EXPERT OPINION

Bioequivalence evaluation of epinephrine autoinjectors with attention to rapid delivery

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Abstract: Timely and proper injection of epinephrine is critical to prevent serious consequences relating to anaphylaxis. In a recent bioavailability study comparing epinephrine delivery from the Auvi-Q™ and EpiPen® epinephrine autoinjectors, the Auvi-Q failed to meet the bioequivalence threshold when using partial area under the curve (AUC) analyses based on zero to T_{max} recommended for highly variable drugs such as epinephrine. Peak plasma epinephrine concentrations for the EpiPen occurred 10 minutes (median T_{max}) after dosing, while peak concentrations for the Auvi-Q occurred 20 minutes after dosing. Though bioequivalence may be concluded for C_{max}, AUC_{inf}, and AUC_{0-t}, for fast-acting therapeutics used to treat life-threatening conditions, such as epinephrine, additional pharmacokinetic parameters such as AUC zero to T_{max} may be important to evaluate when assessing bioequivalence.

Keywords: anaphylaxis, therapy, pharmacokinetics, bioavailability, EpiPen, T_{max}

Anaphylaxis is a rapid-onset allergic reaction that can be life threatening, and its rate of occurrence is increasing, especially in younger people.[1,2] Though the financial impact of anaphylaxis can be difficult to determine, since this condition is likely underreported and underdiagnosed,[2,3] the economic burden of anaphylaxis in the United States was estimated in 2010 at US$1.2 billion in direct expenditures.[4] As anaphylactic reactions often occur in community settings without ready access to a health care professional, the World Health Organization and all published national (US) guidelines list epinephrine as the only first-line option for the initial treatment of anaphylaxis.[1] Epinephrine acts to prevent and relieve upper-airway obstruction and alleviate shock. Intramuscular injection into the thigh is a recommended route of administration,[5] and epinephrine autoinjectors are the primary component of emergency preparedness for anaphylaxis.[1] Timely and proper injection of epinephrine is critical to prevent serious consequences such as hospitalizations or death.[1] Fatalities from anaphylaxis can occur in a time frame ranging from 5 to 30 minutes depending on the type of allergen exposure.[6] Considering the importance of rapid absorption of epinephrine, how best should the delivery of epinephrine be evaluated when assessing the bioequivalence (BE) of a new autoinjector device?

The US Food and Drug Administration (FDA) reviewed the bioavailability of epinephrine from the Auvi-Q™ autoinjector (Sanofi, Bridgewater, NJ, USA) compared with that of the EpiPen® autoinjector. This assessment was based on study INT0802, a randomized, single-dose, single-blind, two-treatment, crossover study to document the bioavailability of epinephrine delivered by Auvi-Q and EpiPen.[7,8] The study design and analysis used the scaled BE approach by Haidar et al,[9] which is currently recom-

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Table 1 Baseline corrected results for comparison of Auvi-Q™ (Sanofi, Bridgewater, NJ, USA) to EpiPen® (Mylan Specialty LP, Basking Ridge, NJ, USA) autoinjectors

| PK parameters | Ratio | 90% confidence interval | | $\mu_T - \mu_R$ | σ_{WR}^2 | Upper 95% confidence limit for $(\mu_T - \mu_R)^2 - 0.8\,\sigma_{WR}^2$ | CV_{WR} (%) | Criterion 1: confidence limit | Criterion 2: point estimate | Bioequivalent |
		Lower	Upper							
C_{max}	0.9446	0.8439	1.0844	−0.0570	0.1931	−0.1046	43.94	Pass	Pass	Yes
AUC_{0-t}	1.1544	1.0575	1.2774	0.1436	0.1279	−0.0373	35.76	Pass	Pass	Yes
AUC_{inf}	1.1747	1.0915	1.3693	0.1610	0.1250	−0.0179	35.36	Pass	Pass	Yes
R1ACOTMX	0.7635	0.6549	0.9219	−0.2698	0.3494	−0.0686	59.11	Pass	Fail	No
R2ACOTMX	0.7896	0.6585	0.9532	−0.2362	0.3154	−0.0670	56.16	Pass	Fail	No

Note: Adapted from Center for Drug Evaluation and Research. Application Number: 201739Orig1s000. *Clinical Pharmacology and Biopharmaceutics Review(s)*. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/201739Orig1s000ClinPharmR.pdf. Accessed February 1, 2013.[7]
Abbreviations: AUC_{0-t}, area under the concentration–time curve from baseline to last measurable concentration in ng · h/mL; AUC_{inf}, area under the concentration–time curve from baseline extrapolated to infinity in ng · h/mL; C_{max}, peak drug concentration in ng/μL; CV_{WR}, coefficient of variation for reference (EpiPen®) in percent; PK, pharmacokinetic; R1ACOTMX, partial AUC based on zero to T_{max} after first administration in ng · h/mL; R2ACOTMX, partial AUC based on zero to T_{max} after second administration in ng · h/mL; T_{max}, time at maximum plasma concentration in hours; μ_R, mean of reference (EpiPen); μ_T, mean of test (Auvi-Q); σ_{WR}^2, intrasubject variability for reference.

mended by the FDA for high-variability substances such as epinephrine (ie, intrasubject variability > 30%). Seventy-one individuals were included in the pharmacokinetic (PK) data analysis; 67 individuals received dosing with Auvi-Q, while 69 subjects received at least one dose using the EpiPen.

The primary PK parameters for BE assessment were peak drug concentration (C_{max}) and area under the curve (AUC); baseline correction was performed to adjust for endogenous levels of epinephrine. Secondary partial AUC parameters were also determined for each individual's concentration–time profiles by calculating the AUC from time zero to the time of the maximum plasma concentration (T_{max}) after injection with the EpiPen. Partial AUC values were higher for the EpiPen than for the Auvi-Q. As shown in Table 1, BE may be concluded for C_{max} and concentration–time curve from baseline to the last measurable concentration (AUC_{0-t}) and AUC from baseline extrapolated to infinity (AUC_{inf}). However, BE was not concluded for the partial AUC analyses based on zero to T_{max} of reference after first administration (R1ACOTMX) or based on zero to T_{max} of reference after second administration (R2ACOTMX).

Further, based on median T_{max} parameters, peak epinephrine concentrations for EpiPen occurred 10 minutes after dosing (0.170 hours, range 0.07–1.00) while peak concentrations for Auvi-Q occurred 20 minutes after dosing (0.330 hours, range 0.08–1.00). While this difference was not considered significant, a numeric T_{max} difference may be highly critical to the therapeutic efficacy of epinephrine administration.

The PK parameters C_{max}, AUC_{0-t}, and AUC_{inf} for Auvi-Q and EpiPen, which met the equivalence criteria using the baseline-corrected data set, were presented by Edwards et al at the American Academy of Allergy, Asthma, and Immunology annual meeting.[10] This presentation did not specifically comment on partial AUC analyses, which failed to meet the BE threshold.[10] However, given the clinical significance of rapid epinephrine delivery, additional PK parameters such as T_{max} and partial AUC analysis may be considered as a requirement for BE. When there is a need for rapid absorption of a life-saving medication, in the case of fast-acting, highly variable therapeutics, additional PK factors might be important to evaluate when assessing BE.

Acknowledgment

Disclosure

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