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Short communication

A pharmacokinetic evaluation of IM administration of bleomycin oil suspension

Margaret Davy [1], Elisabeth Paus[1], Gustav Lehne[2]

[1] The Norwegian Radium Hospital, Oslo, Norway
[2] H. Lundbeck Ltd., Oslo, Norway

Summary. *Bleomycin oil suspension was given IM twice daily to four patients, and bleomycin saline solution infused to three patients with cervical carcinoma. The serum levels of bleomycin were followed for 12 h by radioimmunoassay. Both regimens revealed comparable side effects. Only minor responses were seen. Bleomycin oil suspension produced prolonged levels of bleomycin in serum.*

Introduction

The antitumor antibiotic bleomycin is effective in treating squamous cell carcinomas, malignant lymphomas and testicular tumors. In 1976 Samuels et al. [11] showed a superior clinical response to continously infused bleomycin IV compared to conventional bolus administration in a non-randomised study. This result was confirmed by animal studies showing that sustained plasma levels of bleomycin are related to enhanced inhibiton of tumor growth [9, 12]. Moreover, less toxic effects were seen with the continuous regimen [2]. Lung tissue especially was less vulnerable [5, 12]. It is essential to avoid exposing the pulmonary circulation to high levels of bleomycin as this exerts a direct toxic effect on the capillary endothelium.

The rapid renal clearence of bleomycin demands a continuous infusion to maintain an adequate blood concentration. Pharmacokinetic data obtained in rats, dogs, and rabbits show protracted elimination of bleomycin after IM administration of bleomycin oil suspension (BOS), containing 15 mg bleomycin/ml suspension in sesame oil with 1% aluminium monostearate as dispersing agent [1]. We have studied the depot properties of this BOS preparation in patients with advanced cervical carcinoma. The serum levels of bleomycin were measured by a radioimmunoassay utilizing radioiodinated bleomycin. No optimal therapeutic plasma level has been established, but a range of steady state concentrations of 10–150 ng/ml has been reported as therapeutically effective [4, 6].

Patients and methods

Seven ambulatory patients with recurrent squamous cell carcinoma of the uterine cervix were studied. All had normal renal function. Four were treated with 0.3 ml BOS injections IM into the gluteal muscle twice daily (9 mg bleomycin) with a 4-h interval in order to mimic the sustained serum levels achieved during infusion. Three received a standard regimen with 5 mg bleomycin in saline solution IV infused for 4 h. Both treatments lasted for 5 days. Blood was taken at hourly intervals, beginning just prior to the first bleomycin injection, and continuing for 12 h, on days 1 and 5 of therapy. Serum samples were stored at −20° C until analysis. Informed consent was obtained from all patients.

Assay procedure and calculations. Determination of bleomycin in serum was performed with a conventional radioimmunoassay essentially as described by Broughton and Strong [3]. Bleomycin obtained from H. Lundbeck Ltd., Copenhagen, was iodinated by the iodogen method [8]. The iodination of 1 μg bleomycin with 0.2 mCi $Na^{125}I$ was performed in 0.5 mol/l sodium borate buffer pH 8.5, using 2 μg insolubilized iodogen as the oxidant. The reaction was allowed to proceed for 8 min at room temperature before separating free from bound radioactivity on a Sephadex G-10 column.

Rabbit anti-bleomycin antiserum, purchased from Guildhay Antisera, University of Surrey, was used at a dilution of 1 : 4,800. All dilutions of reagents were made in assay buffer: 0.01 mol/l phosphate buffer pH 7.0, containing 0.15 mol/l NaCl and 0.1% gelatin.

The radioimmunoassay was performed by incubating 50 μl bleomycin standards (3–200 ng/ml) or samples, 100 μl ^{125}I-bleomycin, 100 μl antiserum, and 350 μl assay buffer on ice for 3 h. Dextran coated charcoal, 200 μl, was added to separate free from bound bleomycin. After 10 min at 0° C the tubes were centrifuged and decanted before counting.

Bleomycin dilutions in serum were run as controls at three different levels. The interassay coefficient of variation was in the range 8–12%, and the lower limit of detection 3 ng/ml.

The serum concentrations were graphed over time on semilog paper. The half-lives were calculated according to a one-compartment model, which gave the best fit for the elimination phase. This model was applied together with the trapezoidal method in analysis of the area under the curve, clearence, and distribution volume. Comparisons were performed using van der Waerden's χ-test.

Results

The bleomycin serum levels were slightly increased after the second BOS injection, and with one exception on the 5th day of BOS treatment (Fig. 1). The peak serum concentrations

Offprint requests for: G. Lehne, H. Lundbeck Ltd., Box 188, 1324 Lysaker, Norway

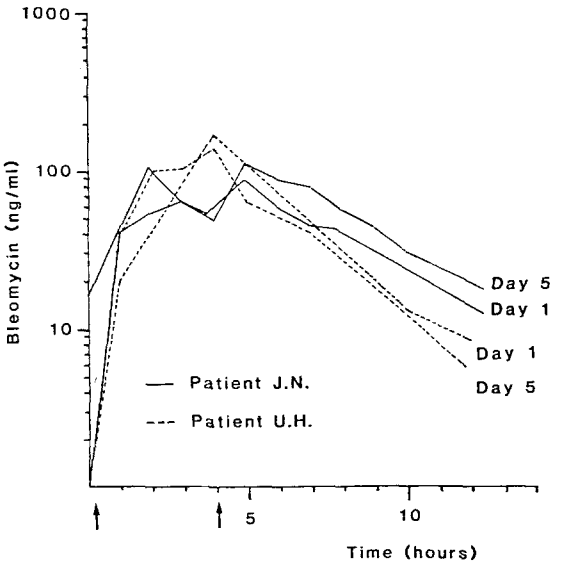

Fig. 1. The time course of bleomycin levels in serum from two patients on day 1 and 5 of therapy graphed on semilog paper. Patient J. N. received 0.3 ml BOS IM twice daily (↑). Patient U. H. received bleomycin IV infusion 5 mg in saline solution for 4 h daily

were obtained approximately 2 h after IM BOS injections. The infusion regimen revealed the higher peak levels, averaging 138 ng/ml vs 97 ng/ml in the BOS regimen (median 140 ng/ml vs 90 ng/ml, respectively). The mean serum half-life was 3.5 h (median 3.7 h) with BOS and 2.4 h (median 2.4 h) for the infusion ($P < 0.01$). Ten hours from the initiation of treatment on day 1 the BOS regimen revealed a mean serum level which was 20 ng/ml higher than found after the infusion. The corresponding difference on day 5 had increased to 31 ng/ml. Before therapy on day 5 the serum levels achieved by BOS ranged from 10 ng/ml to 18 ng/ml compared to less than 3 ng/ml after infusion therapy.

The mean distribution volume (V_D) of bleomycin was 29.4 l/m^2 (median 30.4 l/m^2) with BOS compared to 13.0 l/m^2 (median 13.1 l/m^2) for the infusion ($P < 0.001$). The mean area under the serum concentration curve (AUC) obtained with BOS was not significantly higher than after the infusion regimen (57.0 mg/min/ml vs 49.0 mg/min/ml respectively), despite that the BOS regimen contained almost the double dose of bleomycin. The mean serum clearence rate (Q) for BOS was 101 ml/min/m^2 (median 107 ml/min/m^2) and 66 ml/min/m^2 (median 74 ml/min/m^2) for the infusion.

Clinically, BOS was well tolerated. Fever was seen, but this presented less problems than with the IV infusion. One patient developed a gluteal abcess, a side effect seen also in treatments with other depot preparations, and probably due to the oily vehicle. A 54-year-old woman developed a pulmonary fibrosis after six courses of therapy, totaling 18 ml BOS (270 mg bleomycin) and 60 mg mitomycin-C. The symptoms were relieved with steroids. There were two patients with partial responses. Both had lung metastases, which were reduced in size. These effects were only short lived, such that they did not play a part in prolonging life.

Discussion

The twice daily BOS schedule revealed more favourable pharmacokinetics than the 4-h infusion regimen. The lower AUC yield associated with BOS indicate delayed or incomplete systemic uptake from the injection site. A second phase of retarded elimination was not found during the 12 h of recording in our study, but have been demonstrated by others [13]. However, the delayed peak concentration, the prolonged serum half-life, the maintained therapeutically active concentration, and the huge distribution volume account for some depot effect of the BOS preparation. In contrast, IM administration of bleomycin saline solution is reported with peak levels obtained after one hour [7], a mean half-life of 2.6 h [7], and no detectable levels in serum after 24 h [10, 13].

We have not been able to make a direct comparison between IM injections of BOS and bleomycin saline solution, because a 4-h infusion was used as control. In our department this was previously believed to be the most convenient way of maintaining serum levels within the therapeutic range in a prolonged periode of time. BOS seems even more convenient, and it does not demand hospitalization. Neither of the two schedules was able to show beneficial effect in these patients, but BOS may represent an advantage in treatment of tumors more responsive to bleomycin.

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