Case Report

Medical treatment of insulinomas: The role of diphenylhydantoin

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1. Introduction

Since its first description in the early 1920s, surgical removal of insulinoma is the treatment of choice [1–3]. Medical therapy should be considered for patients with insulinomas missed during pancreatic exploration, and for patients who refuse surgery or have inoperable/metastatic disease. We are reporting here three patients with insulinoma in whom diphenylhydantoin (DPH) was effective in suppressing insulin release and preventing hypoglycemia. A brief review is made of the properties of DPH as an insulin-suppressing agent.

2. Patients and results

2.1. Patient 1

Patient 1 was a 31-year-old male who presented with recurrent nocturnal seizures. Among a variety of antiepileptic drugs, he responded best to DPH. Further investigations led to the final diagnosis of hypoglycemia-induced seizures and imaging revealed a tumor in the pancreatic body. Pre-operatively, treatment with DPH was able to correct the hypoglycemia and thus prevent the seizures. A benign insulinoma was successfully removed and the patient was cured and became free of hypoglycemia and of seizures.

2.2. Patient 2

Patient 2 was a 26 year old female who had a one year history of fasting hypoglycemic episodes and weight gain. Laboratory evaluation showed a low fasting serum glucose level (2.72 mmol/l) with simultaneously elevated serum insulin (30.6 μU/ml) and C-peptide (2 ng/ml) levels. Complete blood count, renal and liver function tests, serum TSH, cortisol and GH levels were all normal. Endoscopic Ultra Sound (EUS) showed a 2 × 2 cm tumor in the tail of the pancreas. Before undergoing a distal pancreatectomy four days later, DPH (400 mg/d) resulted in a fall in insulin levels and a rise in fasting glucose levels (Table 1) and allowed discontinuation of intravenous dextrose infusion. Pathology revealed a benign insulinoma and post-operatively, the patient became totally free of hypoglycemic episodes.

2.3. Patient 3

Patient 3 was a 65-year-old male a known case of previously poorly controlled type 2 diabetes. After 15 years he had ended with end-stage renal disease, requiring chronic hemodialysis. In the preceding year while on hemodialysis, he became euglycemic, even without insulin treatment, and thereafter started having recurrent fasting hypoglycemia with documented endogenous insulin excess. EUS revealed a 2 × 2 cm lesion in the body of the pancreas. As he was not a surgical candidate due to advanced coronary artery disease, medical treatment for insulinoma had to be a substitute...
performed rat pancreas [10]. In humans, several studies have shown that oral administration of DPH results in a higher blood glucose response and diminution of the early and late post-prandial insulin responses [11]. All the above observations, and others [12–14] lead to the conclusion that, at blood levels similar to those attained in the treatment of epilepsy, DPH is a potent inhibitor of insulin release.

The mechanism of the inhibitory effect of DPH on glucose-induced insulin release has also been studied, using isolated pancreatic islet cells. DPH causes hyper-polarization of the plasma membrane in islet cells; an effect that could be brought about by the stimulatory effect of DPH on the membrane sodium–potassium–magnesium ATPase-related pump [15–17], which reduces the uptake of sodium by the islets. Optimal sodium concentration is necessary for insulin secretion [18]. Thus, it seems possible that the effects on cellular sodium are, in part, involved in the inhibitory mechanism of DPH. This pump system, in turn, may influence calcium uptake, an initial requirement for insulin secretion [19]. Furthermore, DPH has also been shown to block calcium uptake via voltage dependent calcium channels [20]. In addition, it also decreases calcium efficacy in the exocytotic system [21]. Peripheral inhibition of the action of insulin by DPH is another possible, but less confirmed, explanation for the DPH-induced hyperglycemia in vivo.

Another well-known effect of DPH is the inhibition of glucagon secretion in vitro [22] and in humans [23]. Due to its inhibitory effect on insulin release, we and others have used DPH to temporarily control hyperglycemia during the preoperative period in patients with insulinoma [24–26]. It has also been used in the treatment of hypoglycemia induced by inoperable insulinomas [27]. The advantages of DPH over Diazoixide, the most widely used drug in the medical treatment of insulinoma, were studied [28]. From the experimental observations of the perfused rat pancreas, it is known that insulin is stored in a labile compartment that is concentration-related to a larger and more stable storage compartment containing 98% of total β-cell insulin [29]. And it is currently accepted that pancreatic insulin secretion is biphasic and involves the immediate release from the small labile pool followed by the subsequent provision of insulin to this labile pool from the larger storage compartment [30]. When Levin et al. [28] compared DPH and Diazoixide with respect to their effects upon insulin secretion by the isolated perfused rat pancreas, it was found that DPH inhibits both secretion from the labile insulin compartment and provision of insulin and/or precursors to this compartment, whereas Diazoixide inhibits insulin release from the labile pool, but continues to allow insulin to be provided by the larger storage compartment. This was translated into constant levels of inhibition by DPH during infusion of the agent, without escape, and without post-inhibitory overshoot, whereas with Diazoixide, although there was an initial fall in secretion, this was followed by an escape towards a pre-inhibition level followed by a post-inhibitory overshoot. Furthermore, Kizer et al. [31] showed that inhibition of insulin secretion by DPH could not be overcome by Tolbutamid, whereas Diazoixide inhibition can be reversed by Tolbutamid [32]. Thus, it is justifiable to state that DPH is advantageous over Diazoixide to blockade insulin release. Fariss and Lutcher [33] defined the optimal dose of DPH required for insulin suppression when they found that in response to oral glucose, the blood glucose levels were within the limits of normal with doses of DPH of 100, 200, 300 mg/d but not with 400 mg/d. The insulin response was further delayed with each increase of DPH to the point where there was little or no further effect during the test period of 400 mg dosage. Therefore, a 400 mg/d of DPH is recommended for adequate suppression of insulin secretion. Finally, our third patient represented a very challenging case in which an insulinoma was diagnosed in a type 2 diabetic patient. Very few similar cases have

### Table 1
Effect of DPH on serum glucose and insulin levels in case 2.

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<tr>
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<th>Before DPH</th>
<th>After DPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum glucose mmol/l (reference range)</td>
<td>2.77 (3.33–5.55)</td>
<td>3.33 (3.33–5.55)</td>
</tr>
<tr>
<td>Fasting serum insulin µU/ml (reference range)</td>
<td>30.6 (4.0–25.0)</td>
<td>20.0 (4.0–25.0)</td>
</tr>
</tbody>
</table>

### Table 2
Effect of DPH on serum glucose and insulin levels in case 3.

<table>
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<th>Before DPH</th>
<th>After DPH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting serum glucose mmol/l (reference range)</td>
<td>2.71 (3.33–5.55)</td>
<td>6.66 (3.33–5.55)</td>
</tr>
<tr>
<td>Fasting serum insulin µU/ml (reference range)</td>
<td>82.0 (4.0–25.0)</td>
<td>31.7 (4.0–25.0)</td>
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for surgery. He was started on DPH, 300 mg/d with an excellent sustained control of his serum glucose and a fall in insulin levels (Table 2). Since the past 20 months the patient is still maintained on DPH and no hypoglycemic episodes.

### Discussion

In the cases presented above, DPH was effective in controlling hypoglycemia in three patients with insulinoma, either temporarily in the preoperative period or as an alternative to surgery. In humans and in animals DPH has been shown to cause hyperglycemia. The intraperitoneal injection of DPH in rabbits [4] and the intravenous administration of DPH in dogs [5] produced a marked increase in blood glucose levels. These observations were soon followed by the clinical recognition of hyperglycemia and even hyperglycemic non-ketotic coma after administration of DPH in humans [6–8].

MORE ABOUT THIS STUDY

Due to the advances in localization techniques and the high surgical success rates, the medical treatment of insulinomas has been a neglected topic in the last three decades. However, the use of agents that suppress insulin release should not be considered only as an alternative to surgery, but also as a temporary measure in the preoperative period.

What is already known about this topic

When surgery fails or cannot be undertaken in a patient with documented endogenous insulin excess, medical measures to suppress insulin releases become a life-saving necessity. Among the agents used in the literature are Diazoxide, Somatostatin analogue (Octreotide), Diphenylhydantoin, Glucocorticoids, Glucagon, Calcium channel blockers, and Beta blockers.

What this study adds

Although Diazoxide is the most widely used drug in the medical treatment of insulinoma, several lines of evidence suggest that, through its ability to affect both the provision and release of insulin, Diphenylhydantoin has a broader action than Diazoxide and, thus, offers a better control of hypoglycemia.

The mechanism by which DPH causes hyperglycemia is believed to be impaired insulin release. This hypothesis was first suggested by Peters and Samaan [9] who reported a delayed and subnormal insulin response to glucose administration when the serum concentration of DPH was at toxic levels. Later on, the inhibition of insulin released by DPH was confirmed using the isolated
previously been reported in both type 1 and type 2 diabetics [34–40]. The clinical implication is that the presence of an insulin-secreting tumor should be considered in a diabetic patient who presents with an otherwise unexplained hypoglycemia.

4. Conclusion

Based on the above facts, we suggest that DPH is suitable as a temporary therapeutic measure in the preoperative period of patients with insulinoma, as well as an alternative to surgery for those who are not surgical candidates.

References