Drug-Induced Disorders of Glucose Metabolism
Mechanisms and Management

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Summary

Glucose homeostasis is maintained by a balance between the release and action of insulin, and the counterregulatory responses mediated principally by glucagon, catecholamines, growth hormone and cortisol. Hence, the effects of a drug on glucose metabolism may be mediated by any of these agents singly or in combination. Host factors, such as inherent gluco regulatory mechanisms, concurrent diseases, organ function and concomitant medications also increase the risk of drug-induced disturbances of glucose homeostasis in susceptible individuals. By far the most important agents causing hypoglycaemia are insulin and the sulphonylureas. Alcohol (ethanol), over-zealous glycaemic control, hypoglycaemic
unawareness, defective counterregulation especially in insulin-dependent diabetes mellitus (IDDM), and renal and liver impairment are all important predisposing factors. Although antihyperglycaemic agents such as metformin and α-glucosidase inhibitors do not cause hypoglycaemia alone, they may enhance the hypoglycaemic effects of potent hypoglycaemic agents such as insulin and sulphonylureas. On the other hand, the potential hypoglycaemic effects of ACE inhibitors, α-blockers, lipid-lowering agents and recombinant human insulin-like growth factor demonstrated in experimental settings, are of potential therapeutic interest.

Iatrogenic hypoglycaemia and intensive insulin treatment are associated with hypoglycaemic unawareness which may be obviated by meticulous avoidance of hypoglycaemia. Effective patient education remains an important preventive measure. Oral glucose is used to treat mild hypoglycaemic episodes while more severe episodes are treated by intravenous glucose or glucagon. Nasal glucagon and theophylline are other experimental measures to improve recovery from hypoglycaemia. In refractory hypoglycaemia due to hyperinsulaemia such as during sulphonylurea overdosage or quinine treatment, the long-acting somatostatin, octreotide, may suppress insulin release and restore euglycaemia.

Diuretics, β-blockers, sympathomimetics, corticosteroids and sex hormones are commonly prescribed drugs which may have adverse effects on carbohydrate metabolism especially in patients with diabetes mellitus or those who are at risk of developing glucose intolerance. Pentamidine was frequently associated with dysglycaemia due to its pancreatic β-cell cytotoxic effects but is now used less often to treat Pneumocystis carinii pneumonia in immunosuppressed patients.

Despite the large number of anecdotal reports of drug-induced disturbances of glucose metabolism, many of the so-called adverse drug reactions were either idiosyncratic or coincidental. Nevertheless, they emphasise the complex nature of glucose homeostasis and its potential interactions with drugs, host factors and disease states. An understanding of these relationships may allow more critical interpretation of these clinical observations, better prediction of drug-induced adverse effects on carbohydrate metabolism and the implementation of more rational therapy. Hence, the hypoglycaemic effects of a drug may be turned to a therapeutic advantage in patients with glucose intolerance. Similarly, the hyperglycaemic effect of a drug may help to treat refractory hypoglycaemia.

1. Insulin Deficiency and Insulin Resistance

An understanding of the mechanisms regulating glucose homeostasis is essential to appreciate fully the hyperglycaemic and hypoglycaemic actions of drugs. Blood glucose level is one of the most closely regulated parameters in humans and is maintained primarily by a balance between insulin release and action and counterregulatory responses. Insulin lowers blood glucose levels by suppressing hepatic glucose production and lipolysis. It enhances the uptake of glucose for utilisation in energy production or storage as glycogen or triglyceride in liver, muscle and adipose tissues. Insulin is synthesised and stored in granules in the pancreatic beta-cells. The main physiological stimulus for insulin secretion is an increase in serum glucose level. Other physiological insulin secretagogues include free fatty acids, ketone bodies and amino acids. These primary stimuli for insulin secretion exert their effects by altering fluxes of cations across both calcium and potassium channels of the beta-cell membrane. These result in an increased