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Treating anaphylaxis with sympathomimetic drugs

In severe anaphylaxis adrenaline by any route is better than none

Acute anaphylaxis is characterised by its rapid, unpredictable onset and progression and usually gratifying, prompt response to treatment. These factors virtually preclude its study by controlled trials. Recommended treatment is therefore based mainly on clinical anecdotes, an understanding of its pathophysiology and the effects of drugs, and, to a lesser extent, animal studies. Animal models generally respond predictably, with a single organ system being affected, unlike humans, who produce variable clinical manifestations. The life threatening effects in humans are cardiovascular collapse (90%), bronchospasm (30%), angio-oedema (25%), and pulmonary oedema (49%).[1,2] Some 90% of patients who develop anaphylaxis outside hospital lose consciousness; only one organ system is affected in 10% of patients.[2]

Controversies still rage over treatment because of the lack of controlled clinical trials. Recently, this journal aired the debate over the best route for giving adrenaline—a controversy that is partially resolvable. Despite the desire for simple recommendations for treatment the nature of the disorder means that no one route of administration is likely to be right in all cases. There are several reasons for this.

The timing of administration of the drug may be critical. Early in anaphylaxis vasodilatation is the main pathological change. Cardiac output and blood flow to skin and muscle may be increased, enabling subcutaneous and intramuscular absorption of adrenaline to be rapid and effective. Indeed, the efficacy of the route is emphasised to those patients who treat themselves using automatic injectors to administer adrenaline subcutaneously. No convincing evidence exists for a difference between the subcutaneous and intramuscular routes. Later in the disease, when intravascular volume is depleted and shock occurs, the intravenous route is necessary to enable absorption. In one study of 27 patients with anaphylaxis that occurred outside hospital two died, and both had received treatment more than 45 minutes after the onset of symptoms. All patients treated within 30 minutes were stable on arrival in hospital. The route of administration of adrenaline did not seem important, although two patients given subcutaneous adrenaline required a second dose of vasopressor.[1]

The effects and rate of progression of anaphylaxis vary. Sympathomimetic drugs are not necessary in cases of slowly progressive oedema or changes restricted to the skin, and oral or parenteral antihistamines are effective. When anaphylaxis occurs outside hospital venous access may be difficult, particularly in small children and obese people, and controlling intravenous adrenaline is more difficult without monitoring. The adverse effects of adrenaline (hypertension, arrhythmias, myocardial infarction, and myocardial depression) are more common when the drug is given intravenously[3] and may be difficult to separate from anaphylaxis itself. Patients with anaphylaxis given sympathomimetic drugs with vasoconstrictor properties usually improve, and the improvement occurs more commonly after adrenaline than other sympathomimetic drugs.[2,4] Furthermore, adrenaline benefits bronchospasm and cardiovascular collapse when compared with pure vasoconstrictors.[2]

These factors suggest the following approach. Adrenaline should be given to patients who have bronchospasm, hypotension, or swelling of the airways due to anaphylaxis. When the disease is treated early and is progressing slowly, venous access is difficult, and the patient is not monitored, intramuscular adrenaline has advantages in terms of safety and is usually effective. When there is shock or severe dyspnoea or the airway is compromised intravenous administration is best. Mostly a single injection is all that is needed, although 10% of people will require a second injection.[1,4] The standard doses of intramuscular and intravenous adrenaline (1 ml of 1:1000 and 10 ml of 1:10 000) are too high in most circumstances. The right adult dose is 0·3 to 0·5 ml of 1:1000 adrenaline intramuscularly or subcutaneously or 3-5 ml of 1:10 000 intravenously. Patients should be observed for six hours when their condition is stable as late deterioration may occur.[5]

In most patients with severe reactions, particularly those who develop anaphylaxis after receiving parenteral drugs, adrenaline on its own may be inadequate. Plasma losses through leaking capillaries produce a volume deficit, and this requires replacement.[4,6,7] The available evidence favours colloid solutions rather than crystalloid solutions.[4,6,7] Indeed, some workers have strongly advocated using colloid solutions alone, avoiding sympathomimetic drugs altogether.[6] Against this policy is the evidence of the efficacy of sympathomimetic drugs; the speed at which they can be given, particularly when intravenous access is difficult; the efficacy of adrenaline in bronchospasm, cardiovascular collapse, and preventing the progression of airway swelling[2]; and adrenaline's stabilising effect on mast cells. Until volume replacement is adequate continuing sympathomimetic drugs are needed,[4] and infusion should be started if hypotension or bronchospasm persists. Adrenaline may also be administered via the airway, either nebulised or by injection through endotracheal tubes. Patients who do not respond to adequate volume replacement and adrenaline infusion may respond to noradrenaline infusion.[4]

H_2 blockers have recently been advocated for treating anaphylaxis and are effective when anaphylaxis is restricted to the skin. A few case reports have recorded their efficacy in hypotension. Until their role has been established they are not drugs of first choice[8]; they may help in protracted cases when release of histamine may be continuing—in such patients H_2 blockers seem to produce a more stable blood pressure. Anaphylaxis may also be associated with heart failure, particularly as a secondary effect in patients with cardiac disease.[4] Despite the well known effects of anaphylactic mediators on the heart evidence of heart failure in patients without cardiac disease during anaphylaxis is extremely rare, although it occurs.[9] In protracted anaphylaxis there is a case for measuring filling pressures or imaging the heart.

Adrenaline is a valuable drug in managing acute, severe anaphylaxis. Factors such as the severity of the condition, the doctor's experience, difficulty of venous access, and the ability to measure the effect of treatment are important in selecting a route of administration. In severe anaphylaxis adrenaline by any route is better than none.

MALCOLM FISHER
Head of Intensive Therapy Unit

Royal North Shore Hospital,
St Leonards,
New South Wales 2065,
Australia

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Familial Alzheimer's disease: second gene locus located

Markers for cases of early onset familial disease may soon be available

Alzheimer's disease is the main cause of neurodegeneration in developed countries, affecting an estimated 750 000 people in Britain and four million in the United States. The characteristic plaque in brains of patients with Alzheimer's disease contains β amyloid protein, which is cleaved from the amyloid precursor protein.

The disease is undoubtedly aetiologically heterogeneous, and the search for clinical or pathological features demarcating subgroups with separate causes has in general been unrewarding. A family history and age of onset are the most useful clinical features that can be related to aetiology. Early onset familial Alzheimer's disease (arbitrarily defined as that below age 65) seems to be transmitted as an autosomal dominant. Genetic studies with early onset familial disease initially showed linkage to chromosome 21,[1] and the identification of mutations of the gene coding for the amyloid precursor protein on that chromosome followed.[2-5]

The inheritance of one of these rare mutations completely predicts the occurrence of the disease. These mutations occur at either end of the β amyloid sequence[5] in the larger amyloid precursor protein molecule. By as yet undetermined mechanisms their presence causes the production of β amyloid in an insoluble form. The demonstration that amyloid itself can initiate the disease process and is not just an "innocent bystander" has prompted the theory that in some way mismetabolism of amyloid precursor protein is always the primary event in Alzheimer's disease. Mutations of the amyloid precursor protein, however, account for probably less than a quarter of early onset familial Alzheimer's disease.

Aided by the human genome project,[6] researchers turned their attention to locating other genes predisposing to early onset Alzheimer's disease. In a recent issue of *Science* Schellenberg and colleagues reported the identification of a second gene for early onset Alzheimer's disease linked to markers on chromosome 14.[7] In their dataset eight out of nine families with early onset disease and differing genetic backgrounds showed evidence of linkage. My group's analysis of nine British families is consistent with linkage to the middle long arm of chromosome 14.[8]

Although the odds for linkage are overwhelmingly in favour of a gene on chromosome 14, further localisation is subject to accurate assessment of genetic heterogeneity in families without mutations of amyloid precursor protein. One key problem arises because statistically it is possible to detect linkage in several families collectively without being able to show that all or any families are individually linked. The fact, however, that most of the families analysed by these two groups (16 out of 18 in total) are consistent with linkage at the chromosome 14 locus suggests that this linkage will account for most very early familial cases. If this is so, genetic risk calculations with markers for either amyloid precursor syndrome or markers on chromosome 14 are imminent in early onset familial Alzheimer's disease.

The hypothesis that amyloid is intimately related to the disease process will be tested when the chromosome 14 gene is identified. This will shed considerable light on the idea that amyloid mismetabolism is the primary error in the common, non-genetic cases of the disease. Several genes localised to chromosome 14 influence the metabolism or processing of amyloid precursor protein, and further genetic analysis will define which ones are important. Previous studies have excluded members of the cathepsin family, at least one of which is known to metabolise amyloid precursor protein.

This research holds out the prospect of improving our understanding of the pathogenic pathways that lead to Alzheimer's disease. Whatever its cause(s), the disease is clinically and neuropathologically homogeneous; therefore the pathological pathways resulting from mutations in either amyloid precursor protein or the second locus must, at some point, converge. Better knowledge of how these two pathogenic pathways relate should improve our understanding of the common late onset form of the disease and may hasten the development of treatments.

MIKE MULLAN
Codirector,
Alzheimer's Disease Research Laboratories,
Department of Psychiatry,
University of South Florida,
Tampa, Florida 33613
USA