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Orgotein (Superoxide Dismutase): A Drug for the Amelioration of Radiation-induced Side Effects

A Double-Blind, Placebo-Controlled Study in Patients with Bladder Tumours

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Summary. Orgotein, the drug version of Cu-Zn superoxide dismutases is a new and safe anti-inflammatory agent. Animal experiments have shown that it does not interfere with the tumourolytic effects of radiation or chemotherapy. A double-blind, placebo-controlled study has demonstrated that orgotein injected after each daily irradiation session can be used safely and effectively to ameliorate or prevent the side effects due to high-energy radiation therapy (8,400 or 6,400 rads) of bladder tumours. Orgotein significantly reduced the signs and symptoms both in the bladder and the bowel, indicating that it provides a therapeutic regimen for control of these side effects, which to date could only be treated symptomatically.

Key words: Orgotein - Superoxide dismutase - Radiation side effects - Bladder tumour - Cystitis - Proctitis.

Orgotein, the generic name for the drug version of Cu-Zn Superoxide Dismutases (SOD) (1), is a new anti-inflammatory agent which is different from all other drugs presently used for the treatment of inflammatory disease. Numerous studies have established that orgotein is a safe drug in animals and man (2). In nature, SODs occur in all cells of oxygen-consuming organisms where they dismutate superoxide anions (O_2^-) formed by a host of intracellular autoxidations. As a very active radical, O_2^- occurring extracellularly can be a threat to the integrity of living systems, since the concentration of SODs in mammalian sera is very low (about 10 ng/ml). It has been shown that exogenous SOD *in vitro* inhibits the cytotoxic effects of the superoxide anion generated by phagocytosing neutrophils and macrophages (3). That irradiation results in cell death with subsequent invasion of phagocytosing cells has been long established (4). The undesirable side effects of radiation therapy are at least partly due to these phenomena.

We initiated our studies based upon the belief that orgotein could reduce inflammatory side effects in patients getting high-dose irradiation for bladder tumours. As destruction of malignant cells by high-energy radiation is largely a direct-hit nuclear event that occurs in the presence of a relatively high concentration of superoxide dismutases in the cytosol, we felt that interference with the tumourolytic events by extra-cellular orgotein would not occur. Radiation experiments in tumour-bearing rodents conducted to date support this assumption. In addition, injection of orgotein at doses up to 400 mg/kg systemically or 2.5 mg intra-tumour did not alter the growth pattern of tumours, such as mammary adenocarcinoma, lymphoid leukaemia L-1210 and P. 388, melanocarcinoma Q-16, Lewis lung carcinoma and KHT sarcoma in mice (5, 6, 7).

MATERIALS AND METHODS

To test the efficacy of orgotein in ameliorating or preventing such side effects, a randomised double-blind, placebo-controlled trial was

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Table 1. Efficacy of orgotein over placebo in ameliorating side-effects due to radiation therapy of bladder tumours

Parameters	Level of Statistical Significance (p)
Maximum voided volume > 200 ml	$<0.05^a$
Interval between voidings during day	$<0.05^a$
Interval between voidings during night	NS^b
Severity of signs and symptoms in bladder	$<0.05^a$
Percent visits with diarrhoea	$<0.025^a$
Percent of "diarrhoea visits" requiring medication	$<0.001^a$
Dose of antidiarrhoeal medication	$<0.0025^c$

[a] Chi-square test [b] Not significant

[c] Student's t-test

undertaken with 38 patients (7 females, 31 males) receiving radiation for bladder tumours.

Four mg orgotein or placebo dissolved in about 1 ml USP saline was injected subcutaneously 15-30 minutes after completion of each daily radiation session. The tumours were classified according to UICC and covered stages T2-T4. Histological grading included malignancy grades 2-4. All patients received high-energy radiation with 6MV X-rays delivered by linear accelerator, using a three-field technique. The dose was either 6400 or 8400 rad, with the CRE factor 1800 or 1890, respectively, and totally similar (6). All patients received antibacterial therapy throughout the trial and were permitted to use a specified anti-diarrhoeal as needed. No other anti-inflammatories in addition to orgotein were permitted.

The effects of the experimental medication were assessed, using parameters such as pain and dysuria, maximum voided volume, interval between voidings during day and night, severity of diarrhoea, and amount of medication to control diarrhea. The patients were evaluated at 0, 2, 5 and 8 weeks after entry into the trial. The 8 week visit coincided with the termination of therapy. A follow-up evaluation was done at about 4 months after termination of therapy and a 2 year follow-up is under way. Haematology and urinalysis were performed at each visit and clinical chemistry at the beginning and end of the treatment. Cystoscopy was performed at the start of the trial and at the 4 months follow-up visit.

RESULTS AND DISCUSSION

The evaluation of the effects of the medication on signs and symptoms in the bladder is complicated by the presence of the tumour. At entry, the tumour affected these parameters to such an extent that the baseline values were considered meaningless as reference points. Orgotein efficacy over placebo was therefore analysed only at termination of therapy. For proctitis which is a side effect which appears early and remains throughout radiation therapy of pelvic tumours, the findings could be analysed using all data collected during the trial. The effects of orgotein over placebo for the evaluated parameters are summarised in Table 1. At completion of radiation therapy 67 % of the orgotein patients had a maximum voided volume over 200 ml compared with 38 % of the placebo patients. Daytime but not night-time voiding intervals showed a similar distribution. The pronounced effect of orgotein on prevention or amelioration of diarrhoea appeared within two weeks, remained throughout the course of radiation therapy, and continued thereafter. Thirteen patients developed pain and/or dysuria during treatment. Orgotein significantly alleviated these symptoms. At the 4 month follow-up, the beneficial effects of orgotein over placebo on bladder and bowel had become even more marked. For example, 4 of the 15 patients in the placebo group who had developed proctitis during the trial still had symptoms, with one patient still requiring substantial antidiarrhoeal medication, whereas none of the patients in the orgotein group showed any symptoms of proctitis.

Analysis of haematological, clinical chemistry, and urinalysis data did not reveal any adverse effects of orgotein. One of the 21 patients in the orgotein group developed some erythema at the site of injection which did not interfere with continuation of therapy.

To date only symptomatic treatment such as anticholinergics, analgesics, and opiates has been available for the treatment of the

sometimes therapy-limiting side effects of radiation. In contrast, the results of this trial indicate that orgotein prevents or ameliorates the side effects of radiation by a therapeutic rather than a symptomatic mechanism.

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