RESPONSE TO COMMENT ON RICKELS ET AL.

Intranasal Glucagon for Treatment of Insulin-Induced Hypoglycemia in Adults With Type 1 Diabetes: A Randomized Crossover Noninferiority Study. Diabetes Care 2016;39:264–270

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We thank Munoz et al. (1) for the opportunity to provide additional rationale for the study design and interpretation of the data supporting the noninferiority of intranasal glucagon for treatment of insulin-induced hypoglycemia. Our study (2) was not designed to test recovery from severe hypoglycemia but rather recovery from insulin-induced hypoglycemia that ethically may only be produced under the controlled conditions available in a clinical research center. Intranasal glucagon was effective in correcting insulin-induced hypoglycemia, and when considering only those subjects with nadir glucose concentrations $<$50 mg/dL, the average time to achieving a glucose concentration of 70 mg/dL or a 20 mg/dL increase was 16 min compared with 13 min with intramuscular glucagon (2). We make no claims that intranasal glucagon and intramuscular glucagon are "equally" effective. The noninferiority margin of 10% was chosen on the basis of the data for glucagon injection in a simulated emergency study where 10% of participants (parents of children and adolescents with type 1 diabetes) entirely failed to administer the injectable glucagon product (3). Despite the preplanned noninferiority margin of 10%, the one-sided 97.5% CI was 4%, with only 1 of 75 participants failing to achieve a glucose concentration of 70 mg/dL or a 20 mg/dL increase by 30 min with intranasal glucagon (2). Although there is always a certain degree of arbitrariness in selecting a noninferiority margin as well as statistical power in planning a study, once the study has concluded, it is the CI that provides the precision of the point estimate that is important for interpreting the results. We believe that physicians will accept a possible 4% less efficacy for the ease of bystander administration of the intranasal glucagon preparation. In a more recent simulated emergency study, 94% of trained caregivers of insulin-using persons administered intranasal glucagon correctly, compared with only 50% for intramuscular glucagon, and, more importantly, 93% of untrained acquaintances administered intranasal glucagon correctly, compared with a mere 20% for intramuscular glucagon (4). An outpatient study of the use of intranasal versus intramuscular glucagon for treatment of severe hypoglycemia in patients with type 1 diabetes is ongoing (ClinicalTrials.gov: NCT02171130). The appropriate use of glucagon in the treatment of severe hypoglycemia is to raise the glucose concentration sufficiently to restore cognition to the point where oral carbohydrate can be ingested. At 15 min following administration, the mean $\pm$ SD glucose had increased from a nadir 44 $\pm$ 8 to 71 $\pm$ 15 mg/dL with intranasal glucagon, and from 47 $\pm$ 8 to 82 $\pm$ 19 mg/dL with intramuscular glucagon; at 20 min following intranasal glucagon the glucose was 85 $\pm$ 18 mg/dL. The average 3-min pharmacodynamic lag with intranasal versus intramuscular glucagon seen in our adult cohort (2) would be offset clinically by

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the 2-min preparation lag with intramuscular versus intranasal glucagon assuming both products are successfully administered (4). Importantly, this pharmacodynamic delay was not seen in a parallel study of intranasal versus intramuscular glucagon in children aged 4–16 years with type 1 diabetes where all 24 intramuscular and 58 of 59 intranasal glucagon administrations produced a ≥25 mg/dL increase in glucose from nadir within 20 min of dosing (5). Because use of intramuscular glucagon is error prone and often omitted in practice, intranasal glucagon can be expected to have a substantial beneficial impact on the treatment of severe hypoglycemia.

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References

1. Munoz AJ, Girish S, Winder MB. Comment on Rickels et al. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. Diabetes Care 2016;39:264–270 (Letter). Diabetes Care 2016;39:e192. DOI: 10.2337/dc16-0955

2. Rickels MR, Ruedy KJ, Foster NC, et al.; T1D Exchange Intranasal Glucagon Investigators. Intranasal glucagon for treatment of insulin-induced hypoglycemia in adults with type 1 diabetes: a randomized crossover noninferiority study. Diabetes Care 2016;39:264–270

3. Harris G, Diment A, Sulway M, Wilkinson M. Glucagon administration – underevaluated and undertaught. Pract Diabetes Int 2001;18:22–25

4. Yale JF, Piche C, Lafontaine M, et al. Needle-free nasal delivery of glucagon is superior to injectable delivery in simulated hypoglycaemia rescue. Presented as a poster at the European Association for the Study of Diabetes (EASD) 51st Annual Meeting, 14–18 September 2015, Stockholm, Sweden

5. Sherr JL, Ruedy KJ, Foster NC, et al.; T1D Exchange Intranasal Glucagon Investigators. Glucagon nasal powder: a promising alternative to intramuscular glucagon in youth with type 1 diabetes. Diabetes Care 2016;39:555–562