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A Double-blind Study of the Efficacy of Metronidazole Gel in the Treatment of Malodorous Fungating Tumours

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A double-blind placebo-controlled trial was undertaken to assess the value of topical metronidazole gel preparation in the palliation of the offensive odour of fungating tumours. This 5 day trial was followed by a 6 day period during which all patients received the active gel. Subjective odour assessments were performed by both patients and medical staff. 11 patients were entered and the randomisation was then halted because of an obvious overall benefit over the whole 11 days. There was a non-significant trend in favour of the active treatment during the initial double-blind placebo-controlled phase of the trial, and no side-effects were observed.
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INTRODUCTION

THE OFFENSIVE odour of fungating tumours is distressing for both patients and their carers, and arises as a consequence of colonisation of a necrotic tumour by anaerobic bacteria. Oral metronidazole has been shown to inhibit anaerobic colonisation [1] and reduce the associated odour of these tumours [2–4]. However, continuous therapy is necessary as organisms rapidly regrow when the treatment is stopped, oral metronidazole frequently causes nausea and vomiting, and the ban on alcohol necessary with oral metronidazole may further impair patients' quality of life [5]. Topical application of metronidazole would circumvent these problems and we have therefore conducted a double blind randomised study to assess its efficacy.

PATIENTS AND METHODS

Patients were randomised for an initial treatment period of 6 days into one of two parallel groups receiving either 0.8% metronidazole gel (Tillotts Laboratories) 1g/cm^2 lesion or placebo gel applied daily. This double-blind randomised placebo-controlled trial period was followed by an open assessment period of 5 days when all patients received active gel. Doses varied between 3.75 and 15 g per day depending on lesion sizes but were constant for each patient. None of the patients received antitumour therapy or antibiotics within the 4 weeks preceding and for the duration of the trial.

The odour of the lesion was graded daily by the patient and by one investigator (AH) at home visits, using visual analogue

scales rated 0–10. Statistical analysis was by paired *t* tests; values are quoted as the mean (S.E.).

RESULTS

11 patients (10 female), mean age 68 years (range 51–85) with open fungating primary or metastatic tumours (9 breast, 1 ovarian, 1 lung) producing an offensive odour graded at least 6/10 on a visual analogue scale by both the patient and medical staff were enrolled.

2 of 11 patients enrolled in this study were withdrawn, 1 from each treatment group. 1 patient required introduction of chemotherapy for systemic disease, and a second required parenteral antibiotics for respiratory infection.

During the first treatment period (days 0–6) the mean patient and medical-staff odour assessment in the placebo group ($n = 5$) remained above 6 (i.e. the minimum severity required for inclusion in the study). In contrast in the treatment group ($n = 4$), the mean patient odour assessment fell from 7.8(0.8) on day 0 to 5.0(2.1) on day 6 ($P > 0.1$). and odour as graded by medical staff fell from a mean of 6.5(0.5) to 4.3(1.9) on day 6 ($P > 0.1$).

At the start of the second open assessment phase of the study the patients initially randomised to placebo therapy had mean odour assessment values of 6.8(0.4) (patient values) and 6.6(0.5) (staff graded). These values fell following 5 days of topical metronidazole to 1.2(0.2) ($P < 0.005$) and 1.1(0.3) ($P < 0.005$), respectively. The 4 patients who had received active gel during the initial treatment period continued to improve over the second period of the study with mean odour assessments falling by day 11 to 2.3(0.9) (patient assessed) and 1.5(0.5) (staff assessed), (see Fig. 1). Overall patients received 5 or 11 days of 0.8% metronidazole gel and in every case there was a subjective improvement in odour as assessed by both patient and medical staff, and these improvements are statistically significant (D0 vs. D11 odour grades $P < 0.001$ (patient assessed), $P < 0.001$ (staff assessed)]. No patient experienced side-effects and there were no adverse events during the study on either treatment arm.

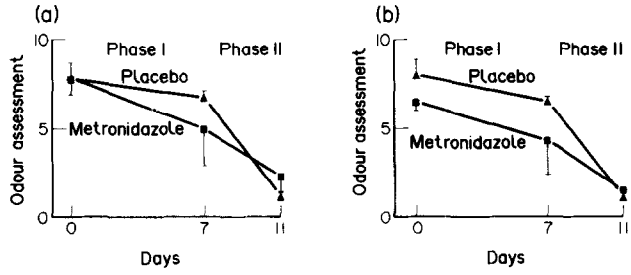

Fig. 1. Mean odour assessments by patients (a) and investigators (b). During phase I (days 0–7) patients receive either metronidazole gel or placebo gel. In phase II (days 7–11) all patients receive metronidazole gel. Bar lines indicate S.E.

DISCUSSION

This is the first double-blind placebo-controlled randomised study of topical metronidazole gel. The trial confirms the efficacy of 0.8% metronidazole in reducing the odour associated with open fungating tumours as assessed subjectively by both the patient and medical staff. All the patients received either 5 or 11 days therapy and all improved. During the initial double-blind placebo-controlled phase of the study there is a trend in favour of the active preparation although this does not achieve statistical significance due to the small number of patients. The moderate improvement in patients whilst treated with placebo gel probably relates to the daily cleaning and redressing of fungating tumours following odour assessment by medical staff. In view of the dramatic and significant overall improvement following therapy it was considered unethical to proceed with the placebo arm of this trial in these terminally ill patients and the trial was stopped.

The results of this small double-blind randomised study indicate a trend in favour of topical 0.8% metronidazole gel over placebo in palliation of offensive smelling tumours. Metronidazole gel is safe, effective and less toxic than orally administered metronidazole. We recommend daily cleaning and redressing for 7 days followed by a 5-day course of topical 0.8% metronidazole gel applied daily at a dose of 1 g/cm^2.

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