CME CREDIT

Drug metabolism in malnutrition and obesity: clinical concerns

NUTRITIONAL STATUS may alter the pharmacokinetics of many drugs enough that their effects are substantially minimized or accelerated, in some cases raising the risk of toxicity. How does nutritional status affect drug metabolism, and what is its impact on therapeutic outcome in undernourished and obese patients?

MECHANISM OF DRUG METABOLISM

A drug's effect on the body depends on how the body handles the drug through the four phases of transition (absorption, distribution, metabolism, and excretion). Many external and internal factors can alter each of these phases of pharmacokinetics.

Although drug metabolism occurs to some extent in the lungs, intestines, and kidneys, it occurs mainly in the liver, which has the greatest effect on the time course of drug action. In addition, compared with the absorption rate or the renal excretion rate, the rate of drug metabolism has a much greater effect on drug concentration.[1]

The role of the mixed function oxidase system

Drug metabolism can occur by two primary pathways or phases. Phase I, also known as oxidation, is a process of the hepatic mixed function oxidase system (MFOS). The MFOS receives electrons from nicotine adenine dinucleotide phosphate. Cytochrome P450 hemoproteins are reduced as the drug is oxidized. Phase II of hepatic metabolism, or conjugation, includes both glucuronidation and acetylation. Each of these phases of hepatic metabolism results in a chemical alteration of the drug to form another compound that may or may not be pharmacologically active.

Exposure to environmental factors that affect the rate or the capacity of the MFOS results in an increase or decrease in the level of enzyme activity, due to induction or inhibition of the enzyme. Environmental factors capable of producing such changes include diet, alcohol, tobacco, other drugs and foreign chemicals, and disease.[1]

One way to measure the ability of the MFOS to oxidize is to follow the elimination kinetics of a drug such as antipyrine. This drug is rapidly and completely absorbed after oral administration. It is distributed throughout the total body water and is not bound to tissue or to plasma proteins. It is almost completely metabolized by oxidative reactions and has negligible renal elimination.[2]

Diet and drug metabolism

The effects of diet on drug metabolism in humans are well documented, although the mechanisms are unclear. Increased dietary protein causes an increase in drug metabolism. Increased dietary carbohydrate results in a decrease in drug metabolism. Increased dietary fat has relatively little effect on drug metabolism. Decreased caloric intake leads to a decrease in drug metabolism.[3]

UNDERNUTRITION AND METABOLIC CLEARANCE OF DRUGS

Decreased caloric intake can also lead to a state of protein-calorie malnutrition. The effects of deficiencies in individual dietary components have been studied in rats: deficiencies in choline[4] and

vitamin A[5] lead to a decrease in MFOS enzymes (cytochrome P450), which results in a decrease in drug metabolism. Bulusu and Chakravarty[6] induced various degrees of protein-calorie malnutrition in rats and showed that decreased protein intake led to decreased enzyme activity when the rats were exposed to subacute doses of certain insecticides. Several studies[7–11] showed decreased metabolism, higher plasma levels, and increased toxicity in malnourished rats when exposed to cancer chemotherapeutic agents oxidized by the MFOS, particularly methotrexate and 5-fluorouracil.

Extrapolating results of MFOS studies in rats to humans is difficult. Cytochrome P450 enzyme systems, drug metabolism rates, and the pharmacodynamics of various chemicals can be substantially different between animals and humans. Also, the laboratory rat shows large sex differences in P450-dependent enzyme activities, a difference not shown in humans.[12]

Manifestations of protein-calorie malnutrition in humans vary widely with age, duration of food deprivation, and associated pathological conditions. Marasmus is a condition characterized by loss of weight, emaciation, loss of skin turgor, disappearance of most subcutaneous fat, and atrophy of muscles. Plasma albumin levels are often normal. In developed countries, patients present in a state of semistarvation and may not have a marked loss of subcutaneous fat. Kwashiorkor is usually seen in children in underdeveloped countries and clinically presents as inadequate growth, hypoalbuminemia, loss of muscular tissue, edema, and hepatomegaly. Other common features include apathy, skin changes, discolored and sparse hair, and mental changes. In the adult in developed countries this presents as malnutrition with accompanying hypoalbuminemia. Frequently, severe protein-calorie malnutrition will have features of both marasmus and kwashiorkor.[13]

The rate of hepatic metabolism of drugs in protein-calorie malnutrition varies depending on the degree of malnutrition. Phase I metabolism (oxidation) of such drugs as antipyrine, acetanilide, theophylline, and carbamazepine is considerably reduced as the severity of malnutrition increases. Phase II metabolism (conjugation) of chloramphenicol, acetaminophen, and sulfonamides is also impaired in malnourished children.[13] A French study looked at antipyrine metabolism in 49 patients with mixed semistarvation and hypoalbuminemia and 25 matched controls. The malnourished patients with plasma albumin levels less than 3.0 g/dL had lower volumes of drug distribution, lower antipyrine clearances, and greater drug half-lives than controls or patients with albumin levels greater than 3.0 g/dL.[14] Patients who are malnourished because of malignant cell growth have been reported to be significantly less likely to respond to chemotherapy than those who are nutritionally normal.[15] Protein-calorie malnutrition is regularly accompanied by multiple nutritional deficiencies.[14] Therefore, the mechanisms of the effects of protein-calorie malnutrition on drug metabolism may be multifactorial. For example, prolonged riboflavin deficiency results in depressed MFOS activities due to increased levels of cytochrome P450.[16]

OBESITY AND METABOLIC CLEARANCE OF DRUGS

Studies in animals and humans have demonstrated the effects of protein-calorie malnutrition on phase I hepatic metabolism. In contrast, studies in animals and humans have demonstrated that obesity has more of an effect on phase II metabolism. From a nutritional perspective, most patients are considered obese if they are more than 20% heavier than their ideal body weight. In most obese individuals, the liver usually has been infiltrated by fat. The degree of fatty infiltration of the liver (hepatic steatosis) appears to be directly proportional to the extent of obesity. In obese patients, clearance of drugs that undergo phase I metabolism can be either increased or unchanged. In contrast, clearance of drugs that undergo phase II metabolism is significantly increased in obese patients. Drugs that undergo phase II metabolism include benzodiazepines, acetaminophen, and aspirin.[17] In one study,[18] enflurane, a volatile halogenated anesthetic, was given to 26 obese (body mass index >30) and eight nonobese patients to observe how obesity affected its metabolism. Pharmacologically equivalent doses were administered, and metabolism was studied by monitoring the nephrotoxic metabolite of enflurane. The results suggested that the metabolism in the obese group proceeded at a rate approximately twice that in the nonobese group.[18]

The mechanism for the increase in metabolic clearance of drugs in obese patients has not been determined. Suggestions include fat infiltration and fibrosis of the liver, changes in the composition of the diet in obese patients (150% to 250% of ideal

body weight), and altered hepatic blood flow.[19]

Abernethy et al[20] suggest that maintenance doses of drugs that undergo phase II metabolism should be increased in proportion to the increase in total body weight of obese patients (>120% of ideal body weight).

SUMMARY

In general, patients who are malnourished tend to have prolonged effects from drugs metabolized by the MFOS. On the other hand, in obese patients, drugs that undergo phase II metabolism tend to be metabolized more rapidly, thus shortening their duration of action. Therefore, clinicians must remember that, in protein-calorie malnutrition, drugs metabolized in the liver may be more likely to cause toxic effects due to the decreased rate of hepatic metabolism. Dose reduction could eliminate these adverse effects. Alternatively, drugs that undergo phase II metabolism may need to be administered at higher doses in obese patients, since the desired clinical effect may not be seen at a normal dose due to the obesity-related increase in hepatic metabolism. This should be considered before discontinuing the drug as a result of its lack of effect.

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