New Approaches to Assessment of Drug Disposition in the Surgical Patient

Three years ago an editorial in these pages described several metabolic complications of total parenteral nutrition. These potential problems include the syndrome of hyperosmolar, hyperglycemic, nonketotic coma; dangerous hypoglycemia following unplanned discontinuation of high concentrations of intravenous glucose; hypophosphatemia; metabolic acidosis; and increased CO₂ production from metabolism of large amounts of glucose. Enhanced CO₂ formation may require initiation of artificial ventilation or may cause failure to wean the patient from long-term ventilation. Other problems and metabolic alterations associated with total parenteral nutrition were enumerated. Caution was suggested in treating such patients. Also, it was recommended that their total energy expenditure be measured before instituting energy replacement.

The article by Pantuck et al. in this issue of ANESTHESIOLOGY extends the list of significant metabolic alterations associated with total parenteral nutrition. Pantuck et al. show that total parenteral nutrition can alter rates of hepatic drug oxidation in divergent ways dependent on the type of nutrition furnished. This has widespread implications. After six healthy young male volunteers had their total nutrition provided parenterally for 4 days with 5% dextrose followed by an isocaloric amount of amino acids (Aminosyn 3.5%) for 1 day, disposition of the model drug antipyrine changed in interesting, divergent ways from that measured under control conditions on a home diet. Compared with antipyrine clearance values obtained on their home diet, the 4 days on dextrose significantly decreased antipyrine clearance.

By contrast, after only 1 day on parenteral amino acids antipyrine clearance increased markedly. Thus, dextrose retarded, whereas amino acids enhanced, rates of drug elimination.

Extrapolation of these results to other drugs may be justified by extensive earlier work on similar effects of isocaloric diets in which the relative proportions of protein to carbohydrate were altered. Collectively these studies suggest that anesthesiologists should consider that the doses of many drugs given to surgical patients may need to be changed on commencement of total parenteral nutrition. Drugs eliminated primarily by hepatic metabolism especially require dosage adjustment. The extent of this dosage adjustment is not determined easily because numerous dynamically changing, interrelated host factors affect it.

Before discussing these factors, we shall describe some earlier experiments that illustrate how various dietary manipulations dramatically alter hepatic drug metabolism. Use of laboratory animals permitted clearer elucidation of the mechanisms of these dietary effects than was possible in human subjects since the activities of hepatic drug-metabolizing enzymes could be assayed directly in laboratory animals. In several species, the specific composition of the diet was demonstrated to influence the biologic fate of drugs, and therefore their intensity and duration of action. Reduction in dietary protein decreased rates of metabolism of some drugs, whereas a high protein diet increased these rates. Overnight starvation of rats markedly altered the activities of certain hepatic drug-metabolizing enzymes, but in obese human subjects starvation produced no changes in antipyrine metabolism. In mice a diet high in carbohydrates diminished hepatic metabolism of drugs in vitro and in vivo.
of drug is oxidized a molecule of oxygen is reduced simultaneously to water. This reaction requires molecular oxygen, NADPH, and a heme protein called cytochrome P-450. The latter is located within the lipid structure of the smooth endoplasmic reticulum. In the rat, more than 10 distinct molecular forms or isozymes of cytochrome P-450 have been isolated and characterized. The amino acid sequence of several cytochrome P-450 isozymes has been defined, and the genes controlling them have been cloned.

Extensive heterogeneity of cytochrome P-450 in humans complicates the interpretation of any factor that can alter rates of metabolism of a particular drug. The question must be asked: how many other drugs will behave similarly? This question often reduces to the molecular mechanism involved in the metabolism of a particular drug and whether the factor under discussion influences all hepatic cytochrome P-450 isozymes to an equal extent. Alternatively, distinct cytochrome P-450 isozymes may be affected differentially. Other nonoxidative pathways that may participate in the hepatic metabolism of the drug under study may be either unaffected or alternatively even more affected than hepatic oxidative reactions. A recent study on effects of switching the ratio of carbohydrate to protein in an isocaloric diet showed that acetaminophen metabolism, and possibly other hepatic con-

Fig. 1. Mean hepatic microsomal values for glucose- and fructose-treated rats expressed as percent of saline-treated controls. Reproduced from Hartshorn et al: Effects of chronic parenteral carbohydrate administration on hepatic drug metabolism in the rat. Pharmacology 18:103–111, 1979, with permission.

In 1951, Lamson et al. first demonstrated an effect of carbohydrate on drug disposition. On awakening from pentobarbital anesthesia, dogs would return to sleep if they received 10 ml of a 50% dextrose solution. In rats, intraperitoneal injection of either glucose or fructose for 7 days decreased cytochrome P-450 content and the activities of several hepatic microsomal drug-metabolizing enzymes; assessment in vivo of this system using antipyrine confirmed decreased drug-metabolizing capacity. Chronic intraperitoneal administration of carbohydrate produced hepatic glycogen depletion and fatty infiltration. These experiments revealed that such variables as time and dose of carbohydrate administered affect the magnitude of the changes produced (fig. 1). Each enzyme measured exhibited a distinctive pattern of change with time.

We now recognize that the hepatic oxidative metabolism of most drugs occurs through an enzymatic system involving several different proteins. One vital reaction is designated a mixed function oxidase because as a molecule

Fig. 2. This circular design suggests the multiplicity of either well-established or suspected host factors that may influence drug response in humans. Reproduced from Vesell: On the significance of host factors that affect drug disposition. Clin Pharmacol Ther 31:1–7, 1982, with permission.
jugation reactions, are unaltered in humans by such dietary manipulations.\textsuperscript{15}

Since three genetically distinct cytochrome P-450 isozymes participate in antipyrine biotransformation,\textsuperscript{16\textendash}18 the pioneering study by Pantuck \textit{et al.}\textsuperscript{2} raises the question of which cytochrome P-450 isozymes are affected by these dietary manipulations. Are they equally depressed by parenteral carbohydrate and elevated to a similar extent by parenteral amino acids or are they differentially affected, as is the case for the inductive effects of rifampicin?\textsuperscript{19}

These questions can be answered satisfactorily now because sensitive, reliable techniques are available to measure antipyrine metabolites in urine.\textsuperscript{20} The specificity of information obtained by calculating rate constants for formation of each antipyrine metabolite recommends this approach, which can help to elucidate at the molecular level mechanisms by which host factors shown in figure 2 produce their effects.\textsuperscript{18\textendash}21 Diet is only one of these dynamically interacting host factors that can affect the elimination of antipyrine and other drugs. Therefore, the extent to which a given factor influences drug elimination depends both on the particular drug and the subject. Because these factors may interact synergistically or antagonistically, they are joined in a circle; the wavy line from each factor to the center circle in figure 2 indicates that these host factors can exert several independent effects on the discrete processes of drug absorption, distribution, metabolism, and excretion.\textsuperscript{22}

In a particular patient receiving total parenteral nutrition, several host factors in figure 2 may be in a state of dynamic change and interaction. The function of critical organs directly involved in drug disposition, including the heart, kidney, and liver, may be rapidly fluctuating. Effective blood concentrations of many drugs can differ from day to day, due not only to addition of new drugs and withdrawal of others, but also to changes in cardiovascular, hepatic and renal function, hormonal status, and diet. In turn, these changes in drug blood concentration can alter in often unpredictable ways rates of drug elimination through effects on hepatic drug-metabolizing enzymes. Presence of infection, fever, and intercurrent disease offers additional opportunities for perturbation of a patient’s normal rate of drug elimination. So many interrelated host factors converge simultaneously and change dynamically in surgical patients receiving total parenteral nutrition that it is often difficult to predict how a particular patient would respond to a particular drug.

To illustrate the difficulty of extrapolating to surgical patients the results of Pantuck \textit{et al.}\textsuperscript{2} on total parenteral nutrition in normal unanesthetized, nonsurgical male subjects, several studies demonstrate a marked but complex effect on antipyrine metabolism of surgery under general anesthesia. In 1976 Elfstrom \textit{et al.}\textsuperscript{23} observed that 37 surgical patients who received general anesthesia for various conditions markedly increased their antipyrine clearance on days four and five postoperatively but not on the second and third postoperative days. These patients were not stated to have received parenteral nutrition. The most marked metabolic change (almost 50\% enhancement of antipyrine elimination) occurred in a subgroup of nine young patients who underwent repair of torn knee ligaments.

In a follow-up investigation, Elfstrom and Lindgren\textsuperscript{24} reported that antipyrine elimination was increased only slightly by bed rest in six normal young males whose antipyrine elimination was studied while ambulant and again after 60 hours of bed rest. In 18 surgical patients and six controls, Pessayre \textit{et al.}\textsuperscript{25} related the effect of surgery and general anesthesia on antipyrine clearance to the duration of the surgical procedure and hence to the magnitude of stress. They measured antipyrine clearance both before and three days after surgery. In patients in surgery 2 h or less, postoperative antipyrine clearance increased 48\%; in patients in surgery 2\textendash}4 h, it decreased 36\%; and in patients in surgery more than 4 h, antipyrine clearance declined by 47\%.

This simplistic interpretation, while possibly correct in general terms, remains to be confirmed. The duration of anesthesia may be an insensitive index of the extent of trauma and stress. Other factors to be considered include the patient’s medical status, effects of different drugs being administered, and the type of surgical procedure being performed.

The conclusion that patients change their basal drug-metabolizing capacity depending on the length and type of surgical procedure must give pause to those who administer drugs under such ill-defined conditions. Drug disposition in the surgical patient deserves more investigation. Elucidation of this problem will have to await better identification of variables involved and their independent manipulation under controlled experimental conditions where individual metabolites of model drugs such as antipyrine are measured instead of only parent drugs. Antipyrine is suited uniquely for this purpose because its decay closely reflects its hepatic metabolism and is largely independent of changes in hepatic blood flow and renal function. Furthermore, under stable environmental conditions a subject’s rate of antipyrine elimination is highly reproducible and conveniently, accurately, and noninvasively measured. For these reasons, antipyrine is used widely as a test of liver function and an index of hepatic drug-metabolizing capacity.\textsuperscript{21}

Therefore, the antipyrine test\textsuperscript{21} and the aminopyrine breath test\textsuperscript{25\textendash}27 can quantify a particular surgical patient’s capacity to metabolize these drugs and can identify
factors that alter this capacity. Caution needs to be exercised in extrapolation of such results to other drugs.\textsuperscript{21} Also, values for these tests of drug-metabolizing capacity can change so rapidly that they may be quite different 6 or 12 h later. In some surgical patients, these tests may be useful, but in others where a drug needs to be given urgently, time may not permit obtaining such information. Currently, these tests are suited particularly for clinical investigation. The time has not yet arrived for their routine clinical use to indicate hepatic drug-metabolizing capacity in surgical patients. In the future, the test drug approach generally may become available to assist anesthesiologists in selecting safe drugs and safe doses. At the present time, the best approach in critical cases is largely empirical: to administer all drugs cautiously and to watch patients closely. Special attention should be focused to assure that the desired therapeutic effect is obtained and to detect adverse drug effects early, thereby permitting appropriate dosage modification before severe toxicity ensues.

While these general therapeutic principles may be difficult to practice, they can be lifesaving. One of the main contributions of the paper by Pantuck \textit{et al.}\textsuperscript{2} is to alert the anesthesiologist to the possibility that rates of drug elimination may change rapidly in surgical patients receiving total parenteral nutrition. Because several host factors shown in figure 2 may be fluctuating simultaneously and interacting dynamically, selection of appropriate doses of many drugs with low therapeutic indexes becomes a difficult task. If the physician recognizes this difficulty and the reasons responsible for it, an initial dose can be chosen that will be understood to represent only a gross approximation. Subsequent close inspection of the patient to detect therapeutic as well as undesired effects of this dose should lead to adjustment of the dose and eventual selection of an appropriate dose and dose interval. This approach to individualization of drug therapy accompanied by a defensible rationale for the introduction of each new drug and a clear estimate in each patient of the end-point desired from each drug administered should help to make drug use in surgical patients safer and more effective. More intensive investigation of drug disposition in the surgical patient using the test drug approach under controlled conditions eventually could provide the information needed to administer drugs more judiciously. Such research is in progress and should be encouraged.

\textbf{References}

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