Metabolic Response to Total Parenteral Nutrition in Cancer Patients

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SUMMARY

In order to evaluate the metabolic response of nutritionally deprived cancer patients to parenteral nutrition, metabolic parameters including glucose turnover, oxidation, and Cori cycle activity were measured in eight patients before and during short-term (5 to 10 days) i.v. nutrition, with solutions containing amino acids and hypertonic glucose. Before parenteral nutrition, five patients had essentially normal glucose turnover, oxidation, and Cori cycle activity, whereas three patients had moderately increased glucose turnover and markedly increased Cori cycle activity. In response to parenteral nutrition, plasma glucose, insulin, and venous lactate concentration increased and free fatty acid decreased. The percentage of respiratory CO₂ from glucose oxidation and the rate of oxidation increased. CO₂ production increased, whereas O₂ consumption was essentially unchanged. Respiratory quotient rose to >1.0. Endogenous glucose production and high basal Cori cycle activity were decreased. Total parenteral nutrition was judged clinically beneficial in five patients, whereas one patient was unchanged. Deleterious responses, including moderate lactic acidemia, occurred in two of three patients with elevated basal Cori cycle activity.

INTRODUCTION

It is generally believed that poor nutritional status contributes to the debility and morbidity of patients with malignant diseases. Because earlier attempts at forced oral feeding of nutritionally deprived cancer patients resulted in variable clinical responses (32), this approach has not been actively pursued until recently, largely due to the acceptance of TPN³ as an important therapeutic modality (6-8, 11, 25, 29).

TPN is known to alter the metabolic and biochemical profile of normal subjects. Because abnormalities of glucose and lactate metabolism can occur in some cancer patients (18, 34, 35), we have studied 8 nutritionally deprived patients before and during short-term TPN by isotope tracer techniques, in order to evaluate resulting host metabolic responses.

MATERIALS AND METHODS

Patients. Eight hospitalized patients with metastatic solid tumors were selected for study. In all cases life expectancy was estimated to be >60 days, and no patient was totally confined to bed. Relevant details pertaining to clinical status are shown in Table 1. At the time of study all patients except C. W. had lost >10% of body weight as a direct result of their disease. No patient was acutely ill, and none was febrile. No patient received chemotherapy or glucocorticoids during the preceding 3 weeks. The purpose and potential risks of hyperalimentation and the isotope tracer procedures were discussed with each patient, and informed consent was obtained.

Metabolic Studies and Methods. Metabolic studies were performed on each patient after an overnight fast of 12 to 14 hr and again after 5 to 10 days of parenteral nutrition. Patients had been maintained on the same quantity of nutrient solution for at least 2 days before the 2nd study. Plasma glucose turnover and Cori cycle activity were measured by previously described methods (18, 27). Fifty to 100 μCi (3 to 6 mg) of [1-¹⁴C]glucose were rapidly administered at zero time, and beginning 1 hr later, blood samples were collected at 30-min intervals for 4 hr. Plasma samples were deproteinized, and the protein-free filtrate was passed through a column of Amberlite MB-3 resin (HCO₃⁻ form). One aliquot of the column eluate was used to determine radioactivity in carbon 6 of glucose by periodate oxidation and formaldehyde precipitation as previously described (27). Radioactivity in all glucose carbons was determined in a 2nd column aliquot by oxidizing glucose to gluconic acid with glucose oxidase, followed by absorption of gluconate to and elution from a column of Amberlite CG-400 resin, with 0.5 M NaCl (14).

Respiratory gas samples were obtained simultaneously with each blood sample and analyzed for O₂, CO₂, and ¹⁴CO₂ content by standard methods (19). Immunoreactive insulin was determined by the method of Hales and Randle (17), free fatty acids were determined by the method of Dole and Meinertz (10), lactate was determined by the modification by Strom (31) of the method of Barker and Summerson (2), and glucose in plasma and parenteral nutrition solution were determined by using Glucostat reagent (Worthington Biochemical Corp., Freehold, N. J.). Total energy balance was estimated in each patient before parenteral nutrition by conventional indirect calorimetry.

The parenteral nutrition solution utilized in these studies contained approximately 218 g glucose and 4.5 g nitrogen
RESULTS

Rates of glucose turnover, oxidation, Cori cycle activity, and other metabolic parameters obtained before TPN in 5 of the 8 patients in this study have been reported previously (18). Patients L. R., R. E., and C. Y. were subsequently added for this investigation. In the present study the volume of parenteral nutrition solution administered to each patient ranged from about 1.5 to 2.5 liters/day. Thus, patients R. S., M. B., and C. W. received glucose at a rate that provided carbohydrate calories 10 to 15% in excess; Patients S. M., L. R., R. E., and C. Y. received it at a rate 22 to 26% in excess; and Patient F. R. received it at a rate 45% in excess of measured basal energy expenditure. Patients L. R., R. E., and C. Y. received 8.1 to 9.4 g nitrogen per 24 hr, whereas the remaining patients received 10.3 to 13.1 g nitrogen per 24 hr. On the basis of urinary nitrogen excretion during the 4-hr glucose turnover study period, positive nitrogen balance (0.3 to 2.9 g nitrogen per 24 hr) was achieved in all but 2 patients. Negative nitrogen balance was observed in M. B. and R. E. with values of −5.6 and −1.7 g nitrogen per 24 hr, respectively.

In response to TPN, plasma glucose, insulin, and venous lactate concentrations increased, and free fatty acid decreased (Chart 1). No patient developed significant hyperglycemia, glycosuria was absent, and no patient required exogenous insulin supplementation. Mean venous lactate concentration before TPN was 1.34 mm and rose to 2.05 mm during TPN. Two patients (M. B. and S. M.) with the highest initial lactate concentrations developed moderate lacticacidemia of 2.7 and 3.5 mm, respectively. Mean O2 consumption rose slightly but not significantly in response to TPN, whereas mean CO2 production increased markedly (p < 0.01) (Chart 2). Respiratory quotient rose to >1.0 except in 1 patient, S. M.

Time-course changes in the specific activity of plasma glucose carbons 1 to 5, carbon 6, and respiratory CO2 in Patient R. S. before and during parenteral nutrition are shown in Chart 3. During each glucose turnover study period the plasma glucose concentration was reasonably constant, averaging 86 mg/100 ml before and 114 mg/100 ml during parenteral nutrition. There was a linear decline in the specific activity of glucose carbons 1 to 5 in each study period, but during TPN the decline was much steeper, indicating a more rapid turnover rate. Before TPN, the specific activity of glucose carbon 6 rose gradually, reached a peak at 2 hr, and then declined. During TPN in this patient, the same general pattern was noted except that the peak occurred at an earlier time, and the entire curve was shifted downward relative to the carbon 1 to 5 specific activity curve. The change in respiratory CO2 specific activity with time in the study before TPN is similar to that previously reported by us and others, by the single injection technique for [14C]glucose administration (1, 24, 28). During TPN, the CO2 specific activity curve reached a peak at an earlier time, and the ratio of CO2 specific activity to that of the carbon 1 to 5 specific activity at each sampling period was somewhat greater than was observed before TPN.

Rates of glucose turnover, oxidation, and Cori cycle activity observed in the 8 patients before and during TPN are shown in Table 2. Before nutritional therapy, 3 patients (R. S., M. B., and S. M.) had moderately increased glucose turnover rates and markedly elevated Cori cycle activity, whereas 5 patients (Table 2, C. W. to C. Y.) had essentially normal glucose turnover and Cori cycle activity. In the latter

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**Table 1**

Clinical data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Diagnosis</th>
<th>Wt* (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. S.</td>
<td>44</td>
<td>M</td>
<td>Cancer of bronchus; retroperitoneal metastases</td>
<td>62.9, 60.5</td>
</tr>
<tr>
<td>M. B.</td>
<td>46</td>
<td>M</td>
<td>Cancer of colon; liver metastases</td>
<td>73.2, 76.4</td>
</tr>
<tr>
<td>S. M.</td>
<td>60</td>
<td>M</td>
<td>Cancer of bronchus; bone and liver metastases</td>
<td>61.8, 62.7</td>
</tr>
<tr>
<td>C. W.</td>
<td>79</td>
<td>M</td>
<td>Cancer of colon; lung metastases</td>
<td>61.4, 65.9</td>
</tr>
<tr>
<td>F. R.</td>
<td>67</td>
<td>M</td>
<td>Cancer of stomach</td>
<td>52.3, 58.6</td>
</tr>
<tr>
<td>L. R.</td>
<td>79</td>
<td>F</td>
<td>Cancer of stomach; liver metastases</td>
<td>44.3, 45.3</td>
</tr>
<tr>
<td>R. E.</td>
<td>53</td>
<td>F</td>
<td>Cancer of breast; liver, bone, and s.c. metastases</td>
<td>31.8, 32.8</td>
</tr>
<tr>
<td>C. Y.</td>
<td>52</td>
<td>F</td>
<td>Cancer of breast; cutaneous, mesenteric and liver metastases</td>
<td>40.9, 44.4</td>
</tr>
</tbody>
</table>

* Denotes weight before and at the completion of TPN.

(Amigen, protein hydrolysate) per liter. The techniques used for parenteral nutrition at this institution have been reported previously (26).

The patient voided before each turnover study, and urine was collected throughout and at the close of the experimental period. A sample of the parenteral nutrition solution which each patient was receiving at the time of the study was also obtained. Nitrogen in urine and parenteral nutrition solution were determined by the method of Ferrari (13).

Calculations. The rate of glucose turnover and Cori cycle activity were calculated by using assumptions and equations described previously (27). In all studies, a linear decline in the specific activity of plasma glucose and reasonably constant plasma glucose concentrations indicated that steady-state conditions were present. The glucose turnover rate was obtained as the product of the glucose pool and the fractional replacement rate, corrected for radioactivity recycled into glucose carbons 1 to 5. The glucose pool was calculated by extrapolating the specific activity of plasma glucose to zero time, a procedure which assumes a single homogenous glucose pool of constant size.

Cori cycle activity, determined from radioactivity recycled into glucose carbon 6, was calculated as a fraction of the fractional replacement rate. The rate of plasma glucose oxidation was obtained from the known rate of CO2 output and the percentage of the exhaled CO2 derived from oxidation of plasma glucose. This latter value was calculated as the ratio of the maximum CO2 specific activity achieved to that of the plasma glucose specific activity at the same time, i.e., at tmax of the respiratory CO2 specific activity curve (1). Values for the percentage of CO2 derived from plasma glucose oxidation and the rate of glucose oxidation obtained in our patients before parenteral nutrition are in good agreement with those reported by others who used this method of calculation (1, 24).
patients, Cori cycle activity was about 22% of the total glucose turnover, a value which is close to that obtained in normal humans by isotope tracer techniques (22, 27). It is also similar to the fraction of hepatic glucose output attributable to lactate uptake determined by direct catheterization of the splanchnic bed in normal humans (22). The rate of plasma glucose oxidation averaged 59 mg/kg/hr (range, 36 to 82) and accounted for 22% (range, 15 to 32) of the total CO₂ output.

In response to TPN, plasma glucose turnover and oxidation increased. The total glucose turnover rates shown in Table 2 include Cori cycle activity. The difference between total glucose turnover and Cori cycle activity should represent endogenous glucose production from all other sources and, during TPN, should be equal to the known rate of glucose administration if endogenous production was completely suppressed. In our studies during TPN, calculated rates of endogenous production averaged 90% of the known rates of glucose administration. There are several possible reasons for this discrepancy. First, in patients receiving TPN, the fractional replacement rate of plasma glucose was increased because of exogenous glucose administration. Although radioactivity was present in glucose carbon 6, the small quantities found preclude accurate assessment of the calculated fractional rate of recycling. This uncertainty, coupled with even small experimental errors involved in estimating the rate of glucose administration and turnover, may account for the differences observed. A 2nd reason is that the small but persistent recycling of radioactivity may be due to processes not reflecting net glucose synthesis from lactate, i.e., isotopic exchange of...
Table 2

<table>
<thead>
<tr>
<th>Patient</th>
<th>Glucose infusion rate (mg/kg/hr)</th>
<th>TGT* (mg/kg/hr)</th>
<th>Cori cycle activity</th>
<th>% of TGT*</th>
<th>% of CO₂ from plasma glucose oxidation rate (mg/kg/hr)</th>
<th>Glucose oxidized Glucose infused x 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>R. S.</td>
<td>0</td>
<td>221</td>
<td>124</td>
<td>56</td>
<td>25</td>
<td>70</td>
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<tr>
<td>331</td>
<td>340</td>
<td>18</td>
<td>5</td>
<td>53</td>
<td>202</td>
<td>61</td>
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<tr>
<td>M. B.</td>
<td>0</td>
<td>283</td>
<td>193</td>
<td>68</td>
<td>27</td>
<td>76</td>
</tr>
<tr>
<td>324</td>
<td>312</td>
<td>62</td>
<td>19</td>
<td>49</td>
<td>161</td>
<td>50</td>
</tr>
<tr>
<td>S. M.</td>
<td>0</td>
<td>209</td>
<td>101</td>
<td>48</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>399</td>
<td>409</td>
<td>76</td>
<td>19</td>
<td>53</td>
<td>170</td>
<td>43</td>
</tr>
<tr>
<td>C. W.</td>
<td>0</td>
<td>108</td>
<td>26</td>
<td>24</td>
<td>18</td>
<td>36</td>
</tr>
<tr>
<td>240</td>
<td>234</td>
<td>19</td>
<td>8</td>
<td>52</td>
<td>120</td>
<td>50</td>
</tr>
<tr>
<td>F. R.</td>
<td>0</td>
<td>105</td>
<td>27</td>
<td>26</td>
<td>15</td>
<td>40</td>
</tr>
<tr>
<td>441</td>
<td>470</td>
<td>62</td>
<td>13</td>
<td>55</td>
<td>203</td>
<td>46</td>
</tr>
<tr>
<td>L. R.</td>
<td>0</td>
<td>148</td>
<td>41</td>
<td>25</td>
<td>32</td>
<td>82</td>
</tr>
<tr>
<td>325</td>
<td>395</td>
<td>32</td>
<td>8</td>
<td>62</td>
<td>203</td>
<td>63</td>
</tr>
<tr>
<td>R. E.</td>
<td>0</td>
<td>177</td>
<td>29</td>
<td>16</td>
<td>18</td>
<td>56</td>
</tr>
<tr>
<td>399</td>
<td>399</td>
<td>31</td>
<td>8</td>
<td>37</td>
<td>150</td>
<td>38</td>
</tr>
<tr>
<td>C. Y.</td>
<td>0</td>
<td>111</td>
<td>19</td>
<td>17</td>
<td>19</td>
<td>53</td>
</tr>
<tr>
<td>335</td>
<td>339</td>
<td>27</td>
<td>8</td>
<td>41</td>
<td>147</td>
<td>44</td>
</tr>
</tbody>
</table>

* TGT, total glucose turnover rate.

labeled glucose carbon (21). Supporting this possibility are reports that lactate extraction by the splanchnic bed of the human was virtually abolished during suppression of endogenous glucose production by p.o. or i.v. glucose administration (12, 33).

During TPN, Cori cycle activity, expressed as mg per kg per hr, apparently decreased or remained essentially unchanged, whereas, when expressed as a fraction of the total glucose turnover, a uniform decrease was noted in all patients. Because of the previously mentioned uncertainties concerning the calculations and significance of Cori cycle activity during TPN, firm conclusions regarding the physiological significance of these changes cannot be stated at this time.

The rates of plasma glucose oxidation were increased 2- to 5-fold during TPN and, although the data are limited, were apparently proportional to the rates of glucose administration. The percentage of CO₂ derived from the immediate oxidation of plasma glucose ranged from 37 to 62%, indicating that glucose provided a major share of the total energy expenditure of the patient. Oxidation accounted for 38 to 61% of the glucose administered in the parenteral nutrition solution.

Parenteral nutrition was judged clinically beneficial in 5 patients; 1 patient (R. S.) was unchanged, whereas 2 patients (M. B. and S. M.) deteriorated clinically. The latter 2 patients both had initially high Cori cycle activity and developed the described moderate lactic acidemia in response to TPN. Clinical response was judged solely on the basis of subjective changes, and no attempt was made to evaluate objective changes in measurable lesions during the short-term study. Thus, beneficial responses occurred in patients claiming an improved sense of well-being, whereas, deleterious responses occurred in patients who described a significant worsening of all symptoms before TPN.

It should be noted that weight changes during TPN are included for the purposes of calculation and, with the exception of R. S., are likely to reflect short-term fluid accumulation. Two patients (R. E. and M. B.) developed modest ascites during nutritional therapy, but this factor alone did not affect the final subjective evaluation of response.

Although M. B. and S. M., with adverse responses to TPN, had liver dysfunction secondary to metastases, similar degrees of liver dysfunction were noted in C. R., R. E., and C. Y., in whom beneficial responses were reported.

DISCUSSION

It is recognized that the patients selected for this initial study are both clinically and metabolically heterogeneous, reflecting the diverse nature of the hospitalized cancer patient population. Because TPN alters the metabolic and biochemical profile of even normal subjects (9) and because abnormalities of glucose and lactate metabolism may preexist in some cancer patients in the basal state (18, 34, 35), TPN was delivered as a strictly short-term adjunct before specific anticancer therapy in this group of patients.

In response to TPN, plasma glucose and insulin concentrations increased, and free fatty acids decreased as would be anticipated after an infused glucose load. Impaired glucose tolerance has been described in nutritionally deprived cancer patients (5) and in some trauma patients receiving TPN (16). The absence of significant induced hyperglycemia during TPN, however, excludes the possibility of major disturbances of carbohydrate tolerance in the patients studied.

The administration of exogenous glucose to normal humans results in a decrease in its endogenous production (12, 23, 33). At least qualitatively, the suppression of endogenous glucose production observed in our patients during TPN is in agreement with those observations.

Major increases in O₂ consumption and basal metabolism rate were not observed in our patients, contrasting with previous reports by Terepka and Waterhouse (32) on the metabolic response to forced feeding in some cancer patients. The percentage of CO₂ derived from immediate oxidation of plasma glucose during TPN averaged 50% (range, 37 to 62), indicating that glucose provided a major share of the total energy expenditure of the patient. The wide range of values is probably related to the nutritional status of the...
patients and to the rate of exogenous glucose administration.

That glucose was apparently not a more important energy-yielding fuel during TPN is somewhat surprising. The percentage of CO₂ derived from glucose oxidation and the rate of glucose oxidation may have been underestimated because of isotopic exchange of the labeled glucose carbon with and into other compounds (21). However, amino acid and fatty acid oxidation probably also contributed to the caloric requirement of patients during TPN. The urinary nitrogen excretion in our patients, calculated from a 4-hr urine collection during each metabolic study period, averaged 10.7 g/24 hr (range, 5.9 to 18.7). Since the caloric equivalent of urinary nitrogen is 26.4 kcal/g, this rate of urinary nitrogen excretion is equal to about 280 kcal/24 hr or 20% of the estimated total energy expenditure of these patients (18). Rates of plasma free fatty acid oxidation have not been measured in the human during periods of sustained glucose administration. However, a short-term glucose administration to the human (36) or animals (15) has been shown to decrease but not abolish fatty acid oxidation. By using an average plasma free fatty acid concentration of about 0.2 μEq/ml, which was observed in our patients during TPN, and on the basis of data extrapolated from normal humans studied over a wide range of plasma concentrations (19), it is possible to calculate that about 15% of their total caloric expenditure was probably derived from oxidation of plasma free fatty acids. Thus, during TPN, about 85% of the total caloric expenditure of our patients could be accounted for by oxidation of glucose, amino acids, and plasma free fatty acids. The remainder of the total caloric expenditure may have been satisfied by glucose oxidation which was underestimated because of methodological and experimental errors involved in estimating this process.

With the exception of 1 patient, respiratory quotients values exceeded 1.0 during TPN, implying the synthesis of fat from carbohydrate. Diets rich in carbohydrate have been shown to increase triglyceride-fatty acid synthesis in the human (3). It is therefore possible that some glucose administered during TPN was converted to triglycerides in liver and subsequently oxidized in peripheral tissues. Dilution of the administered [14C]glucose carbon and delayed appearance of 14CO₂ resulting from this process could result in an underestimation of the extent to which glucose contributed to total energy expenditure during TPN.

The elevation of venous lactate concentration after TPN requires special comment. Blood lactate concentration is known to rise after glucose administration (12) and during TPN (20), but the mechanism has not been clearly determined. Felig et al. (12) have suggested that the hyperlactatemia after p.o. glucose administration may be due, at least in part, to a decreased splanchnic uptake. During TPN, 2 patients in our study (M. B. and S. M.) developed moderate lacticacidemia of 2.7 and 3.5 mM, respectively, after apparent suppression of high Cori cycle activity. Although this may represent decreased clearance of lactate by means of glucose resynthesis, increased lactate production may also be involved. The possibility exists that increased lactate production may reflect enhanced tumor growth rates, since this phenomenon has been observed during animal studies involving forced feeding (4, 30).

Although it is recognized that patient numbers are small, the clinical response to parenteral nutrition during this study is worthy of comment. Five patients were subjectively improved, and 1 patient was unchanged, whereas 2 patients felt significantly worse and appeared to deteriorate at an accelerated rate. We have not attempted to distinguish between the possibly deleterious effects of glucose versus infused amino acids in this initial study. The greatest benefit occurred in 2 patients with intestinal obstruction who subsequently responded to additional chemotherapy. The deleterious responses occurred in 2 of 3 patients with initially high Cori cycle activity and moderately increased glucose turnover rates, O₂ consumption, and total caloric expenditure. Neither of these latter patients responded to treatment. It seems evident that parenteral nutrition can play a valuable adjunctive role in the management of patients with malignant disease. Our general observations, however, are in accord with those of Terepka and Waterhouse who commented on the sometimes adverse clinical response of cancer patients to forced p.o. feeding (32). Clearly, further studies are required in a more homogeneous population of patients before general acceptance of parenteral nutrition as an adjunct to cancer therapy can be established.

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REFERENCES

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