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Epinephrine Administered in Anaphylaxis: The Evolution of 0.3 mg Dosage

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Abstract

Background: Despite epinephrine's historical use for over a century and Food and Drug Administration (FDA) approval for EpiPen's use in 1987 to treat anaphylaxis, little information exists regarding selection of the 0.3 mg adult dose. A review of literature was conducted to provide a historical retrospective regarding the evolution of the dosage selected for today's EpiPen. The first adrenal gland extract, isolation of the epinephrine active ingredient, observation of physiological effect, selection of the intramuscular route for administration, the dosage range recommended by independent physicians based on their clinical observations and selection of the ultimate standardized dosage are profiled.

Conclusion: This retrospective review illustrates the drug development process prior to the rigors required for today's clinical trials and provides clinical evidence supporting the dose in EpiPen and other similar life-saving epinephrine products.

Keywords: adrenal extract, adrenaline, anaphylaxis, asthma, dosage, epinephrine, epiPen, hay fever, hormone, intramuscular

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Introduction

Epinephrine, the drug of choice to arrest anaphylactic shock, is commonly administered by an autoinjector in both healthcare and nonhealthcare settings at a dose of 0.3 mg for adults and 0.15 mg for children. There is a lack of information regarding the origins of how the adult dosage arose as well as confirmation that the dosage regimen is, in fact, ideal. Within the 2015 "Anaphylaxis practice parameter update" put forth by the AAAAI (American Academy of Allergy, Asthma, and Immunology) and the ACAAI (American College of Allergy, Asthma, and Immunology), the predominant organizations which preside over the treatment of anaphylaxis, it is stated that "the optimal dose of epinephrine is unknown".[1] Epinephrine has been certified for use within the United States since 1939 but has been employed as early as 1901 for medical use.[2,3] The recommended dosage varied broadly before and even after the patenting of the EpiPen in 1977 and its official approval by FDA for use to treat anaphylaxis in 1987. As late as 1988, the dosage of 0.3 to 0.5 mL of 1:1000 solution by intramuscular (IM) injection in adults for administration immediately after diagnosis was still recommended by physicians.[4–6] Epinephrine used to treat anaphylaxis in pediatric cases was also commonly presented as a range, such as in the 1973 American Academy of Pediatrics guidelines which stated "0.1 to 0.3 mL of 1:1000 epinephrine was to be used for pediatric use,"[7] presumably on the basis of the child's weight. In the year 1994, the AAAAI Board of Directors published a position statement recommending 0.3 mL of 1:1000 solution due to the increased availability of the standardized dosage of epinephrine contained in EpiPen.[8] This recommendation still stands today. Understanding how this standard dosage evolved and the background information that was relied upon by the scientists/medical practitioners making the recommendation will allow us to better understand the history of one of the most ubiquitous and critical drugs in use today.

Discovery and Purification of Epinephrine

In 1895, George Oliver and E. A. Schäfer extracted the supernal glands (adrenal medulla) from a variety of animals, including calves,

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sheep, guinea pig, a dog, and a cat, which were then prepared in an alcohol and glycerin solution to be diluted and injected into dogs.[9] Oliver and Schäfer discovered that the extract generated increases in heart rate, dilation of blood vessels, blood pressure, as well as a slowing of respiratory rate.[9] These findings initiated the effort to purify the adrenal extract into the active ingredient to ensure consistency in obtaining the physiological actions described above. The first scientist to do so was the American scientist, John Abel. Abel attempted to expand further upon Oliver and Schäfer's work in 1899 when he published a paper claiming that he had extracted and isolated the active principle of the adrenal medulla.[10] He opted to name what he thought to be the active ingredient "epinephrin."[10] The product's purity was challenged by Otto von Fürth, a German scientist who named the substance of his extraction "suprarenin," and Jokichi Takamine, a Japanese scientist who named his extract "adrenalin."[11,12] Jokichi Takamine alleged and correctly found that the product isolated by John Abel was not the active ingredient and was an inactive benzoylated derivative of epinephrine.[13] Jokichi Takamine also developed a simple extraction method of adrenalin, which would be used by T. B. Aldrich, to determine the final formula of epinephrine ($C_{10}H_{10}NO_3$) using combustion analysis.[14] Now that the extract's purity was certain and the empirical formula was determined, the product was then patented in 1903 under the name "Adrenaline" by Parke-Davis & Company, which would later become a subsidiary of Pfizer.[15] The product of Parke-Davis would be the most widely used product in experiments, which was packed into 1 mL ampules of 1:1000 dilution of the adrenaline solution.[15] As reported by J. K. Aronson,[16] there was a debate between Henry Dale and Henry Wellcome regarding what should be the correct generic name. Dale insisted on the use of the name adrenaline arguing that the term epinephrine had been used to describe extracts that were not physiologically the same as extracts called adrenaline. On the other hand, Wellcome preferred the name epinephrine. However, he was eventually convinced by Dale's assertion that "In physiological literature the terminology is settled by those who describe the physiological action."

Epinephrine's Use in the Treatment of Anaphylaxis and Other Fundamental Developments

The 1902 experiments of French scientists Charles Richet and Paul Portier formally recognized the phenomenon of anaphylaxis for the first time.[17] In these experiments, dogs were injected with a small dose of toxin followed by a larger dose to determine if the animals became less sensitive to the toxin. In fact, the scientists found the opposite to be true in that the dogs had become much more sensitive to the toxin; this effect was then initially termed as aphylaxis but then changed to anaphylaxis.[18] Within treatment guidelines and early published physician anecdotes, anaphylaxis was commonly grouped with hay fever and spasmodic asthma, with the same prescribing information of epinephrine used for all despite the life-threatening severity of anaphylaxis.[19,20]

The first medical use of epinephrine occurred in 1901 by Solomon Solis-Cohen, who used desiccated adrenal extract to treat patients with hay fever.[21] Cohen applied dosing based on the unique tolerance of the individuals and identified the need for a purified active ingredient for more accurate clinical use, which would become broadly available through the Park-Davis in 1903.[21,22] The first published clinical study after the extraction method was developed by Takamine[14] studied treatment of asthma by hypodermic injection of 1:1000 adrenal chloride solution in doses of 3 to 6 minims (estimated to be 0.18-0.37 mg).[22] Minims were a common apothecary measurement at the time representing approximately 1 480 of a US fluid ounce and were phased out of common use in favor of metric system measurements. Minims represent a less accurate unit of measurement when delivering specific doses of medicine and their use was more common before the proliferation of US Pharmacopeia (U.S.P.) standards for purity, potency, and quality.

Through the assertions of Carl J. Wiggers in his 1905 Croonian Lecture, it was stated for the first time that epinephrine is a hormone, building the groundwork that would be fundamental for future physicians and researchers understanding the mechanisms of action for epinephrine.[23] Another important development that occurred within the same year was the first study that compared different modes of epinephrine administration in rabbits: subcutaneous, intraperitoneal, intravenous, and intramuscular.[24] The study used blood pressure (BP) as the primary proxy for absorption and concluded that IM injections

were the most convenient to elicit a rapid rise in BP while not imposing the dangers presented by intravenous injections of epinephrine.[24] No dosages were recommended at the time.

Further expanding epinephrine's role beyond local vasomotor uses, H. O. Butler was the first to utilize epinephrine as a systemic cardiac stimulant in 1906.[25] Harold W. L. Waller's 1914 clinical note emphasized that over multiple years of use in his clinical practice, a dose of 5 to 6 minims of 1:1000 adrenal chloride solution (estimated to be 0.31-0.37 mg) to treat spasmodic asthma is ideal for reducing the possibility of any negative side effects, and no more than 5 to 6 minims should be used for the first dose.[26] This dose was again emphasized in a paper published the same year stating that no more than 5 minims of 1:1000 adrenal chloride solution (estimated to be 0.31 mg) should be used.[27] This represents two physician assessments of dosage published independently of each other and based on clinical use observations.

Within a pharmacology guide published in 1918 following the dosing previously used for hay fever and spasmodic asthma, it is recommended to use a dose of 0.3 cc's administered by hypodermic injection to treat anaphylactic shock. In addition, this guide notes that deep IM injection has been shown to enter the bloodstream and produce a distinct rise in blood pressure.[28] With practitioners' guides published in the 1930s, dosages ranging from 0.5 to 1.0 cc's were put forth as the ideal doses to sufficiently treat anaphylactic shock.[29–31] Within another guide that groups together spasmodic asthma and anaphylactic reactions, the use of 0.1 to 0.5 cc of 1:1000 solution by IM injection is deemed as sufficient and is recommended to be given as early as possible.[32]

Conclusion

Epinephrine was the first hormone to be successfully isolated and has been used in the treatment of anaphylaxis since the turn of the 20th century. The primary evidence for ideal dosing of epinephrine to treat anaphylaxis for much of the 20th century was based upon clinical observation rather than rigorous clinical trials. The dosages of epinephrine administered and recommended by physicians varied within a consistent range until the adult dose was standardized via the introduction of the EpiPen. This analysis of how the dosage of epinephrine evolved and the factors that played a role in its development help to increase our understanding of the historical origins of this life-saving drug that was developed before the rigors of dose–response relationships and formal clinical trials were introduced into the drug development process.

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