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Exploding more myths around adrenaline

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Conflicts of interest: The authors are co-authors of the European Academy of Allergy and Clinical Immunology Anaphylaxis Guideline.

Abbreviations: EMA: European Medicines Agency.

Funding: Southampton National Institute of Health Research Biomedical Research Centre

Word count: 988.

For decades, we've been told that intramuscular adrenaline is the first line treatment of anaphylaxis. Any suggestion that a randomised control effectiveness trial study is needed has been met with the analogy of undertaking a randomised control trial to assess the effectiveness of a parachute when jumping out of an aircraft.

As a result of concerns around the performance of adrenaline autoinjectors, the European Medicines Agency (EMA) requested companies to undertake pharmacokinetic and pharmacodynamic studies on their adrenaline autoinjectors [1]. For the first time, we have some data related to the effectiveness of our current autoinjector devices. These data have

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/all.15767

exploded one of the accepted myths around autoinjectors, namely, that the needle length is important. Anapen was developed as a subcutaneous delivery device with a relatively short needle (11mm). Newer devices have longer needles, in particular the Emerade has a needle length of 23mm. The concern was that short needles result in subcutaneous injection delivery, especially in overweight individuals, which would not be effective in terms of delivering adrenaline rapidly to the circulation. The pharmacokinetics studies however demonstrate that the EpiPen (16mm needle) delivers much higher concentrations of adrenaline than Emerade [2]. So whether adrenaline has been delivered subcutaneously or intramuscularly appears not to be major factor in explaining the rapidity of adrenaline appearing in the circulation.

The EMA requested both pharmacokinetic and pharmacodynamic data. Pharmacokinetics describes the concentration of the drug in the circulation. It's very much a surrogate endpoint and we have assumed that a "high" concentration is equivalent to effectiveness. Actually we do not know what concentration of adrenaline is required to successfully treat an episode of anaphylaxis [3]. It's therefore important that we also have pharmacodynamic information. This describes the endorgan effects of the drug in the body and so gives a much better idea of whether a specific dose is likely to have the desired clinical outcome.

In this issue of the journal, Patel et al publish pharmacodynamic data on intramuscular adrenaline, comparing two devices [4]. Their data suggests that the two devices are bioequivalent in terms of adrenaline delivery to the circulation, albeit circulating adrenaline levels appear to increase more rapidly with EpiPen 0.3mg than Emerade 0.3mg [4]. They also demonstrate that Emerade 0.5mg delivers higher peak plasma adrenaline levels and areas under the curve adrenaline levels than Emerade 0.3 or Epipen 0.3mg [4].

The novel aspect of the Patel et al study is the measurement of cardiac output [4]. In anaphylaxis there is extensive vasodilation which results in a drop in blood pressure and therefore tissue perfusion. The body's response is to increase cardiac output, driven by endogenous adrenaline release. This is one of the rationales for using adrenaline as a therapy given that it increases both the stroke volume and the heart rate giving increased cardiac output. This was seen with the Emerade devices but surprisingly there was a substantial reduction in cardiac output with the EpiPen [4].

Adrenaline has a rather complicated pharmacology because it acts on numerous receptors. We are most familiar with its activity on the beta-adrenergic receptor giving bronchodilation and alpha-adrenoreceptor receptor giving vasoconstriction. However, at high concentrations of adrenaline, the beta-2-adrenergic receptor activates an inhibitory G-protein [5]. This is thought to be the mechanism underlying Takotsubo cardiomyopathy which has been associated with high doses of adrenaline [6]. In this condition, transient cardiac dysfunction is seen. So an interpretation of the results from Patel et al is that the very rapid and large increase in plasma adrenaline after the Epipen 0.3mg results in a negative inotropic effect where as a positive inotropic effect is seen with the slow rise seen with the Emerade devices. These data provides more clues as to the therapeutic dose range for adrenaline; higher plasma levels are not necessarily better.

What is the ideal dose of adrenaline to treat anaphylaxis? Some patients do not respond to multiple doses of intramuscular adrenaline but will respond to an intravenous infusion [7]. So in some cases, a higher dose is beneficial. In others cases a high plasma adrenaline level is associated with reduced cardiac output [4] or even Takotsubo syndrome [6]. The data presented by Patel et al illustrates how different adrenaline autoinjectors give very different plasma adrenaline profiles making it difficult to extrapolate from one device to another. They demonstrate that Emerade 0.5mg gives higher plasma adrenaline levels and better cardiac output than Emerade 0.3mg. However, we can not extrapolate to say that an EpiPen 0.5mg would also be better than a EpiPen 0.3mg device as the former is likely to deliver even higher first peak plasma adrenaline levels which may depress cardiac output further impairing its effectiveness.

There is a very large caveat about all of these studies, they have all been undertaken in patients who are not experiencing anaphylaxis. Many participants were not even at increased risk of anaphylaxis. During anaphylaxis, there are massive changes in the body's physiology in response to an immunological mediator cascade and subsequent endogenous adrenaline release. This preferentially directs blood to muscles and away from tissues such as the skin and the gastrointestinal tract. It could be argued that in this situation a longer needle length able to deliver intramuscularly may be more important. Equally, with endogenous adrenaline release, getting the therapeutic dose right may be even more important.

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So it appears that we still do not have good evidence around the optimal dose and approach to delivering adrenaline therapy in anaphylaxis. Although it is obvious that timely administration is important, we now have evidence that rapidly increasing plasma adrenaline to very high levels may be deleterious. What we need are observational data from clinical situations where patients experiences anaphylaxis and are treated with intramuscular adrenaline. One opportunity would be studies where food challenges or oral immunotherapy are being undertaken as they are both associated with a relatively high risk of anaphylaxis. Participants could be randomised to receive one of a number of different autoinjector devices if they experienced an episode of anaphylaxis with subsequent pharmacokinetic and pharmacodynamic parameters monitored. The data collected would markedly improve our understanding of the pharmacokinetics and pharmacodynamics of adrenaline during anaphylaxis. This information is essential if we are to understand how to optimise the clinical use of adrenaline in managing anaphylaxis.

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