Cutaneous Complications of Chronic Continuous Subcutaneous Insulin Infusion Therapy

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The cutaneous complications that can develop with continuous subcutaneous insulin infusion constitutes a significant concern when using this innovative and highly effective form of treatment for type I diabetes. These complications are twofold, the first being infection with abscess formation at the infusion needle site. Proper hygiene and frequent changing of the infusion site are helpful and effective measures. The second complication is the development of local allergic skin reactions, again at the infusion needle site, even with highly purified pork insulin. These may subside after several weeks on their own but switching insulin preparations also may be helpful. DIABETES CARE 4: 624–626, NOVEMBER–DECEMBER 1981.

Local skin reactions to insulin occur in 15–55% of insulin-treated patients at some time in the course of their treatment. Many of these reactions subside spontaneously, while others require the use of purified pork insulin and antihistaminics.[1–3] With the recent introduction of highly purified pork insulin preparations in this country, it is hoped that these reactions will be less frequent. Over the past two years we have had extensive experience with 20 patients on continuous subcutaneous insulin infusion using portable insulin infusion pumps.[4–6] The purpose of this communication is to report our experience in regard to cutaneous complications in this group. We noted two types of cutaneous complications to CSII. The first is abscess formation at the infusion site. The second is local allergic reactions to insulin. Interestingly, these occurred when using highly purified pork insulin preparations.

METHODS

Our CSII group consisted of 20 insulin-dependent diabetic patients. Their ages ranged from 15 to 42 yr. The duration of CSII treatment ranges from 2 to 22 mo with a mean of 12.6 ± 1 mo. All patients were hospitalized in the General Clinical Research Unit at the Parkland Memorial Hospital, Dallas, Texas. During this time they were oriented to CSII therapy. The protocol for the "orientation" used in our patients has been previously described.[4,5] After variable periods of hospitalization (a minimum of 3 wk) they are followed as outpatients while continuing CSII treatment. They are expected to follow rigid diabetic diets, and measure their capillary blood glucose levels from 3 to 6 times a day in order to monitor their therapy. Capillary blood glucose levels were measured on the Ames Eyetone or Dextrometer (a gift from the Ames Division, Miles Laboratory, Elkhart, Indiana) on blood samples obtained by finger stick. All have been able to follow this program while continuing their normal daily routine. Nine patients were receiving Lilly Iletin II pork insulin (Eli Lilly and Company, Indianapolis, Indiana), 10 were receiving Novo Actrapid pork insulin (Novo Industries, Copenhagen, Denmark), and one was on a less purified insulin preparation. They were instructed to report any abnormal complications to their treatment program.

RESULTS (TABLE 1)

Skin infections. Six patients on seven occasions had evidence of infection at the site of needle insertion. Four of these infections were minor (twice on one patient), resulting in a small area of induration and erythema with no significant accumulation of pus. They responded well to withdrawal of the needle, local heat, and antibiotics. The other three patients developed larger areas of erythema and induration with subcutaneous abscess formation. Cultures done on these three abscesses showed *Staphylococcus aureus.* These required incision and drainage in addition to antibiotic therapy. Initially, we permitted our patients to leave their infusion needle (25-gauge butterfly infusion set) in place for 4–6 days without changing the infusion site. Because of the high frequency of infection, we have stressed the need for careful attention to proper hygiene and care during needle insertion to all of our

TABLE 1
Allergic manifestation during CSII treatment

Patient	History of insulin allergy	Type of insulin Conventional	Type of insulin CSII	Response to Novo Actrapid
R.H.	None	Iletin beef-pork NPH	Iletin II pork	Good
J.G.	None	Iletin beef-pork NPH	Iletin II pork	Good
D.C.	Yes (semi-lente)	Iletin beef-pork NPH	Iletin II pork	Good
M.F.	Yes (beef-pork NPH)	Iletin pork NPH	Iletin II pork	No change
N.L.	Yes (beef-pork NPH)	Iletin pork NPH	Iletin II pork	No change

patients. We have also insisted on more frequent changing of the infusion site (at least every other day) and a change of the needle at the first sign of inflammation. After this change in operating procedure we have had no further skin infections.

Allergic reactions. Five patients developed local skin reactions to insulin during CSII in the form of local induration and erythema at the site of the infusion (Figure 1). These generally appeared 4–8 h after the insulin infusion began in the area. The induration and tenderness persisted 24–36 h after the infusion site was changed.

All five patients who developed these reactions (Table 1) were receiving Iletin insulin preparations before the start of CSII. This insulin preparation accounts for almost 95% of all the insulin sold in the United States. One was using lente insulin and another one was receiving an NPH beef-pork combination. None of these two patients had a previous history of allergic reactions to insulin. A third patient, who also received beef-pork NPH before CSII treatment without any problems, gave a history of previous allergic-type reactions to semi-lente insulin. The other two patients were using Iletin pork NPH due to a previous history of local skin reactions to beef-pork insulin. However, they had no skin reactions to pork insulin.

All five of these patients began CSII treatment using Lilly Iletin II pork insulin. The local skin reactions appeared from 1 day to 3 mo after the start of CSII. All patients who developed these local reactions were then switched to Novo Actrapid insulin. The results of the change in insulin preparation were variable.

In two patients, the skin reactions persisted irrespective of the type of insulin preparation used. These two patients were those who gave a previous history of allergic skin reactions to beef-pork NPH. Treatment with oral Benadryl gave them partial relief. Their reactions became less marked and gradually disappeared after several weeks. One of these patients still experiences occasional induration at the injection site. Conversion to the Novo insulin preparation resulted in an immediate cessation of the skin reaction in all three of the remaining patients. None have had a recurrence. One of these patients was rechallenged with Iletin II pork insulin while under close supervision to see if the disappearance of the skin reaction was due to the change of insulin or if it was merely coincidental. On rechallenge, the patient again developed an area of erythema, induration, and tenderness at the site of the insulin infusion.

DISCUSSION

The use of CSII in the treatment of insulin-dependent diabetes mellitus is a major advance. Most investigators who have had experience with it report long-term normoglycemia and improvement in many metabolic and other parameters not generally attained with usual forms of treatment.[4–9] Surprisingly, untoward ef-

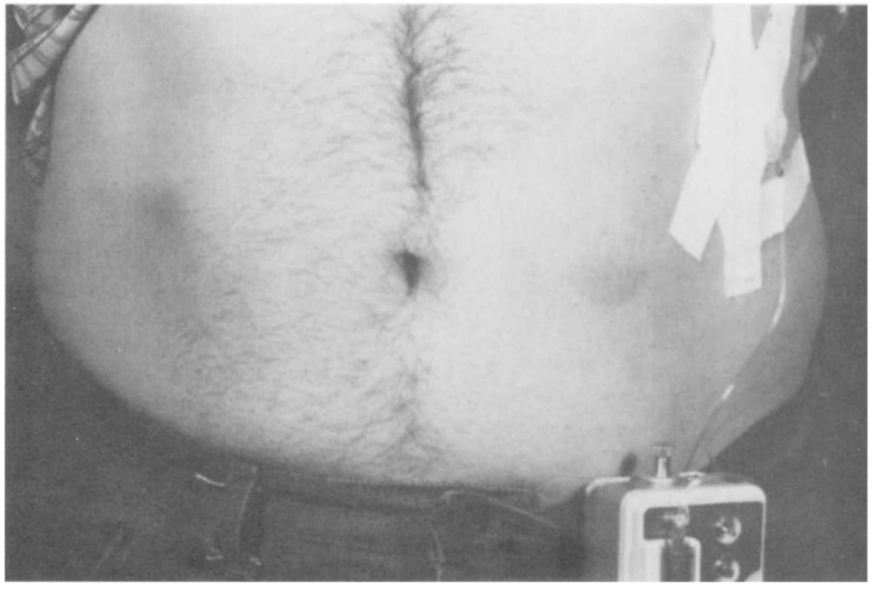

FIG. 1. Appearance of local skin reaction to purified pork insulin during continuous subcutaneous insulin infusion. Note the local induration and erythema at the sites of insulin infusion.

fects of this form of treatment have been minimal. Cutaneous complications from CSII have not as yet been reported. In our experience, these represent a significant problem which must be dealt with as the use of CSII proliferates.

The incidence of skin reactions in our patients with CSII therapy is fairly high. The most worrisome of the two types of cutaneous complications is infection with abscess formation. Although only 3 of our 20 patients have had significant infections, this could become a problem when using CSII on a large scale. However, this problem has been minimized with the frequent change in injection site and careful attention to proper hygiene. We believe this to be a reasonable approach to prevent infection at the infusion site.

We do not consider the local allergic manifestations to have occurred more frequently than might be expected. Surprisingly some of our patients without previous history of allergic manifestations with beef and pork insulin mixtures developed allergic skin reactions when switched to a highly purified pork insulin preparation. Although this may be a coincidence, we have to consider the possibility that CSII facilitates the development of local allergic skin reactions. The mechanism for this obvious speculation is unknown.

Another interesting aspect of this problem is that in some patients these skin reactions disappeared after the patient was switched from one form of highly purified pork insulin to another. One patient who was rechallenged with the Lilly purified pork preparation after his local skin reaction cleared up with the use of the Novo preparation again developed a skin reaction. In all patients whose skin reaction cleared up, the improvement occurred when they were switched from the Lilly to the Novo preparation. It is claimed that Iletin II contains less than 10 parts per million of impurities while Actrapid is said to have less than 1 part per million. We do not know if this accounts for the difference we observed between the two insulin preparations. Another possibility is that each insulin preparation may contain different types of additives used in preventing insulin polymerization, which might enhance local skin reactions.

Even though we have not as yet had this experience, it is also conceivable that there will be patients who develop local skin reactions to the Novo insulin preparation that clear up when they are switched to Iletin II. In any case, if patients develop local allergic skin reactions while using one form of highly purified pork insulin, it seems reasonable to try another form of purified insulin before instituting other measures of treatment.

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REFERENCES

[1] Arkins, J. A., Engbring, N. H., and Lennon, E.: The incidence of skin reactivity to insulin in diabetic patients. J. Allergy 33: 69–72, 1962.

[2] Lamkin, N., Lieberman, P., Hashimoto, K., Morohashi, M., and Sullivan, P.: Allergic reactions to insulin. J. Allergy Clin. Immunol. 58: 213–23, 1976.

[3] Kahn, C. R., and Rosenthal, A. S.: Immunologic reactions to insulin: insulin allergy, insulin resistance, and the autoimmune insulin syndrome. Diabetes Care 2: 283–95, 1979.

[4] Raskin, P., Pietri, A., and Unger, R. H.: Changes in glucagon levels after four to five weeks of glucoregulation by portable insulin infusion pumps. Diabetes 28: 1033–35, 1979.

[5] Pietri, A., Ehle, A., and Raskin, P.: Changes in nerve conduction velocity after six weeks of glucoregulation with portable insulin infusion pumps. Diabetes 29: 668–71, 1980.

[6] Pietri, A., Dunn, F., and Raskin, P.: The effect of improved diabetic control on plasma lipid and lipoprotein levels: a comparison of conventional therapy and continuous subcutaneous insulin infusion. Diabetes 29: 1001–1005, 1980.

[7] Tamborlane, W. V., Sherwin, R. S., Genel, M., and Felig, P.: Restoration of normal lipid and amino acid metabolism in diabetic patients treated with a portable insulin infusion pump. Lancet 1: 1258–61, 1979.

[8] Pickup, J. C., Keen, H., Parson, J. A., Alberti, K. G. M. M., and Rowe, A. S.: Continuous subcutaneous insulin infusion: improved blood-glucose and intermediary-metabolite control in diabetics. Lancet 1: 1255–57, 1979.

[9] Tamborlane, M. W., Sherwin, R. S., Koivisto, U., Hendler, R., Genel, M., and Felig, P.: Normalization of growth hormone and catecholamine response to exercise in juvenile-onset diabetic subjects treated with a portable insulin infusion pump. Diabetes 28: 785–88, 1979.