Use of Premixed Insulin Among the Elderly

Reduction of errors in patient preparation of mixtures

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OBJECTIVE — To evaluate the accuracy of elderly patients in their mixing of regular and intermediate insulins, to assess the safety and efficacy of premixed insulins compared with extemporarily mixed insulins, and to determine patients' preferences.

RESEARCH DESIGN AND METHODS — We conducted a crossover multicenter study of 5 mo duration. Premixed insulins and patient-mixed, human biosynthetic (rDNA) insulins were used among 64 insulin-treated patients with NIDDM. After a 4-wk run-in period, eligible patients were randomly assigned to treatment 1 (extemporarily mixed insulins) or treatment 2 (premixed insulins) for 8 wk. After that period, the two treatments were crossed for an additional 8-wk period. A blood glucose profile was recorded monthly and HbA_{1c} was measured at the beginning and at the end of each treatment period. An in vitro skills test was performed to assess the accuracy and reproducibility of the patient preparation of insulin doses, and a questionnaire was used to determine their personal preferences for premixed versus extemporarily mixed insulin.

RESULTS — In our study, the quality of the metabolic control was the same whether patients used self-mixed or premixed insulin. The differences in blood glucose profiles and HbA_{1c} were negligible between type and periods of treatment. The overall number of hypoglycemic episodes increased during the trial in both groups, but the difference between treatments was not significant.

The in vitro skills test, however, indicated that the accuracy in the preparation of insulin doses was significantly higher when patients aspirated from one vial compared with preparation from two vials ($P < 0.001$). The CVs were 3.7% when drawing up a single dose and 5.0% when preparing a mixture, but the ranges were rather elevated (0.1–20.7 and 0.6–35.8%, respectively). Forty-two patients described the preparation of their daily insulin dose as very easy and 21 described it as easy when using premixed insulins versus 11 and 43, respectively, when using extemporarily mixed insulins ($P < 0.001$).

CONCLUSIONS — While the quality of the metabolic control was the same whether patients used self-mixed or premixed insulin, the in vitro skills test indicated that insulin preparation by elderly patients is highly inaccurate. In some patients, a modification of the contents of the insulin is likely to occur in a few days. The use of premixed insulins should lessen the errors that occur in mixing insulins and from the contamination of the second insulin vial. Draw-up errors could partially account for the lack of improvement of glucose control during the period when patients received premixed insulins. A longer observation period probably is needed to assess appreciable changes in the quality of diabetes control.

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rDNA, RECOMBINANT DNA; NIDDM, NON-INSULIN-DEPENDENT DIABETES MELLITUS; CV, COEFFICIENT OF VARIATION; BMI, BODY MASS INDEX; ANOVA, ANALYSIS OF VARIANCE; LDL, LOW-DENSITY LIPOPROTEIN; HDL, HIGH-DENSITY LIPOPROTEIN.

In the last decade, problems of unsatisfactory metabolic control have been reported among diabetes patients who receive mixtures of short-acting and intermediate-acting insulin. Their problems have been attributed to *1*) inaccurate insulin mixing and lack of reproducibility of insulin dosage (1–5), *2*) erratic absorption of intermediate-acting insulins (6–7), and *3*) modifications of the kinetics of rapid insulin because of an excess of the intermediate insulin medium (8).

The use of fixed-ratio, premixed insulins has been suggested as a means to ameliorate patient compliance and accuracy in insulin mixing, especially among elderly patients (8–12), who are likely, to have difficulty in mixing insulins because of visual and motor impairment (3–5).

The objectives of our study were *1*) to evaluate the accuracy of elderly patients in mixing regular and intermediate insulins (measured using ^{125}I-labeled solutions), *2*) to assess safety and efficacy of premixed insulins compared with extemporarily mixed insulins in combinations with the same ratio of rapid to intermediate insulins, and *3*) to determine patients' preferences.

RESEARCH DESIGN AND METHODS

— Premixed insulins (with short- to intermediate-acting ratios ranging from 10/90 to 40/60) and patient-mixed, human biosynthetic (rDNA) insulins (Humulin, Lilly, Firenze, Italy) have been used in 64 insulin-treated patients with NIDDM participating in a crossover multicenter study of 5 mo duration. The mean age was 66.8 ± 5.7 yr; 30 were men and 34 were women. The average duration of diabetes was 15.7 ± 8.5 yr (range, 1–37 yr), and the mean BMI was 26.8 kg/m^2 (±3.8 SD).

A blood glucose profile was recorded monthly. HbA_{1c} was measured at the beginning and at the end of each treatment period. The values of HbA_{1c} were standardized within and among

participating centers, according to the Kroc Collaborative Study Group's criteria (13).

All patients were on a low-fat, high-carbohydrate diet and maintained their dietary habits and levels of physical activity throughout the study.

Careful records of hypoglycemic episodes were kept by the patients and reported at each medical visit. At the end of each treatment period, patients were asked to answer a questionnaire on the preparation of their daily insulin dose (e.g., degree of difficulty, number of errors per period). At the end of the study, the patients expressed their opinions on the insulin preparation they would prefer to use in the future (self-mixed versus premixed). Informed consent was obtained from all patients.

Assessment of accuracy and reproducibility in preparing insulin doses

To quantify the ability of the individuals in this study to prepare insulin mixtures, each patient used 6 Microfine (Becton Dickinson, Milan, Italy) U-40 syringes (which have no dead space), a 10 mL vial of a solution containing ^{125}Iodine and isotonic saline (vial A), and three insulin vials filled with 1.5 mL of saline (vials B1, B2, and B3). To test the accuracy and reproducibility of the preparation of a 20-IU dose, each patient aspirated three times, consecutively, 0.5 mL of the iodinated solution from vial A. Syringes 4–6 were used to test a 40-U mixture in the following manner: A volume of 0.5 mL was withdrawn from the ^{125}I-saline solution (vial A) followed by 0.5 mL from vials B1, B2, and B3. The volume in each syringe provided an estimate of the accuracy of fluid withdrawal from the vials. The amount of radioactivity found in vials B1, B2, and B3 reflected the amount of contamination from vial A.

Statistics

Student's t tests for paired and unpaired data, the χ^2 test, and crossover ANOVA were used to test the significance of the differences.

RESULTS

Blood glucose and HbA_{1c}

The differences in blood glucose profiles and HbA_{1c} were negligible between type and periods of treatment. At crossover analysis, only the after-dinner glucose value was significantly lower after treatment with extemporarily mixed insulins than after premixed insulins ($P < 0.05$). The difference was attributable to the treatment and not to a period or sequence effect.

Serum lipids

Total cholesterol, LDL cholesterol, and triglyceride levels changed slightly during the observation periods. Only the HDL cholesterol fraction increased after both treatments, and the crossover analysis excluded effects of the treatment on the change of HDL cholesterol.

Hypoglycemic episodes

The overall number of episodes increased during the trial in both groups, but the difference between treatments was not significant. The daily insulin requirement remained the same for all over the study period. Of the four Humulin R:I (short-acting to intermediate insulin) ratios available for use in the trial, the 10/90 ratio was used in <10% of the cases, the 20/80 in ~20%, whereas the 30/70 and 40/60 R:I insulins were each used in ~35% of the patients.

Bias in the preparation of insulin injections

The accuracy in preparation of insulin doses was significantly higher when patients aspirated from one vial compared with preparation from two vials ($P <$ .001). The CVs were 3.7% when drawing up a single dose and 5.0% when preparing a mixture, but the ranges were rather elevated (0.1–20.7 and 0.6–35.8%, respectively).

The volume of the contents unintentionally transferred from the first vial to the second in insulin mixture preparation was 1.3 ± 1.5%, with an extreme range of 7.11%.

Questionnaire on difficulties and errors in the preparation of insulin mixtures

In our study, 42 patients described the preparation of their daily insulin dose as very easy and 21 described it as easy when using premixed insulins versus 11 and 43, respectively, when using extemporarily mixed insulins ($P < 0.001$). The number of errors that each patient reported during the preparation of insulin mixtures resulted significantly in favor of premixed insulins (χ^2 trend $P < 0.02$). The majority of patients (94%) also stated their preference for the use of premixed insulins in the future.

CONCLUSIONS — In our study, the quality of the metabolic control was the same whether patients used self-mixed or premixed insulin. The number of hypoglycemic episodes increased from the run-in period to the treatment period in both groups, probably because of higher dietetic compliance and/or the research of a tight glycemic control. The number of errors and the difficulties in the preparation of insulin were significantly higher when patients used self-mixed insulin, and results of the questionnaire indicated a patient preference for premixed insulins.

The in vitro skills test revealed that insulin preparation by elderly patients is highly inaccurate, and that their skill level is lower in mixing of insulins than in drawing up of a single dose. Furthermore, we have shown that the magnitude of error was significantly higher when the same patient mixed insulins from two vials, and that contamination of the second vial was rather frequent (and in some cases remarkable); in some patients, a modification of the content of an insulin vial is likely to occur in a few days. The percentage error was lower than described previously in older

subjects (1), possibly because subjects with visual problems were excluded from our study.

Use of premixed insulins should lessen the errors that occur in mixing insulins and contamination of the second insulin vial, whereas errors in drawing up insulin are likely to decrease with the use of injection devices such as pens. Such draw-up errors could account partially for the lack of improvement of glucose control during the period when patients received premixed insulins. Finally, a longer observation period probably is needed to assess appreciable changes in the quality of diabetes control.

References

1. Kesson CM, Baillie GR: Do diabetic patients inject accurate doses of insulin? (Letter) *Diabetes Care* 4:333, 1981
2. Corcoran JS, Yudkin JS: How inaccurate is insulin mixing? Patient variability and syringe dead space effect. *Diabetic Med* 2:131–33, 1985
3. Puxty JAH, Hunter DH, Burr WA: Accuracy of insulin injection in elderly patients. *Br Med J* 287:1762, 1983
4. Berne C, Eriksson G, Lundgren P: How accurate are insulin mixtures prepared by the patient? *Diabetes Care* 9:23–26, 1986
5. Bell DS, Clements RS Jr, Perentesis G, Roddam R, Wagenknecht L: Dosage accuracy of self-mixed vs. premixed insulin. *Arch Intern Med* 11:2265–69, 1991
6. Henriksen JE, Vaag A, Hansen IR, Lauritzen M, Djurhuus MS, Beck-Nielsen H: Absorption of NPH (isophane) insulin in resting diabetic patients: evidence for subcutaneous injection in the tight as the preferred site. *Diabetic Med* 8:453–57, 1991
7. Lauritzen T, Pramming S, Gale E, Deckert T, Binder C: Absorption of isophane insulin and its clinical implications. *Br Med J* 285:159–62, 1982
8. Nolte MS, Poon V, Grodsky GM, Forsham PH, Karam JH: Reduced solubility of short-acting soluble insulins when mixed with longer-acting insulins. *Diabetes* 32:1177–81, 1983
9. Schlichtkrull J: New insulin crystal suspensions with various timing of action and containing no added zinc. In *Diabetes Mellitus III, IDF Congress* 1958. Oberdisse K, Jahnke K, Eds. Stuttgard, Germany, George Thieme, 1959, p. 737–45
10. Corcoran JS, Yudkin JS: A comparison of premixed with patient-mixed insulins. *Diabetic Med* 6:246–49, 1986
11. Cucinotta D, Mannino D, Lasco A, Di Cesare E, Musolino C, Alessi R: Premixed insulins at ratio 3/7 and regular + isophane insulin at mixing ratios from 2/8 to 4/6 achieve the same metabolic control. *Diabete Metab* 17:49–54, 1991
12. Haupt MH, Etti H, Bamber E, Hilgenfeld J: Clinical trial with semi-synthetic human insulin in fixed combination and individual mixture of intermediate- and short-acting preparations. *Med Klin* 80: 131–35, 1985
13. The Kroc Collaborative Study Group: Blood glucose control and the evolution of diabetic retinopathy and albuminuria. *N Engl J Med* 311:365–72, 1984