Peak expiratory flow rate in case 2. Shaded areas indicate periods when patient was at work

investigated, and thus the bronchoconstriction is unlikely to have been a non-specific irritant reaction. The absence of airway hyperresponsiveness may have been because the measurements were taken some weeks after the last exposure to the spray, but hyper-

responsiveness is not invariably present in patients with occupational asthma.^{4,5} Challenge with the disinfectant spray produced an asthmatic response in both patients and supported the clinical diagnosis of occupational asthma due to this agent. The use of chlorhexidine-alcohol aerosols was stopped in the departments where these nurses worked, and they remained free of symptoms.

As this form of disinfection is widely used within the health service a large number of employees could be exposed to it. We have highlighted the risk within this health board and have notified both the manufacturers and the Committee on Safety of Medicines.

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Impaired filterability of white cells in acute cerebral infarction

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The outcome of cerebral infarction after thromboembolism depends on the extent of residual microvascular perfusion. Whole blood filterability is reduced in acute stroke,¹ but whether this reflects changes in plasma viscosity, fibrinogen concentration, packed cell volume, or the filterability of erythrocytes or leucocytes is not known. We therefore measured these variables in patients with acute stroke and in controls.

Subjects, methods, and results

We studied 39 patients with acute hemiparetic cerebral infarction, which had been confirmed by computed tomography in 24 and by the Guy's clinical score² in 15, on the morning after admission. We also studied 11 patients of similar age with radiological evidence of acute chest infection (acute phase controls) and 61 asymptomatic controls, who were hospital staff or patients without vascular, infective, inflammatory, or malignant disease. Venous blood was anticoagulated with edetic acid (1.5 g/l) for measurement of the packed cell volume, plasma viscosity (Coulter-Harkness capillary viscometer; 37°C), and fibrinogen

concentration (by heat precipitation). Suspensions of blood cells in phosphate buffered saline (pH 7.4, 290 mmol/kg) were filtered at 25 (± 1)°C through filters with pores of diameter 5 μ m (Nuclepore, Pleasanton, California) after filtration of buffer. Flow variables were calculated relative to the values obtained with buffer. Erythrocytes were suspended at a packed cell volume of 0.10 and filtered (Carri-Med Filtrometer, Dorking) at constant pressure (3 cm water), the relative initial flow rate being measured.³ Polymorphonuclear and mononuclear leucocytes were separated by Ficoll-Hypaque density gradient centrifugation, suspended at 10⁶/ml, and filtered at constant flow (1.5 ml/min), the relative pressure at six minutes being measured.⁴

The table shows that there were no significant differences among the groups in the packed cell volume or filterability of erythrocytes. Plasma viscosity and fibrinogen concentration increased with age in the asymptomatic controls and were further increased in the patients with cerebral infarction. The most striking findings, however, were impaired filterability of leucocytes (increased relative pressure) in those controls aged 40 and over (mean difference from value in controls under 40=0.54 (95% confidence interval 0.02 to 1.06) for polymorphonuclear leucocytes and 1.69 (0.80 to 2.58) for mononuclear leucocytes). Further impairment was seen in the patients with cerebral infarction compared with controls matched for age (mean difference 1.17 (0.63 to 1.71) for polymorphonuclear leucocytes and 2.75 (1.69 to 3.81) for mononuclear leucocytes). Filterability of leucocytes was unrelated to sex, smoking habit, or death in hospital (n=15), but in the patients with stroke fibrinogen concentration correlated with the filterability of polymorphonuclear leucocytes (Spearman's rank test, $r=0.43$, $p=0.01$) and of mononuclear leucocytes ($r=0.30$, $p=0.08$). Filterability of leucocytes in the patients with stroke was similar to that in the patients with chest infection, who also showed similar acute phase increases in fibrinogen concentration and viscosity.

Comment

We showed that reduced filterability of blood in patients with acute cerebral infarction¹ is not due to changes in packed cell volume or the filterability of

Results in four groups studied, expressed as means (SD)

	Controls		Patients with cerebral infarction	Patients with chest infection
	<40 Years	≥ 40 Years		
No in group	30	31	39	11
No of men	15	15	17	6
Age (years)	28 (4)	68 (11)	71 (11)	73 (11)
Packed cell volume	0.42 (0.03)	0.42 (0.04)	0.44 (0.05)	0.41 (0.05)
Viscosity (mPa.s)	1.41 (0.10)***	1.46 (0.10)***	1.59 (0.12)	1.54 (0.20)
Fibrinogen (ml/l)	26.8 (6.9)***	34.2 (7.1)***	49.3 (11.6)	47.3 (13.6)
Filtration variables†:				
Erythrocytes	0.496 (0.036)	0.498 (0.041)	0.497 (0.053)	0.486 (0.041)
Polymorphonuclear leucocytes	3.66 (1.10)***	4.20 (0.90)***	5.37 (1.23)	4.83 (1.95)
Mononuclear leucocytes	5.88 (1.62)***	7.57 (1.84)***	10.32 (2.44)	9.58 (2.38)

*** $p<0.001$. Compared with values obtained in patients with cerebral infarction (unpaired Wilcoxon test).

†See text for definitions.

erythrocytes. It is partly explained by acute phase increases in plasma fibrinogen concentration and viscosity. In particular, however, we found that the filterability of both polymorphonuclear and mononuclear leucocytes is reduced in acute cerebral infarction. This may not only explain the reduced filterability of blood but also promote malperfusion of the microcirculation and infarction.

Reduced filterability of leucocytes may be part of the acute phase response to injury, as suggested by the correlation with fibrinogen concentration in the patients with stroke and by similar findings in the controls with chest infection. Preceding infection is an important risk factor for cerebral infarction.⁵ The risk of infarction also increases with age, and we observed decreased filterability of leucocytes in controls aged over 40. We suggest that mechanisms by which increasing age and infections increase the risk of cerebral infarction include increased plasma fibrinogen

concentration and viscosity and decreased filterability of leucocytes, each of which tends to reduce capillary flow.

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Progesterone cream for cyclic breast pain

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Breast pain and nodularity during the luteal phase of the menstrual cycle may be due to insufficiency of progesterone. Local application of progesterone cream has been claimed to relieve these symptoms without affecting uterine function, but evidence that oral progesterone is effective is disputed. The use of progesterone cream for treating cyclic mastalgia has become popular in France after uncontrolled trials.¹ A randomised trial of cream (C Conti, unpublished data) gave sufficiently favourable results to justify further studies.

Patients, methods, and results

Women attending our breast clinic with cyclic breast pain of at least two months' duration were included in the study. Women not menstruating regularly, taking the contraceptive pill, or with breast abnormalities were excluded. The women were asked to record their pain on a linear analogue scale from one to 100 daily from the first day of menstruation.² The nodularity of the breasts was assessed by palpation on one day of the luteal phase of the cycle each month.

Patients who kept full records during a control month were randomised into the six month trial. They were asked to apply 5 g of cream each evening from the tenth day of one menstrual cycle to the first day of the next. Two different preparations in identical containers labelled first or second were used; one contained 1% natural progesterone and the other was without the active hormone. The active and placebo creams were applied for three months, each in random order, and only the statistician knew the order of the treatments. For each patient a mean pain score was calculated from the seven worst daily pain scores during the premenstrual phase each month. The seven worst days were usually consecutive and most often the days before the next period. The pain and nodularity scores for each patient were analysed by non-parametric tests, which compared differences within patients.

Thirty two women were entered into the study; 17 were randomised to use the active drug first and 15 the

placebo. Seven did not return for their monthly appointments (usually after the first month). Thus complete data were available for 25 of the women, 14 of whom used the active treatment first and 11 the placebo.

The data were first analysed for trends in the pain and nodularity scores over time, but no evidence of any such trends was found. To compare the drugs a mean pain score and a total nodularity score were calculated for each patient's three month exposure to each drug.

Pain and nodularity scores in 25 patients with cyclic breast pain

Outcome	Median score	Median (95% confidence interval) difference (active-placebo)
Mean pain score at 3 months	44	3.3* (-3 to 12)
Total nodularity score over 3 months†	4	1.0* (0 to 1.5)

*Not significantly different from zero by Wilcoxon's signed rank test.

†Sum of three monthly ratings, each of which was scored 0 = none, 1 = slight, 2 = mild, 3 = severe.

The results (table) showed a small but non-significant benefit from the placebo over the active drug. The confidence intervals indicated that any difference between the two preparations was small.

Comment

We have found that progesterone cream applied locally was no better than placebo cream in relieving breast discomfort. Attempts to determine whether the cream was absorbed into the circulation by daily measurement of salivary hormone concentrations was unsuccessful; this was because the samples contained high concentrations, which we found to be the result of contamination from cream on the patients' fingers.

Many of the oral treatments for mastalgia—for example, bromocriptine, danazol, and tamoxifen—can have troublesome side effects,^{3,4} and for a condition that can be self limiting their use is thus questionable.⁵ A topical treatment would be preferable, but unfortunately we showed that progesterone had no effect.

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