peak activity. Attendance rose to 140 per day during war fighting, but with far fewer minor injury presentations.

Experience in Oman in 2001, Afghanistan in 2002, and again in Iraq in 2003 has confirmed that a substantial proportion of a field hospital's work will be soldiers incapacitated by an enteric virus. Particularly important lessons were learned by 34 Field Hospital at Bagram airbase in Afghanistan when an outbreak of Norwalk-like virus

manifested in a novel and severe form among the hospital's 76 staff. Forty per cent of the staff were ill and a further 20% quarantined, with five cases of meningitis (two requiring ventilation, and one with DIC). This was particularly clear in my own mind as I had been the emergency physician and had required to take the additional roles of consultant ITU, consultant general medicine, and junior doctor for the whole hospital because of staff shortages. It is convenient to point the finger at "poor hygiene" in both instances, but this group of viruses is notorious for its high attack rate among institutions, including NHS hospitals. Traditional cases of dysentery (salmonellosis, shigellosis, amoebiasis) were very rare compared with historical precedents in war because of improvements in field hygiene and perhaps, as the Professor of Military Medicine observed, this was simply nature expanding to fill a vacuum. This experience was translated into a process of assessing infectious disease patients separately from conventional patients. A 14 bay assessment tent was placed adjacent to A&E and infectious patients streamed to this area for assessment by staff with appropriate protective equipment. The broader concern was for recognising and separating those patients showing the first symptoms of biological warfare (particularly those highly contagious conditions such as smallpox and pneumonic plague). Distant from us our NHS colleagues had the real and present threat of controlling the global SARS crisis, no doubt working through similar thought processes.

With domestic normality at 34 Field Hospital rapidly restored after the morning's storm, focus was drawn to the clinical activity. It was lunchtime when we had an influx of critical patients over 90 minutes. A soldier with an acute onset dilated cardiomyopathy and fast atrial fibrillation. Two escaping prisoners of war with gunshot wounds, one with damage to a popliteal artery and a shattered tibia, the other with multiple limb wounds. A 15 year old Iraqi boy unconscious with a closed head injury after a road accident. An 18 month old Iraqi girl who had fallen into a burning pit of oil sustaining facial and limb burns. A 7 year old Iraqi girl with an amputation of the hand and abdominal

fragments from playing with a landmine. A 14 year old Iraqi girl with 60% burns. A 3 year old Iraqi boy with a compound tibia fracture after a road accident. A 12 year old Iraqi girl with 20% burns from two weeks ago and septic shock. And a prisoner of war with appendicitis.

So what? Nothing you could not cope with in your own practice. But what if the nearest CT scanner and neurosurgeon is in another country? Would your general surgeons perform burr holes or a craniotomy on clinical grounds alone? What if your burns services are also in another country: can you really spare an anaesthetist for the inter-hospital transfer, as it may take a day for them to return? How will you manage the patients in A&E when your two surgical teams are occupied; there are no surgical reinforcements? How will you improvise if your paediatric resuscitation equipment is "limited"? And what if your intensive care unit is full? These were a day's worth of challenges.

So few words cannot do justice to the intensity of this experience, of frustrations balanced with fulfillment and spiced with a little anxiety. Nothing has yet been said of the effort required to simply sustain yourself in a desert environment, without climate control, washing out of a mess tin, and eating packet meals (termed *Meals Ready to Eat*, or less charitably *Meals Rejected by Everyone*). The personal challenge to anticipate and manage the requirements of equipment, people, and procedures to provide the emergency medicine service across three field hospitals and within the medical regiment was enormous, is not one I would have missed, and was only achievable with the quality and resourcefulness of my staff. It is quite amazing, I thought as I lay on my sleeping bag under the mosquito net that night of 13 April listening to the tanks trundling behind the protective berm (a wall of sand), the wind and rain, and the indiscernible crackle of the tannoy, how quickly you can adapt to the most bizarre circumstances. And almost regard them as normal.

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