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Delayed-release bleomycin

Comparative pharmacology of bleomycin oil suspension and bleomycin in saline

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Summary. *Experimental and clinical evidence indicates that bleomycin by continuous infusion is superior to intermittent administration. Continuous infusion is less convenient, however. It has been suggested that a suspension of bleomycin in sesame oil, given by IM injection, simulates a continuous infusion.*

The pharmacokinetics of this formulation have been compared with those of bleomycin in saline following IM injection, in six patients.

The pharmacokinetic profiles of the two formulations were similar. The only difference between the profiles was the long terminal half-life at very low concentrations between 12 and 48 h after injection of the oil suspension. This difference is of unknown, but doubtful, clinical significance.

Introduction

Bleomycin is an anti-tumour antibiotic that is cell cycle phase-specific, acting predominantly in the G2 and M phases [4]. Such drugs are generally more effective when administered by continuous infusion [5].

Animal studies comparing continuous infusion of bleomycin with intermittent administration have demonstrated a greater anti-tumour effect with the former [11, 14, 18], without an increase in the pulmonary toxicity.

In man, studies of continuous infusion of bleomycin have also suggested increased activity. In testicular teratoma continuous infusion of single-agent bleomycin led to the achievement of partial remission in a high percentage of patients (69%) who had been refractory to bleomycin by intermittent-dose schedules [10]. Similarly, Samuels et al. [12] found a higher complete response rate in patients with testicular teratoma treated with continuous infusion of bleomycin compared with twice-weekly IM injection (49% vs 34%). In advanced uterine cervical cancer the importance of bleomycin schedule has been demonstrated, with twice-weekly and continuous infusion schedules shown to be superior to a once-weekly injection in one study [3] and continuous infusion superior to daily injections in another study [11]. The toxicity associated with continuous infusion has been no greater than with the intermittent schedule [10].

Continuous infusion of bleomycin has not gained wide acceptance because of the disadvantage of requiring patients to be in hospital, while the intermittent schedule can be given on an outpatient basis.

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Recently it has been claimed that a suspension of bleomycin in sesame oil might delay the release of bleomycin from the injection site, and animal studies have suggested that this suspension may be more effective than conventional bleomycin [17]. The local and systemic toxicity following IM injection of bleomycin oil suspension in man appeared similar to that previously reported for conventional bleomycin injections [13]. Shimoyama et al. [13] found a higher complete response rate in patients with non-Hodgkin's lymphoma treated with bleomycin oil suspension than in those treated with bleomycin saline solution (35% vs 10%). Intra-tumour injection of bleomycin oil suspension has been evaluated in several hundred patients [6, 7, 16]. Effective local control has been obtained with this therapy but it is difficult to evaluate the role of the bleomycin.

There are few data, in man, on the pharmacokinetics of bleomycin given in this new formulation [6, 9, 10]. Therefore, the pharmacokinetics of bleomycin following injection of bleomycin oil suspension and bleomycin in saline have been compared.

Materials and methods

Patients. Six patients (three with testicular teratoma, two with ovarian cancer, and one with uterine cervical cancer) were studied. All patients were fully ambulant and had normal renal and hepatic function. Each patient was studied following both bleomycin oil suspension and bleomycin in saline on consecutive occasions, and all thus acted as their own controls. The order in which the two formulations were given was randomised.

Methods. Bleomycin and bleomycin oil suspension were supplied by Lundbeck. The bleomycin oil suspension comprises bleomycin sulphate (15 mg/ml) in a sesame oil base containing 1% aluminium monostearate. The bleomycin saline solution was prepared by adding 1 ml saline to 15 mg bleomycin sulphate powder. Each formulation was given at a dose of 15 mg (total volume 1 ml) by IM injection into the deltoid muscle.

Sampling. Blood samples were taken after the injection of bleomycin at the following times: 0, 15, 30, and 45 min; 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 24, and 48 h. Samples 4 ml in volume were taken and allowed to clot. The serum was separated and frozen at −20° C until assay.

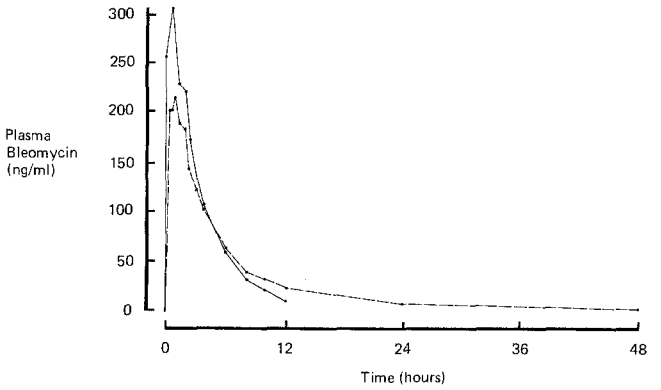

Fig. 1. Mean plasma bleomycin concentrations in six patients after IM injection of 15 mg bleomycin in saline (———) or 15 mg bleomycin oil suspension (– – –)

Assay. Serum levels of bleomycin were measured using a specific and sensitive radioimmunoassay [16]. The limit of detection of this assay is less than 1 ng/ml, with a coefficient of variation of 6% within and 10.8% between assays [2].

Statistics. The pharmacokinetic analysis was performed using an interactive computer program, STRIPE [8]. Student's *t*-test was used for statistical analysis.

Results

Both formulations were well tolerated with no local toxicity from either. Bleomycin oil suspension and bleomycin in saline were both rapidly absorbed following IM injection. The mean peak levels were not significantly different but there was greater inter-patient variation following bleomycin oil suspension. Serum levels following bleomycin oil suspension declined with a mean initial elimination half-life of 1.9 ± 0.23 h, which accounted for 75% of the AUC and a terminal half-life of 10.8 ± 5.6 h. This terminal half-life occurred at very low concentrations (less than 12 ng/ml; mean 4.1 ng/ml). Serum levels after bleomycin in saline declined with a single exponential (mean half-life 2.5 ± 0.9 h) which was similar to the initial half-life following injection of bleomycin oil suspension.

No bleomycin was detected more than 24 h after bleomycin in saline, but bleomycin was present after bleomycin oil suspension at 48 h in five of the six patients. The apparent difference in the elimination half-lives of the two formulations was due to the long terminal half-life of the oil suspension at concentrations near the limit of detection of the assay. The similarity of the two concentration/time profiles is clearly illustrated in Fig. 1. The mean serum bleomycin concentrations following injection of each formulation are given in Table 1. The pharmacokinetic data are shown in Table 2. The areas under the curve (AUC) are shown for individual patients in Table 3. The mean AUC and total body clearances were not significantly different for bleomycin oil suspension and bleomycin in saline.

Table 1. Plasma concentrations of bleomycin[a]

Time (h)	Bleomycin in saline (ng/ml)	Bleomycin oil suspension (ng/ml)
0	0	0
0.25	254 ± 81	115 ± 54
0.50	283 ± 47	208 ± 85
0.75	308 ± 79	207 ± 120
1	272 ± 60	221 ± 147
1.5	234 ± 47	193 ± 108
2	219 ± 62	184 ± 92
2.5	182 ± 59	147 ± 67
3	150 ± 53	131 ± 50
4	109 ± 31	106 ± 43
6	59 ± 26	66 ± 39
8	32 ± 20	41 ± 25
10	20 ± 15	30 ± 21
12	12 ± 9	22 ± 17
24	–	6 ± 4
48	–	2 ± 1

[a] Means and standard deviations of data recorded in six patients

Table 2. Bleomycin pharmacokinetics[a]

	Bleomycin in saline	*P*-value	Bleomycin oil suspension
Absorption $T_{1/2}$ (min)	7 ± 3	NS	22 ± 19
C max (ng/ml)	318 ± 56	NS	243 ± 130
T max (min)	45		60
Elimination $T_{1/2_1}$ (h)	–		1.9 ± 0.23
Elimination $T_{1/2_z}$ (h)	2.5 ± 0.9	$P < 0.05$	10.8 ± 5.6
AUC (ng/ml · h)	1,192 ± 376	NS	1,303 ± 689
Total clearance (ml/min)	230 ± 83	NS	229 ± 80

[a] Means and standard deviations of data recorded in six patients

Table 3. Comparison of AUC in individual patients following bleomycin 15 mg IM

Patient	Bleomycin in saline (ng/ml · h)	Bleomycin oil suspension (ng/ml · h)
P.M.	1,383	1,574
P.L.	1,224	866
I.A.	976	971
M.S.	1,140	2,599
P.P.	1,769	937
P.M.	657	869
Mean	1,192	1,303
SD	376	689

Discussion

The pharmacokinetics of bleomycin following injection of the two formulations were remarkably similar. The only difference between the two plasma profiles was the long terminal half-life following bleomycin oil suspension, which occurred at very low concentrations between 12 and 48 h after injection. These concentrations of bleomycin (mean 4 ng/ml) are considerably lower than those found during continuous IV infusion of 15 mg/24 h (mean 50 ng/ml; unpublished observations). It seems unlikely that such levels are clinically significant. The difference between the terminal half-lives of the two formu-

lations is probably irrelevant. The failure to detect bleomycin beyond 12 h following bleomycin in saline has led, by convention, to the comparison of a single exponential decay curve following bleomycin in saline with the second of two such curves following bleomycin oil suspension. If the initial exponentials are considered these are not significantly different. The plasma concentration profiles are clearly very similar, as shown in the figure. This is in contrast to previous reports of the pharmacokinetics of bleomycin oil suspension in man [6, 9], in which bleomycin oil suspension produced significantly longer plasma concentrations than did bleomycin in saline. Kimura et al. [9] treated a single patient with bleomycin in saline by IV bolus and by IM injection and with bleomycin oil suspension by IM injection. Ikeda et al. [6] compared the pharmacokinetics of bleomycin following IM injection of saline solution and oil suspension, also in a single patient. These data are difficult to evaluate, however, because the AUC is much greater following the oil suspension, suggesting that the dose of bleomycin in oil suspension may have been larger than that of the bleomycin in saline.

In contrast to these studies the results of the current study are similar to those found in a single patient studied by Krakoff et al. using ^{111}I-labelled bleomycin in saline or oil suspension [10].

A formulation of cytotoxic drug in vegetable oil similar to bleomycin suspension has been used in an attempt to delay the release of cytosine arabinoside from subcutaneous tissues (M. L. Slevin et al. [15]. Cytosine arabinoside was suspended in arachis oil plus 2.5% aluminium distearate and was compared with cytosine arabinoside in saline. There was no delay in the release of this drug either in animal studies or in man. Bleomycin sulphate and cytosine arabinoside are both highly water-soluble drugs and it is likely that they pass rapidly from the oil suspension into solution in the surrounding interstitial fluid from where they are absorbed.

The similar plasma concentration profiles following bleomycin oil suspension or bleomycin in saline suggest that the oil suspension cannot be considered an alternative to IV infusion.

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