PAPERS AND SHORT REPORTS

Naftidrofuryl and the nitrogen, carbohydrate, and lipid responses to moderate surgery

J M JACKSON, H T KHAWAJA, P C WEAVER, S T TALBOT, H A LEE

Abstract

The effect of twice daily infusions of 200 mg naftidrofuryl on the six day cumulative losses of urinary nitrogen after moderate surgery was studied in 32 patients maintained on an intravenous infusion of 4% dextrose and saline. A previous report of the ability of naftidrofuryl to reduce loss of nitrogen was not substantiated, although changes in metabolism in the immediate postoperative period suggested that the drug might exert some advantageous metabolic effect. Further investigations with other nutritional regimens are warranted.

Introduction

The major metabolic effect of trauma or operations is to increase the net degradation of muscle protein to provide alternative energy substrates and to maintain the synthesis of visceral protein.^{1,2} This is usually associated with a negative nitrogen balance, the extent of which reflects the severity of trauma.³ The various methods used to moderate this net nitrogen loss have included infusions of fat, carbohydrates, and amino acids.⁴

Burns *et al* suggested that infusion of naftidrofuryl into patients undergoing operations was the first example of a drug successfully reducing urinary excretion of nitrogen.⁵ This could be invaluable in the treatment of severely injured patients, in whom a negative nitrogen balance may present a serious problem. The study of Burns *et al* was limited to the nitrogen losses on the operative and first two postoperative days.⁵ Maximum nitrogen excretion may, however, occur beyond this

period,⁶ and we therefore studied the effect of naftidrofuryl over the first five postoperative days. We wanted to establish the accompanying biochemical changes in more detail so that the mode of action could be examined more clearly and to determine whether the nitrogen loss was also reduced when naftidrofuryl treatment was started postoperatively (as would be the case in traumatic injury).

Patients and methods

The protocol was approved by the local ethical committee, and all patients gave informed consent.

We studied 45 patients undergoing elective intra-abdominal operations. Only patients aged under 75 who had lost less than 5 kg in weight in the previous month were considered. We excluded patients with metastatic cancer, septicaemia, intra-abdominal sepsis, localised abscesses, endocrine disorders, severe cardiac insufficiency, or atrioventricular block and those receiving treatment with steroids or the contraceptive pill. The patients were randomised into three groups: one was given placebo twice daily, one was given naftidrofuryl 200 mg twice daily starting with the induction of anaesthesia, and one was given naftidrofuryl 200 mg twice daily starting on the morning after operation. The naftidrofuryl and the placebo were kept in plain phials in coded boxes, one box being allocated to each patient, and were infused in saline for two hours. All groups received a regimen of 4% dextrose and saline according to body weight, and only water was allowed by mouth. We measured the preoperative height, weight, mid-arm circumference, and triceps skinfold thickness for each patient.

Twenty four hour collections of urine were started on the morning of the operation and were continued for five days postoperatively. Total urinary nitrogen excretion was measured by a semiautomated Kjeldahl method (Technicon industrial methods No 334-74A/A and No 369-75A/A), and urinary urea and creatinine excretions with Beckman BUN and Creatinine 2 analysers after dilution 1/20 in 0.8% saline.

Fasting blood samples were taken preoperatively (day 0) and further samples were taken on days 1, 3, and 5 after operation between 7 and 9 am while the patient was receiving the infusion of 4% dextrose and saline and seven to eight hours after the end of the previous naftidrofuryl infusion. Whole blood lactate, 3-hydroxybutyrate, and glycerol were measured by the automated fluorometric methods of Lloyd *et al*⁷ with minor modifications to buffer strength and reaction delay time. Pyruvate and acetoacetate were measured on the day of sampling by manual enzymatic methods.^{8,9} Total ketones were expressed as the sum of 3-hydroxybutyrate and acetoacetate.

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Serum albumin, total protein, urea, and glucose concentrations were measured with a Technicon SMA 12/60 by standard methods. Serum lipoproteins were fractionated, using the manganese and heparin method to isolate high density lipoprotein¹⁰ and the method of Burstein and Scholnick to isolate low density lipoprotein plus high density lipoprotein.¹¹ Cholesterol and triglyceride concentrations were measured by enzymatic methods (Boehringer). The cholesterol reagent was modified by the addition of disodium edetic acid to a final concentration of 0.016 M to remove manganese interference. Very low density lipoprotein triglyceride and low density lipoprotein cholesterol concentrations were calculated by subtraction.

The differences in concentrations between days and between groups were analysed for significance with two tailed paired and

the total six day nitrogen excretion and weight ($r=0.46$, $n=32$, $p<0.01$), mid-arm muscle circumference ($r=0.54$, $n=30$, $p<0.01$), and height $\times$ mid-arm muscle circumference ($r=0.64$, $n=25$, $p<0.001$) the expression of nitrogen as a factor of these variables did not show any differences between groups, although improved coefficients of variation were obtained.

Table III shows the mean blood analyte concentrations (SEM for non-skewed data). Only for lactate concentrations were any significant ($p<0.05$) differences shown between the groups. Serum albumin concentration was significantly reduced on day 1 ($p<0.001$) in all groups, and no further change occurred over the study period. Blood glucose concentration was raised in all groups on day 1 ($p<0.001$) and then fell during the study period. Serum urea

TABLE I—Preoperative anthropometric data and operations in the three groups

	Control group		Naftidrofuryl started:			
			Before operation		After operation	
	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)	n
Weight (kg)	67.8 (2.8)	13	69.1 (3.4)	11	66.6 (4.5)	8
Mid-arm muscle circumference (cm)	24.2 (0.73)	13	25.6 (0.96)	8	24.1 (0.71)	8
Height (m)	1.68 (0.025)	11	1.69 (0.025)	11	1.70 (0.05)	8
Men: women	5:8		4:7		4:4	
No of patients undergoing:						
Cholecystectomy	10		6		4	
Cholecystectomy + transverse colectomy	1					
Sigmoid colectomy					1	
Restoration of colonic continuity					1	
Anteroposterior resection			2		1	
Laparotomy	1					
Highly selective vagotomy			1		1	
Partial gastrectomy			1			
Aortobifemoral graft	1		1			

TABLE II—Mean (SEM) three and six day cumulative urinary excretions in the three groups

	Controls (n = 13)	Patients given naftidrofuryl		
		Starting before operation (n = 11)	Starting after operation (n = 8)	All (n = 19)
Urine volume (l):				
Over 6 days	12.0 (0.58)	12.7 (1.22)	12.2 (1.1)	12.5 (0.82)
Urinary total nitrogen (g):				
Over 3 days	19.0 (1.38)	22.7 (1.55)	24.5 (2.62)	23.4 (1.40)
Over 6 days	41.01 (3.15)	45.5 (3.35)	48.2 (3.74)	46.7 (2.45)
Urinary urea (g):				
Over 3 days	14.4 (1.19)	17.6 (1.49)	18.2 (2.13)	17.9 (1.21)
Over 6 days	30.6 (2.47)	34.0 (3.14)	35.7 (3.24)	34.7 (2.22)
Urinary creatinine (mmol):				
Over 3 days	22.8 (1.82)	28.6 (2.52)	26.0 (3.46)	27.5 (2.02)
Over 6 days	49.8 (3.78)	56.9 (4.80)	52.7 (4.71)	55.1 (3.36)

Conversion: SI to traditional units—Creatinine: 1 mmol $\approx$ 1113 mg.

unpaired t tests respectively for non-skewed data. Total ketone concentrations were skewed and were analysed with the two tailed Wilcoxon rank sum test. The increases in lactate concentrations between days 0 and 1 and in total ketone concentrations between days 1 and 3 were analysed with the single tailed Wilcoxon rank sum test.

Results

We analysed the data on 32 of the 45 patients in the study. Thirteen patients were excluded because of failure to complete the study, postoperative sepsis, incomplete urine collection, or discovery of latent diabetes. Table I shows the operations carried out and the preoperative anthropometric data for each group, and shows a satisfactory comparability between the groups. The measurements of mid-arm muscle circumference did not indicate that any patient was malnourished preoperatively.

Table II shows the cumulative three and six day urinary volume and total nitrogen, urea, and creatinine excretions for the three groups and for all patients treated with naftidrofuryl. No significant differences in these variables were found between any of the groups ($p>0.05$). Furthermore, despite a significant correlation between

concentration was lower on day 5 than preoperatively ($p<0.001$) in all groups. Serum total triglyceride concentrations were significantly depressed on day 1 ($p<0.001$) but had risen to preoperative values ($p>0.05$) by day 5. Serum low density lipoprotein cholesterol concentrations were also reduced, the lowest values occurring on day 3 ($p<0.001$).

Peak blood lactate concentrations occurred on day 1 in all groups ($p<0.05$). Concentrations in the group given naftidrofuryl before operation were significantly lower than those in the controls on all postoperative days ($p<0.05$) and were also lower than those in the group in whom naftidrofuryl was started on the morning after operation, although significantly so only on day 3. On day 0, however, the concentration in the group given naftidrofuryl before operation was lower than that in the controls ($p>0.05$) and significantly lower than that in the other treatment group ($p<0.05$). As the patients in the latter group did not receive their first infusion of naftidrofuryl until after the blood sampling on day 1 they were pooled with the controls to examine the changes occurring between days 0 and 1. Lactate concentrations in this pooled group were significantly higher on both days than those in the group given naftidrofuryl before operation ($p<0.05$). When the magnitude of the increase in lactate concentrations occurring between days 0 and 1 was compared between the groups the increase in the group given naftidrofuryl before operation was significantly lower than the increase in the pooled group ($p<0.05$).

TABLE III—Blood concentrations of variables measured before and after operation in controls and patients given naftidrofuryl (before operation=patients in whom drug was started with induction of anaesthesia; after operation=those in whom it was started after operation)

	Day 0		Day 1		Day 3		Day 5	
	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)	n	Mean (SEM)	n
Lactate (mmol/l):								
Controls	0.760 (0.065)	12	1.467 (0.153)	12	0.882 (0.111)	12	0.779 (0.063)	12
Before operation	0.610 (0.044)	11	0.847 (0.114)	11	0.572 (0.051)	11	0.585 (0.030)	11
After operation	0.796 (0.073)	7	1.190 (0.163)	8	0.958 (0.116)	8	0.711 (0.076)	8
Pyruvate (mmol/l):								
Controls	0.066 (0.003)	11	0.139 (0.019)	11	0.083 (0.009)	11	0.070 (0.006)	11
Before operation	0.063 (0.005)	11	0.099 (0.016)	11	0.066 (0.006)	11	0.069 (0.007)	10
After operation	0.065 (0.007)	8	0.107 (0.020)	7	0.077 (0.008)	8	0.058 (0.005)	8
Lactate:pyruvate:								
Controls	11.77 (0.95)	11	11.81 (1.18)	11	10.91 (0.76)	11	11.89 (1.23)	11
Before operation	9.82 (0.45)	11	8.96 (0.67)	11	8.75 (0.37)	11	8.78 (0.54)	10
After operation	11.77 (0.62)	6	11.62 (1.03)	5	12.31 (1.16)	7	11.91 (1.64)	7
Total ketones* (mmol/l):								
Controls	0.069	12	0.098	12	0.153	12	0.180	12
Before operation	0.077	11	0.055	11	0.234	11	0.269	11
After operation	0.094	8	0.114	8	0.222	8	0.267	8
Glucose (mmol/l):								
Controls	4.71 (0.18)	12	7.43 (0.52)	12	5.88 (0.42)	11	4.90 (0.26)	12
Before operation	4.53 (0.21)	11	6.86 (0.53)	11	5.78 (0.51)	11	5.15 (0.28)	10
After operation	4.31 (0.21)	8	7.41 (0.48)	7	6.40 (0.44)	8	5.80 (0.57)	6
Albumin (g/l):								
Controls	44.0 (0.56)	12	39.5 (0.65)	12	36.7 (1.58)	12	37.5 (1.31)	12
Before operation	43.3 (1.10)	11	37.9 (0.96)	11	36.3 (0.78)	11	37.0 (0.52)	11
After operation	43.7 (0.96)	8	37.9 (0.67)	8	36.0 (0.88)	8	36.8 (1.04)	8
Urea (mmol/l):								
Controls	4.58 (0.51)	12	5.57 (0.76)	12	3.50 (0.58)	11	3.57 (0.50)	12
Before operation	5.05 (0.25)	11	4.61 (0.45)	11	3.25 (0.40)	11	3.53 (0.31)	11
After operation	4.47 (0.30)	8	4.56 (0.36)	8	3.61 (0.45)	8	2.73 (0.37)	7
Total triglycerides (mmol/l):								
Controls	1.47 (0.12)	12	0.81 (0.06)	12	1.22 (0.11)	11	1.40 (0.09)	13
Before operation	1.34 (0.10)	11	0.82 (0.07)	11	1.11 (0.06)	11	1.35 (0.05)	11
After operation	1.42 (0.15)	8	0.72 (0.10)	7	1.13 (0.07)	8	1.33 (0.09)	8
VLDL triglycerides (mmol/l):								
Controls	0.78 (0.09)	11	0.27 (0.04)	10	0.31 (0.04)	9	0.45 (0.04)	12
Before operation	0.57 (0.08)	11	0.22 (0.05)	11	0.19 (0.03)	11	0.34 (0.04)	11
After operation	0.60 (0.10)	6	0.14 (0.03)	5	0.28 (0.06)	6	0.35 (0.18)	6
LDL cholesterol (mmol/l):								
Controls	3.96 (0.25)	12	3.02 (0.22)	12	2.94 (0.32)	12	3.21 (0.33)	12
Before operation	4.43 (0.29)	11	3.36 (0.26)	11	3.02 (0.24)	11	3.14 (0.27)	11
After operation	3.63 (0.32)	8	2.59 (0.23)	8	2.82 (0.22)	8	3.04 (0.14)	8
Glycerol (mmol/l):								
Controls	0.080 (0.009)	12	0.085 (0.010)	12	0.077 (0.011)	12	0.090 (0.012)	12
Before operation	0.076 (0.005)	11	0.064 (0.007)	11	0.071 (0.008)	11	0.065 (0.004)	10
After operation	0.104 (0.016)	8	0.088 (0.007)	8	0.063 (0.007)	8	0.086 (0.012)	8

VLDL = Very low density lipoprotein. LDL = Low density lipoprotein.

*Derived from logarithmic transformation.

Conversion: SI to traditional units—Lactate: 1 mmol/l $\approx$ 9 mg/100 ml. Pyruvate: 1 mmol/l $\approx$ 8.8 mg/100 ml. Glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Urea: 1 mmol/l $\approx$ 6 mg/100 ml. Triglycerides: 1 mmol/l $\approx$ 88.6 μ g/100 ml. Cholesterol: 1 mmol/l $\approx$ 38.7 mg/100 ml. Glycerol: 1 mmol/l $\approx$ 9.2 mg/100 ml.

and there was no correlation between the increase and the original concentration on day 0 ($p > 0.1$).

Peak blood pyruvate concentrations occurred on day 1, and although the mean concentration in the group given naftidrofuryl before operation was lower than that in the controls and the group started on naftidrofuryl after operation, the difference was not significant. The ratio of lactate to pyruvate concentrations in the group given naftidrofuryl before operation was significantly lower than that in the control group on all days, but no other significant differences between the groups could be shown.

Total ketone concentrations showed no significant differences between the groups although some general trends emerged. Concentrations in the group given naftidrofuryl before operation were all below 0.2 mmol/l on day 1 and had increased by day 3. However, six patients out of the 21 who had not received naftidrofuryl (controls plus patients started on naftidrofuryl after operation) had total ketone concentrations above 0.2 mmol/l on day 1. The mean increase in total ketone concentrations between days 1 and 3 in the control group (0.004 mmol/l) was significantly lower than the mean increase in the group given naftidrofuryl before operation (0.287 mmol/l; $p < 0.01$). There was a significant linear correlation between log (total ketone concentrations) and lactate concentrations postoperatively in all three groups ($r = 0.62$, $n = 36$, $p < 0.01$ in the controls; $r = 0.46$, $n = 32$, $p < 0.01$ in patients given naftidrofuryl before operation; and $r = 0.56$, $n = 24$, $p < 0.01$ in patients started on naftidrofuryl after operation). Four patients (two controls, two given naftidrofuryl before operation) had total ketone concentrations below 0.1 mmol/l in all samples taken postoperatively.

Discussion

Table II shows that a naftidrofuryl infusion does not result in any measurable nitrogen sparing effect in patients who have undergone operations and received only 4% dextrose and saline.

These results complement the findings of Inglis *et al.*,¹² who failed to show any nitrogen sparing effect when naftidrofuryl 400 mg daily was given as a constant intravenous infusion. They indicated, however, that this result might have been due to their use of a constant infusion of naftidrofuryl as opposed to a slow bolus infusion as used by Burns *et al.*⁵ and in our study.

In addition to the evidence from urinary measurements, there were no differences in albumin concentrations between the control and treatment groups. After the initial fall in albumin concentration on day 1, due to the effects of fluid retention associated with trauma the concentrations remained constant as these effects diminished and net degradation increased.¹³

In studies of surgical injury it has always been important to distinguish between effects due to trauma and effects due to the nutritional support regimen.¹⁴ Our results represent those after injury with a minimal carbohydrate infusion (1.3–1.7 MJ (300–400 kcal)/24 h), and thus the postoperative blood concentrations are not fasting concentrations.

The rise in blood glucose concentration on day 1 indicates the usual hyperglycaemia with insulin resistance that follows injury.¹³ The concentrations later fell towards the normal values for patients receiving an infusion of dextrose and saline. The decline in blood urea concentrations during the study is difficult to explain considering the expected increase in ureagenesis after injury. The pronounced decrease in triglyceride concentrations on day 1 results from the ebb phase of lipolysis induced by catecholamines and cortisol.¹³ Thereafter the triglyceride concentrations rose, but it should be noted that the very low density lipoprotein triglyceride concentration remained low and the major increase was in the triglyceride carried by the low density lipoprotein plus high density lipoprotein fraction.

No reason was apparent for the difference in lactate con-

centrations on day 0 between the group given naftidrofuryl before operation and the controls, and it may have been an artefact of selection. Catecholamines cause an increased production of lactate from the muscle and an acceleration of the alanine shuttle. If the critical factor after trauma is a cellular, rather than a hormonal, modification affecting nitrogen conservation then the utilisation of pyruvate decarboxylation and fatty acid β oxidation as sources of acetyl coenzyme A may be reduced. Under these conditions of immediate postoperative injury—namely, increased muscle lactate production from glycogen, lipolysis, and glucose intolerance—then a rise in elevation of blood ketone, lactate, and pyruvate concentrations would be expected. Smith *et al* showed that early ketoadaptation is associated with improved conservation of nitrogen.¹⁵ In contrast, an agent that is able to increase the utilisation of carbohydrate and fat in the citric acid cycle and reduce the need for protein degradation, as has been suggested for naftidrofuryl,⁵ would therefore be expected to diminish the increases in both lactate and total ketone concentrations that occur at this stage. This would indicate a resetting of the regulation that links lactate and pyruvate with ketone production, and the usual inverse relations would still operate. The result reported here for the diminished rise in lactate concentration, although without a change in the ratio of lactate to pyruvate concentrations, and the possibility of a diminished rise in the total ketone concentration on day 1 are not inconsistent with this mode of action on day 1, although it has not been possible to show any nitrogen sparing effect. We believe that further investigation with other nutritional regimens is warranted, and this is currently being undertaken. Nevertheless, the claim that naftidrofuryl alone will reduce the loss of nitrogen postoperatively cannot be generally applied.

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Protein synthesis in muscle measured in vivo in cachectic patients with cancer

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Abstract

Rates of synthesis of protein were measured in vivo in skeletal muscle and in the whole body of cachectic patients with cancer and in normal healthy men, using a tracer infusion of leucine labelled with a stable isotope. Synthesis of protein in muscle was significantly reduced in the patients with cancer (0.030 v 0.198%/hour; $p < 0.01$), whereas whole body rates of protein synthesis and

degradation did not differ significantly between the two groups. Thus depression of synthesis of protein in muscle appeared to be the immediate cause of muscle wasting in cancerous cachexia.

Any therapeutic intervention that aims at preventing the onset of cachexia should be designed to stimulate the synthesis of protein in muscle, and measurement of turnover of protein may be used to evaluate such treatment provided that rates of protein synthesis are measured directly in specific tissues.

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Introduction

The most common cause of death in patients with cancer is the generalised wasting of body tissues known as cachexia.¹ This is also one of the most distressing features of cancer both for the patients and for their relatives. Skeletal muscle makes up more than 40% of the body, and wasting of the muscles is a prominent feature of cachexia in cancer. Indeed, the outcome of the disease is most often determined by the wasting of the respiratory muscles and the consequent inability to overcome respiratory infections.

The mechanism by which this muscle wasting occurs is at present poorly understood. Because of the phenomenon of protein turnover the same degree of muscle wasting could