An Analysis of Dosage Volume for Halfway Doses in the Victoza Pen

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King and Wolfe[1] assessed the accuracy of liraglutide doses at the halfway marks between the three indicated or marked doses (0.6, 1.2, and 1.8 mg) of the Victoza® pen device. The presumed doses at each halfway mark was 0.3, 0.9, and 1.5 mg. The clinical rationale the authors provided for using a dose other than the marked doses is that patients could use a slightly lower dose if the 1.2 or 1.6 mg doses were not tolerable due to side effects. The main side effects associated with liraglutide that can be challenging for patients are gastrointestinal (GI) effects, primarily nausea and vomiting. The Victoza pen is a prefilled, multidose pen that is designed to deliver 0.6, 1.2, or 1.8 mg and contains 3 ml of solution with a 6 mg/ml concentration of liraglutide. The halfway marked doses are 5 clicks between the marked dose settings (as there are 10 clicks between the marked dosages). Using a 6 × 6 randomization schedule, volume measurements for each halfway dose and the three marked doses (i.e., six doses) were determined and then converted to milligrams. All six doses were found to be linear and equivalent to the marked and assumed halfway doses: 0.3, 0.6, 0.9, 1.2, 1.5, and 1.8 mg.

The recommended dosing schedule for liraglutide (Victoza) is to initiate therapy with the 0.6 mg dose daily for 1 week and then titrate to 1.2 mg; the 0.6 mg dose is considered a starting dose, to alleviate GI symptoms during the dose titration period. After 1 week taking 1.2 mg, the dose can be increased to 1.8 mg if the 1.2 mg dose does not result in the desired glycemic control. In the phase 3 clinical trials with liraglutide, the Liraglutide Effect and Action in Diabetes (LEAD) program, both the 1.2 and the 1.8 mg dose resulted in significant reductions in hemoglobin A1c (A1C) compared with baseline (~1–1.5% lowering when added as combination therapy and 0.8–1.1% as monotherapy);[2–5] in two of the LEAD studies, only the 1.8 mg dose was studied.[6,7] It is important to note that the difference in A1C lowering achieved with a 1.2 and 1.8 mg dose may not be clinically significant. In LEAD-1 (liraglutide added to glimepiride), the A1C change was -1.08% and -1.13% for the 1.2 and 1.8 mg doses, respectively, and in LEAD-2 (liraglutide added to metformin), both the 1.2 and the 1.8 mg dose resulted in the same A1C lowering on average (-1.0%).[2,3] Therefore, it seems reasonable to use a dose lower than 1.8 mg if this dose causes intolerable GI side effects. Additionally, since some studies have demonstrated clinical efficacy with just the 1.8 mg dose (e.g., LEAD-5, which compared liraglutide with insulin glargine, and LEAD-6, which compared liraglutide with exenatide),[6,7] if a patient is not able to tolerate the 1.8 mg dose, using the dose of 1.5 mg (the halfway dose) seems like a logical approach to alleviate the GI effects.

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Abbreviations: (GI) gastrointestinal, (A1C) hemoglobin A1c, (LEAD) Liraglutide Effect and Action in Diabetes

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Liraglutide has been demonstrated to have dose-dependent GI symptoms.[8] The GI symptoms associated with liraglutide are seen early in treatment and are most often transient. In LEAD-5, which studied the 1.8 mg dose, 14% of patients initially experienced nausea; this decreased after 1 to 3 weeks, and by 4 weeks, the incidence of nausea was only 1.5%.[6] As liraglutide is dose titrated, if the marked dose (1.2 or 1.8 mg) is not tolerated, a lower dose (the halfway doses studied by King and Wolfe[1]) could be tried. Then, after the GI symptoms resolved, it would be reasonable to reattempt the higher marked dose if needed for the desired glycemic control. Prior to considering use of a nonmarked dose, it would be important to assess that a patient was taking Victoza properly, such as not increasing the dose too rapidly (e.g., less than 1 week titration), which could increase the chance for GI symptoms.

One consideration in using a halfway unmarked dose is that this would require a patient to count clicks (i.e., five clicks between a marked dose), as there are no visible lines on the pen device at these interim clicks. If a patient were not diligent with accuracy in counting the necessary clicks, it could result in difficulty determining the actual dose a patient is taking and further confusion in how to dose adjust liraglutide. However, there should be no concern for overdosing if a halfway unmarked dose is used, as the pen can only deliver a maximum of 1.8 mg per dose.

Another consideration is the accuracy of the halfway unmarked dose after repeated use of the Victoza pen device. While King and Wolfe[1] determined the dose at each halfway point to be 0.3, 0.9, and 1.5 mg, it is possible with repeated use of the pen that the accuracy of these doses could be affected. Therefore, a conservative approach would be to use the halfway unmarked dose on a temporary basis until a patient's GI symptoms were alleviated and then increase back to the marked dose (1.2 or 1.8 mg).

In conclusion, King and Wolfe[1] demonstrated the accuracy of the dose volume for the halfway doses in six Victoza pens. From a practical standpoint, use of a halfway dose (0.3, 0.9, and 1.5 mg) could be considered on a temporary basis until GI symptoms are alleviated, and then liraglutide could be retitrated to the marked dose.

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