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Double-blind, placebo-controlled cross-over study of oral pilocarpine for the prevention of chemotherapy-induced oral mucositis in adult patients with cancer

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Abstract

This study aimed to investigate the effect of oral pilocarpine (OP) in reducing the incidence of chemotherapy-induced oral mucositis. 32 adult cancer patients completed a total of 82 courses of chemotherapy in which either OP or placebo was given prophylactically in a double-blind cross-over design to prevent mucositis. Mucositis was documented in 20 out of 41 courses in which patients were given placebo, whereas mucositis was documented in only six out of 41 courses when patients were given OP ($P<0.005$). OP treatment was found to significantly reduce the mucositis score when assessed by the method of Donnelly and colleagues (Donnelly JP, Muus P, Schattenberg A, De Witte T, Horrevorts A, De Pauw BE. *Bone Marrow Transplant* 1992, **9**, 409–413). Using this score, all patients scored a total of 52 when they were given the placebo versus eleven when they were treated with OP ($P<0.001$). A similar reduction in mucositis score was noticed using the World Health Organization (WHO) mucositis score; the total patient score was 25 for the placebo-treated group versus 6 for the OP group ($P<0.001$). We therefore conclude that oral pilocarpine is highly effective in the prevention of oral mucositis when given prophylactically to adult patients receiving a variety of cancer chemotherapy regimens.

Keywords: Pilocarpine; Mucositis; Chemotherapy; Cancer

1. Introduction

Muscositis is a painful, debilitating, dose-limiting side-effect of cancer chemotherapy and following therapeutic irradiation of the head and neck [1]. After chemotherapy, the cells in the basal layers of the mucous membranes in the upper airways and upper gastrointestinal (G.I.) tract are unable to replace the cells that are lost. The most severe manifestation of mucositis is ulceration of the mucosa. This may be aggravated by concomitant chemotherapy-induced neutropenia and exacerbated by the colonisation of the ulceration by bacterial flora which may be an important source of systemic infection. 20–50% of septicaemia in immune-suppressed patients originate from the mouth [2]. Almost all cases of *candidiasis* originate from the oral cavity. Various chemotherapeutic agents may be associated with mucositis including 5-flourouracil (5-FU), methotrexate, bleomycin, doxorubicin, cyclophosphamide, ifosfamide, cisplatin, VP-16, high dose cytarabine, vinblastine, mitoxantrone and the taxanes. Mucositis may be a dose-limiting toxicity associated with a variety of regimens. Up to 80% of the patients receiving 5-FU and folinic acid may develop mucositis. Ulceration of the oropharynx with dysphagia reaches its peak on or near to day 10 post-chemotherapy. Doses of chemotherapeutic drugs may have to be reduced or delayed because of mucositis.

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There is no standard, widely accepted treatment to prevent or ameliorate chemotherapy-induced mucositis. A wide range of remedies have been used including traditional remedies, anti-ulcer agents, granulocyte-colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), ice in the mouth, capsaicin, amifostine, oral glutamine and mouthwash with various agents [1,3–5]. Oral pilocarpine (OP) has been effectively used to prevent or ameliorate radiation-induced mucositis and xerostomia [6–8]. OP has been used to treat mucositis during bone marrow transplantation in a pilot study consisting of 16 patients and resulted in a significant reduction of Bearman Grade II mucositis [9]. It was found to relieve xerostomia in chronic graft versus host disease (GVHD) in bone marrow transplantation patients [10]. The use of OP to prevent oral mucositis in chemotherapy setting has not been studied.

The aim of this study was to evaluate the effectiveness of OP in preventing or ameliorating mucositis when given prophylactically to patients with cancer who had received chemotherapy alone without radiation.

2. Patients and methods

2.1. Patients

From 6 February 2000 through to 5 December 2000, a total of 38 patients were studied in a randomised double-blind, placebo-controlled cross-over design (Fig. 1). Only patients with an expected survival of 3 months or more were included. 6 patients were excluded for protocol violation. 32 patients completed a total of 82 courses equally divided between each of the study drugs (pilocarpine or placebo) with all patients completing a minimum of one course of each. 7 patients received an additional two courses; one of each of the study drugs and 1 patient received an additional four courses, two of each drug. There were a total of 23 females (who received a total of 58 courses) and 9 males (who received a total of 24 courses). Mean age was 45.8 years (range 23–62 years). There were a total of 18 patients with breast cancer, 3 with Non-Hodgkin's lymphoma, 3 with Hodgkin's disease, 2 with acute myeloid leukaemia (AML), 2 with adrenal carcinomas, and one of each of ovarian carcinoma, carcinoma of the cervix, thyroid carcinoma and bladder carcinoma. Table 1 shows the patients' characteristics, courses and diagnosis.

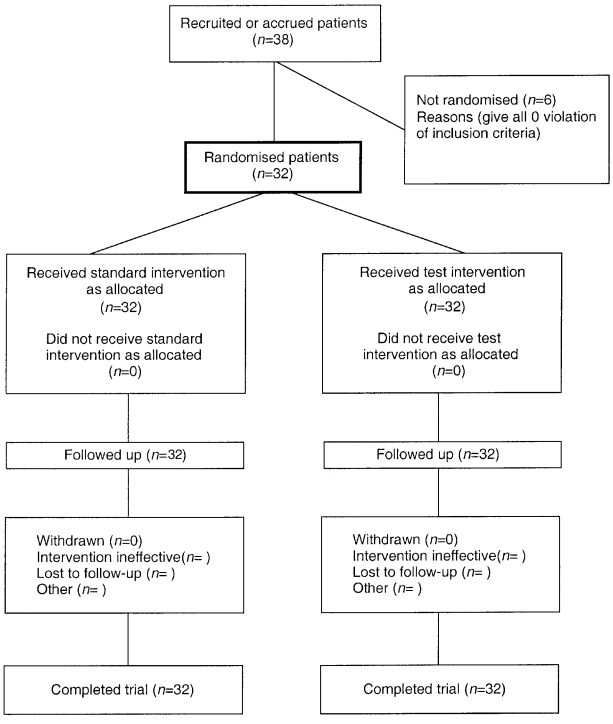

Fig. 1. Flow chart of the progress of patients through the trial (adapted from Ref. [14]).

2.2. Study protocol

Study protocol was approved by the institution review board and patient's consent was obtained in accordance with the Helsinki declaration.

2.2.1. Study drugs

Pilocarpine and placebo were supplied in the form of 5 mg tablets, 10-tablet blister packs were supplied free of charge by Advanced Pharmaceutical Company, Sahab, Jordan. The investigators and patients were blinded. The patient was started on a 5 mg tablet of the study drug 1 h before chemotherapy and was continued on one tablet every 8 h for a total of 7 days. The patient was asked to return the empty drug packs and the remaining tablets were counted. Any discrepancy in the number was considered a violation of protocol. The

Table 1
Patients characteristics and diagnosis

Gender	Males	Females	Total
	9	23	32
Mean age (range)/year	46.1 (24–61)	45.65 (23–62)	45.8 (23–62)
Courses	24	58	82
Diagnosis			
Breast	–	18	18
NHL/HD	5	1	6
AML	1	1	2
Adrenal	1	1	2
Others[a]	2	2	4
Total (patients)	9	23	32

NHL, Non-Hodgkin's lymphoma; HD, Hodgkin's disease; AML, acute myeloid leukaemia.

[a] One of each of the following neoplasms: cervix, ovary, thyroid and urinary bladder.

patient was seen daily on days 7 through to 11 post-chemotherapy. On these days, the patient was checked for any signs and symptoms of mucositis and these were carefully recorded. Additionally, patient was asked about side-effects and the results of blood counts were recorded. A period of 2 weeks had to elapse from receiving the study drug before the patient was given the other study drug with a repeat of the same chemotherapeutic protocol. Normosaline mouthwash was allowed, but no other mouthwash mixtures were permitted. Prophylactic use of G-CSF or GM-CSF was not allowed during the first week. No modification of chemotherapy was allowed while the patient was on the study drug.

2.3. Chemotherapy protocols

7 patients received doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC), 4 patients received CAF (cyclophosphamide 500 mg/m^2 doxorubicin 50 mg/m^2, 5-FU 500 mg/m^2 all on one day, 3 patients received paclitaxel 175 mg/m^2 and carboplatin, area under the concentration curve (AUC) 6, 3 patients received CHOP (cyclophosphamide 750 mg/m^2 day 1, doxorubicin 50 mg/m^2/day 1, vincristine 2 mg day 1 and prednisolone 100 mg or orally (p.o.) days 1–5, 2 patients received Ara-C 200 mg/m^2 continuous intravenous (i.v.) days 1–5 and mitoxantrone 12 mg/m^2 days 1 and 2, 2 patients received doxorubicin 60 mg/m^2 and vinorelbine 35 mg/m^2 on day 1. The remaining 11 patients received other combinations. Each received a different individualised chemotherapy as follows: 1 CMF, 1 cisplatin/paclitaxel, 1 docetaxel alone, 1 paclitaxel alone, 1 vinorelbine, doxorubicin and cyclophosphamide, 1 paclitaxel/gemcitabine, 1 paclitaxel/vinorelbine, 1 accelerated bleomycin, etoposide, doxorubicin, cyclophosphamide, oncovin, procarbazin, prednisolone (BEACOPP), 1 standard BEACOPP, 1 doxorubicin, bleomycin, viriblastine, dacarbazine (ABVD), 1 doxorubicin/cisplatin.

2.4. Mucositis score

Mucositis was scored using the following methods simultaneously in each of the days the patient was seen. (1) Score A: a modification of the score described by JP Donnelly and colleagues [6]. Each patient was scored for ulceration, erythema, oedema, pain and dysphagia. Each of these was given a score of 0 if absent, 1 if mild or less than three ulcers, 2 if moderate or three to six ulcers, 3 if severe or extensive ulceration. The maximum score per patient per course possible was 15 (see Table 2). (2) Score B: World Health Organization (WHO) score method was adopted as follows: grade 1, painless ulcers, erythema or mild soreness; grade 2, painful erythema, oedema or ulcers but can eat; grade 3: inability to eat solid food; grade 4: use of total parenteral nutrition (TPN)/IV narcotics for the pain control. Maximum score per patient per course possible was 4. (3) Score C: in which the most prominent sign or symptom was given a score as follows: 1 if mild, 2 if moderate and 3 if severe. The peak score in each of A, B, C scores was taken as the reference mucositis score to compare OP and placebo. Additionally, in any course in which mucositis was noted, it was considered positive for mucositis. If no mucositis was observed, it was considered negative for mucositis.

2.4.1. Statistics

The non-parametric matched-pairs Wilcoxon rank test was used to analyse the mucositis scores.

3. Results

3.1. Effectiveness of pilocarpine in preventing mucositis

As shown in Table 2, mucositis was recorded in 20 out of the 41 courses (49%) in which patients were given placebo with a total mucositis score of 52 for score A, 25 for score B and 23 for score C. When the same patients were given OP, mucositis appeared in six out of 41 courses with a total mucositis score of 11 for score A, 6 for score B and 6 for score C. The differences in mucositis score, between the OP and placebo groups were highly significant when comparing score A $P<0.001$, score B $P<0.001$, score C $P<0.001$ and the presence or absence of mucositis $P<0.005$. This indicates the effectiveness of OP in preventing mucositis, as well as in reducing the severity of mucositis when it appears.

Table 2
Mucositis and P value using Wilcoxon signed ranks test taking the peak score day during the follow-up from days 7 through to 11 post-chemotherapy

Mucositis score	Total in all courses		P value
	Placebo	Pilocarpine	
A[a]	52	11	<0.001
B[b]	25	6	<0.001
C[c]	23	6	<0.001
No. of courses in which mucositis appeared	20	6	<0.005

[a] Components in score A are as follows: 1, lesion (oral ulceration) score: 0 if absent, 1 if <3 ulcers, 2 if 3–6, 3 if >6; 2, erythema score: 0 if absent, 1 if mild, 2 if moderate, 3 if severe; 3, oral oedema score: as in erythema score; 4, pain score: as in erythema score; 5, dysphagia: as in erythema score. Maximum possible score per patient per course is 15.

[b] Score refers to scoring of oral mucositis in accordance with World Health Organization (WHO) score as follows: grade 1, painless ulcers, erythema or mild soreness; grade 2, painful erythema, oedema or ulcers, but can eat; grade 3, inability to eat solid food; grade 4, use of TPN/intravenous (i.v.) narcotics to control pain. Maximum score per patient per course is 4.

[c] Score refers to the most prominent single sign or symptom and is scored as follows: 1 if mild, 2 if moderate, 3 if severe. Maximum score per patient per course is 3.

Table 3
Side-effects

Patient	Age (years)	Gender	Diagnosis	Chemotherapy	Study drug	Side-effects
1	44	Female	Ca Breast	ADR/Txre	Pilocarpine	Palpitations[a], chest pains
2	23	Female	AML	ARAC/Novant	Placebo	Palpitations, abdominal pain, SOB
3	46	Female	Ca Breast	ADR/CTX	Placebo Pilocarpine	General weakness, sweating
4	55	Female	Ca Breast	CAF	Pilocarpine	Palpitations
5	52	Female	Ca Breast	ACT	Placebo	Abdominal pain
6	46	Female	Ca Breast	CEF	Pilocarpine	Epigastric pain, vomiting
7	49	Female	Ca Breast	Txre/CPP, LipoADR	Pilocarpine	Abdominal pain

ADR or A, doxorubicin; Txre, docetaxel; Novant, novantrone; ARAC, cytosine arabinoside; CTX or C, cyclophosphamide; E, epirubicin; CPP, carboplatin; Lipoadr, liposomal doxorubicin; T, paclitaxel, F, 5-fluorouracil; AML, acute myeloid leukaemia; Ca, cancerous; SOB, shortness of breath.

[a] Sinus tachycardia confirmed by electrocardiogram (ECG) tracing.

3.2. Side-effects

There were a total of eight courses in which side-effects were detected, three courses with placebo and five with pilocarpine (Table 3). One patient had palpitations, abdominal pain and shortness of breath, while 1 had generalised weakness and a third had abdominal pain while they were on placebo. Of the 5 patients who were on pilocarpine, 2 had palpitations of whom had a tachyarrhythmia (sinus tachycardia) confirmed by an electrocardiogram (ECG), 1 had troublesome sweating and 2 had abdominal pain including 1 who also experienced vomiting.

4. Discussion

Stomatitis or oral mucositis is acutely distressing to patients causing pain, ulceration and dysphagia. When oral ulcers are present, they may be the portal for systemic entry of infectious pathogens [2]. The sense of taste and smell, as well as the overall nutritional and hydration status of the patient may be affected by mucositis and the patient may require parenteral nutrition and hydration [12].

Several studies have found oral pilocarpine to be effective in relieving xerostomia induced by radiation, high-dose chemotherapy and chronic graft versus host disease (GVHD) [6–8,10]. One pilot study found oral pilocarpine to be useful when given concurrently with high-dose chemotherapy in a bone marrow transplantation setting [9]. There has been no reported randomised study to address the usefulness of oral pilocarpine in preventing oral mucositis following chemotherapy. This work was specifically designed to address this issue in a double-blind placebo-controlled cross-over study. We chose several methods to evaluate oral mucositis simultaneously in the same patient including, the World Health Organization (WHO) method and a modification of the method by Donnelly and colleagues [11]. We found the latter method very useful.

We also found OP to be extremely effective in preventing mucositis ($P<0.005$) and in preventing severe mucositis ($P<0.001$) following various chemotherapy regimens. We chose to start OP treatment 1 h before chemotherapy and continued it for 1 week. The dose of 5 mg and frequency of every 8 h were arbitrarily chosen based on the pharmacokinetics of the drug, previous protocols and personal observation. Factors which may influence the prevention of mucositis were avoided during the first week post-chemotherapy. These included G-CSF, GM-CSF, chlorhexidine mouthwash and oral cryotherapy. We thus believe that the reduced incidence of mucositis was due to the oral pilocarpine treatment. Reasons for this positive effect are not clear. OP is known to increase saliva flow [6,13] by stimulating the salivary glands, especially the minor salivary glands [8]. Saliva from the minor salivary glands contributes to 70% of the total mucin in the saliva [6]. OP stimulates the production of salivary mucin, proteins and glycoproteins [6]. It seems that mucin and other salivary constituents play a protective role in the prevention of chemotherapy-induced mucositis.

OP seems to be a safe drug and is well tolerated by patients. The case of tachyarrhythmia documented in this study was a sinus tachycardia and was directly linked to the OP treatment. The other cases with palpitations had no ECG documentation of arrhythmia. The other side-effects were minor in nature.

In conclusion, based on this study, we believe that OP is an effective and safe treatment in the prevention of oral mucositis in standard dose chemotherapy and should be used with all protocols know to be associated with a high incidence of oral mucositis.

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