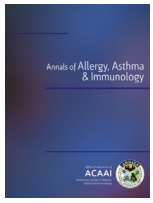
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Correspondence

Pharmacokinetic parameters for assessing bioequivalence of epinephrine autoinjectors

We were interested in the recent publication regarding a bioavailability study comparing epinephrine delivery from the EpiPen (Mylan Specialty LP, Basking Ridge, New Jersey) and Auvi-Q (sanofi-aventis US LLC, Bridgewater, New Jersey) epinephrine autoinjectors (EAIs) by Edwards et al.[1] The stated objective of the study by Edwards et al was "to compare the bioavailability of 0.3 mg of epinephrine (adrenaline) injected with Auvi-Q and EpiPen in healthy adults." Although the reported data suggested that Auvi-Q EAI was bioequivalent with respect to total exposure (overall area under the curve [AUC]) and peak exposure, these findings represent only a subset of pharmacokinetic parameters that might be evaluated in a formal bioequivalence study relative to EpiPen EAI, which may include partial AUC (ie, AUC evaluated from time zero to the median time of peak exposure [T_{max}] of the reference), which allows for assessment of early exposure and speed of absorption.[2]

As a matter of note, Mylan has conducted a study similar to that reported by Edwards et al using the currently marketed EpiPen EAI, which features an ergonomically designed oval barrel and a built-in needle guard that reduces the risk of needle-related injuries.[3,4] In this study, we included partial AUC in our evaluation, which is based on the area under the epinephrine plasma concentration-time curve from time zero to the median T_{max} of the reference product, EpiPen EAI in this case. Although we generally had findings similar to those reported by Edwards et al, we failed to find bioequivalence based on partial AUC, owing to lower epinephrine levels that result from Auvi-Q EAI relative to EpiPen EAI during the first 15 minutes after dosing (median T_{max} was 15 minutes for EpiPen EAI and 25 minutes for Auvi-Q EAI in our study).

The manner in which Edwards et al[1] used specific frequency intervals to reflect T_{max} results appears confusing. For example, by including T_{max} results that occurred at 15 and 20 minutes after dosing in the same frequency interval ($\geq$15 to $<$21 minutes), a reader cannot disaggregate the results to approximate the median T_{max} results for Auvi-Q EAI. T_{max} by itself may be viewed as having somewhat limited utility in assessing bioequivalence because of the discrete nature of the data. Partial AUC, on the other hand, is more amenable to bioequivalence inferences and can provide linkage to T_{max} based on the appearance of drug, after dosing, up until the time of median T_{max} for the reference. The article does not include a report on partial AUC findings.

The clinical significance of any difference in partial AUC is not completely understood, and there are challenging ethical issues with conducting direct clinical studies in patients with anaphylaxis. Nevertheless, given that prompt injection of epinephrine remains first-line therapy for the emergency treatment of life-threatening allergic reactions,[5] assessment of early systemic exposure (partial AUC) is worthy of further study.

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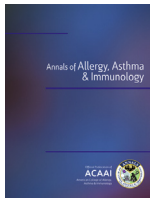
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Author response

Dr Rackley makes 2 primary assertions in his letter, both of which do not appear to be supported by available information. First, he questions selection of the industry standard parameters area under the curve (AUC) and maximum plasma concentration (C_{max}) to demonstrate that EpiPen and Auvi-Q have comparable bioavailability while partial AUC (derived from time after administration of a drug when the maximum plasma concentration is reached [T_{max}]) is excluded. Second, he suggests that the newly designed Epipen "reduces the risk of needle-related injuries" (presumably compared with the original EpiPen for which unintentional injections were previously reported).[1,2]

The first point is best addressed by the Food and Drug Administration (FDA) in their review of the data where they state that "primary parameters of interest were AUC and C_{max}" and "due to the high and overlapping variability associated with T_{max}, strict evaluation of similarity in T_{max} is not meaningful."[3] Dr Rackley notes that his own study had findings similar to ours and then attempts to make a distinction based on a parameter derived from T_{max}, a parameter that was found as not meaningful for evaluation by the FDA.[3] As previously stated by Dr Rackley, partial AUC is complex and there is uncertainty related to obtaining a consensus from industry, academia, and health authorities on harmonization of this parameter.[4]

The FDA concluded from our study that, based on appropriate evaluation criteria, epinephrine exposure from Auvi-Q is equivalent to EpiPen.[3] Multiple FDA reviewers, including reviewers from the medical and clinical pharmacology teams highlighted this, and the division director concluded the "study provides useful information in that it confirms that delivery of epinephrine for the two products [EpiPen and Auvi-Q] was the same."[3,5]

With regard to Dr Rackley's second point, continuous product quality improvement is an admirable goal for which all companies should strive. However, any improvement in the safety (or efficacy) of a product should be substantiated by results from adequate and well-controlled studies (ie, not a company press release).[2] Although design changes have been implemented, evidence that individuals continue to unintentionally inject themselves into a digit with the new EpiPen still remains.[6]

As a result of Auvi-Q's approval and availability, physicians, patients, and caregivers have more options regarding which epinephrine autoinjector (EAI) they care to use. Health care decision makers can now select an EAI based on critical considerations, such as the likelihood the patient will carry an EAI with them and the likelihood it will be used correctly during an allergic emergency, knowing that the epinephrine levels provided by Auvi-Q and EpiPen are the same.

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