Trial of glucose versus fat emulsion in preparation of amphotericin for use in HIV infected patients with candidiasis

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Abstract

Objectives—To compare the tolerance, efficacy, and pharmokinetics of amphotericin deoxycholate (Fungizone) prepared in a parenteral fat emulsion (Intralipid 20%) or glucose in HIV patients with candidiasis.

Design—Non-blind randomised controlled trial.

Setting—University hospital; tertiary clinical care.

Patients—22 HIV positive patients with oral candidiasis.

Interventions—Amphotericin 1 mg/kg/day given on four consecutive days as a one hour infusion dissolved in either 5% glucose (amphotericin-glucose) or parenteral fat emulsion at a final concentration of 2 g/l fat emulsion (amphotericin-fat emulsion).

Main outcome measures—Clinical tolerance (fever, chills, sweats, nausea, arterial pressure, and pulse rate); biological tolerance (serum creatinine, electrolyte, and magnesium values); clinical score of candidiasis; and serum concentrations of amphotericin.

Results—11 patients were enrolled in each group. All the amphotericin-fat emulsion infusions were given without serious problem whereas four amphotericin-glucose infusions were stopped because of renal impairment (n=3) or severe chills (n=2), or both. For patients completing the amphotericin-glucose treatment creatine concentration increased by 42 μmol/l; four of seven patients had at least one creatinine value ⩾133 μmol/l versus one of 11 receiving amphotericin-fat emulsion. Magnesium concentration fell significantly with amphotericin-glucose but not with amphotericin-fat emulsion. Clinical side effects were noted in 36/38 infusions with amphotericin-glucose but 10/44 with amphotericin-fat emulsion. Oral candidiasis score was reduced similarly in both groups. Serum amphotericin concentrations were significantly lower and the volume of distribution of the drug higher after infusion of amphotericin-fat emulsion than after amphotericin-glucose.

Conclusions—Clinical and renal toxicity of amphotericin are reduced when the drug is prepared in fat emulsion. Preparation is simple and cost effective. Its efficacy is similar to that of conventional amphotericin.

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Introduction

Amphotericin remains the standard treatment of the main systemic mycoses.[1] In patients infected with HIV fungal infections such as candidiasis are very frequent and aspergillosis is increasing.[1-6] Although azole compounds such as ketoconazole, fluconazole, or itraconazole are widely used, incomplete response or failures of these treatments or decreased susceptibility of yeasts are increasing.[7-11] In these situations amphotericin remains the ultimate recourse. However, toxicity is the main limitation of amphotericin. Indeed, infusion related toxicity is very frequent (up to 80% of cases) and includes chills, fever, and nausea, nephrotoxicity being the most severe limiting factor.[1 12-16] Other side effects, such as cardiac arrhythmia, are rare.[16 17 18]

Amphotericin is a lipophilic drug that binds to sterols and intercalates among lipid bilayers. These properties suggest that amphotericin should be suitable for use with a lipid based delivery system. Indeed, its incorporation with or use in association with liposomes or lipid complexes reduces toxicity such that the therapeutic index is increased.[19]

Kirsh *et al* reported that mixing the parenteral lipid emulsion Intralipid with amphotericin greatly reduces amphotericin related toxicity both in vitro and in vivo.[20] Since in routine practice these two compounds are widely given together (but through different catheters) we decided to prepare amphotericin directly in the lipid emulsion. We report a randomised clinical trial comparing the tolerance and efficacy of amphotericin deoxycholate (Fungizone) prepared either in Intralipid 20% or in glucose in HIV patients with candidiasis. The pharmacokinetics of these two formulations were also investigated.

Patients and methods

Patients were eligible for the study if they were aged 18 or over, infected with HIV, and had oral candidiasis. Patients were excluded if they had oesophagitis, oral Kaposi's sarcoma, known intolerance of amphotericin, pancreatitis, hyperlipidaemia, or a serum creatinine concentration above 115 μmol/l. All eligible patients gave signed informed consent. The protocol was accepted by the local ethics committee. All patients included in the study were hospitalised in our medical unit.

Treatment—Amphotericin deoxycholate was dissolved either in 5% glucose at a final concentration of 1·6 g amphotericin/l (amphotericin-glucose) or in parenteral fat emulsion (Intralipid 20%) at a final concentration of 2 g amphotericin/l (amphotericin-fat emulsion). Whatever the preparation, amphotericin was given as a one hour infusion of 1 mg/kg/day on four consecutive days.[13 15 21-24] The rationale for using 1 mg/kg/day was the need to attain sufficiently bioactive concentrations.[25 26] No premedication was given before the infusions. Amphotericin was infused into a peripheral (n=9) or central (n=13) vein. No other antifungal drug was given nor any intravenous lipid emulsion for parenteral nutrition. Hydration and electrolyte supplementation were given as needed. Magnesium supplementation was not given. After giving informed consent patients were assigned randomly to one of the two treatment groups. Group selection was determined by sequential assignment from a table of random numbers, by using the sealed envelope technique. Each envelope was opened immediately before the treatment was given. The treatments could not be given in blind fashion since the lipid emulsion has a distinctive milky appearance.

Assessment of tolerance—Clinical tolerance was monitored by using a standard data form. Sweating, chills, fever (defined as a temperature above 37·5°C

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and rise of more than 1°C during the infusion), nausea, pulse rate, and systolic and diastolic blood pressure were recorded at the beginning, middle, and end of the infusion and one hour afterwards. Mean blood pressure was calculated as follows: mean blood pressure = (diastolic blood pressure + (systolic blood pressure − diastolic blood pressure)/3). At these times the transcutaneous saturation of oxygen was measured (OSP-200 apparatus, SATLITEtrans, Datex, Helsinky, Finland). Biological tolerance was monitored by daily electrolyte and creatinine measurements. In addition, full blood count; magnesium, triglyceride, and cholesterol concentrations; aspartate and alanine aminotransferase, γ-glutamyltransferase, lipase, and amylase activities; and electrocardiograms were obtained on days 1 and 5. Amphotericin was stopped if severe clinical side effects occurred or if the creatinine concentration reached 159 μmol/l. Paracetamol (1 g orally or intravenously) or dexamethasone (4 mg) were given if severe chills or fever occurred during or after the infusion.

Assessment of efficacy—We devised a simple clinical score to monitor the state of the oral candidiasis. Each day the following nine sites were inspected for the presence or absence of candidiasis: upper, right, and left sides of the tongue; left and right sides of the jaw; both tonsil regions; and the smooth and hard portions of the palate. Each site was examined for confluent, patchy, or scattered lesions, which were scored 3, 2, and 1 respectively. Thus a clinical score could be calculated daily. A swab of one or two lesions was taken for mycological analysis before and at the end of treatment.

Pharmacokinetics—Serum samples were obtained daily before (trough) and five minutes (peak) and 12 hours after the one hour infusion of amphotericin and stored at −20°C till assayed. Amphotericin was bioassayed with *Paecilomyces varioti* used as test organism.[13] Sensitivity of the assay was 0·2 mg/l; within day and between day variations were 8% at 0·5 mg/l and 4% at 1·5 mg/l. Area under the curve was calculated by the trapezoid method. The following formulas were used to calculate the pharmacokinetic parameters. Total body clearance (l/kg/h) was calculated as dose divided by the area under the curve, volume of initial distribution (l/kg) was calculated as dose/concentration after the infusion; volume of distribution at steady state (l/kg) was calculated as clearance divided by k, where k is the terminal rate constant; half life of elimination was calculated as 0·693/k.

Statistics—There is an 80-100% incidence of side effects with amphotericin-glucose[12 14 15 16] but only a 5% incidence of side effects with amphotericin-fat emulsion (personal data from pilot study). We decided that a 75% reduction in the incidence of side effects could be obtained with amphotericin-fat emulsion. For a type I error of less than 5% and statistical power of at least 95% we calculated that we should need to have 11 patients in each group.[17] Discrete variables were compared by means of χ^2 contingency analysis and Fisher's exact test. Continuous variables were compared by Student's *t* test, one way analysis of variance on repeated measures as indicated, or the Mann-Whitney U test. A p value of <0·05 was taken as significant. Measurements are reported as means and SD.

Results

From June to December 1991, 22 patients (11 in each group) were enrolled in the study. The two groups were comparable for all the characteristics tested, including demographic variables, status of HIV infection and candidiasis, renal function and electrolyte equilibrium, and the concomitant use of other nephrotoxic drugs (table I).

TABLE I—*Baseline characteristics of two groups of patients receiving amphotericin either in glucose or in parenteral fat emulsion*

	Amphotericin-glucose	Amphotericin-fat emulsion
No of patients	11	11
No male	11	9
Mean (SD) age (years)	35 (7)	34 (7)
Mean (SD) weight (kg)	61 (8)	53 (9)
Centres for Disease Control classification of HIV (No of patients):		
IV C2	3	3
IV D	0	1
IV C1	8	7
Concurrent treatment (No of patients):		
Zidovudine	8	6
Foscarnet	1	1
Co-trimoxazole	2	2
Pyrimethamine	3	5
Sulphadiazine	2	3
Mean (SD) white cell count (×10⁶/l)	3445 (1747)	2809 (1444)
Mean (SD) CD4 count (×10⁶/l)	121 (161)	48 (88)
Mean (SD) creatinine (μmol/l)	79·6 (13·1)	77·8 (19·4)
Mean (SD) potassium (mmol/l)	3·8 (0·3)	3·9 (0·3)
Mean (SD) magnesium (mmol/l):		
Serum	10·7 (1·4)	10·8 (1·5)
Erythrocytes	24·5 (13·0)	29·5 (10·5)
Oral candidiasis:		
Prior treatment: Fluconazole	7	6
Prior treatment: Oral polyene	1	2
Fungal strain: *Candida albicans*	9	10
Fungal strain: Other	2	1
Mean (SD) clinical score*	6·0 (7)	6·3 (4)

*See methods.

All the amphotericin-fat emulsion infusions were given without serious problem whereas four amphotericin-glucose treatments were stopped. Two patients had shaking chills during the first two amphotericin-glucose infusions and three patients had a striking increase in creatinine concentration (>159 μmol/l) on day 3 (one of whom also had chills). All these renal insufficiencies reversed within a few days.

Clinical side effects were much more frequent with amphotericin-glucose than with amphotericin-fat emulsion (36 per 38 infusions (94·7%) *v* 10 per 44 (22·7%); p=0·0001 (χ^2 test)). Only two patients receiving amphotericin-glucose (18% (95% confidence interval 2·2% to 37%)) were free of clinical reactions compared with eight in the amphotericin-fat emulsion group (72% (50% to 94%); p=0·03 (Fisher's exact test)). Moreover, the reactions were severe enough to warrant treatment (paracetamol, dexamethasone) in five patients given amphotericin-glucose (45·5%) compared with none given amphotericin-fat emulsion (p=0·04 (Fisher's exact test)). Chills and fever were the most frequent side effects—66% (25) in the amphotericin-glucose group versus 4% (2) in the amphotericin-fat emulsion group (p=0·001 (Fisher's exact test)). Seven patients given amphotericin-glucose complained of chills compared with one given amphotericin-fat emulsion (p=0·001 (Fisher's exact test)). The same picture was observed with fever (seven patients given amphotericin-glucose compared with one given amphotericin-fat emulsion (p=0·001; Fisher's exact test)). Five of the seven patients given amphotericin-glucose had both chills and fever whereas these side effects occurred in different patients in the amphotericin-fat emulsion group. Sweating and nausea were slightly less frequent in the amphotericin-fat emulsion group (table II).

There were no significant variations in pulse rate, blood pressure, or transcutaneous oxygen saturation either during the infusions or during the whole treatment course (table III). No electrocardiographic abnormalities were seen before or after amphotericin.

With respect to patients who completed the four days of treatment the mean increase in creatinine concentration from baseline (table II) was higher in the amphotericin-glucose group (42 (SD 31) μmol/l *v* 14 (19) μmol/l). The daily increase in creatinine concentration was also higher in this group (p=0·01 (one way analysis of variance on repeated measures,

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not shown)). The numbers of patients with at least one creatinine value ≥133 μmol/l during the five days of observation were four among seven compared with one among 11 for patients given amphotericin-fat emulsion (p=0·04 (Fisher's exact test)). No significant variation in potassium or sodium value was observed in either group. Magnesium concentration was not decreased with amphotericin-fat emulsion whereas a significant decrease in serum and erythrocyte magnesium concentrations was observed with amphotericin-glucose (table II). No correlation was found between the variations in magnesium concentration and renal function in patients who completed treatment with amphotericin-glucose (not shown).

Triglyceride concentrations at day 0 and day 5 were not appreciably different in the two groups (1·4 (SD 0·6) and 1·9 (0·6) mmol/l in the amphotericin-glucose group; 1·6 (0·8) and 1·5 (0·7) mmol/l in the amphotericin-fat emulsion group). Serum cholesterol concentrations also were very similar in the two groups at entry and day 5 (3·6 (1·6) and 3·3 (0·8) mmol/l in the amphotericin-glucose group; 3·7 (1·5) and 3·7 (0·7) mmol/l in the amphotericin-fat emulsion group). Platelet and white cell counts, haemoglobin concentration, and serum aminotransferase, γ-glutamyltransferase, lipase, and amylase activities were not appreciably different in the two groups at entry and did not change after completion of either amphotericin treatment (not shown).

Applying our clinical score of oral candidiasis showed the two groups to be comparable (table I). All the patients improved with either treatment. The reduction in clinical score of oral candidiasis was similar in the two groups (3·5 (SD 5) in the amphotericin-fat emulsion group; 4·6 (6) in the amphotericin-glucose group (p=0·38; Mann-Whitney U test)). Only two patients in each group had a sterile swab at the completion of treatment, including a patient in the amphotericin-fat emulsion group whose swab at day 1 had grown *Candida tropicalis*. Only one patient given amphotericin-fat emulsion had *Torulopsis glabrata* isolated at day 5; in all the other patients *C albicans* was isolated at both day 1 and day 5.

TABLE II—*Side effects of amphotericin 1 mg/kg/day in one hour infusion for four days prepared either in glucose or in Intralipid 20%*

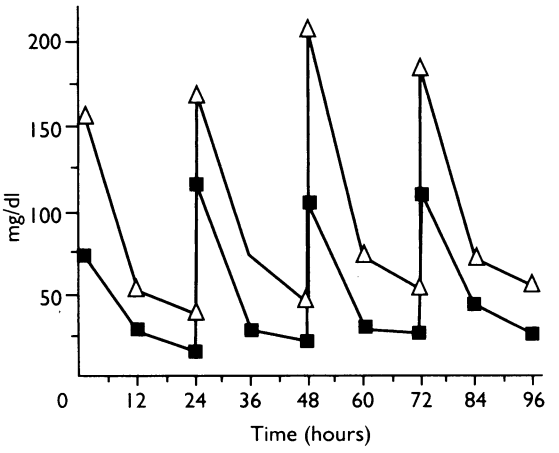
	Amphotericin-glucose	Amphotericin-fat emulsion
No of patients	11	11
No having interruption of treatment	4	0*
Day of interruption (No of patients)	Day 2 (1), day 3 (3)	
Causes of interruption (No of patients):		
Chills	2	
Creatinine >159 μmol/l	3	
No of infusions	38	44
No of patients without any clinical side effects	2	8*
Total No of clinical side effects	36	10*
Chills	15	1
Sweats	5	4
Fever	10	1
Nausea	6	4
Mean (SD) creatinine (μmol/l)†:		
Day 0	79·6 (13·3)	77·8 (19·4)
Day 5	121·1 (31·8)	91·9 (23·9)‡
No of patients with at least one creatine value >133 μmol/l during treatment†	4	1*
Mean (SD) change of magnesium (mmol/l):		
Serum	−1·22 (1·7)	0·22 (1·2)§
Erythrocytes	−6·7 (9·5)	0·6 (4·3)‖

*p≤0·05 With Fisher's exact test.
†The four patients whose treatments were stopped were not included.
‡Comparison between treatments significant at p=0·04 (analysis of variance) from days 3 to 5.
§p=0·05 With Student's *t* test.
‖p=0·03 With Mann-Whitney U test.

TABLE IV—*Comparative pharmacokinetic parameters of amphotericin 1 mg/kg/day in one hour infusion on four days prepared either in glucose or in parenteral fat emulsion*

	Amphotericin-glucose	Amphotericin-fat emulsion
Mean (SD) area under curve (mg/h)	21·9 (8)	12·6 (4·4)*
Mean (SD) total body clearance at day 4 (l/kg/h)	0·509 (0·0176)	0·879 (0·0305)*
Mean (SD) half life of elimination at day 4 (h)	12·7 (3·2)	11·6 (4·3)
Mean (SD) volume of distribution (l/kg):		
Day 1	0·795 (0·226)	1·544 (0·564)†
Day 4	0·916 (0·381)	1·6 (1·06)

*p=0·01 With Mann-Whitney U test.
†p=0·0046 With Mann-Whitney U test.



Pharmacokinetics of amphotericin 1 mg/kg daily given as one hour infusion on four days prepared either in glucose (Δ) or in parenteral fat emulsion (■). (Blood was sampled for bioassay before, at end, and 12 hours after each infusion of amphotericin. Results are means of data from nine patients in each group)

Amphotericin concentrations at trough, peak, and 12 hours after the daily infusion and at day 5 (last trough) were available for nine patients in each group (figure). There were significant differences in each of these three concentrations between treatments (p=0·01 for peak and 12 hour concentrations; p=0·0024 for trough concentrations (analysis of variance on repeated measures)). The area under the curve was greater for amphotericin-glucose than for amphotericin-fat emulsion (table IV). Total body clearance on the fourth day of treatment and the volume of initial distribution were significantly higher with amphotericin-fat emulsion than with amphotericin-glucose whereas the volume of distribution at steady state (day 4) was slightly higher with amphotericin-fat emulsion (NS; table IV). The half life at day 4 was similar with the two preparations.

TABLE III—*Haemodynamic tolerance of amphotericin 1 mg/kg/day in one hour infusion for four days prepared either in glucose or in parenteral fat emulsion*

		Baseline value	Changes at: Day 1	Day 2	Day 3	Day 4
Mean (SD) pulse (beats/min)	Amphotericin-glucose	90 (15)	−6·3 (24)	−7·1 (22)	−11·9 (33)	−13 (34)
	Amphotericin-fat emulsion	78 (15)	0·4 (8·5)	−2·8 (9·7)	−1·3 (8·8)	3·3 (11)
Mean (SD) blood pressure (mm Hg)	Amphotericin-glucose	90 (15)	−0·7 (1)	−0·3 (1·1)	1·2 (1·8)	0 (1·3)
	Amphotericin-fat emulsion	92 (18)	0·3 (1·6)	0·8 (1·3)	0·2 (1·3)	0·5 (1·4)
Mean (SD) transcutaneous saturation of oxygen (%)	Amphotericin-glucose	97 (4)	0·3 (1·5)	0 (2·9)	0·8 (3·4)	−1·2 (5·1)
	Amphotericin-fat emulsion	98 (1)	−0·8 (2)	0·4 (1·5)	−2 (9)	0·9 (2)

The three haemodynamic measurements were done at end of each infusion.

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Discussion

The main finding of our study was that the combination of amphotericin deoxycholate with a parenteral lipid emulsion is much better tolerated than amphotericin prepared in glucose. Indeed, in this study clinical side effects were fourfold to 16-fold less frequent with amphotericin-fat emulsion than with amphotericin-glucose. There were no differences in blood pressure or pulse rate between the two treatment groups.[24] Moreover, renal impairment occurred in seven of the 11 patients who received amphotericin-glucose compared with only one of the 11 who received amphotericin-fat emulsion. There was a fall in magnesium values in serum and erythrocytes in patients given amphotericin-glucose but not in patients given amphotericin-fat emulsion.

Experience suggests that a prolonged duration of infusion should result in fewer side effects associated with infusion. Several case reports and one randomised study, however, did not confirm this with respect to amphotericin.[13 15 21-24 26 28] Furthermore, the toxicity of amphotericin-glucose observed in this study was similar to that usually recorded.[1 12 13 15 16 21 29] On the other hand, both the efficacy and toxicity of amphotericin in vitro are considered to be concentration dependent.[13] Hence rapid intravenous injections, which give higher serum concentrations,[26] could be more toxic. We failed to find any correlation between serum amphotericin concentrations and either clinical effects and serum creatinine values or magnesium concentrations in patients receiving amphotericin-glucose (not shown). Thus we cannot incriminate the brief duration (one hour) of the infusion to explain the observed toxicity of amphotericin-glucose. Therefore, the comparison between the two formulations of amphotericin is valid and clinically useful.

Some of the reported reactions with amphotericin are probably mediated by tumour necrosis factor or prostaglandin release.[30 31] Probably they are also related to the direct effects of free amphotericin on mammalian cells.[32-35] We speculated that parenteral fat emulsion might act as other lipid structures in reducing the toxicity of amphotericin,[19 20 34] and in this respect our clinical findings confirm experimental data obtained in vitro and in vivo. Indeed, parenteral fat emulsion reduced amphotericin related toxicity in erythrocytes[20] and human renal tubular cells[35] and renal toxicity in rats.[20] Furthermore, the maximal tolerated dose in mice was ninefold higher with amphotericin-fat emulsion than with amphotericin alone.[20]

We expected a very low incidence of toxicity related to the parenteral fat emulsion itself, given the small volume infused. Indeed, although nausea could be related to the fat emulsion, no increase in hepatic or pancreatic enzyme activities was observed.[36 37]

Amphotericin is easy to prepare in parenteral fat emulsion and is chemically stable,[20] cost effective, and well tolerated at a dose of 1 mg/kg/day for four consecutive days. However, further studies are warranted to investigate the tolerance of this mixture over a longer period of treatment.

The pharmacokinetic analysis of amphotericin was based on only three samples per day, and plainly our results with respect to amphotericin-glucose were very similar to those previously reported.[1 13 23 38 39] Conversely, the pharmacokinetics of amphotericin were modified when the drug was prepared and infused with parenteral fat emulsion. Indeed, all calculated parameters indicated that the diffusion of amphotericin-fat emulsion was greater than the diffusion of amphotericin-glucose. It is of particular interest that the volume of initial distribution of amphotericin-fat emulsion was twice that of amphotericin-glucose whereas the difference was not so great for the volume of distribution at steady state. This could indicate that the diffusion of amphotericin-fat emulsion is much more rapid than the diffusion of amphotericin-glucose. This could have clinical implications for the treatment of tissue infections.

We did not set out to compare the relative efficacy of amphotericin-glucose and amphotericin-fat emulsion on mucosal candidiasis in patients infected with HIV. Nevertheless, we note that the reduction in the clinical score of candidiasis was similar with both treatments. This supports the argument that egg lecithins (a major component of parenteral fat emulsion) do not alter the bioactivity of amphotericin[40] and confirms in vitro[41] and in vivo experimental data on both candidal and cryptococcal infections[20 41] (V Joly, L Saint-Julien, C Carbon, P Yeni, paper presented to 31st interscience conference on antimicrobial agents and chemotherapy, Chicago, 29 September to 2 October, 1991 (abstract 578)). More importantly, a pilot study of amphotericin-fat emulsion in our institution in patients with neutropenia showed that this formulation is effective against candidaemias. Similarly, we have recorded cure of candidal oesophagitis in patients with HIV.

Conclusion

We conclude that the clinical and renal tolerance of amphotericin is dramatically improved when the drug is prepared and infused in parenteral fat emulsion. This simple and cost effective preparation of amphotericin avoids the usual need for escalating doses. In addition, its efficacy in candidal infection is similar to that of conventional amphotericin at the same dosage.

These results prepare the way for further controlled and comparative studies of amphotericin-fat emulsion in different clinical settings. For example, investigations could be done to shorten antifungal treatment by giving the full dose at once, to increase the daily dose of amphotericin, or to lengthen the duration of amphotericin treatment.

Finally, the respective benefits, limits, and indications for amphotericin-glucose, amphotericin-fat emulsion, and the new liposomal formulations of amphotericin remain to be investigated.

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Vitamin C depletion and pressure sores in elderly patients with femoral neck fracture

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Abstract

***Objective*—To evaluate the contribution of specific nutritional deficiencies (as indicated by zinc; vitamin A, C, and E; albumin; and haemoglobin concentrations) to the risk of pressure sores.**

***Design*—Observational cohort study.**

***Setting*—St James's University Hospital, Leeds.**

***Subjects*—21 elderly patients presenting consecutively to the orthopaedic unit with femoral neck fracture.**

***Main outcome measure*—Full thickness epidermal break over a pressure bearing surface.**

***Results*—10 patients (48%) developed a pressure sore during their hospital stay. Indices of zinc status and concentrations of albumin, haemoglobin, and vitamins A and E were similar in patients who developed a pressure sore and those who did not. Mean leucocyte vitamin C concentration, however, was 6·3 (SD 2·2) μg/10⁸ cells in patients who developed a pressure sore as compared with 12·8 (4·6) μg/10⁸ cells in patients who did not.**

***Conclusions*—Low concentrations of leucocyte vitamin C appear to be associated with subsequent development of pressure sores in elderly patients with femoral neck fractures.**

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Introduction

Up to 10% of all hospital patients and 30% of all elderly patients suffer from pressure sores.[1] Elderly patients with femoral neck fractures are particularly at risk, and as many as 60% may develop sores, most of which occur within the first five days of admission to hospital.[2] Many such patients spend unacceptably long periods on high pressure surfaces, particularly in casualty and in the operating theatre, and many go on to develop sores, though the relation may not be causal.[3] It is possible that acute illness may be more important by exacerbating liability to pressure necrosis because of reduced feeling and mobility, pain, low blood pressure, and nutritional deficiency. Other factors, such as confusion and incontinence, may also be important.[4,5]

The benefits of supplementary nutritional support in patients with femoral neck fracture have been reported,[6,7] and there is evidence that undernutrition may be a predisposing factor in pressure sore development.[8] However, the contribution of pre-existing specific nutritional deficiencies to the risk of pressure sore development has not been studied.

Zinc is an essential element which has a crucial role in immunity and healing and for which interactions with other vitamins have been described.[9] Both topical and oral zinc supplementation have a beneficial effect on wound healing in zinc depleted subjects.[10] Vitamin C has also been shown to promote wound healing and may have a role in immunological regulation.[9] Elderly people are particularly at risk from both nutritional deficiencies and depressed immunity, and studies in this hospital have shown a high prevalence of zinc[11] and vitamin[12] depletion in elderly inpatients.

This study was undertaken to assess the contribution of nutritional status to the development of pressure sores in elderly patients with femoral neck fractures.

Subjects and methods

Twenty one unselected patients aged 75 or more admitted to the orthopaedic unit with a diagnosis of femoral neck fracture were invited to participate in the study, which was approved by the local clinical research (ethics) committee. Written informed consent was obtained from all patients or their next of kin. Pressure sores were defined as a full thickness epidermal break over a pressure bearing surface.

A preoperative fasting blood sample was obtained at 8-9 am on the day after admission for assay of various biochemical nutritional indices, including plasma and polymorphonuclear leucocyte zinc; plasma albumin

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