Severe Hypoglycemia in Diabetic Patients: Frequency, Causes, Prevention

ANTON F. CASPARIE, M.D., AND LAMMY D. ELVING, M.D.

Over a 12-mo period, the frequency of severe hypoglycemic episodes was measured in a population of approximately 400 (50% type I) diabetic patients treated with insulin. There were 32 severe insulin reactions in 26 patients, a patient-yr incidence of 8%. The major precipitating causes were patients' errors (nine), and too much insulin or a wrong combination (six). In seven cases no cause could be found. For the group as a whole there was clear evidence of overtreatment as measured by insulin doses (0.89 ± 0.43 U/kg/day versus 0.65 ± 0.34 U/kg/day in a convenience group of 100 patients from the same diabetic population [$P < 0.05$]). Furthermore, 6–12 mo after the event the mean insulin dose had decreased from 0.82 ± 0.25 to 0.69 ± 0.27 U/kg/day in the subgroup of 20 hypoglycemic patients that could be followed ($P < 0.001$). The mean HbA_{1c} levels of the hypoglycemic group and the control group differed significantly (8.1 ± 1.3% versus 8.7 ± 1.7%, $P < 0.05$). Six to 12 mo after the reaction, the mean HbA_{1c} level in the follow-up subgroup rose from 8.1 ± 1.3% to 9.1 ± 1.1% ($P < 0.05$). Patients' errors as a cause of the insulin reaction were not only the result of the patients' deficient knowledge but more often of lack of alertness and carelessness. We conclude that it is not possible to prevent all the severe hypoglycemic reactions in diabetic patients. However, besides avoiding overtreatment by the physician, teaching patients to respond more adequately to changing circumstances in daily life or to warning signs could also reduce the incidence of hypoglycemia. DIABETES CARE 1985; 8:141–45.

Hypoglycemia is a continuous threat for the diabetic patient treated with insulin; it can disturb his social life, and, under certain circumstances, be very dangerous. The frequent occurrence of many severe hypoglycemic episodes may in time cause encephalopathy.[1] Meticulous control of diabetes may lead inadvertently to a higher incidence of hypoglycemia. In patients treated with continuous subcutaneous insulin infusion (CSII), death as a result of severe hypoglycemia has been described.[2] For the physician, a severe hypoglycemic event in one of his patients can be frustrating, because the causal factor can be improper insulin therapy or insufficient education of the patient.

We were interested in the frequency and causes of severe hypoglycemic reactions in our diabetic population. During 1 yr we measured its incidence in a population of about 400 patients with type I and type II diabetes mellitus. Our primary goal was to study the different causes in order to identify means for prevention. We have compared our findings with the results of some recent publications on this subject.[3–7]

PATIENTS AND METHODS

The patients in this study are part of an outpatient diabetes clinic that consists of approximately 400 patients treated with insulin, 10 of whom were treated by CSII. This number of 400 patients was estimated by counting all the insulin-using diabetic patients who successively attended our clinic during 3 mo in the middle of 1982. The patients were seen every 2–3 mo or sooner in case of temporary deterioration of diabetes control. About 50% of these patients had type I diabetes. Distinction between type I and type II diabetes mellitus was made on data from medical history and on clinical criteria such as episodes with ketosis and use of oral medication in the past. C-peptide levels were not measured. During 1 yr (1982) all severe hypoglycemic events were recorded. Severe

Downloaded from http://diabetesjournals.org/care/article-pdf/8/2/141/532569/8-2-141.pdf by guest on 19 May 2024

TABLE 1
Individual characteristics of 26 patients with severe hypoglycemia at the moment of the reaction* and 6–12 mo afterward

Patient	Age (yr)	Duration of diabetes (yr)	Type of diabetes	Insulin medication†		Time of hypoglycemia	Insulin dose (U/kg/day)		HbA_{1c} (%)	
				8 a.m.	5 p.m.		During	After	During	After
1	36	23	1	18 SL, 4 A	16 SL, 4 A	12 a.m.	0.57	0.50	9.5	8.0
2	46	11	1	28 L, 8 A	8 A	10 p.m.	0.58	0.58	6.8	8.5
3	74	15	2	40 MT, 8 A		2 p.m.	0.64	0.30	7.6	8.6
4‡	24	2	1	40 L, 12 A		9 a.m.	1.04	0.96	7.5	6.7
5	48	12	2	60 MT		3 a.m.	0.81	0.61	7.0	9.7
6	22	12	1	36 MT, 12 A	28 MT, 8 A	9 a.m.	1.17	1.08	7.8	8.6
7	28	14	1	52 MT, 8 A	4 MT	4 a.m.	0.64	0.63	7.8	8.3
8	58	17	2	40 L		7 a.m.	0.51	0.30	9.0	9.3
9	33	6	1	26 MT	8 MT	9 a.m.	0.59	0.33	7.4	9.8
10	16	11	1	48 MT, 16 A	12 MT§	1 a.m.	0.99	0.83	7.9	8.7
11	54	4	2	20 MT, 12 A	12 MT, 4 A	10 a.m.	0.64	0.58	7.2	8.9
12	32	11	1	40 MT	20 MT	2 a.m.	0.86	0.77	9.6	8.9
13	57	36	1	16 SL, 12 A	12 A-16 SL§	11 a.m.	0.71	0.67	9.1	8.4
14	26	15	1	32 MT, 20 A	12 MT, 12 A	12 a.m.	1.06	0.85	9.4	9.0
15	15	4	1	40 MT, 16 A	16 MT, 16 A	1 a.m.	1.44	1.25	7.4	8.0
16	84	49	2	40 L, 8 A		9 a.m.	0.78	0.70	6.8	12.6
17	52	4	2	36 MT, 8 A	16 MT	8 a.m.	0.71	0.56	7.6	9.1
18	42	4	1	40 MT, 8 A	8 A	9 a.m.	0.76	0.66	7.1	9.0
19	31	28	1	12 MT, 12 A	16 MT, 4 A	9 a.m.	0.71	0.56	7.6	9.1
20	76	27	2	20 MT, 24 A	12 MT	7 a.m.	1.04	0.85	12.3	10.8
21	18	12	1	40 MT, 16 A	16 A	5 p.m.	1.21	1.28	8.6	9.0
22‖	25	12	1	52 L, 20 A	12 A	5 a.m.	0.98	0.73	9.2	8.6
23¶	44	19	1	CSII		1 p.m.	0.82	0.73	7.9	8.1
24	24	7	1	CSII		3 p.m.	0.48	0.67	6.7	8.4
25	83	30	2	32 MT, 16 A	12 A	9 a.m.	0.86	Died	?	Died
26	70	24	2	40 L, 88 A	44 A	6 p.m.	2.64	Died	7.7	Died

*In patients with more than one reaction, the data of the first hypoglycemic reaction were used.
†A = Actrapid MC; SL = Semilente MC; L = Lente MC; MT = Monotard MC.
‡Patient with three hypoglycemic episodes.
§Injected at 10 p.m.
‖Patient with two hypoglycemic episodes.
¶Patient with three hypoglycemic episodes on CSII and one episode on conventional insulin administration.

hypoglycemia was defined as an insulin reaction that could not be treated by the patient alone but required assistance from a relative, friend, or physician who injected glucagon intramuscularly or glucose intravenously, or for which hospital admission followed. On each outpatient visit, the patient was asked about the occurrence of hypoglycemic events as defined above. Also, every admission to our hospital because of hypoglycemia was recorded. Some hypoglycemias were recorded after telephone contact with the patient or the physician who had treated the reaction at home.

Every patient filled in a checklist to find out what could have been the cause of the hypoglycemic event. In consultation with the patients, the causes were fitted into one of the following classifications:

(1) Patients' errors (too little food, too much exercise without taking precautions).

(2) Inadequate response by the patient to previous minor signs of hypoglycemia that could be seen as indicating a decreasing insulin need.

(3) Too much insulin or improper combinations of short-, intermediate-, and long-acting insulins.

(4) Intercurrent disease with reduced food intake.

(5) Labile diabetes mellitus.

(6) Unknown reasons.

"Too much insulin" listed as a cause meant that in the previous period the insulin dose had been increased, after which minor signs of hypoglycemia occurred. In addition, after the severe hypoglycemic event the insulin dose could be decreased without apparent deterioration in the control of blood glucose. A wrong combination meant that the ratio between short-, intermediate-, or long-acting insulin in the morning or in the evening was clearly different from that advised in recent literature.[8] Moreover, there was evidence to suggest that a surplus of one of these insulins caused the

Downloaded from http://diabetesjournals.org/care/article-pdf/8/2/141/532569/8-2-141.pdf by guest on 19 May 2024

hypoglycemic episode. Labile diabetes mellitus as a cause meant that the patient often had insulin reactions without clear reason. An unknown cause meant that the patient had never before had an insulin reaction and that no reasons for this reaction could be identified.

The daily insulin dose was measured as U/kg. HbA_{Ic} was measured by a chromatographic method using a microcolumn (normal range 4.5–6%).[9] Six to 12 mo after the hypoglycemic episode, HbA_{Ic} was remeasured and insulin doses recorded. These figures were compared with those from 100 patients selected as a convenience sample from the same outpatient diabetes clinic. This group was composed of the first 100 insulin-using diabetic patients who successively visited our clinic from 1 April 1982. Statistical analysis was performed using both the Wilcoxon rank-sum test and the chi-square test on unpaired samples and the Student *t*-test on paired samples.

RESULTS

In 1982 we recorded 38 severe hypoglycemic events in 32 patients. Six patients were excluded from this study for the following reasons: three patients admitted to our hospital used oral hypoglycemic drugs prescribed by a general practitioner, two patients were being treated elsewhere, and one patient appeared to have an insulinoma. In the remaining 26 patients, there were 32 severe hypoglycemic events. They occurred in 12 women and 14 men, with a mean age of 43 yr (15–84 yr). Table 1 shows the characteristics of these patients. Seventeen patients from this group (65%) had type I diabetes mellitus. Two patients with four episodes were treated with CSII. All patients but two had a normal renal function. In patient no. 19 serum creatinine was 1.5 mg/dl, and in patient no. 25 the level was 2.8 mg/dl. These values had remained unchanged during the previous 6 mo. Two patients (nos. 13 and 20) had clinical signs of autonomic neuropathy.

In 20 episodes treatment was given at home; in the other 12, the patient was admitted to the hospital. In these 12 patients, 10 had already been given glucose intravenously or glucagon intramuscularly at home. Most of the hypoglycemic episodes occurred at night or in the morning (respectively, 10 between 12 a.m. and 7 a.m., and 12 between 7 a.m. and 12 p.m.). Of the 10 episodes at night, intermediate-acting insulin had been given as an evening dose in 6, and long-acting insulin as a morning dose in 3 cases. In one case, an intermediate-acting preparation was injected in the morning. Actrapid (Novo, Copenhagen, Denmark) injected between 7 and 8 a.m. was used in all but one of the patients with hypoglycemic episodes in the morning.

TABLE 2
Causes of severe hypoglycemic reactions in 26 patients (see text for explanation)

Cause	Cause in no. of hypoglycemic reactions
Patients' error	9
No reaction to previous warning signs	2
Too much insulin or wrong combination	6
Intercurrent disease	3
Labile diabetes mellitus	5
Unknown	7
Total	32

TABLE 3
Clinical data of 26 patients with severe hypoglycemia and of 100 randomly selected diabetic patients

	Hypoglycemic group (N = 26)	Random group (N = 100)	P
Age (yr)	43 (15–84)	44.6 (14–88)	
Duration of diabetes (yr)	15.7 (4–49)	12.2 (0.9–46)	
Type I diabetes mellitus	17 (65%)	47 (47%)	<0.05
HbA_{Ic} (%)*	8.1 ± 1.3	8.7 ± 1.7	<0.05
Insulin dose (U/kg/day)*	0.89 ± 0.43	0.67 ± 0.34	<0.05

Values are expressed as mean ± SD.
*In patients with more than one reaction, the data of the first hypoglycemic reaction were used.

Table 2 shows the causes of the hypoglycemic reactions as established in consultation with the patients. Patients' errors were the most important cause (9 of 32 episodes), and in two episodes the patient did not pay attention to previous warning signs. Too much insulin or a wrong combination of insulin, i.e., physician's error, was the cause in 6 of 32 reactions. In seven cases no apparent reason for the hypoglycemic reaction could be determined. All these reactions with unknown causes appeared in type I diabetic patients. There were no differences in causes between the nocturnal and daytime hypoglycemic episodes.

In comparing the clinical data of the 26 patients with severe hypoglycemic reactions with that of 100 randomly sampled patients in our diabetic population, we found a significant difference in mean HbA_{Ic} level (Table 3). Furthermore, the insulin dose was significantly higher in the hypoglycemic group than in the control group. Table 4 shows the HbA_{Ic} level and insulin dose in 20 patients at the time of the hypoglycemic reaction and 6–12 mo afterward. After the hypoglycemic episode, the insulin dose was decreased. Excluded from this table were two patients treated with CSII, two patients with more than one hypoglycemic reaction, and two patients who died during the follow-up period.

DISCUSSION

In our diabetic population, 6.5% of the patients had one or more severe hypoglycemic reactions during 1 yr, and per patient-yr the incidence was 8%, i.e., 32 episodes in 26 of

Downloaded from http://diabetesjournals.org/care/article-pdf/8/2/141/532569/8-2-141.pdf by guest on 19 May 2024

TABLE 4
Mean HbA_{Ic} level and insulin dose in 20 patients with severe hypoglycemia at the moment of the reaction and 6–12 mo afterward

No. of patients	Mean HbA_{Ic} (%)		Mean insulin dose (U/kg/day)	
	During	After	During	After
20	8.1 ± 1.4	9.0 ± 1.1	0.82 ± 0.25	0.69 ± 0.27
	$P < 0.05$		$P < 0.001$	

Values are expressed as mean ± SD.

approximately 400 patients. It is possible that this figure could be somewhat higher because not all patients will report a hypoglycemic episode.[5] However, with the stringent control of our diabetic population, it does not seem very likely that many severe insulin reactions escaped our attention. In the literature, different frequencies of severe hypoglycemia are given, depending partly on the definition of a severe insulin reaction and partly on the patient group studied. Potter et al.[4] noted 200 severe hypoglycemic episodes in 130 patients during 1 yr by measuring visits to the emergency clinic. This figure represents 9% of their known diabetic population treated with insulin, but this only concerns hospital admissions and perhaps more episodes were treated at home. Basdevant et al.[6] reported that as many as 30% of their diabetic patients experienced a severe insulin reaction during 1 yr. They used the same definition of a severe insulin reaction as we did, but they did not note if all these patients had type I diabetes. From the same hospital a group of 172 patients with type I diabetes mellitus were questioned, and at least one severe episode was described by 26% of these patients during the past year.[5]

Goldstein et al.[3] reported only a 4% incidence per year in 147 children and adolescents with type I diabetes mellitus. They characterized a severe reaction by altered central nervous system function or prolonged sympathetic nervous system symptoms. On the other hand Koch et al.[7] recently described that out of 388 patients with type I diabetes mellitus, 10% experienced at least one severe reaction per year.

Our diabetic population contains type I as well as type II diabetic patients and probably represents more the average outpatient population attending outpatient diabetes clinics. Therefore, our figure of 8% seems to be rather realistic and must be compared with the already mentioned figure of 9% from Potter et al.[4] from a comparable diabetic patient group. In our group of patients with severe hypoglycemia, the percentage of type I diabetes mellitus was significantly higher than in our random group. However, it must be emphasized that severe hypoglycemic reactions can also occur in patients with type II diabetes.

In accordance with the findings of others, we can conclude that the precipitating cause is not always easy to find. Goldgewicht et al.[5] could not identify a cause in 11% of the severe hypoglycemic events and Potter et al.[4] could not in one-third of their patients. In our study the cause was unknown in 22% of the episodes, all of which occurred in type I diabetic patients.

Labile diabetes mellitus was not a very frequent cause in our study group since it was only present in 5 of the 32 reactions. This is in agreement with Goldstein et al.[3] However, it may have played some role in the unexplained episodes of type I diabetic patients, assuming that this type of diabetes is more labile than type II diabetes mellitus.

We found evidence that overtreatment was an important cause of severe hypoglycemic reactions. First, in six (20%) patients too much insulin or a wrong combination of short- and intermediate-acting insulin was prescribed. Second, the mean insulin dose of the patients with hypoglycemia was significantly different from a random group of diabetic patients. Third, 6–12 mo after the event, the mean insulin dose had been decreased and the HbA_{Ic} level did increase. It is, of course, possible that the insulin dose at this moment was too low for fear of recurrence of a hypoglycemic reaction. Our findings, however, are partly in agreement with those of Goldstein et al.[3] They found a significantly lower HbA_{Ic} level in patients with severe hypoglycemia, but there was no difference in insulin dose. Potter et al.[4] found evidence of overtreatment in the group with two or more hypoglycemic reactions per year: The mean insulin dose had been decreased from 1.2 to 0.8 U/kg/day 1 yr after the last episode. HbA_{Ic} levels were not measured.

The cause of more than one-quarter (28%) of the hypoglycemic reactions was patients' errors, i.e., they had not taken their normal meal or did too much exercise without taking precautions. From the data of Potter et al.[4] it can be calculated that in 30% of the episodes the cause was a missed meal or excessive exercise. Goldstein et al.[3] mentioned that all but one of their six patients with eight severe hypoglycemias reported mild but frequent reactions preceding the severe episode, but none had decreased their insulin dosage as was advised. It was striking that after the reaction nearly all our patients admitted that they had done something wrong or had not taken the necessary precautions.

Although most of the hypoglycemic reactions occurred either at night or in the morning, it was not possible to analyze the contributory factors in relation to the time of the event, owing to the smallness of the sample. All causes manifested themselves at all times of the day. It is notable that not all reactions at night were due to an evening dose of intermediate-acting insulin. It must be noted that intermediate-acting insulin given as a morning dose resulted in a hypoglycemic reaction at night in the case of one patient. Hypoglycemia occurred in the morning in another patient.

CONCLUSIONS

Our findings agree mainly with the available data from other studies; therefore, some general statements can be made. From our study it is apparent that, since in about one-quarter of severe hypoglycemic reactions a cause could not be identified, it does not seem possible to prevent all these reactions. How-

Downloaded from http://diabetesjournals.org/care/article-pdf/8/2/141/532569/8-2-141.pdf by guest on 19 May 2024

ever, because overtreatment was present for the group as a whole, the physician must always be aware of the possibility of too much insulin in the daily treatment of his patients, in his attempts to prevent severe hypoglycemia. However, in the individual patient with hypoglycemia, the insulin dose was not necessarily more than the mean dose of the control group. Furthermore, in one-quarter to one-half of the patients with severe hypoglycemia, a lack of care or alertness on the part of the patient was present. Therefore, it is not necessary to sacrifice glucose control in all patients in an attempt to prevent severe hypoglycemic reactions. In those patients who make mistakes or who take an improper combination of insulins, education or altering the combination of insulins can minimize or eliminate severe hypoglycemia without loosening diabetes control. Educating the patient to respond adequately to changing circumstances in daily life or to warning signs could reduce the 8% annual incidence of severe hypoglycemic reactions.

From the Department of Internal Medicine, Hospital "de Weezenlanden," Groot Wezenland 20, 8011 JW Zwolle, The Netherlands.

Address reprint requests to Dr. A. F Casparie at the above address.

REFERENCES

[1] Gale, E.: Hypoglycaemia. Clin. Endocrinol. Metab. 1980; 9:461–75.

[2] Unger, R. H.: Meticulous control of diabetes: benefits, risks and precautions. Diabetes 1982; 31:479–83.

[3] Goldstein, D. E., England, J. D., Hess, R., et al.: A prospective study of symptomatic hypoglycemia in young diabetic patients. Diabetes Care 1981; 4:601–605.

[4] Potter, J., Clarke, P., Gale, E. A. M., Dave, S. H., and Tattersall, R. B.: Insulin-induced hypoglycaemia in an incident and emergency department: the tip of an iceberg? Br. Med. J. 1982; 285:1180–82.

[5] Goldgewicht, C., Slama, G., Papoz, L., and Tchobroutsky, G.: Hypoglycaemic reactions in 172 type I (insulin-dependent) diabetic patients. Diabetologia 1983; 24:95–99.

[6] Basdevant, A., Costagliola, D., Lanöe, J. L., et al.: The risk of diabetic control: a comparison of hospital versus general practice supervision. Diabetologia 1982; 22:309–14.

[7] Koch, K., Mühlhauser, I., Jörgens, V., et al.: Incidence and management of severe hypoglycaemia in 402 type I (insulin-dependent) diabetic patients. Abstract. Diabetologia 1983; 25:171.

[8] Skyler, J. S., Skyler, D. L., Seigler, D. E., and O'Sullivan, M. J.: Algorithms for adjustment of insulin dosage by patients who monitor blood glucose. Diabetes Care 1981; 4:311–18.

[9] Boer, M.-J., Miedema, K., and Casparie, A. F.: Glycosylated haemoglobin in renal failure. Diabetologia 1980; 18:437–40.

Downloaded from http://diabetesjournals.org/care/article-pdf/8/2/141/532569/8-2-141.pdf by guest on 19 May 2024