

A Review of a Family of Ultra-Rapid-Acting Insulins: Formulation Development

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Abstract

This review summarizes the clinical development of a family of ultra-rapid-acting recombinant human insulin formulations. These formulations use ethylenediaminetetraacetic acid (EDTA) to chelate zinc and thereby destabilize insulin hexamers. In addition, insulin monomer surface charges are chemically masked with citrate to prevent reaggregation. The first phase 1 trials were performed using BIOD-090, an acidic 25 unit U/ml insulin formulation, which contained disodium-EDTA (NaEDTA). When compared with regular human insulin (RHI) and/or insulin lispro in multiple phase 1 studies, BIOD-090 consistently showed more rapid absorption and/or onset of action. A standard meal challenge study also demonstrated improved postprandial glucose profiles associated with BIOD-090. However, increased patient exposure in larger phase 3 trials showed that this formulation was associated with an increased incidence of local injection site reactions, most commonly pain. A next generation formulation, BIOD-100, contained the same excipients as a standard insulin concentration of 100 U/ml. BIOD-100 maintained an ultra-rapid action profile and was associated with modest but significantly improved toleration when compared with BIOD-090. In order to further improve toleration, the hypothesis that NaEDTA contributed to discomfort by chelating endogenous calcium was tested by either substituting calcium-EDTA for NaEDTA or by adding calcium chloride to the NaEDTA formulation. These calcium formulations essentially eliminated the excess discomfort associated with BIOD-090 but were associated with less optimal pharmacokinetic profiles in humans. Recent efforts have succeeded in developing ultra-rapid-acting human insulin formulations with acceptable injection site toleration by optimizing concentrations of calcium (BIOD-125) and with the use of magnesium sulfate to mitigate discomfort (BIOD-123). Similar formulation technology has also been shown to accelerate absorption of insulin analogs in animal models.

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Abbreviations: (AUC) area under the curve, (AUCGIR) area under the glucose infusion rate curve, (CaEDTA) calcium ethylenediaminetetraacetic acid, (EDTA) ethylenediaminetetraacetic acid, (GIR) glucose infusion rate, (HbA1c) hemoglobin A1c, (LIS) insulin lispro, (NaEDTA) disodium ethylenediaminetetraacetic acid, (PD) pharmacodynamic, (PK) pharmacokinetic, (RHI) regular human insulin, (SC) subcutaneous, (SD) standard deviation, (tGIR) duration of action, (tGIR_{max}) time to maximum GIR, (t_{max}) time to maximal insulin concentration, (VAS) visual analog scale

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