he was taking a minimum of 256 units daily. Thereafter the dosage dropped progressively, but seven weeks later he still needed up to 188 units daily. He was then transferred to Actrapid MC. In three days his insulin requirement fell by 36% to 102 units daily. He was stabilised on twice daily Actrapid MC in a total dose of 112-124 units daily and remained well controlled, with a mean mid-morning blood sugar level of 6.1 mmol/l (110 mg/100 ml). His daily diet (9.2 MJ; 2200 kcal) and weight remained unchanged. At the time of maximum insulin resistance there was no evidence of severe infection or any other precipitating factor; in particular, his growth hormone levels were normal.

Discussion

Although claims that monocomponent insulins are highly purified and virtually non-antigenic²⁻⁴ have been challenged,⁵ they may be of benefit to patients with insulin resistance¹ and allergies and in atrophic and hypertrophic types of lipodystrophy. Their use in newly diagnosed diabetics might help to avert complications due to the formation of insulin antibodies, although the significance of this is still under debate.² A potential disadvantage is that they may have a shorter duration of action than conventional insulins because binding to circulating antibody is thought to delay availability of active free insulin to the tissues.

Our patient was clearly coming out of his insulin-resistant phase before changing to monocomponent insulin, but his immediate fall of 36% in insulin requirements on transfer to Actrapid MC could have had serious consequences had the changeover been attempted outside hospital. This fall was probably more drastic than average, but the overall frequency of decreased requirements compared with less pure insulins has been reported to occur in some two out of three such transfers. The packaging of the new monocomponent insulins is closely similar to that of the standard insulins marketed by the manufacturer (Novo Industri), and we are concerned that patients already taking the latter may unwittingly be supplied with monocomponent insulins as a renewal of prescription and may therefore be at risk of severe hypoglycaemic reactions. We therefore suggest that patients changing to monocomponent insulins from beef insulins should make a 20% cut in dosage, and those changing from monospecies pork insulins, which are less antigenic, a 15% reduction initially, and that finer adjustments should be made thereafter under close supervision.

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Serum levels of doxycycline in normal subjects after a single oral dose

Doxycycline (Vibramycin) gives prolonged and therapeutic serum levels after single oral doses of 100, 150, and 250 mg per day. This, compared with other tetracyclines, makes a once a day treatment schedule possible and rational.¹ Single-dose therapy at 100 mg and

200 mg for louse-borne typhus fever² and tick-borne relapsing fever,³ 300 mg for uncomplicated gonorrhoea,⁴ and 500 mg for uncomplicated lobar pneumonia (unpublished, Pfizer Ltd), have been reported. We therefore measured serum levels after a single dose of 500 mg in healthy adults to establish a rationale for this dose level.

Methods and results

Fourteen female and six male healthy, adult Nigerians between 20 and 45 years of age volunteered for the study. After a zero blood sample taken after breakfast, five doxycycline hyclate capsules (500 mg) were given orally with a glass of water over 5-10 minutes. Serial blood samples were then taken initially from nine volunteers up to 48 hours and subsequently from 11 volunteers up to 120 hours and from three up to 144 hours. Light refreshments were served during the first few hours and the subjects then returned home to their routine lives, reporting on subsequent days for blood sampling after breakfast. The serum concentration of doxycycline was determined by the fluorometric method of Kohn,⁵ using a Farrand Model A fluorometer.

The results are summarised in the table. Two subjects, who vomited during the second hour after taking the capsules, had peak serum concentrations of 11.30 and 8.00 mg/l. Two other subjects complained of abdominal rumblings on the first evening of the study. Using an aqueous solution of doxycycline in three experiments, and doxycycline powder in two, mean percentage recoveries of doxycycline from whole blood *in vitro* were 37% and 24% respectively. A further extraction of the haemolysed red cell "debris" gave a mean percentage recovery of 55%, which gave a total recovery of 92% and 79% with the aqueous solution and the powder respectively.

Discussion

Doxycycline was rapidly absorbed by all subjects, with peak serum levels after four hours. The mean peak level of 15.29 mg/l is much higher than those reported for lower doses,¹ but the fluorometric measurement of doxycycline gives higher values than the microbiological assay. The *in-vitro* experiments suggest that serum doxycycline represents only a fraction of the level in blood. The association of a larger percentage with the red cell "debris" suggests that serum doxycycline binds to these cells. While the significance of this cannot be fully inferred now, it indicates that much higher levels are present in whole blood than in serum.

The fact that the generally accepted clinically effective serum level of 1 mg/l was maintained for up to four days with a single 500-mg dose of doxycycline establishes a rationale for clinical trials of single-dose therapy. This could be particularly useful in areas of the world where patients missing doses, or taking too many capsules, present as problems in the prescription of antibiotics in outpatient and general practice clinics. Its proved efficacy may also be of advantage in dealing with acute illnesses of bacterial origin where facilities do not permit close and frequent supervision of patients by a medical team.

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Mean serum concentrations of doxycycline ($\pm$ SE of mean)

Hours:	0	1	2	4	6	24	48	72	96	120
Mean (mg/l)	0.50	7.03	11.15	15.29	10.86	6.60	3.42	1.24	1.00	0.40
SE of mean	0.10	0.65	0.57	0.80	1.65	0.66	0.62	0.17	0.04	0.07
No of subjects	20	20	20	11	9	20	20	9	9	9

At 144 hours in three subjects levels were 0.40, 0.20, and 0.20 mg/l.