Changes in Nerve Conduction Velocity After Six Weeks of Glucoregulation With Portable Insulin Infusion Pumps

ANGEL PIETRI, ALBERT L. EHLE, AND PHILIP RASKIN

SUMMARY
Near normal glucoregulation was maintained in 10 patients with insulin-dependent (type I) diabetes mellitus for 6 wk with preprogrammed continuous subcutaneous insulin infusion using a portable battery-powered infusion pump (CSII). This form of therapy resulted in a statistically significant increase in motor nerve conduction velocity in the median and peroneal nerves compared with baseline values. There was no significant change in the motor nerve conduction velocity in the ulnar nerve or in the sensory nerve conduction studies. No changes occurred in five additional patients studied in similar fashion while on a conventional insulin regimen. These results suggest that the prevention of sustained hyperglycemia with CSII could theoretically result in the prevention of diabetic neuropathy. However, only long-term studies of CSII will provide the information necessary to determine the clinical relevance of the findings. DIABETES 29:668–671, August 1980.

The role of hyperglycemia in the pathogenesis of diabetic microvascular disease has not yet been proved.1 Since most diabetic patients receiving conventional, intermittent subcutaneous insulin injections are hyperglycemic for a major portion of each day,2,3 it is difficult to define the role of hyperglycemia in the development of diabetic complications.

The recent development of portable "open-loop" insulin infusion pumps has made possible the maintenance of normal or near-normal 24-h plasma glucose profiles,3–7 allowing correction of certain of the metabolic and endocrine abnormalities found in diabetics receiving insulin by conventional methods.7–10 There is as yet no evidence that this improved level of glycemic control has any effect on the progression of microvascular diabetic complications.

In this communication we report improvement in motor nerve conduction velocity in type I diabetics after 6 wk of continuous subcutaneous insulin infusion (CSII) delivered with a portable insulin pump. No changes occurred in diabetic patients treated with conventional insulin delivery methods over a similar period of time.

METHODS
Ten patients with typical type I (insulin-dependent) diabetes mellitus of 5-yr duration or longer (mean age, 15.8 ± 2.5 yr) were studied. Four of the patients had clinically evident diabetic neuropathy, two had symptoms typical of the carpal tunnel syndrome, and the other two had mild polyneuropathy with painful paresthesia of the feet.

All patients were admitted to the General Clinical Research Unit of Parkland Memorial Hospital and placed on a metabolic diet consisting of 45% carbohydrate, 35% fat, and 20% protein. The meal plan and CSII protocol has been previously described.7

With each patient receiving his or her usual daily dose of subcutaneous insulin, the initial baseline studies were performed. These studies included a 24-h glucose profile, measurement of glycosylated hemoglobin, and the nerve conduction tests. No attempt was made to achieve optimal control on conventional treatment. The Auto-Syringe pump model AS-2C (Auto-Syringe, Inc., Hooksett, New Hampshire) was used in all patients but one; that patient was treated with the Mill-Hill infuser (Muirhead Ltd., Beckenham, Kent, England).

All patients were hospitalized for at least the first 2 wk of CSII therapy, after which they were sent home and followed as outpatients. While at home they were required to adhere to their diabetic diet and to monitor their capillary blood glucose levels several times each day. Capillary blood was obtained by finger stick and the glucose level measured on the Ames Eyetone or Dextrometer.1 All managed to continue

From the University of Texas Health Science Center at Dallas, Southwestern Medical School, and the Dallas Veterans Administration Medical Center, Dallas, Texas.

Address reprint requests to Philip Raskin, M.D., University of Texas Health Science Center at Dallas, 5323 Harry Hines Blvd., Dallas, Texas 75235.

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with their usual daily activities, returning to work or to school. Most reported a marked increase in their feeling of well-being after institution of CSII. They were readmitted to the Clinical Research Unit periodically for reevaluation, during which time another profile was done. All studies were repeated after 2 and 6 wk of treatment.

Blood samples for the 24-h glucose profile were obtained at hourly intervals from 0700 to 2300 and then at 2-h intervals from 2300 to 0700 through an indwelling 19-gauge butterfly needle placed in a large forearm vein. The glucose was measured immediately on a Beckman glucose analyzer. Total glycosylated hemoglobin was determined by ion exchange chromatography using a prepacked microparticle (Quik-Column, Helena Laboratories, Beaumont, Texas).

An additional 5 type I diabetic patients (13 ± 2 yr duration) who served as controls were also studied. Each underwent the nerve conduction studies on three occasions (baseline, 2 wk, and 6 wk) while on their usual daily dose of intermittent subcutaneous insulin. Before the nerve conduction studies at the baseline and 6-wk time points, a blood sample was drawn for measurement of total glycosylated hemoglobin.

The motor nerve conduction velocities were measured in the right median and ulnar nerve forearm segments and in the peroneal nerve in the right lower extremity. In the upper extremity the distal stimulating electrodes were located 1.5 cm proximal to the palmar crease with an electrode spacing of 2 cm. For the median nerve a proximal electrode was placed in the antecubital fossa, and for the ulnar nerve proximal stimulation was performed approximately 2 cm distal to the elbow. At the time of initial recording, the distance of the proximal electrode from the distal stimulating site was recorded and this distance was used subsequently to determine the proximal site of stimulation. Latencies were determined to the onset of the surface-recorded muscle action potential.

The peroneal conduction velocity was performed in a similar manner. Proximal stimulation was just distal to the course of the nerve around the head of the fibula. Distal stimulation was performed at the ankle and the distance recorded for subsequent reproducibility. Normal motor nerve conduction velocity is greater than 40 m/s for the peroneal nerve and greater than 50 m/s for the ulnar and median nerves.

The sensory conduction study was performed using the right median nerve. Stimulating ring electrodes were placed at the distal interphalangeal crease of the index finger. The recording electrode was placed over the median nerve at the wrist with the 2-cm spacing and the distal electrode located 1.5 cm from the palmar crease. An averager was used to average 10 responses, and the latency to the negative peak of this sensory-action potential and the peak-to-peak amplitude of the deflection was recorded for all subjects. Skin temperature was measured on the back of the right hand. All measurements were within ±1°C for the studies on each subject.

The Student's t test for paired groups was used for comparison within groups. The t test for nonpaired groups and chi-square analysis was used for comparison between treatment groups.

RESULTS

Table 1 shows the mean 24-h glucose level and total glycosylated hemoglobin values before and after 2 and 6 wk of CSII treatment. The 24-h glucose profile was normal after 2 wk of CSII treatment, and after 6 wk of treatment the glycosylated hemoglobin level had fallen into the normal range, demonstrating the effectiveness of this form of treatment in achieving long-term normal or near-normal levels of glycemia. Also shown in this table are the glycosylated hemoglobin values for those patients studied over a 6 wk period on conventional insulin treatment. Total glycosylated hemoglobin levels were elevated initially and remained high for the period of observation.

Table 2 shows the results of the nerve conduction tests. For those diabetics treated with CSII, the median nerve conduction velocity averaged 50.7 ± 2 m/s before the initiation of CSII and was unchanged at 51.4 ± 0.8 m/s after 2 wk of therapy. However, after 6 wk of CSII, there was a statistically significant increase (P < 0.05) to 53.5 ± 0.8 m/s. A similar significant increase in the motor nerve conduction velocity was seen in the peroneal nerve, which increased from 39.5 ± 1.6 to 41.7 ± 2 m/s at 2 wk (P < 0.05) and to 44.4 ± 1.8 m/s after 6 wk (P < 0.01) of CSII. Of the 30 individual motor nerve conduction tests performed after CSII therapy, 23 improved while conduction slowed in seven instances (Table 3). Motor nerve conduction velocity increased in all but one case in which the initial velocity was abnormal. There were no significant changes in the motor nerve conduction velocity in the ulnar nerve or in the median nerve sensory conduction studies. In those diabetics treated by conventional means, there were no statistically significant differences in the baseline values from those patients treated with CSII, and no significant changes in the nerve conduction studies occurred on repeated testing. In contrast to those patients treated with CSII, motor nerve conduction velocity tended to decrease with time, although this decrease was not statistically significant. Of the 15 individual motor conduction velocities performed, nerve conduction velocity diminished or was unchanged in 10 cases and improved in only 5 (Table 3). This is significantly different from the CSII-treated group (P < 0.01 by chi-square analysis). There was no correlation between the duration of diabetes and the nerve conduction studies.

All 4 patients with clinical neuropathy treated with CSII reported a marked improvement in their symptoms within 6

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TABLE 1
Mean 24-h plasma glucose and glycosylated hemoglobin levels in type I diabetics after either 6 wk of continuous subcutaneous insulin infusion or conventional therapy

<table>
<thead>
<tr>
<th></th>
<th>Plasma glucose (mg/dl)</th>
<th>Glycosylated hemoglobin (%)</th>
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<tbody>
<tr>
<td><strong>CSII</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>214 ± 17*</td>
<td>10.4 ± 0.9†</td>
</tr>
<tr>
<td>2 wk</td>
<td>107 ± 9†</td>
<td>7.3 ± 1†</td>
</tr>
<tr>
<td>6 wk</td>
<td>103 ± 8†</td>
<td>6.0 ± 0.4†</td>
</tr>
<tr>
<td><strong>Conventional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>—</td>
<td>10.1 ± 0.9</td>
</tr>
<tr>
<td>6 wk</td>
<td>—</td>
<td>9.5 ± 0.9</td>
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</tbody>
</table>

* Mean ± SEM.
† P < 0.01 by paired analysis.

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wk. However, there were no striking differences between changes in the motor nerve conduction velocities in this subset of patients as compared with the groups without symptoms.

**DISCUSSION**

This study clearly shows that the improved glucoregulation obtained with CSII has an effect on motor nerve conduction velocity. Both the median and peroneal nerves showed statistically significant increases in conduction velocities after only 6 wk of treatment with CSII as compared with values obtained in these patients before institution of CSII. There was also a small improvement in the peroneal nerve at 2 wk. We showed no effect on conduction velocities in the ulnar nerve or in sensory function. In contrast, in patients studied in a similar fashion while on a conventional insulin regimen, resulting in persistent elevation of total glycosylated hemoglobin levels, motor nerve conduction velocities tended to decrease. However, these changes were not statistically significant.

These data fit well with those of Greene et al.11 who showed that in rats with streptozotocin-induced diabetes, significant decreases in motor nerve conduction velocities occur within several weeks of the induction of diabetes. These abnormalities in motor nerve conduction velocity could be corrected with insulin treatment. However, exquisite diabetic control was required before a complete return to normal conduction velocity occurred.

These data, although exciting, must be viewed cautiously. While the methods used to study nerve conduction velocity are well established, they provide only a limited evaluation of the overall function of peripheral nerves. Motor nerve conduction studies provide only information about the fastest conducting fiber population at the time of study. Sensory conduction studies, while reflecting a different fiber population, also examine only the function of large myelinated axons. While the amplitude of the potential can provide some indication of the number of fibers present, the low signal-to-noise ratio of this potential makes detection of small changes difficult. Other factors, such as the degree of dispersion of conduction velocities, also affect amplitude.

Although most of our patients had no clinical suggestion of diabetic neuropathy, all 4 who did noted a marked improvement in their symptoms. One must ask what these findings mean in relation to the long-term development of diabetic neuropathy. The small changes we observed could have nothing to do with long-term complications, but merely reflect a reversible effect due to reduction in the plasma glucose levels. Graf et al. showed a correlation between the level of hyperglycemia and the slowing of motor nerve conduction velocity in maturity-onset diabetics.12 The fact that the 24-h glucose profile was normal after 2 wk of CSII, yet the conduction velocity in the median nerve was unchanged from baseline values and that the peroneal nerve showed only a small change, suggests that the improvement in motor nerve conduction velocity that we observed was not due merely to the acute reduction in plasma glucose levels but was the result of a more long-term effect of improved glucoregulation.

It must be remembered that sustained hyperglycemia has been shown to result in postsynthetic glycosylation of many proteins, including hemoglobin, albumin, and the proteins of the lens.18 Perhaps the proteins of nervous tissue are also glycosylated, which could be one of the pathogenic mechanisms for the development of the neurologic complications of diabetes. Prevention of sustained hyperglycemia with CSII could, thus, theoretically result in the prevention of diabetic neuropathy. Only long-term controlled studies of CSII will provide the necessary information to determine the clinical relevance of these findings.

**ACKNOWLEDGMENTS**

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### TABLE 2

Nerve conduction tests in type I diabetics after either 6 wk of continuous subcutaneous insulin infusion or conventional therapy

<table>
<thead>
<tr>
<th></th>
<th>Motor nerve conduction velocity (m/s)</th>
<th>Median nerve sensory</th>
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<tbody>
<tr>
<td></td>
<td>Ulnar</td>
<td>Median</td>
</tr>
<tr>
<td>CSII</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>52.9 ± 1.6*</td>
<td>50.7 ± 1.2</td>
</tr>
<tr>
<td>2 wk</td>
<td>53.9 ± 1.3</td>
<td>51.4 ± 0.8</td>
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<tr>
<td>6 wk</td>
<td>54.2 ± 1.3</td>
<td>53.5 ± 0.8†</td>
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<tr>
<td>Conventional</td>
<td></td>
<td></td>
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<tr>
<td>therapy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>55.8 ± 2.2</td>
<td>53.0 ± 0.9</td>
</tr>
<tr>
<td>2 wk</td>
<td>51.0 ± 1.4</td>
<td>51.7 ± 1.1</td>
</tr>
<tr>
<td>6 wk</td>
<td>53.4 ± 2.3</td>
<td>52.0 ± 1.5</td>
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</table>

* Mean ± SEM.
† P < 0.05 by paired analysis.
‡ P < 0.01 by paired analysis.

* P < 0.01, CSII versus conventional therapy by chi-square analysis.
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REFERENCES