

# Treatment of Insulin Hypoglycemia in Diabetic Campers

## A Comparison of Glucagon (1 and 2 mg.) and Glucose

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### SUMMARY

The change in concentration of blood glucose in hypoglycemic diabetic boys and girls after treatment with glucagon (1 or 2 mg. given subcutaneously) or glucose (20 gm. orally) was determined. Following glucagon, at both dose levels, the concentration of blood glucose was increased after five minutes, was within the physiologic range by fifteen minutes and did not return to hypoglycemic levels during one hour. Symptoms of hypoglycemia were relieved in ten minutes in each instance. The time course of change in the concentration of blood glucose was identical at both dose levels of glucagon. With glucose orally a similar response was noted during the first fifteen minutes but the concentration of blood glucose was lower at thirty and at sixty minutes. It is concluded that the hyperglycemic response to glucagon in hypoglycemic diabetic boys and girls was identical with a 1 or 2 mg. dose.

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The prompt and predictable increase in the concentration of blood glucose following glucagon administration to hypoglycemic subjects has been well documented. This response to glucagon has been observed in normal individuals,<sup>1,2</sup> in patients with mental disease treated with large doses of insulin to induce coma,<sup>3-6</sup> and in patients with diabetes mellitus during spontaneous,<sup>7-12</sup> and insulin-induced,<sup>9</sup> hypoglycemia.

Doses from 0.33 mg. to 2.0 mg. have been successfully used to reverse hypoglycemia in children and in adults. Schulman and Greben<sup>8</sup> showed that the hyperglycemic effect of glucagon in schizophrenic patients made comatose by large doses of insulin was related to the dose of glucagon, being maximal with 0.2 mg. per kg. Evidence relating response to dose is less clear in the case of the hypoglycemic diabetic treated with glucagon. Eli Lilly and Company recommends a dose of 1 mg. However, several authors<sup>9-11</sup> have suggested, without

supporting evidence, that hypoglycemia in the diabetic be treated with a 2 mg. dose. Previous studies at this camp indicated a prompt response to this dose.<sup>12</sup> Because of the importance of a prompt reversal of hypoglycemia, and the known safety of glucagon, it seemed desirable to determine whether the response to 1 and/or 2 mg. of glucagon differed. The purpose of this study was to determine the time course of change in concentration of blood glucose of hypoglycemic diabetic boys and girls treated with: (A) 1.0 mg. of glucagon, (B) 2.0 mg. of glucagon, and (C) 20 gm. of glucose.

### METHODS AND MATERIALS

Subjects were diabetics whose disorder varied from one to eleven years in duration attending Camp Immokalee, Florida's Summer Camp for Diabetic Boys and Girls. Those suspected of being hypoglycemic were brought to an infirmary; the concentration of blood glucose was estimated by a rapid screening method.\* Campers with a concentration of blood glucose of less than 50 mg. per 100 ml. were treated in rotation by Method A (1.0 mg. glucagon), B (2.0 mg. glucagon), or C (20 gm. of glucose given orally as 40 ml. of a 50 per cent solution containing lemon flavoring). If a hypoglycemic camper had been treated previously he was purposely given another form of treatment. Glucagon at both dose levels was given as a one ml. subcutaneous injection. Venous blood samples were taken before and 5, 15, 30 and 60 min. after treatment. Glucose was determined on 0.1 ml. of venous blood by the method of Dubowski.<sup>12</sup>

### RESULTS

In each instance, an appreciable increase in the concentration of blood glucose was evident within five minutes; by fifteen minutes the glucose concentration

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\*Glucospot, Worthington Biochemical Corporation, Freehold, New Jersey.

TREATMENT OF INSULIN HYPOGLYCEMIA IN DIABETIC CAMPERS

TABLE 1

Effect of glucagon and glucose on concentration of blood glucose during insulin hypoglycemia in diabetic boys and girls\*

| Treatment               | Camper No. | Age years | Sex | Weight kg. | Duration of Diabetes | Insulin* before |        | Time of hypoglycemia | Concentration of blood glucose, mg. per 100 ml. (minutes after treatment) |     |     |     |     |     |
|-------------------------|------------|-----------|-----|------------|----------------------|-----------------|--------|----------------------|---|-----|-----|-----|-----|-----|
|                         |            |           |     |            |                      | Breakfast       | Supper |                      | 0   | 5   | 15  | 30  | 60  |     |
| A.<br>Glucagon<br>1 mg. | 33         | 14        | M   | 46         | 2                    | 60 L            | 15 L   | 1800                 | 50  | 87  | 136 | 180 | 237 |     |
|                         | 15         | 11        | M   | 44         | 4                    | 16 L            | 4 L    | 1745                 | 45  | 50  | 91  | 125 | 77  |     |
|                         | 26         | 14        | M   | 44         | 11                   | 80 L            | 20 R   | 1200                 | 31  | 38  | 69  | 96  | 109 |     |
|                         |            |           |     |            |                      | 80 R            |        |                      |   |     |     |     |     |     |
|                         |            | 21        | 10  | M          | 36                   | 6               | 38 L   | 0                    | 1230  | 35  | 78  | 114 | 127 | 121 |
|                         |            | 47        | 9   | F          | 30                   | 1               | 10 L   | 0                    | 1220  | 45  | 50  | 69  | 91  | 114 |
|                         |            | 54        | 14  | F          | 52                   | 2               | 38 NPH | 0                    | 1152  | 63  | 63  | 91  | 145 | 181 |
|                         |            | 43        | 9   | F          | 35                   | 6               | 14 L   | 0                    | 1214  | 36  | 46  | 91  | 112 | 101 |
|                         |            |           |     |            |                      |                 | 12 UL  |                      |   |     |     |     |     |     |
|                         |            |           |     |            |                      |                 | 12 R   |                      |   |     |     |     |     |     |
|                         |            | 50        | 13  | F          | 51                   | 2               | 42 L   | 0                    | 1615  | 48  | 117 | 90  | 114 | 156 |
|                         |            |           |     |            |                      |                 | 4 R    |                      |   |     |     |     |     |     |
|                         |            |           |     |            |                      |                 | 6 UL   |                      |   |     |     |     |     |     |
|                         |            | 56        | 15  | F          | 50                   | 6               | 26 L   | 0                    | 0725  | 50  | 92  | 96  | 122 | 176 |
|                         | 26         | 14        | M   | 44         | 11                   | 80 L            | 20 R   | 1745                 | 35  | 56  | 99  | 169 | 164 |     |
|                         |            |           |     |            |                      | 80 R            |        |                      |   |     |     |     |     |     |
| B.<br>Glucagon<br>2 mg. | 50         | 13        | F   | 51         | 2                    | 44 NPH          | 6 NPH  | 1115                 | 30  | 67  | 74  | 112 | 114 |     |
|                         |            |           |     |            |                      | 8 R             |        |                      |   |     |     |     |     |     |
|                         | 26         | 14        | M   | 44         | 11                   | 80 R            | 20 R   | 1805                 | 48  | 62  | 123 | 170 | 225 |     |
|                         |            |           |     |            |                      | 80 L            |        |                      |   |     |     |     |     |     |
|                         |            | 31        | 15  | M          | 50                   | 3               | 38 L   | 0                    | 1158  | 39  | 58  | 75  | 103 | 96  |
|                         |            |           |     |            |                      |                 | 12 UL  |                      |   |     |     |     |     |     |
|                         |            | 33        | 14  | M          | 46                   | 2               | 60 L   | 15 L                 | 1220  | 35  | 60  | 128 | 147 | 181 |
|                         |            | 28        | 10  | M          | 43                   | 4               | 32 NPH | 0                    | 1230  | 35  | 40  | 77  | 101 | 75  |
|                         |            | 9         | 12  | M          | 36                   | 1               | 16 NPH | 0                    | 1050  | 51  | 80  | 98  | 98  | 94  |
|                         |            | 63        | 12  | F          | 34                   | 7               | 28 NPH | 0                    | 1225  | 46  | 67  | 86  | 114 | 127 |
|                         |            |           |     |            |                      |                 | 6 R    |                      |   |     |     |     |     |     |
|                         | 21         | 10        | M   | 36         | 6                    | 38 L            | 0      | 1535                 | 45  | 70  | 78  | 131 | 153 |     |
|                         | 54         | 14        | F   | 52         | 2                    | 44 NPH          | 0      | 1023                 | 20  | 38  | 66  | 111 | 123 |     |
|                         | 45         | 9         | F   | 30         | 7                    | 60 L            | 0      | 1735                 | 35  | 38  | 88  | 144 | 138 |     |
| C.<br>Glucose<br>20 mg. | 50         | 13        | F   | 51         | 2                    | 44 NPH          | 6 NPH  | 0950                 | 48  | 58  | 107 | 134 | 115 |     |
|                         |            |           |     |            |                      | 8 R             |        |                      |   |     |     |     |     |     |
|                         | 29         | 14        | M   | 53         | 7                    | 24 NPH          | 18 NPH | 1200                 | 47  | 62  | 87  | 110 | 125 |     |
|                         |            |           |     |            |                      | 5 R             |        |                      |   |     |     |     |     |     |
|                         | 61         | 12        | F   | 54         | 8                    | 44 L            | 15 L   | 1212                 | 47  | 58  | 101 | 128 | 104 |     |
|                         |            |           |     |            |                      | 14 R            |        |                      |   |     |     |     |     |     |
|                         | 54         | 14        | F   | 52         | 2                    | 40 NPH          | 0      | 1050                 | 39  | 58  | 90  | 103 | 75  |     |
|                         |            |           |     |            |                      | 4 R             |        |                      |   |     |     |     |     |     |
|                         | 31         | 15        | M   | 50         | 3                    | 42 L            | 0      | 1235                 | 39  | 44  | 69  | 92  | 44  |     |
|                         |            |           |     |            |                      | 14 UL           |        |                      |   |     |     |     |     |     |
|                         | 21         | 10        | M   | 36         | 6                    | 38 L            | 0      | 1800                 | 40  | 50  | 97  | 132 | 169 |     |
|                         | 26         | 14        | M   | 44         | 11                   | 80 L            | 20 R   | 1200                 | 55  | 77  | 115 | 92  | 54  |     |
|                         |            |           |     |            | 80 R                 |                 |        |                      |   |     |     |     |     |     |
| 47                      | 9          | F         | 30  | 1          | 10 L                 | 0               | 1224   | 54                   | 71  | 107 | 114 | 65  |     |     |
| 33                      | 14         | M         | 46  | 2          | 60 L                 | 0               | 2030   | 54                   | 63  | 84  | 69  | —   |     |     |
|                         |            |           |     |            |                      | 8 UL            |        |                      |   |     |     |     |     |     |
| 61                      | 12         | F         | 54  | 9          | 40 L                 | 0               | 1045   | 19                   | 35  | 47  | 97  | 123 |     |     |
|                         |            |           |     |            |                      | 10 R            |        |                      |   |     |     |     |     |     |
|                         |            |           |     |            |                      | 12 UL           |        |                      |   |     |     |     |     |     |

\*Certain clinical features, the insulin dosage, the hour of hypoglycemia and the concentration of blood glucose after treatment are shown. Insulin is designated: L = Lente, R = Crystalline, NPH = Isophane and UL = Ultralente.

was within the physiologic range (table 1). More variation was noted during the second thirty minutes. Symptoms of hypoglycemia, in each instance, were less after five minutes and were relieved within ten minutes with each type of treatment. The mean concentrations

of blood glucose during the sixty minutes studied were identical after 1 and 2 mg. of glucagon; the mean concentration of glucose in those campers given 20 gm. of glucose was less at 30 ( $p < 0.2$ ) and at 60 ( $p < 0.02$ ) min. than that observed with glucagon (table 2, figure

TABLE 2

Concentration of blood glucose after treatment of insulin hypoglycemia in diabetic boys and girls\*

| Treatment                 | Concentration of blood glucose (mg. per 100 ml.) |           |           |            |             |
|---------------------------|--|-----------|-----------|------------|-------------|
|                           | 0  | 5         | 15        | 30         | 60          |
| A. Glucagon, 1 mg.        | 44<br>± 3  | 68<br>± 8 | 95<br>± 6 | 128<br>± 9 | 144<br>± 15 |
| B. Glucagon, 2 mg.        | 38<br>± 3  | 58<br>± 5 | 89<br>± 7 | 123<br>± 8 | 133<br>± 14 |
| C. Glucose, 20 gm. Orally | 44<br>± 3  | 58<br>± 4 | 90<br>± 6 | 107<br>± 7 | 97<br>± 14  |

\*The mean concentration of blood glucose, and Standard Error of diabetic campers of table 1 are shown.

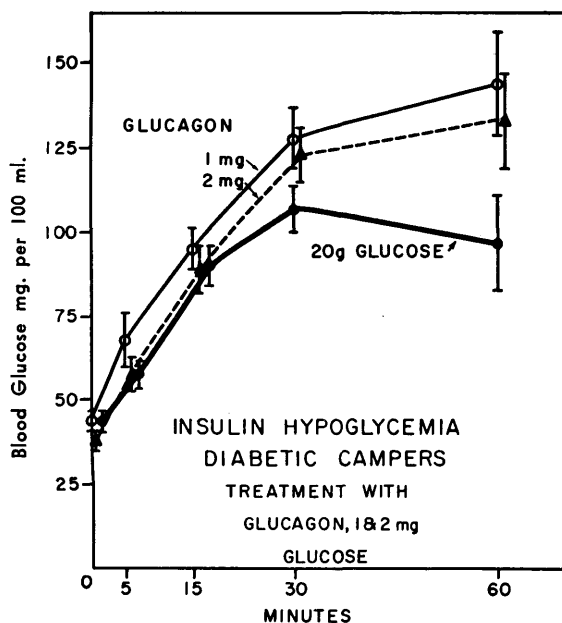


FIG. 1. The concentration of blood glucose (mean ± S. E.) after treatment of insulin hypoglycemia with glucagon (1 and 2 mg.) and glucose.

1). Among hypoglycemic campers who received glucagon, the mean concentration of blood glucose was greater than 100 mg. per 100 ml. after sixty minutes; at sixty minutes one camper who received 1 mg. of glucagon and three who received 2 mg. of glucagon had a concentration of blood glucose of less than 100 mg. per 100 ml. In those given 20 gm. of glucose, four of nine had a blood glucose concentration of less than 100 mg. per 100 ml. at sixty minutes. In the glucose treated group, six of nine had a lower concentration of blood glucose at sixty than at thirty minutes; two (No. 26, No. 31) were hypoglycemic at sixty minutes.

DISCUSSION

It is realized that the time of day with respect to the peak action of the injected insulin, the magnitude of counter-regulatory responses to hypoglycemia, and other factors, may have influenced the response to treatment. The number in each group tended to balance out factors not directly related to treatment. Five campers (Nos. 33, 26, 50, 54 and 21) were treated by all three methods; Camper 26, who received 180 U. of insulin daily, was treated by all three methods, and he received one milligram of glucagon on two occasions. The period up to fifteen or thirty minutes after treatment represented the time during which the concentration of blood glucose was most directly influenced by the treatment.

The response to each of the three forms of treatment appeared to be the same regardless of the hour at which the hypoglycemia occurred, the amount of insulin received, the age of the camper and the duration of diabetes. Others<sup>2,9</sup> have suggested that the change in concentration of blood glucose after glucose was not related to the degree of hypoglycemia or the previous insulin dosage. The hyperglycemic response with one and two mg. of glucagon was not related to the weight of the patient; the dose of glucagon used was from approximately 0.02 to 0.06 mg./kg. Thus, in this study, the hyperglycemic effect was obtained with approximately one tenth the dose used by Schulman and Greben.<sup>3</sup> This difference may be explained by the fact that their patients were deeply comatose after receiving large doses of insulin; furthermore, in Schulman's study even a dose of 0.2 mg./kg. did not produce normoglycemia.

Those results indicate the consistent and predictable hyperglycemic effect of glucagon. The consistency of response during the first thirty minutes confirms that glucagon was promptly absorbed from the subcutaneous site and had an immediate hyperglycemic action. No camper failed to respond and there were no adverse reactions to glucagon.

Elrick and co-workers<sup>9</sup> suggested that glucagon has advantages over glucose for the treatment of hypoglycemia in the patient with diabetes mellitus. Glucagon treatment utilizes endogenous glucose and the hyperglycemia produced is more predictable and rarely as excessive as may occur with a large intake of glucose. An unexpected finding in this study was the failure of 20 gm. of glucose, an amount greater than is usually recommended for symptoms of hypoglycemia,<sup>14</sup> to maintain normoglycemia for sixty minutes. The most significant advantage of glucagon is for the treatment of the unconscious or uncooperative hypoglycemic patient. In a

camp for diabetic boys and girls its use for hypoglycemia prevents feigned reactions<sup>11,12</sup> and provides a practical means of acquainting the young diabetics with glucagon.

## SUMMARIO IN INTERLINGUA

*Tractamento de Hypoglycemia Insulinogene in Juvene Diabeticos Sojornante in un Campo de Vacantia*

Le alteration del concentration de glucosa del sanguine post tractamento con glucagon in administrationes subcutanee de 1 o 2 mg o con glucosa in administrationes oral de 20 mg esseva determinate in pueros e pueras diabetic in stato de hypoglycemia. Post glucagon, a ambe nivellos de dosage, le concentration sanguinee de glucosa esseva augmentate intra cinque minutas; illo attingeva valores physiologic intra dece-cinque minutas; e illo non retornava a nivellos hypoglycemic durante un hora. Le symptomatas de hypoglycemia esseva alleviate in omne caso intra dece minutas. Le curso temporal del alteration in le concentration sanguinee du glucosa esseva identic a ambe nivellos de glucagon. Con glucosa in administration oral, un simile responsa esseva notate durante le prime dece-cinque minutas, sed le concentration de glucosa sanguinee esseva plus basse post trenta e post sexanta minutas. Es concludite que le responsa antihypoglycemic a glucagon in hypoglycemic pueros e pueras diabetic esseva identic in le caso de un dose de 1 mg e in le caso de un dose de 2 mg.

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