Case report

A 59-year-old woman with severe multiple sclerosis was admitted for the management of a decubitus ulcer over the mid-sacral area. This included spraying the base of the ulcer daily with 1-2 ml of bovine soluble insulin (insulin injection BP, 20 units/ml). She was turned two-hourly, given a high-protein diet and all possible nursing care. Her general condition deteriorated suddenly 3-4 hours after her insulin treatment. Her mental state changed and she became restless, aggressive, and disorientated. She was flushed and sweating, though afebrile. Her pulse was 110 beats/min and blood pressure 120/70 mm Hg. The only abnormal physical sign was a positive Babinski response on the left side. An electrocardiogram was within normal limits.

During the next hour her condition deteriorated further and she became comatose and unresponsive to deep pain. Dextrostix showed a blood glucose concentration of less than 2.5 mmol/l (45 mg/100 ml) and urinary sugar concentration at this time was 1.2 mmol/l (20 mg/100 ml). 100 ml of 50% dextrose intravenously resulted in total physical and mental recovery within 10 minutes.

Discussion

Undoubtedly this patient suffered hypoglycaemic coma from absorption of topical insulin through the ulcer. Subsequent inquiry showed that a more concentrated preparation (80 units/ml) had been used on this occasion.

Although reports of the effect of topical insulin on wound healing in rats are conflicting,^{1,2} Van Ort and Gerber³ concluded in a small pilot study that topical insulin was "a safe and effective agent in the healing of small uncomplicated decubitus ulcers." This case shows that the possibility of absorption of insulin through a large raw area should not be underestimated and suggests that great care is required when administering insulin in this way.

I thank Mr C P Bates for permission to report this case and Dr R B Tattersall for his helpful comments.

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² Grewal, R S, *et al*, *International Surgery*, 1972, **57**, 229.

³ Van Ort, S R, and Gerber, R M, *Nursing Research*, 1976, **25**, 9.

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20-hour combination chemotherapy in advanced breast cancer

Breast cancer is one of the most responsive of the so-called "solid" tumours to combinations of anticancer drugs.¹ Nevertheless, drug treatment has usually been given over several days, often five, often associated with varying degrees of toxicity to normal tissues, particularly the bone marrow. In 1971 we showed that intensive combination chemotherapy could be given over 24 hours with a definite reduction in toxicity to normal tissues, and without loss of therapeutic effect.² Here we report the application of these principles to the treatment of advanced breast cancer.

Patients, methods, and results

A total of 45 patients were treated, of whom 42 were assessable. All had had a mastectomy as initial treatment, and most had been given postoperative radiotherapy. Thirty-five patients had had some previous hormone treatment, two ablative endocrine surgery, but only one had been given chemotherapy.

At time zero in the drug treatment the patients were given intravenously vincristine sulphate, 1.0 mg/m²; cyclophosphamide, 600 mg/m²; and 5-fluorouracil 500 mg/m². Immediately after this, an infusion of methotrexate, 100 mg/m² in physiological saline, was given over 16 hours. Four hours

after the end of the methotrexate infusion, calcium folinate was given in two doses of 21 mg four hours apart, followed by 6 mg intravenously six-hourly for four injections. In patients with impaired renal function, the leucovorin "rescue" was extended appropriately. A phenothiazine antiemetic was given at the beginning of treatment and repeated as necessary; the treatment cycle was usually repeated every three weeks. If the peripheral blood platelet and total white cell counts had not returned to pretreatment levels, treatment was postponed for one week, when full doses could always be given. Patients with evidence of progressive disease were treated with at least two cycles. If the disease progressed in spite of this, the patient was considered a non-responder and treatment was altered. Patients who showed objective evidence of regression were continued on the same treatment for as long as the response continued. Response was defined as a 50% reduction in the size of the primary tumour without evidence of progressive disease in other affected sites. The regression had to last for at least one month. Subjective improvements were counted as a non-response. The duration of response was timed from the initial treatment until unequivocal evidence of progressive disease, and not from the beginning of treatment to death.

Of 42 assessable patients, 28 (67%) responded and 14 did not (see table).

In all patients who responded there was relief of pain and an overall improvement in performance. Four patients had complete regression of all clinical manifestations of tumour. The side effects of treatment were nausea and occasional vomiting during treatment, loss of tendon jerks, and alopecia. There were no drug-induced deaths and no episodes of severe thrombocytopenia or neutropenia.

Menopausal status, response, and survival in 42 patients

	Menopausal		Response duration (months)		Survival (months)	
	Pre-	Post-	Mean	Median	Mean	Median
Responders	18	10	6+	5½	13	9 (5 patients still alive)
Non-responders	9	5	—	—	5½	<2 (1 patient still alive)

One month = 28 days

Discussion

The results of this study confirm our original findings² that combinations of the above drugs can be given perfectly safely provided certain kinetic principles³ are applied and the drugs are given over short periods. This approach has also been shown to improve the selectivity of drug combinations in other tumours.⁴ Therefore it is now possible to give effective and quite intensive chemotherapy more safely than in the past, provided certain precautions are rigorously observed. We suggest that for adjuvant therapy studies in breast cancer protocols such as ours have certain advantages—for example, low toxicity; at least equal effectiveness in advanced disease compared with more toxic regimens; and minimal interference with the quality of the patient's life. It is true that the protocol requires admission to hospital for one night every three or four weeks, but this is an advantage in a controlled study since it is certain that the patients receive the drugs. Finally, increases in survival time are more likely if adjuvant chemotherapy is given optimally.⁵ We think that our approach makes it possible to meet this requirement safely.

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