Management guidelines for use of oral hypoglycemic agents (OHA) in complex clinical situations and important drug interactions with OHA's

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ABSTRACT

Special precautions need to be exercised with the use of oral hypoglycemic drugs (OHA) in complex clinical situations. These precautions are based on the pharmacologic properties of the drugs in the normal and disease state. We describe the use of OHA in hepatic and renal diseases. Drug interactions of OHA and lactic acidosis due to biguanides is also described.

1. USE OF OHA IN HEPATIC DISEASES:

Information regarding effects of OHA in hepatic dysfunction is meagre (1, 2). Usually, hepatic metabolism of sulfonylurea involves inactivation by a process of oxidation rather than conjugation. Conjugation involves either a glucuronidation or acetylation. This occurs only in case of acetohexamide, which is converted by liver to a more active metabolite. Most sulfonylureas are metabolised more exclusively in the liver to compounds with little or no activity. Therefore, in liver diseases the inactivation of the drugs is reduced, thereby prolonging their half-life. Hypoglycemic action is potentiated.

Hypoalbuminemia in hepatic disorders makes the drugs more free and thereby the availability of the drug is enhanced. This leads to frequent hypoglycemia. Drug metabolism in alcoholic liver disease is complicated by the fact that alcohol can induce enzymes that degrade sulfonylureas and thus their effects can be reduced.

Liver function tests usually do not correlate well with the ability of liver to metabolise drugs, hence the liver function test (LFT) should not be used as a criterion for adjustment of dosage (3). Therefore it is recommended that sulfonylurea be cautiously administered in reduced doses to patients with liver disease.

2. USE OF OHA IN RENAL DISEASES:

Renal diseases result in the decreased renal elimination of sulfonylureas and their active metabolites, thus prolonging their action. Therefore in renal failure, hypoglycemia is likely to develop regardless of the drugs used (4, 5). The half-life of all sulfonylureas is prolonged in patients with renal disease. This is of little clinical importance as far as tolbutamide and glipizide are concerned, since only small amounts are excreted intact in the urine. Acetohexamide, on the other hand has more active metabolites (hydroxyhexamide) which can accumulate in renal insufficiency and can produce pronounced hypoglycemia (6). Chlorpropamide, because of its long half-life, also should not be used in patients with renal disease. Tolazamide and glibenclamide have active metabolites that accumulate in patients with severe renal insufficiency (with creatinine clearance less than 30 ml/mt (1). Tolbutamide and glipizide are therefore preferable for patients with moderately severe renal insufficiency.

3. BIGUANIDES AND LACTIC ACIDOSIS:

The commonly used biguanides are metformin and phenformin. Metformin is not bound to plasma proteins and does not undergo biotransformation. It is excreted by the kidneys (8). Phenformin is converted to parahydroxyphenethyl biguanide by hydroxylating enzymes in the liver. The detoxifying enzymes are genetically regulated. Therefore, some patients are genetically more prone to have lactic acidosis with these agents while others are not. These drugs are contraindicated in the setting of congestive cardiac failure as well as pulmonary, hepatic and renal diseases, which are likely to produce tissue anoxia and precipitate lactic acidosis (9). Lactic acidosis is treated by insulin and glucose administration. Bicarbonate is used very cautiously, since it can lead to a fluid overload. In severe lactic acidosis, it should be combined with frusemide. Even in severe cases the use of bicarbonate remains a dilemma since alkaline media will lead to free entry of phenformin into the cells and production of more lactic acid. Very rarely, dialysis is indicated.

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4. Drug Interactions:

Other drugs may influence the hypoglycemic actions of sulfonylurea through pharmacodynamic and pharmacokinetic interactions (1, 2, 10). In the latter mechanism, drugs displace sulfonylurea from plasma protein binding sites. (clofibrate, salicylates and sul-phonamides) and produce hypoglycemia. Certain drugs reduce metabolism of sulfonylurea (dicoumarol, chloramphenicol, monoamino-oxidase inhibitors and phenylbutazone) and enhance action of a sulfonylurea. Certain drugs can decrease urinary excretion of sulfonylurea and enhance its action-these are allopurinol, probenecid, phenylbutazone and salicylates. Certain drugs like insulin, alcohol, beta-adrenergic blockers, monoamine-oxidase inhibitors and guanethidine can increase the intrinsic hypoglycemic activity (by pharmacodynamic mechanism) of sulfonylureas.

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