Title

Relative Hypoinsulinemia after Short-Term Diphenylhydantoin Administration in Therapeutic Doses

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Reversible hyperglycemia has been described as a toxic effect of diphenylhydantioin (DPH) overdosage in man (1-3), and a recent in vitro study on rats has shown that DPH-induced hyperglycemia results from direct impairment of insulin secretion (4).

In this paper, we report a relative impairment of insulin secretion in response to glycemic stimulus induced by short-term DPH administration in therapeutic doses in man.

Materials and Methods

Seven non-obese healthy subjects (six males and one female, aged 18 to 40 years) mostly physicians & laboratory workers volunteered for this study. No one had a history of diabetes in the family; and none was on any medication. In each case, an informed consent was obtained prior to the study. After standard dietary preparation and an overnight fast, each volunteer drank a standard solution of 100 G of glucose dissolved in 250 ml of water & remained in bed throughout the test period. Blood samples were drawn at 0,30,60,90,120, and 180 minutes and analyzed for glucose (5) and for insulin by radioimmuno-assay (6). Each subject was then put on oral DPH 100 mg every eight hours, and glucose tolerance test (GTT) was repeated 5-7 days later while the subject was still on DPH.

The GTT was interpreted as normal or abnormal according to the criteria of Fajans (7). Thus two additional volunteers who did not fulfill the normal criteria before DPH administration were not included. In each case, an "insulinogenic index" (8) was calculated by dividing the area circumscribed by the insulin curve (i.e the change from the

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fasting level) by the corresponding area circumscribed by the glucose curve before and after DPH administration. Similarly "insulin: glucose" ratios were obtained by dividing the change in plasma insulin from the fasting value divided by corresponding change in blood glucose (8).

Results

The results of this study are shown in table I

a) Glucose levels:

No gross differences in mean blood glucose levels were discernible before and after DPH administration; in fact, the values in both instances were quite normal. However, in 3 out of seven (43%) subjects, some changes in glucose tolerance were detectable after DPH when examined individually. Thus, in two subjects, blood glucose was above 160 mg per 100 ml at 60 minutes, and both showed clinical hypoglycemia at 180 minutes (blood glucose 30 and 42 mg per 100 ml), reminiscent of early diabetes (9). In an additional subject, the blood glucose was still above 120 mg per 100 ml at 2 hour interval.

b) "Insulin: Glucose Ratios": Fig I shows the mean "insulin: Glucose ratios" before and after DPH administration. At all time intervals, the mean "insulin: glucose ratio" was found to be higher before DPH administration with an earlier peak than after DPH where the rise was slower and lesser in magnitude. At thirty minutes, the "ratio" after DPH was significantly lower ($p < 0.05$), while at other times the difference in the mean values was not statistically significant (10).

c) "Insulinogenic Index": The "insulinogenic index" fell after DPH administration in all cases, and the difference in the mean values 4.56 ± 0.99 and 3.10 ± 0.59 (SEM) respectively before and after DPH administration was statistically significant. ($p < 0.05$) (10).

Discussion

The "insulinogenic index" as described by Seltzer et al (8) can be regarded as the most sensitive index of pancreatic islet-cell secretory function, because it tells the cumulative insulin output per unit of secretory stimulus. This study has conclusively demonstrated that DPH, even in therapeutic concentrations, impairs the insulin output in response to a glycemic stimulus. As the mean "insulin: glucose" ratio was significantly depressed only during the first thirty minutes of the GTT, it is tempting to speculate that DPH affects mainly the small rapid insulin release pool rather than the larger sustained pool coupled with insulin synthesis (11), although the latter possibility can not be ruled out from the available evidence. The insulin inhibition caused by DPH may be the result of intracellular sodium depletion (12).

The relative hypoinsulinemia as the result of short term administration of DPH in doses that are generally used in medical practice may have clinical implications in view of the widespread use of this drug for neurological and other disorders. It would be of interest to conduct a similar study on patients on long term DPH therapy.

Abstract

In 7 healthy adults a standard glucose tolerance test, done before and after oral diphenylhydantoin (DPH) (300 mg per day) administration for 5-7 days, showed a relative impairment of insulin secretion as judged by decreased "insulinogenic index" calculated by dividing the area circumscribed by the insulin curve by the corresponding area of the glucose curve. The mean "index" was found to be 4.56 ± 0.99 and 3.10 ± 0.59 (SEM) respectively before and after DPH administration, and the difference was statistically significant ($p < 0.05$). This finding of relative hypoinsulinemia induced by therapeutic concentrations may have clinical implications, in view of the widespread use of DPH in medical practice.

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Table I

Glucose Tolerance Test Before and After DPH*

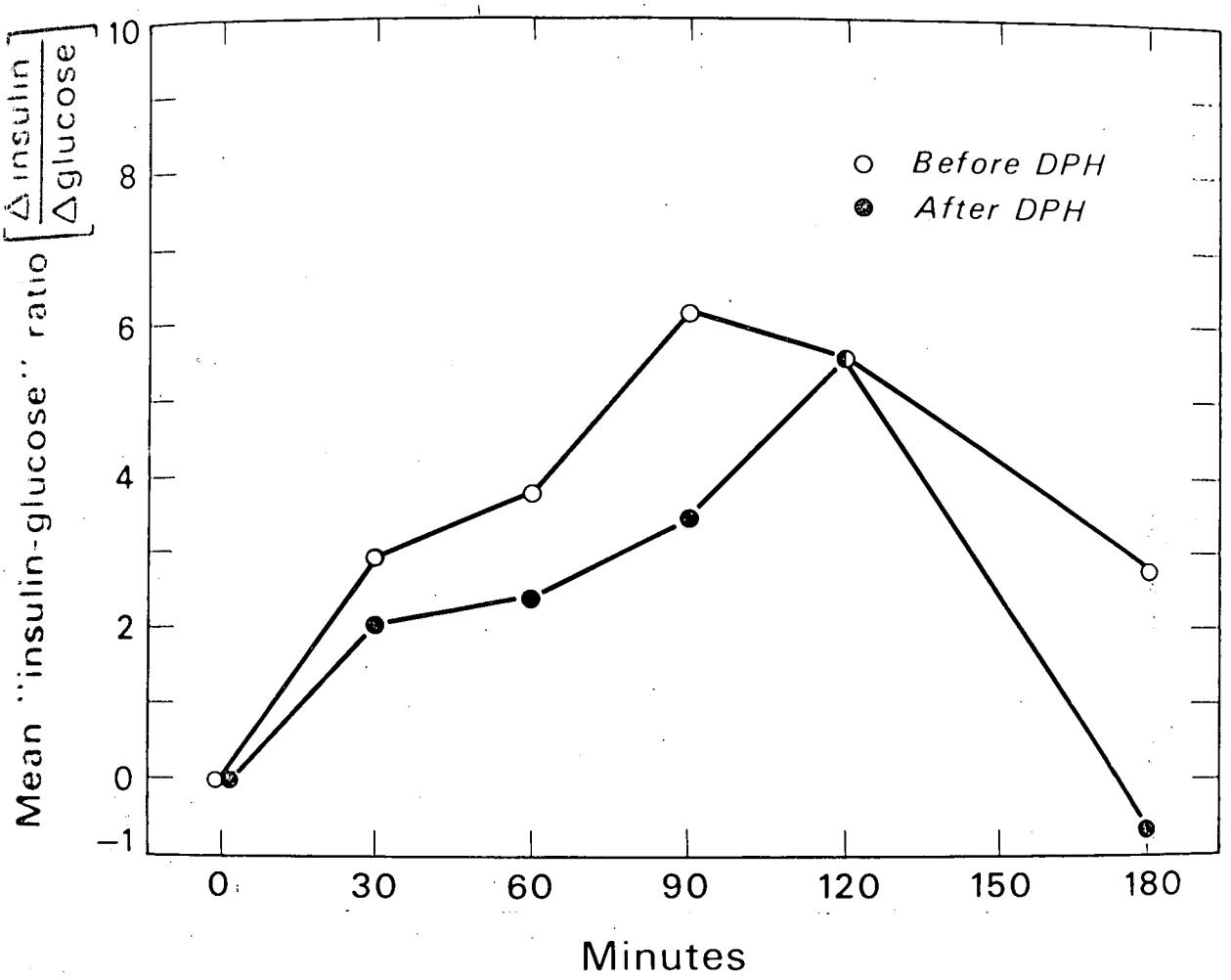
Name	Glucose (mg/100 ml.)						Insulin (mug/ml)						Insulinogenic Index**
	Minutes						Minutes						
	0	30	60	90	120	180	0	30	60	90	120	180	
1. M.O.	76 (64)	130 (132)	112 (134)	106 (130)	96 (122)	62 (102)	25 (27)	157 (144)	248 (213)	151 (210)	147 (135)	60 (134)	5.12 (2.83)
2. W.L.	74 (80)	108 (134)	128 (126)	102 (106)	96 (88)	68 (78)	21 (26)	88 (106)	93 (131)	134 (100)	130 (98)	40 (54)	3.03 (3.00)
3. D.R.	76 (62)	106 (140)	124 (88)	106 (88)	94 (70)	90 (88)	22 (36)	124 (258)	212 (120)	181 (125)	205 (51)	127 (132)	5.57 (3.06)
4. R.S.	74 (71)	152 (148)	140 (162)	100 (110)	100 (110)	76 (42)	39 (35)	204 (152)	183 (149)	113 (200)	132 (183)	71 (38)	2.63 (2.62)
5. R.L.	72 (67)	102 (110)	102 (110)	106 (106)	110 (76)	90 (94)	38 (34)	125 (158)	114 (72)	160 (108)	166 (72)	136 (87)	3.40 (2.09)
6. B.O.	68 (64)	124 (153)	104 (191)	92 (158)	120 (87)	52 (30)	34 (35)	346 (286)	305 (521)	428 (712)	462 (376)	85 (50)	9.38 (6.23)
7. D.O.	80 (73)	112 (110)	108 (95)	90 (82)	100 (83)	104 (102)	34 (30)	108 (81)	109 (90)	102 (47)	90 (63)	82 (63)	2.81 (1.88)
Mean	74 (69)	118 (132)	116 (129)	100 (111)	102 (91)	77 (76)	30 (32)	164 (169)	180 (185)	181 (214)	190 (140)	86 (79)	4.56 (3.10)
S.E.M. ±	1.53 (2.61)	7.20 (6.93)	5.77 (15.06)	2.77 (10.53)	3.84 (7.59)	7.43 (11.89)	3.10 (1.69)	36.04 (30.89)	32.57 (63.18)	45.76 (92.49)	50.98 (46.49)	14.16 (16.07)	0.99 (0.59)

* The numbers appearing within parenthesis refer to values after DPH administration.

** The area circumscribed by the insulin curve divided by the area circumscribed by glucose curve.

Legend for Fig. I

The "insulin: glucose" ratios plotted here are successive mean ratios of Δ insulin: Δ glucose at each sampling interval. After DPH, the mean ratios are always lesser in magnitude and the peak is delayed. The "insulin: glucose ratio" at 30 minutes is significantly lower after DPH.


Mean "insulin-glucose" ratio [Δ insulin / Δ glucose]
10
8
6
4
2
0
−1
0
30
60
90
120
150
180
Minutes
Before DPH
After DPH

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RELATIVE HYPOINSULINEMIA AFTER SHORT-TERM DIPHENYLHYDANTOIN ADMINISTRATION IN THERAPEUTIC DOSES

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