SHORT COMMUNICATION

THE EFFECT OF DIPHENYLHYDANTOIN ON INSULIN RESPONSE

A. G. CUDWORTH and J. L. CUNNINGHAM

Department of Medicine (Nuffield Unit of Medical Genetics),
University of Liverpool, Liverpool

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SUMMARY

1. Serum immunoreactive insulin, glucose tolerance and growth hormone levels were estimated in healthy volunteers before and after receiving diphenylhydantoin sodium (DPH) for 14 days.

2. With a standard oral dose of DPH all subjects showed a reduced insulin response to oral glucose (11–44%). This correlated with the serum concentration of the drug, which ranged from 30.5 to 90.0 μmol/l (7.7–22.7 μg/ml).

3. Glucose tolerance remained normal and no changes in growth hormone levels were observed.

4. Different doses of DPH have been employed in the treatment of insulinoma and as a screening test for detecting latent insulin secretory defects. This study confirms the wide inter-individual variation in the metabolism of DPH, and stresses both the importance of measuring the serum concentration of DPH and the comparative irrelevance of dosage levels in these situations.

Key words: insulin response, diphenylhydantoin.

The diabetogenic effect of DPH has been known for several years. Belton, Etheridge & Millilchlap (1965) and Sanbar, Conway, Zweiffler & Smet (1967) demonstrated that intravenous administration of large quantities of DPH in animals produced a reversible hyperglycaemia. Klein (1966) reported a case of marked hyperglycaemia after inadvertent oral administration of excessive DPH and other similar case reports followed (Goldberg & Sanbar, 1969; Dahl, 1967; Said, Fraga & Reichelderfer, 1968). More recently, hypoinsulinaemia has been recorded accompanying hyperglycaemia in certain individuals on chronic DPH therapy (Peters & Samaan, 1969; Fariss & Lutcher, 1971), and studies in vitro have indicated that DPH inhibits the release of insulin from the pancreas (Levin, Booker, Smith & Grodsky, 1970; Kizer, Vargas-Cordon, 1971).

Correspondence: Dr A. G. Cudworth, Department of Medicine (Nuffield Unit of Medical Genetics), University of Liverpool, Liverpool L69 3BX.
Brendel & Bressler, 1970; Levin, Grodsky, Hagura & Smith, 1972). Fariss & Lutcher (1971) described a case in which hyperglycaemia and hypoinsulinaemia were related to increasing dosage of the drug. DPH is emerging as a possible form of therapy in the treatment of insulinoma and as a diagnostic tool in the detection of early diabetes. The difficulty is that blood level and dose of DPH are poorly related (Kutt & McDowell, 1968).

The aim of this study was to determine whether administration of a standard dose of DPH to normal, healthy volunteers produced any impairment of glucose tolerance and whether there was any reduction in insulin response that could be related to the serum level of the drug. The clinical effectiveness of DPH in relation to insulin response would depend on such a correlation.

MATERIALS AND METHODS

Eight non-obese medical students with no family history of diabetes mellitus were studied. They were not taking any other therapy during the investigation.

Each individual had a standard 50 g oral glucose tolerance test (GTT) after a 9 h overnight fast. DPH was administered in capsules, 396.3 μmol (100 mg) 8-hourly, for 14 days. On the morning of the repeat GTT, the subject took a capsule on rising, 2 h before the commencement of the test. Blood was collected for serum DPH estimation midway through the second test.

Blood sugar was estimated using a Technicon AutoAnalyzer (ferricyanide method). Serum immunoreactive insulin was measured by using the double-antibody method of Hales & Randle (1963). Insulin levels for each subject before and after taking DPH were assayed simultaneously to avoid inter-assay variability. Growth hormone (GH) was measured by double-antibody radioimmunoassay according to Schalch & Parker (1964). Serum DPH was measured by the method of Dill, Baukema, Tsun-Chang & Glazko (1971). Estimations were carried out in duplicate with 3 ml aliquots of serum. A standard line, from aqueous standards, was incorporated with each assay. The mean recovery of DPH from plasma has been shown to be 99.8% of that obtained from water (Dill et al., 1971).

RESULTS

Serum insulin

DPH did not influence the standard curve for immunoassay of insulin. The inter-assay coefficient of variation was 2.6%. No difference occurred in fasting levels of insulin but all subjects whilst taking DPH showed a general reduction in insulin response to glucose up to 2 h after ingestion. By using the t test for paired data, this reduction is most significant at 30 and 60 min (P<0.01) (Table 1).

Calculating total insulin response as the sum of the insulin values (0–120 min), the percentage reduction in insulin response on DPH correlates with the serum concentration of the drug (Spearman's rank correlation coefficient r = 0.75; P<0.05).

Oral glucose tolerance

Glucose tolerance remained normal. Any elevations in blood sugar whilst DPH was taken were not significant even in two subjects with a serum DPH level in excess of 79.3 μmol/l (20 μg/ml).
TABLE 1. Diphenylhydantoin and insulin response in eight subjects

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<thead>
<tr>
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<th>Subject</th>
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<tr>
<td>Serum insulin</td>
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<tr>
<td>30 min Pre-DPH</td>
<td>103.9</td>
<td>64.5</td>
<td>84.7</td>
<td>50.7</td>
<td>33.4</td>
<td>22.0</td>
<td>49.1</td>
<td>33.8</td>
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<tr>
<td>On DPH</td>
<td>81.1</td>
<td>62.1</td>
<td>72.0</td>
<td>26.1</td>
<td>20.0</td>
<td>20.5</td>
<td>36.9</td>
<td>27.0</td>
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<tr>
<td>60 min Pre-DPH</td>
<td>73.5</td>
<td>73.2</td>
<td>105.4</td>
<td>75.9</td>
<td>37.6</td>
<td>19.6</td>
<td>45.8</td>
<td>48.2</td>
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<tr>
<td>On DPH</td>
<td>54.4</td>
<td>52.7</td>
<td>72.7</td>
<td>56.2</td>
<td>23.6</td>
<td>19.9</td>
<td>45.5</td>
<td>24.7</td>
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<td>Serum concentration of DPH</td>
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<td>µmol/l</td>
<td>30.5</td>
<td>63.0</td>
<td>90.0</td>
<td>35.7</td>
<td>84.0</td>
<td>50.7</td>
<td>38.0</td>
<td>44.0</td>
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<td>(µg/ml)</td>
<td>(7.7)</td>
<td>(15.9)</td>
<td>(22.7)</td>
<td>(9.0)</td>
<td>(21.2)</td>
<td>(12.8)</td>
<td>(9.6)</td>
<td>(11.1)</td>
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<td>Reduction in insulin response (%)</td>
<td>23.0</td>
<td>23.3</td>
<td>44.0</td>
<td>11.4</td>
<td>39.1</td>
<td>11.7</td>
<td>11.4</td>
<td>27.3</td>
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Growth hormone

No alteration in GH levels was observed during DPH administration. All subjects showed normal suppression with glucose.

Serum DPH

Serum levels ranged from 30.5 to 90.0 μmol/l (7.7–22.7 μg/ml). These values would be expected to represent the steady-state serum concentrations (vide infra). No side effects were noted.

DISCUSSION

The mechanism of this reduction of insulin response due to DPH is not yet clear. It has been demonstrated that DPH inhibits the secretion of insulin in vitro (Levin et al., 1970; Kizer et al., 1970). Kizer et al. (1970) showed that this inhibition cannot be overcome with tolbutamide, which is contrary to observations made on diazoxide, another known powerful inhibitor of insulin secretion. Levin et al. (1972) produced evidence that DPH affected the synthesis as well as the release of insulin from the beta cell. Hales & Milner (1968) reported reduced insulin secretion in situations associated with depletion of intracellular sodium. This could be a mechanism through which DPH exerts its effect, as it is known to reduce intracellular sodium in brain and muscle tissue (Woodbury, 1955).

During investigation of a 42-year-old negro woman (Fariss & Lutcher, 1971), delayed insulin response was demonstrated with increasing doses of DPH and hyperglycaemia developed at 1585 μmol (400 mg) daily. These changes were reversible, and this was also the case in another report by Peters & Samaan (1969). Hyperglycaemic non-ketotic coma has been reported after administration of DPH (Goldberg & Sanbar, 1969). Insulin assay in this type of coma has shown very low circulating peripheral insulin (Johnson, Conn, Dykman, Pek & Starr, 1969).

Cummings, Rosenbloom, Kohler & Wilder (1972) compared mean insulin and glucose responses in twenty children (8–18 years) on chronic DPH therapy with a normal group. Glucose tolerance was normal but an apparent augmented mean insulin response was observed. It is doubtful whether comparing mean insulin values between groups is valid. Furthermore, no correlation was demonstrated between insulin response and serum level of the drug. No mention is made of possible ingestion of other drugs; phenobarbitone in particular influences the metabolism of DPH (Kristensen, Hansen & Skovsted, 1969).

Recently DPH has been used successfully in the management of a patient with an insulinoma using a dose regime of 1585 μmol (400 mg) daily (Cohen, Bower, Fidler, Johnsonbaugh & Sode, 1973), but drug levels were not apparently estimated. Levin, Reed, King-Nien Ching, Davis, Blum & Forsham (1973) have further shown that DPH may be used to unmask insulin secretory defects in patients with mild glucose intolerance, but only after post-glucose arginine stimulation was used. A large dose of DPH, 33.7 μmol/kg (8.5 mg/kg), was administered for 4 days, which would not be long enough to achieve a steady state. It has been confirmed in this laboratory that a steady state of DPH is achieved within 13 days for twenty-three normal individuals not taking any other drugs, and Kutt & McDowell (1968) have stated that when a dose of 300 mg daily is used, levels stabilize between 5 and 15 days.

Serious hyperglycaemia occurs only in certain individuals in association with overdosage or long-term therapy. The results in this study confirm the finding of most workers that insulin
response to DPH is significantly reduced, and further demonstrate that this reduction is variable and directly correlates with the serum concentration of the drug for each individual. It is well known that there is wide inter-individual variation in the metabolism of DPH and these data indicate that blood concentration more than dosage of the drug must be considered when assessing effects on insulin metabolism.

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REFERENCES


