Letters and Comments

Heparin Addition to Insulin in Implantable Pumps to Prevent Catheter Obstruction

Now that stable insulin solutions are available (1), coagulation, fibrin, and tissue deposition are the major causes of implantable insulin pump failures because they cause catheter malfunction. (2). Heparin may prevent this phenomenon by blocking fibrin formation and/or other coagulation processes. We have reported that heparin may be mixed with insulin (Organon, Saint Denis, France) in pumps (Siemens, FRG) without altering the stability or other basic properties of either compound (3). This study expands on the above data by evaluating the miscibility of heparin with the only special insulin (Hoechst-Roussel, Somerville, NJ) and programmable implantable pump (MiniMed, Sylmar, CA) available and currently under clinical trial in the United States (C. Saudek, J.-L.S., C. Pitt, K. Waxman, M.A. Charles, and R.E. Fischell, unpublished observations).

Four solutions were tested: U-400 human buffered neutral insulin stabilized by a surfactant (Genapol, Hoeschst-Roussel, Somerville, NJ), pure sodium heparinate (500 U/ml, Organon), a combination of insulin at 400 U/ml and heparin at 500 U/ml, and a control solution of phenol and water. Each solution was used to fill four implantable pumps (model MIP 2001, MiniMed). Pumps were set at 0.7 U/h and shaken horizontally at 83 Hz, 6.4 × *g* and placed at 37°C for 3 mo. Eluates were collected at the extremity of the pump catheter (polyethylene covered externally with Silastic; length 25 cm, internal diam 0.3 mm) every week.

The turbidity of the solution was assessed visually. High-performance liquid chromatography (HPLC; Waters system, Axxiom columns, and absorbance detection at 220 nm) was used to analyze insulin solutions as previously described (1,3). To improve accuracy, each peak area was adjusted by the corresponding extinction coefficient, determined by ultraviolet spectroscopy at 280 and 220 nm. Zinc, phenol, and pH were measured by standard methods. Heparin activity was assessed by biological (clotting times with the Sigma panel of reagents) and chemical (colorimetry with orthotoluidine blue) methods.

No significant changes were noted in clarity or pH. Over the 3-mo period, zinc was reduced by 10% and phenol by 12–15% from both insulin and heparinized insulin. HPLC analysis of insulin, expressed in percentages of total insulin at time 0, gave the following results. Pure insulin solution results at peak 1 (unmodified insulin) were 89.8 and 66.4% at 0 and 3 mo; at peak 2 (denatured insulin), 5.0 and 2.9%; and at peak 3 (other products), 5.2 and 10.2%. Heparinized insulin solution results at 3 mo were 65.3% (peak 1), 13.5% (peak 2), and 10.7% (peak 3).

Heparin activity, expressed in percentage of initial heparin activity (500 U/ml = 100% activity) was 43 and 65% for the heparinized insulin solution, assessed biologically and chemically at 3 mo, and 46 and 76% for the pure heparin solution.

In summary, a significant drop in pure insulin and heparin content was noted after 3 mo. However, further analyses (data not shown) indicated that most of the alterations were caused by shaking rather than by temperature, storage, or material contact; that the heparin drop is still very compatible with full anticoagulant effect; and, most important, that heparin addition did not further affect any of the parameters tested.

We conclude that addition of heparin to insulin in conditions reproducing those of in vivo implanted devices did not alter the chemical stability of either com-

pound, and further research is necessary to determine whether heparinized insulin is effective in preventing catheter obstruction.

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Clinical Comparison of Glipizide and Glyburide

Glyburide and glipizide are two of the most commonly used second-generation sulfonylureas. Glyburide has been reported to produce a higher basal serum insulin level than glipizide (1) and has also been claimed to be the more potent of the two agents in controlling hyperglycemia (2). In addition, because of the relationship between basal insulin level and appetite, patients on glyburide might have increased body weight when compared with those treated with glipizide (3). Despite the possible differences between the two agents, there have been few randomized studies of these drugs.

Forty patients with non-insulin-dependent diabetes mellitus (mean age 62 yr, mean weight 180 ± 5 lb, mean fasting plasma glucose 282 ± 12 mg/dl) who were refractory to diet were randomly placed on 5 mg/day glipizide or glyburide and followed at 1- to 2-mo intervals. If fasting plasma glucose was >200 mg/day, an additional 5 mg of the oral agent was administered to a maximum daily dose of 20 mg.

At the end of 6 mo, mean fasting plasma glucose on glipizide was 180 ± 18 vs. 188 ± 16 mg/dl on glyburide (n = 20, NS). There was also no significant difference in weight between the patients receiving the two agents (181 ± 5 vs. 175 ± 8 lb). The mean daily dose of glipizide was 15.0 ± 2 vs. 14.4 ± 2 mg of glyburide (NS) at the end of the treatment period.

These data agree with the recent report of Groop et al. (1) and indicate that glipizide and glyburide are equally potent in controlling plasma glucose and that the differing insulin profiles of the two agents do not affect body weight.

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Role of Protein in Diabetes Control

In a recent article (1) evaluating protein in the dietary management of diabetes, Wylie-Rosett emphasized that half of exogenous protein is available as glucose. We take issue with this statement and the basis on which it was made. The article that was referenced stated that 50% was a good estimate of the amount of exogenous protein converted to glucose in diabetes (2). However, this figure was not derived experimentally but rather as an assumption based on the previous studies of Janney (3), who studied phlorhizinized diabetic dogs by administering meals of protein and estimating glucose yield through evaluation of glycosuria. He found a marked rise in glycosuria within 2 h of ingestion of protein. Unfortunately, phlorhizin, which is known to cause renal glucose osmotic diuresis without hyperglycemia (4,5) and stimulates glycogen breakdown in the liver (6), is a very poor model for evaluating the physiologic contribution of dietary protein to gluconeogenesis.

In circumstances of insulin deficiency, the oxidation of branched chain amino acids in muscle and uptake of alanine (the principle glycogenic amino acid) by liver are accelerated, resulting in increased gluconeogenesis and augmented protein catabolism (7). Wahren et al. (8) studied the effect of protein ingestion in patients with diabetes and found a three- to fourfold increment in splanchnic glucose output. Insulin was withheld for 24 h before subjects were studied. However, in the presence of hyperinsulinemia, alanine uptake by the liver is reduced to virtually zero (9), and hepatic glucose production falls by 85% (10). The abnormal branched chain