Epidural Steroid Shots Up Diabetics' Blood Sugars

BY FRAN LOWRY
Orlando Bureau

ORLANDO — Glucocorticosteroids that are epidurally administered produce a transient increase in fasting blood glucose levels in patients with diabetes, according to data presented at the annual meeting of the American Academy of Pain Medicine.

In a trial of 40 patients, fasting blood glucose levels rose significantly—about 30% above baseline—the first morning after the epidural and stayed elevated for an average of 7 days in one subset of patients, said Dr. Adam Stoller of Beth Israel Deaconess Medical Center, Boston.

"It's important to know that there is this potential for bad outcomes, especially since epidural steroid injections are the most common pain clinic procedure and there is an increasing number of diabetics," Dr. Stoller said in an interview.

He and his associates at Beth Israel Deaconess were prompted to study the effect of epidural steroid injections on blood sugar after a diabetic patient went into a ketoacidosis coma following the procedure.

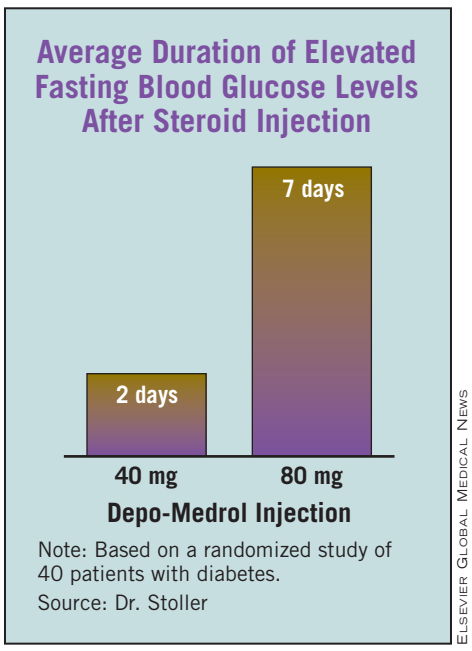
The patients were randomized to receive epidural administration of 40 mg or 80 mg of methylprednisolone acetate (Depo-Medrol). Hemoglobin A_{1c} (HbA_{1c}) levels were drawn on the day of the epidural, and baseline blood sugars were obtained from the patients' glucose log, or from a glucose monitoring device. Fasting blood sugars were monitored for 2 weeks after the epidural.

Fasting blood glucose levels were elevated for an average of 7 days in the patients who received the 80-mg dose of Depo-Medrol and for an average of 2 days in those on the 40-mg dose.

The magnitude of the rise in blood sugar was correlated with HbA_{1c} levels at the time of the injection, Dr. Stoller said. "The higher the hemoglobin A_{1c}, the greater the derangement in fasting blood glucose. Hemoglobin A_{1c} of 7[%] or greater predicted a more significant increase in blood glucose."

Baseline fasting blood sugars did not correlate with the subsequent rise that occurred after the epidural steroids, which surprised the investigators.

"We often use fasting blood sugar as an indication of whether we should or should not give epidural steroids. In this study, we found fasting sugars had no correlation with what their rise after the epidural steroids would be. The thing that most correlated with a rise in blood sugar was the [HbA_{1c}], and levels that started at 7 were linked to the greatest rise." Dr. Stoller said he had no conflicts of interest to report. ■



ELSEVIER GLOBAL MEDICAL NEWS

Unanswered Questions, Lack of Data Complicate Incretin Therapy

BY SHERRY BOSCHERT
San Francisco Bureau

SAN FRANCISCO — The new incretin mimetic exenatide and the incretin enhancer sitagliptin both have unique properties that need to be taken into account when prescribing them, American Diabetes Association president Dr. John B. Buse said at a meeting sponsored by the association.

Injections of exenatide (Byetta) were approved in 2005 as adjunctive therapy for patients with type 2 diabetes. Orally administered sitagliptin (Januvia) was approved in 2006 for use as monotherapy or in combination with metformin or thiazolidinedione for patients who have type 2 diabetes.

Dr. Buse has received research funds from Amylin Pharmaceuticals and from Eli Lilly & Co., which market exenatide. He is an adviser and speaker for those companies and for Merck & Co., which markets sitagliptin.

Incretin augments glucose-stimulated insulin secretion by intestinally derived peptides. Exenatide and sitagliptin augment the incretin pathway, which appears to be attenuated in type 2 diabetes. The incretin effect is composed mainly of the peptides glucose-dependent insulinotropic polypeptide and glucagonlike peptide-1 (GLP-1), which are normally inactivated by the enzyme dipeptidyl peptidase-4 (DPP-4). Exenatide is a GLP-1 receptor analogue resistant to DPP-4 degradation and slows gastric emptying. Sitagliptin selectively inhibits DPP-4, giving the incretin enzymes a longer half-life to enhance their effects.

"We don't have long-term safety and efficacy data" for these medications "as we do with the other four classes of medications for diabetes mellitus," cautioned Dr. Buse, who discussed several aspects of the use of these drugs.

► **Combination with insulin.** "This is a very exciting combination," he said, though it has not been adequately studied in clinical trials. Sparse data on five patients treated for 5 days with exenatide and insulin at his institution are buried in a larger study published in 2001, said Dr. Buse, professor of medicine at the University of North Carolina, Chapel Hill. However, he warned against combining exenatide with rapid-acting insulin. "I'd be exceptionally cautious about doing [that]."

► **Fitting exenatide into the diabetes care algorithm.** Experts are wondering whether exenatide might be a reasonable alternative to sulfonylureas or glitazones. Decisions on whether to include exenatide in treatment algorithms will depend "on whether we have data demonstrating its long-term safety and efficacy, and what the effects are on β-cell biology," he said.

► **Rhinorrhea as a side effect of sitagliptin.** Studies of sitagliptin persistently show an elevated but low rate of rhinorrhea—around 11%, compared with 7% in placebo groups—and few other side effects. The drug affects chemokine levels, which has raised concerns that the rhinorrhea is "a hint that there are immune effects that we haven't been able to measure yet." But many drugs are associated with an increased rate of rhinorrhea, so it could be something more benign, he added.

► **Which patients will respond to these agents.** Because exenatide dramatically increases GLP-1 levels, "my guess is that virtually anybody would respond" to it, though it's unclear whether the level of response would justify two injections daily and a cost of around $200 per day, said Dr. Buse. Sitagliptin produces more modest increases in GLP-1 levels, but "I don't know what the effects would be in a patient who has severely impaired β-cell function."

► **Their use in bariatric surgery patients.** "Part of the benefit of bariatric surgery is you actually increase the levels of GLP-1 and perhaps other incretin hormones, so it's an intriguing notion," Dr. Buse said. "The concern with exenatide would be the nausea from the surgery plus the nausea from the exenatide maybe getting somebody in a bad place in that regard."

► **Effects on gastroparesis patients.** The clinical trials excluded patients with chronic, serious GI issues, "so we don't really know" the answer, he said. For some patients whose intermittent "gastroparesis" is a result of overeating that produces bloating and nausea, exenatide may limit their eating and help them feel better, "but you want to be cautious." ■

Data Suggest HbA_{1c} Can't Be Switched to Mean Blood Glucose

BY MIRIAM E. TUCKER
Senior Writer

Attempts to translate hemoglobin A_{1c} into mean blood glucose via a mathematical formula are likely to introduce substantial error, according to data from an analysis of continuous glucose monitoring data in 47 children with type 1 diabetes.

A recent multinational trial identified a formula for converting HbA_{1c} to mean blood glucose, based on continuous glucose monitoring (CGM) data from 643 diabetic and nondiabetic subjects. Pending the final results of that study, the American Diabetes Association, the European Association for the Study of Diabetes, the International Federation of Clinical Chemistry and Laboratory Medicine, and the International Diabetes Federation have called for laboratories to report that mean glucose value in addition to the HbA_{1c} itself (Diabetes Care 2007;30:2399-400).

However, new data from the Diabetes Research in Children Network (DirectNet) Study Group suggest that although HbA_{1c} does clearly reflect mean glucose, there is substantial variability in individual mean glucose concentrations for a given HbA_{1c} value. Moreover, the strong relationship between HbA_{1c} and the risk for diabetic complications may reflect not only mean blood glucose but also a patient's propensity to glycosylate other structural proteins, said Dr. H. Peter Chase of the University of Colorado, Denver, and colleagues (Diabetes Care 2008;31:381-5).

The 47 patients, aged 4-18 years, included 28 pump users and 19 who took multiple daily injections using glargine as their basal insulin. They wore Abbott Laboratory's FreeStyle Navigator continuous glucose monitor for an average of 115 hr/wk. The slope of mean glucose over the previous 3 months was 18 mg/dL per 1.0% HbA_{1c}, with considerable variation in glucose concentrations for any given HbA_{1c}. This relationship was similar between the pump users and those taking injections, and at both 3-month and 6-month visits.

"For any given A_{1c} level, mean sensor glucose levels differed by up to 50 mg/dL or more, making the conversion of A_{1c} into mean glucose equivalents as suggested by a recent American Diabetes Association consensus statement tenuous at best," the study group commented.

Two measures of a patient's rate of glycation—a simple ratio of mean glucose to HbA_{1c} and a derived "glycation index"—remained relatively constant over the 6 months of the study, suggesting that individuals glycate proteins at different rates and the tendency to be a fast or slow "glycator" persists over time.

After controlling for mean glucose over the previous 3 months, HbA_{1c} was not significantly associated with measures of glucose lability, thus refuting findings in other studies that high glucose values contribute disproportionately to the HbA_{1c} value. "We found no evidence to contradict the simple hypothesis that A_{1c} directly reflects the integral of glucose level over time," they said.

The group cautioned that because children and adolescents may have higher glycemic variability than do adults, the findings may not be directly applicable to adult patients.

Funding for the study was provided by the National Institutes of Health; Abbott Diabetes Care provided the continuous glucose monitors and test strips. ■