

When every second counts: ampoule versus adrenaline auto-injector administration for life-threatening allergy

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Gold-standard treatment for anaphylaxis in the community is with adrenaline auto-injectors (AAIs).¹ The WHO in recognition of this has been involved in developing an action plan to increase the global availability of AAIs and specifically ensure adequate access to AAIs at an affordable cost.² A proposal is currently being prepared to support inclusion of AAIs in the WHO essential medicines list to be formally submitted for their forthcoming edition.² Despite this, AAIs are not funded by PHARMAC and are only available to individuals privately, at considerable cost, further increasing health inequities and decreasing access to essential healthcare.

Worldwide there has been a marked increase in the rate of anaphylactic reactions³ with studies reporting increases in Australia, Asia, America and Europe.⁴ Evidence highlights that for adrenaline to be effective in the treatment of anaphylaxis it should be administered intramuscularly rather than subcutaneously or intravenously.⁵ Intramuscular administration of adrenaline provides superior consistency of absorption in comparison to subcutaneous administration.⁶ Adrenaline auto-injector, EpiPen®, delivers adrenaline deep into the muscle with the aid of the force of the spring action needle.⁷ Alternative delivery is from an ampoule, needle and syringe that must be prepared and administered manually. There are justifiable concerns about the timely and safe intramuscular delivery of adrenaline manually by lay persons in the community. As PHARMAC currently only funds an ampoule of adrenaline for this purpose, many people are left with no other financially viable choice. AAIs ensure

the ability of individuals to administer the correct dose of adrenaline via the correct route in a timely and effective manner.

There are difficulties conducting randomised controlled trials investigating efficiency of adrenaline in anaphylaxis, with respect to dosing and delivery. Conversely, one could also argue that it is ethically wrong to not conduct trials that inform evidence-based best practice in life-threatening situations. A Cochrane Systematic Review on use of AAIs in the community concurred that trials on different auto-injector devices would be practically challenging to conduct.⁸ The review concluded that in the absence of appropriate trials, adrenaline administration via auto-injector should still be regarded as the most effective first-line option for management of anaphylaxis in the community.⁸ Interestingly, the review only advocated for trials comparing auto-injectors to adrenaline administered by ampoule, needle and syringe in countries where auto-injectors are not commonly used or are unaffordable.⁸ Despite the ethical dilemmas identified, studies have been conducted to address this clinical question. A randomised, single-dose, single-masked study in children between 4–12 years old who had a history of anaphylaxis secondary to severe allergy, received either intramuscular adrenaline via EpiPen® or a subcutaneous injection of adrenaline.⁹ The plasma adrenaline concentrations following anaphylaxis reported the mean time to C-max was eight minutes with an EpiPen®, significantly shorter than 34 minutes with subcutaneously delivered adrenaline.⁹ A study investigating the pharmacokinetics of

adult and paediatric EpiPens® both prior to and exceeding their expiry dates, confirmed the prompt systemic exposure to adrenaline with an unexpired EpiPen®.¹⁰

Moreover, a porcine study examined the length of the needle in an auto-injector device and the projection of the adrenaline past this point (N=24).¹¹ EpiPen® with a needle length of 1.43cm was investigated. Prior to EpiPen® injection into the pig's thigh, 0.1ml of methylene blue was added to allow tracing of the injection.¹¹ On dissection and evaluation of the subcutaneous thigh tissue, it was revealed that the location of the dye was intramuscular with a mean depth of 2.78cm, considerably past the end of the needle.¹¹ Thus, EpiPen's® spring-loaded needle drives adrenaline 94.4% beyond the needle length, sufficient to reach the muscle in even obese individuals.¹¹ In the study, pressure was gradually applied to the EpiPen® until it was triggered, implying minimal pressure (2lbs or 0.9kgs) when activated.¹¹ This highlights the 'worst case' for delivery depth, suggesting that with more force, as recommended in guidelines, the adrenaline from an EpiPen® could be delivered even deeper for faster action.¹¹ Despite studies demonstrating the effectiveness of EpiPen®, it is not always administered correctly, especially in community situations. Even with written instructions on EpiPen® use, and education delivered on how to correctly administer the auto-injector, some parents report that within three months they have forgotten how to use the device.¹² Although, a recent study investigating the most effective way to train first responders to administer adrenaline via auto-injector, identified that simulation training improves essential skills and retention of knowledge at three months compared to non-simulation-based training.¹³

A recent review by Grissinger highlighted that the incorrect dose and/or route were reported to have been administered when adrenaline was drawn from ampoules by healthcare professionals (HCPs).¹⁴ Grissinger recognised that choosing between an auto-injector and ampoule, needle and syringe can be a difficult decision. While auto-injectors may be convenient, there can also be misuse issues with auto-injectors, specifically EpiPen®, such as holding the auto-injector upside down, pressing

and injecting the user's thumb or the risk to children who may access the device and press the wrong end.¹⁴ Despite these concerns, delivery of an inaccurate dose of adrenaline was more frequent with ampoule, needle and syringe among HCPs.¹⁴ This begs the question, if HCPs have difficulty accurately drawing up and delivering adrenaline in the event of anaphylaxis, how can a parent or member of the public be expected to do so and in particular a person on their own experiencing anaphylaxis?

There is limited research around adrenaline administration in the community for infants and children; however a prospective, controlled study comparing the time and accuracy of parents drawing up a 0.09ml dose of adrenaline compared with HCPs was conducted.¹⁵ The study reported that not only did parents take a significantly longer time (142±13 seconds (P<0.05)), compared to HCPs (mean time 40±2 seconds) to draw up adrenaline from an ampoule, most parents also drew up an inaccurate dose.¹⁵

With the available evidence, it is recommended that AAIs may provide New Zealanders with the best chance of survival from anaphylaxis in the community, reducing mortality and morbidity. Considering that the international incidence and prevalence of anaphylaxis appears to be increasing in certain populations,¹⁶ why are there still questions around mode of delivery? As HCPs, we need to be advocating for those with severe allergy to have funded access to AAIs. It is concerning that the general population may not be sufficiently equipped to deliver adrenaline through an ampoule, needle and syringe in a timely and effective manner. There is insufficient evidence to support PHARMAC's currently funded form of adrenaline, which raises the question as to why PHARMAC does not fund this life-saving mode of adrenaline delivery or at the very least provide funding for those who are in financial hardship in New Zealand?

PHARMAC state that funded adrenaline ampoules are a suitable treatment for anaphylaxis in the community, in direct conflict with the guidelines released by the Australian Society of Immunology and Allergy that stress that adrenaline ampoules and syringes are not suitable for non-medical settings.¹⁷ PHARMAC

support their funding decision by stating that individuals who have an AAI often do not have them on their person at all times and owning an AAI does not reduce anxiety around anaphylaxis treatment. Thus, PHARMAC conclude, there is not a strong indication for funding.¹² The issue of funding AAIs has been ongoing at PHARMAC; however, a PHARMAC Health Technology Assessment detailing AAI cost utility analysis reported the cost of funding auto-injectors would only save 1.5 quality-adjusted life years (QALYS), instead of the generally acceptable 50 QALYS, per million dollars spent, therefore AAI funding has only received moderate priority.¹⁸ Although the above mentioned report included at least three AAIs (EpiPen®, Anapen® and Twinject®) among others, a decision was still made not to fund these devices.

In 2014, Pharmacology and Therapeutics Advisory Committee (PTAC) Committee recommended PHARMAC fund one AAI in a 12-month period for patients who had experienced anaphylaxis to venom or food, with moderate priority,¹⁹ but still AAIs remain unfunded in New Zealand. Unfortunately, since then, only one AAI is currently available in New Zealand—EpiPen® limiting choice in New Zealand's pharmaceutical tender market. In a recent news release²⁰ the PHARMAC Operations Director identified that the high cost of adrenaline auto-injectors in New Zealand was because one drug company held the monopoly. There does not appear to be any basis to the claim

as other companies have entered the New Zealand market with auto-injectors but subsequently withdrew their products. In fact, the cost utility analysis commissioned by PHARMAC¹⁸ included more than three AAIs and still funding was not granted. However, the current supplier (Mylan, New Zealand) has remained in the market, continually providing New Zealanders with an auto-injector, and has not increased their price to pharmacies for over a decade. The variable pricing of EpiPen® in pharmacies is largely due to the differing profit margins imposed by each pharmacy, with a single EpiPen costing the consumer between \$120–\$180. Therefore, consumers are encouraged to shop around for price and ensure the 'use by' date remains valid for at least 12 months.

Since 2014, European and UK guidelines have recommended that people with allergies are prescribed two AAIs which need to be carried at all times, including those with allergic asthma.²¹ Australian and New Zealand guidelines recommend prescription of two AAIs in children.¹⁷ With commercial availability of various AAIs such as Emerade®, Jext®, Fastjekt®, FastPen®, ChenPen®, Adrenalina WZF®, Altellus®, Anapen®, Nepipe® and EpiPen® in the European Union alone,²² surely PHARMAC could source affordable, bioequivalent, device-equivalent, adrenaline auto-injector alternatives. However, in the absence of viable competition, PHARMAC should fund the only currently available AAI in New Zealand, EpiPen®.

Competing interests:

Nil.

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