

# An Endocrinologist's View on the Practical Use of Insulin

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The use of sliding-scale SC insulin for glycemic control in hospitalized patients with diabetes mellitus can produce clinically important fluctuations in blood glucose concentrations over time. Although the plasma concentration of insulin peaks after ~2 hours, the stimulation of glucose utilization by insulin does not peak until 3 to 4 hours after SC administration. Thus, the repeated administration of sliding-scale SC insulin every 4 hours can create a large cumulative effect on glucose utilization and a precipitous decline in blood glucose concentration in a relatively short period of time. Even rapid-acting insulin analogues reach their peak effects on glucose utilization after ~2 hours. At the University of Washington Medical Center in Seattle, Washington, a hospital-wide protocol has been developed for the use of IV insulin for hospitalized diabetic patients who are not eating or eating very little. An initial IV insulin dose is selected on the basis of the patient's insulin sensitivity, and subsequent doses are adjusted in response to changes in blood glucose values over time. The use of IV insulin reduces the likelihood that patients will develop hypoglycemia or hyperglycemia in both critical and noncritical care settings. Standardized methods, which are valuable for patient care and for educating clinicians about insulin use, have also been developed to transition patients to SC insulin.

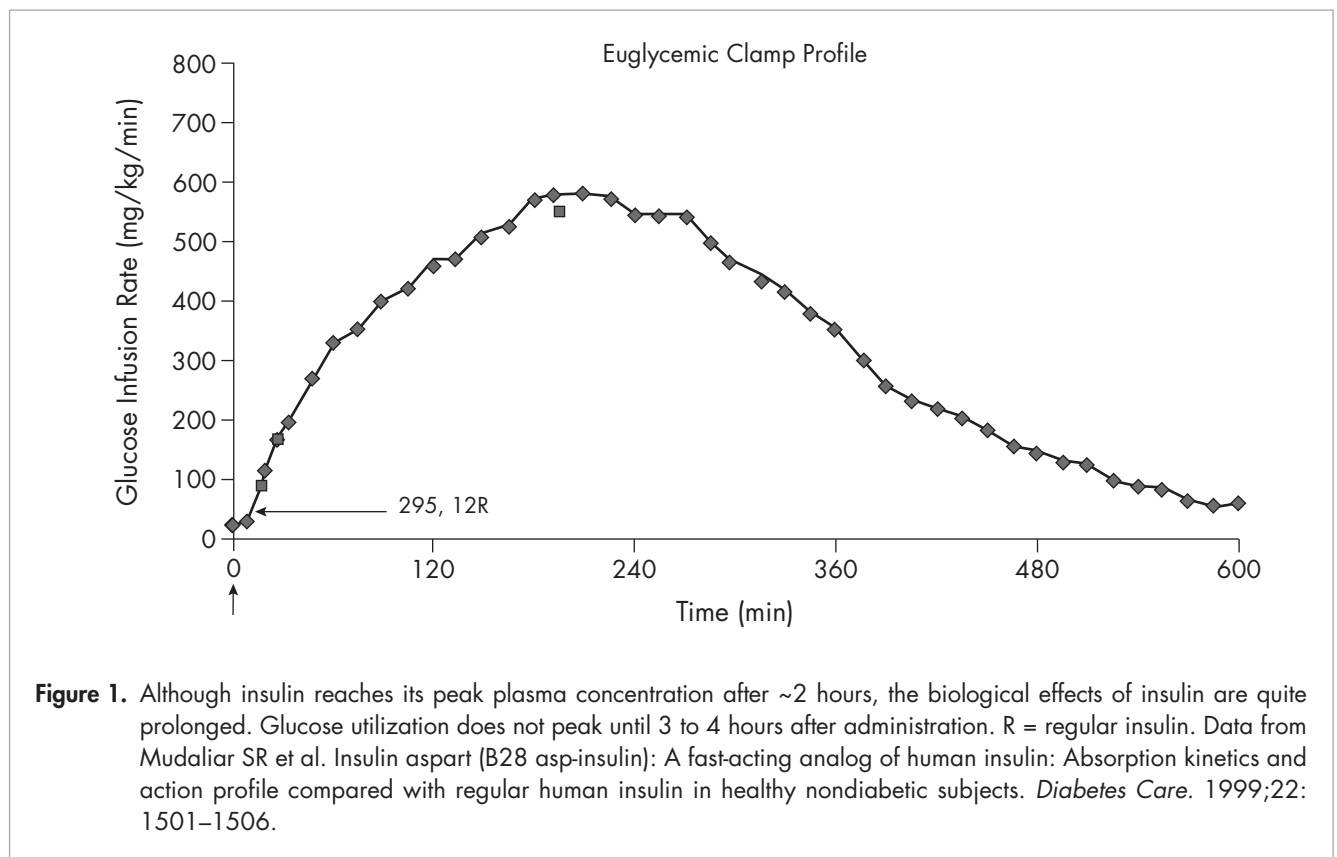
## LIMITATIONS OF SC INSULIN IN HOSPITALIZED DIABETIC PATIENTS

As described by Dr. Dandona and Dr. Nesto in this supplement, both insulin and glucose modulate inflammatory processes that are important in the development of vascular injury. Although some studies have demonstrated significant anti-inflammatory effects of insulin administration, clinical trials that have examined the infusion of glucose and insulin solutions in patients with acute myocardial infarction have shown that insulin administration alone does not improve clinical outcomes when glucose levels are not adequately controlled.<sup>1</sup> In addition, it is necessary to protect hospitalized diabetic patients against hypoglycemia. Despite the importance of maintaining blood glucose concentration within a relatively narrow range in hospitalized diabetic patients, the reality for most patients is a pattern of highly variable changes in blood glucose values from day to day.

Insulin treatment for hospitalized diabetic patients has traditionally been performed by discontinuing the patient's home insulin regimen and instituting sliding-scale SC insulin.<sup>2</sup> This approach often leads to potentially dangerous variability in blood glucose concentrations, as illustrated by a recent case. A 59-year-old man was hospitalized with decompensated heart failure. He had type 2 diabetes mellitus, and his glycosylated hemoglobin value at the time of hospitalization was 8.9%. He had an infection and was too ill to eat. At the time of hospitalization, his home insulin regimen of 70% neutral protamine Hagedorn and 30% regular

human insulin was discontinued and replaced by sliding-scale SC insulin every 4 hours. His initial glucose value was 295 mg/dL. Based on the sliding scale, the nurse administered 12 U of regular insulin at 6:00 PM. At 10:00 PM, his blood glucose value was 180 mg/dL, and he received another 6 U of insulin. At 12:00 AM, he received an antibiotic in a 5% dextrose solution. At 2:00 AM, his glucose value was 180 mg/dL, and he received another 6 U of regular insulin. At 6:00 AM, he developed hypoglycemic seizures and his glucose was 35 mg/dL.

This patient's hypoglycemic crisis was a consequence of the prolonged effect of SC insulin on glucose utilization, which persists much longer than most clinicians realize. The pharmacodynamic effects of single doses of SC insulin have been examined using a glycemic clamp procedure, in which insulin is injected subcutaneously and glucose is continuously infused to maintain a constant plasma glucose at the patient's baseline glucose value.<sup>3</sup> The administration of insulin results in increased glucose utilization, and therefore an increased rate of glucose infusion is required to maintain a constant plasma glucose concentration. Most clinicians believe that SC insulin reaches its peak effect ~2 hours after administration. However, as shown in **Figure 1**, this study found that although insulin reaches its peak plasma concentration after ~2 hours, the biological effects of insulin are actually quite prolonged.<sup>3,4</sup> Glucose utilization did not peak until 3 to 4 hours after administration. Because of this long duration of action, administration of repeated SC insulin doses in a relatively short period of time can produce poten-



tially dangerous cumulative effects on glucose utilization. These effects are illustrated for the case study described using the results of the glycemic clamp study (Figure 2). At time 0, the patient had a plasma glucose concentration of 295 mg/dL and received 12 U of insulin. On the basis of the glycemic clamp study, this insulin dose was expected to produce a large increase in glucose utilization over the next several hours. At approximately the time that glucose utilization was reaching its peak, the patient had a glucose concentration of 180 mg/dL and received another 6 U of insulin. This second dose produced a second peak of insulin activity, which is shown at the bottom of Figure 2.<sup>3,4</sup>

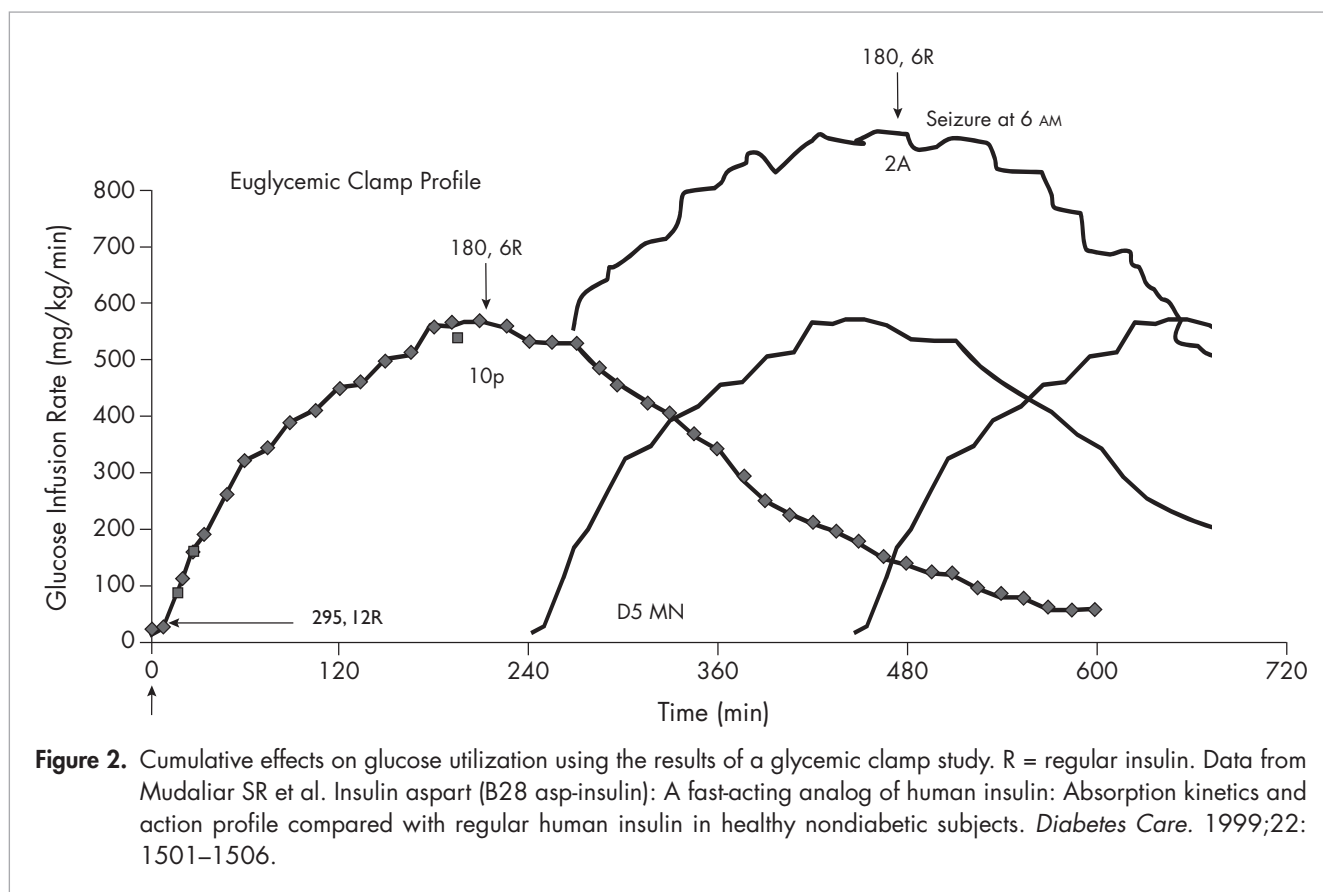
The combined net effect of the 2 insulin doses is shown in the upper curve. At midnight, the patient received an antibiotic administered in a 5% dextrose solution, and glucose was checked again at 2:00 AM. The combined effects of the 2 insulin injections created a large effect on glucose utilization, but the patient's plasma glucose value was sustained by the dextrose infusion. The nurse administered a third insulin dose, and the cumulative effects of the stacked insulin doses (also called "insulin stacking"), combined with the termination of the dextrose infusion, rapidly created a dangerously large drop in plasma glucose concentration. It should be noted that even with rapid-acting insulin analogues, glycemic clamp studies similarly have shown that the peak effects on glucose utilization occur much more slowly (at ~2 hours) than the peak plasma insulin concentration (at ~1 hour).<sup>3</sup>

#### DEVELOPMENT OF AN INSULIN PROTOCOL FOR HOSPITALIZED DIABETIC PATIENTS

Should IV insulin be considered as an alternative to sliding-scale SC insulin for hospitalized diabetic patients who are not eating? As suggested by the case study described earlier, the effects of SC insulin are often too slow and too dangerous for very ill hospitalized patients, especially if they are not eating properly. Hospital physicians are often unfamiliar with current outpatient insulin regimens, which make inpatient insulin use even more challenging and dangerous. It is not reasonable to expect patients to reach glycemic targets with SC insulin when insulin requirements are changing rapidly.

Two IV insulin formulations were recently approved by the US Food and Drug Administration: recombinant human insulin and insulin aspart.<sup>5</sup> Although the concentration of insulin in plasma reaches a peak value within a few minutes after IV injection, glycemic clamp studies show that, similar to SC insulin and long-acting analogues, the peak biological effect of IV insulin is attained more gradually. After IV administration, both insulin lispro and regular insulin produced peak effects on glucose utilization after ~30 minutes to 1 hour.<sup>6</sup> Thus, although faster than SC administration, IV administration produces its peak effect on glucose utilization more gradually than most physicians realize.

Our initial IV insulin protocol was first developed in 1992 for use in the intensive care unit and other medical services at the University of Washington Medical Center, in Seattle,



Washington. When the IV insulin program began, knowledge about the effects of insulin among health care providers was generally limited, and the program had to overcome significant concern from physicians, nurses, and administrators about the safety and costs of IV insulin. Originally, each unit developed its own insulin protocol, resulting in a number of different approaches to insulin use within our institution. However, after van den Berghe and colleagues<sup>7</sup> reported in 2001 that intensive insulin therapy and control of blood glucose to <110 mg/dL reduced morbidity and mortality among patients in surgical intensive care, insulin protocols were standardized across the hospital. A standardization committee was composed of a clinical pharmacist, a nurse practitioner, an endocrinologist, a surgeon, and an anesthesiologist. The most difficult and controversial decision that the committee faced was the seemingly simple decision about the concentration of insulin to use. Before the attempt at standardization, the insulin concentration used in surgery was different from the concentrations used in other settings. At our institution, ~150 patients are receiving IV insulin at any given time.

The insulin infusion protocol that we developed uses a series of 5 insulin administration algorithms (Table).<sup>8</sup> The initial infusion rate is selected on the basis of the patient's insulin resistance and is subsequently adjusted as shown in the table. Most patients begin at columns 1 or 2, and no patient begins at columns 4 or 5. Patients may move from one

algorithm to another as required: those who are not meeting glycemic targets with one algorithm move up to a more aggressive insulin treatment schedule, and those with large decreases in blood glucose may move down. The use of this protocol to adjust the insulin infusion rate is illustrated in Figure 3.<sup>4</sup> The patient in this example had an initial glucose value of 180 mg/dL, and an infusion rate of 4 U/h was selected. One hour later, the patient's glucose concentration had dropped to 100 mg/dL. If the patient continued on column 3, the infusion rate would be reduced to 1 U/h. However, as a result of the large drop in plasma glucose between evaluations, a more conservative insulin rate was selected. The patient was shifted down to column 2, and a new infusion rate of 0.5 U/h was selected. Similarly, a patient with persistently high glucose values despite increasing infusion rates would be moved up to a more intensive algorithm. This infusion protocol in some ways mimics the release of insulin by normal pancreatic  $\beta$ -cells, which continue to increase insulin production as long as the plasma glucose concentration remains elevated. Using an algorithm similar to this one, we have found that patients in critical and non-critical care settings are less likely to develop hyperglycemia or hypoglycemia than are historical control patients from our institution.<sup>9</sup>

Experience with this protocol has taught us several lessons. Health care providers need to agree about glycemic targets and philosophies of insulin use. Each group of health

**Table.** Insulin infusion rates for postoperative glycemic management in patients undergoing heart surgery.

Column 1*		Column 2†		Column 3‡		Column 4§		Column 5	
BG, mg/dL	U/h	BG, mg/dL	U/h	BG, mg/dL	U/h	BG, mg/dL	U/h	BG, mg/dL	U/h
		<100	Off	<100	Off	<100	Off	<100	Off
<120	Off	100–119	0.5	100–119	1.0	100–119	1.0	100–119	1.0
120–149	0.5	120–149	1.0	120–149	1.5	120–149	2.0	120–149	2.0
150–179	1.0	150–179	1.5	150–179	2.0	150–179	3.0	150–179	4.0
180–239	1.5	180–239	2.0	180–209	3.0	180–209	4.0	180–209	8.0
				210–239	4.0	210–239	6.0	210–239	12.0
240–299	2.0	240–299	3.0	240–269	5.0	240–269	8.0	240–269	16.0
				270–299	6.0	270–299	10.0	≥270	20.0
300–359	2.5	300–359	4.0	300–329	7.0	300–329	12.0		
				330–359	8.0	330–359	14.0		
≥360	3.0	≥360	6.0	≥360	12.0	≥360	16.0		

BG = blood glucose.

\*For patients whose estimated rate is ≤1.0 U/h for maintenance.

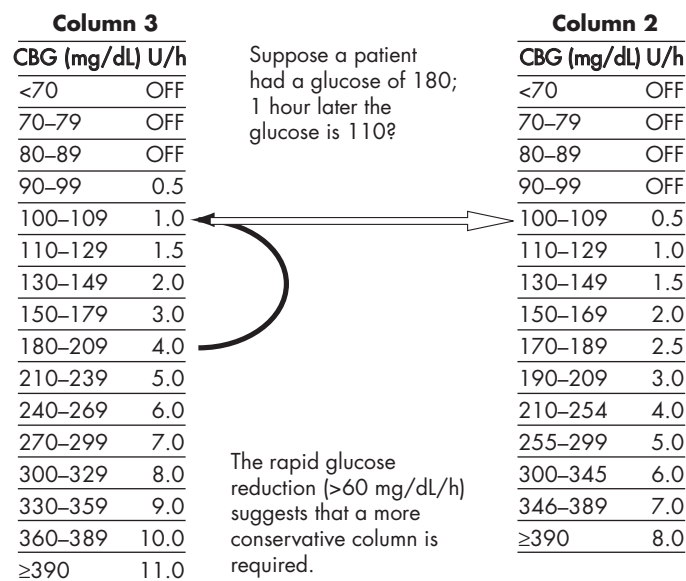
†For patients whose estimated rate is 1.1–1.5 U/h for maintenance; most patients start here.

‡For patients whose estimated rate is 1.6–2.0 U/h for maintenance and for patients in whom column 2 has failed; some post-heart surgery patients, insulin-requiring patients who use >80 U/d, and corticosteroid-treated patients start here.

§For patients whose estimated rate is >2 U/h for maintenance and in whom column 3 has failed; no patient starts here.

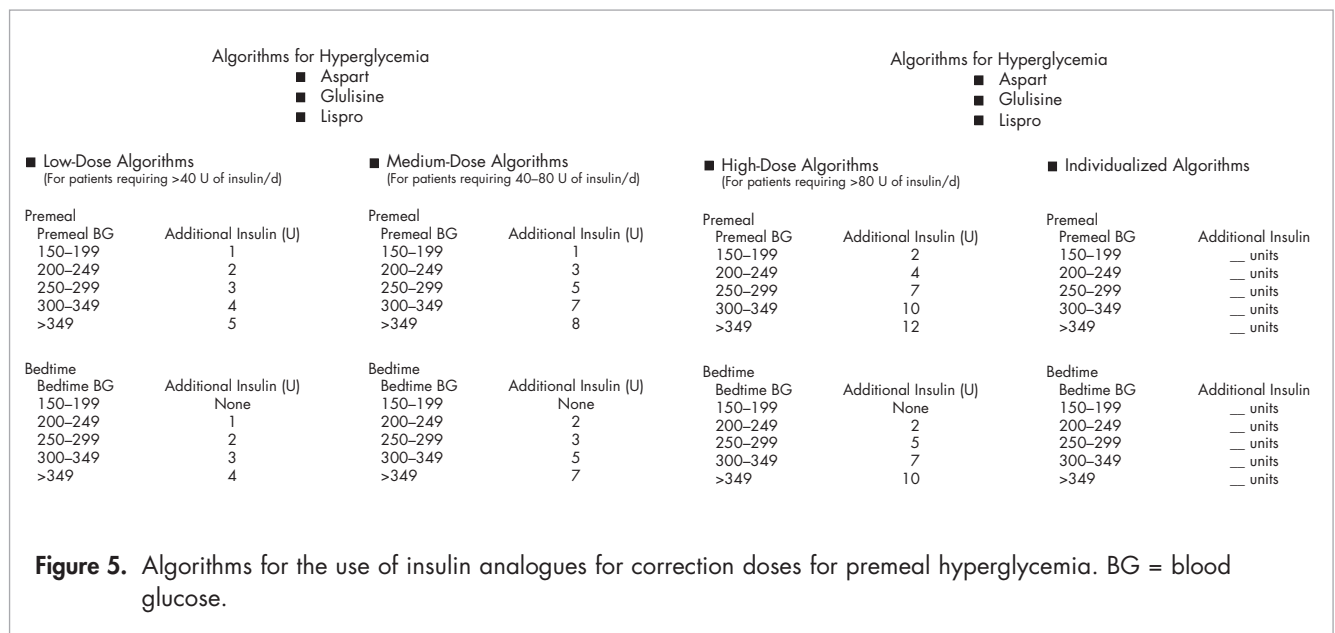
||For patients whose estimated rate is ≥4 U/h for maintenance and in whom column 4 has failed; candidates include patients receiving high-dose corticosteroids or patients with intra-aortic balloon pumps; no patient starts here.

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**Figure 3.** Use of an insulin infusion protocol to adjust a patient’s insulin infusion rate. CBG = calculated blood glucose.





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