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Pergamon

European Journal of Cancer Vol. 30A, No. 5, pp. 584–587, 1994
Elsevier Science Ltd
Printed in Great Britain
0959–8049/94 $7.00 + 0.00

0959-8049(94)E0058-C

Efficacy and Tolerance of Oral Dipyrone Versus Oral Morphine for Cancer Pain

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In a double-blind, randomised and parallel clinical trial, two oral doses of dipyrone (1 and 2 g) administered every 8 h were compared with 10 mg of oral morphine given every 4 h for the relief of chronic cancer pain. A total of 121 patients with cancer pain without gastric involvement participated in a 7-day treatment course and were allocated to receive either dipyrone 1 g (n = 41), dipyrone 2 g (n = 38) or morphine (n = 42). Drug efficacy was analysed according to the degree of pain relief using a 100-mm visual analogue scale, and the number of patients who decided to increase the dose of the analgesic drug on day 4. The analgesic effect of dipyrone, 2 g every 8 h, was similar to that of morphine. The efficacy of both schedules was significantly greater than that of dipyrone, 1 g every 8 h. Dipyrone at either 1 or 2 g doses tended to be better tolerated than morphine, although the differences were not statistically significant.

Key words: dipyrone, morphine, analgesia, efficacy, tolerance, cancer pain
Eur J Cancer, Vol. 30A, No. 5, pp. 584–587, 1994

INTRODUCTION

SEVERE CANCER pain is usually mitigated by opiates, particularly meperidine and morphine [1, 2]. Dipyrone has a potent analgesic action and has been extensively used in the treatment of acute painful conditions. The use of high doses of orally administered dipyrone to relieve severe pain including chronic cancer pain is a common practice in Spain. However, the optimal dose of dipyrone still has to be determined, and no clinical trials have been conducted to elucidate this question.

The aim of the present study was to compare the efficacy and tolerance of two different oral doses of dipyrone (1 and 2 g), administered every 8 h, with 10 mg of oral morphine given every 4 h for the relief of cancer pain. Morphine was selected as

the control drug, since treatment of cancer pain often requires the use of opiates in advanced stages.

PATIENTS AND METHODS

Between January 1991 and May 1992, patients of both sexes with primary malignancies presenting with cancer pain (Foley IIa grade) at the departments of oncology of the participating hospitals were eligible to be included in a 7-day study. Eligibility requirements were: age over 18 years, absence of other causes including gastric disorders, either related or unrelated to the malignant neoplasm to which pain could be attributed, mental status sufficient to be able to complete efficacy and tolerance tests and Karnofsky performance > 30%. Patients undergoing adjuvant therapy at the time of entering the study or who had completed radiotherapy of chemotherapy within 15 days prior to the study were excluded, as were patients with contraindications and/or hypersensitivity to the study drugs, clinical evidence of brain or liver metastases, severe underlying diseases and pregnant women. The protocol was approved by the ethical committee of the participating centres, and written informed consent was obtained from all patients.

Patients included in the study were randomly assigned to three groups of active treatment as follows: group 1, dipyrone 1 g (Nolotil®, Europharma; half an ampoule) every 8 h; group 2, morphine 10 mg orally every 4 h; and group 3, dipyrone 2 g (Nolotil®, Europharma; one ampoule) every 8 h. Patients were instructed to take medications at 4 a.m., 8 a.m., noon, 4 p.m., 8 p.m. and midnight. In order to keep the double-blind design of the study, patients in the dipyrone groups were given placebo at 4 a.m., noon and midnight.

Pain intensity was evaluated by the patient according to a 100-mm visual analogue scale (from point 0 'no pain' to point 10 'the most severe pain imaginable') [3–7]. On entering the study, a level of ≥ 70 mm was required. Assessments of pain intensity were carried out daily. Patients were allowed to increase the dose of the analgesic drug on day 4 (up to 2 g of dipyrone every 8 h for patients in group 1, and 30 mg of morphine every 4 h for patients in group 2) if they considered that relief of pain during the first days of treatment had been insufficient. Routine haematological and biochemical laboratory tests were carried out at baseline and on day 7. At the same time as pain was evaluated, data on the appearance of possible adverse effects as a result of the drugs administered were recorded. A checklist was used to register adverse effects, but in no case was the occurrence of unwanted effects reported to patients. The severity of adverse effects was judged by the investigators and classified as follows: mild, sign or symptom which was easily tolerated by the patient; moderate, discomfort sufficient to cause interference with the patient's daily activities; and severe, discomfort incapacitating the ability to work or to undertake usual daily activities.

No other medication was given during the 7-day study period except for rescue treatment (paracetamol 300 mg plus codeine phosphate 15 mg) in those patients in whom relief of pain was not achieved.

Statistical analysis

A total of 123 evaluable patients were needed in order to ensure that differences as small as 8 mm (S.D. = 10 mm) in the visual analogue scale would be detected among the three groups of active treatment, given a beta error of 0.05 and an alpha error of 0.05. The statistical analysis was carried out by variance analysis (ANOVA), Student's *t*-test, Wilcoxon test, Mann–Whitney U test, χ^2 test and Kruskal–Wallis test. The level of significance was set at $P < 0.05$. Data are presented as mean ± S.D.

RESULTS

Of a total of 149 patients eligible to be included in the study, 28 were excluded because self-evaluation of pain prior to the study was < 70 mm ($n = 18$), no fulfilment of the inclusion criteria ($n = 3$), incomplete baseline data recording ($n = 3$), concomitant use of other analgesics ($n = 2$), and other reasons ($n = 2$). The study population consisted of 121 cancer patients of whom 41 (mean age 59 ± 12.4 years, 51% males) were assigned to group 1, 42 (mean age 62 ± 10.4 years, 76% males) to group 2, and 38 (mean age 61 ± 9.4 years, 79% males) to group 3. The percentage of male patients was significantly lower in group 1 ($P < 0.05$) as compared with the other two groups, but ages of the patients showed no differences among the three treatment groups. The location of the primary malignant neoplasm is shown in Table 1. Although the type of pain was related to the site of malignancy, a multifactorial origin, i.e. somatic and visceral pain, was present in most patients. Bone metastases were diagnosed in 37% of patients.

The course of pain according to the visual analogue scale is shown in Table 2. All three analgesic schedules induced significant improvements in cancer pain (Wilcoxon test, $P < 0.001$ day 1 versus day 7). However, patients given dipyrone 1 g every 8 h showed significantly less pain relief on days 2, 3, 4 and 7 as compared with patients given dipyrone 2 g every 8 h ($P < 0.05$), and on days 3, 4 and 5 as compared with patients given morphine ($P < 0.01$). There were no significant differences among patients receiving dipyrone 2 g or morphine.

Table 1. Location of primary cancer in patients treated with dipyrone 1 g every 8 h (group 1), morphine 10 mg every 4 h (group 2) or dipyrone 2 g every 8 h (group 3)

Location	Group 1	Group 2	Group 3
Lung	6	14	8
Breast	7	2	1
Pancreas	2	2	2
Kidney	1	0	2
Bowel	3	5	3
Mouth	3	1	7
Oesophagus	0	1	0
Larynx	2	2	3
Rectum	0	2	1
Ovary	1	0	1
Endometrium	4	0	3
Bladder	2	1	4
Prostate	3	2	0
Others	7	10	3

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Revised 21 Dec. 1993; accepted 28 Jan. 1994.

Table 2. Efficacy of dipyrone 1 g every 8 h (group 1), morphine 10 mg every 4 h (group 2) or dipyrone 2 g every 8 h (group 3) according to results of the visual analogue scales

Day	Group 1	Group 2	Group 3
Baseline	82.9 ± 8.5	83.5 ± 9	81.8 ± 0.6
1	69.6 ± 22.8	64.1 ± 30.9	64.0 ± 19.9
2	66.0 ± 19.6	52.6 ± 30.4	57.2 ± 22.9
3	65.9 ± 23.2	46.4 ± 30.9	53.1 ± 24.4
4	61.8 ± 25.3	43.7 ± 29.6	49.4 ± 27.1
5	55.4 ± 26.4	42.5 ± 28.	44.9 ± 25.4
6	50.5 ± 29.6	40.6 ± 28.4	37.4 ± 25.0
7	51.3 ± 31.5	39.9 ± 31.1	34.9 ± 25.8

Group 1, $P < 0.05$ day 1 versus day 7; group 2, $P < 0.01$ day 1 versus day 2 and $P < 0.01$ day 1 versus day 7; group 3, $P < 0.05$ day 5 versus day 6 and $P < 0.05$ day 1 versus day 7.

The mean percentage of pain decrease on day 7 as compared to baseline was 64.4 ± 37.9% in group 1, 49.6 ± 38.8% in group 2, and 51.9 ± 33.8% in group 3. There were no statistically significant differences within groups (Mann–Whitney U test), but there were significant differences between groups 1 and 2 ($P < 0.05$).

When differences in pain intensity between day 1 and day 7 were analysed, there were no significant differences between groups (group 1, 30.9 ± 32.6; group 2, 42.6 ± 32.9; group 3, 39.8 ± 28.6), although the lowest values were found in patients assigned to dipyrone 1 g every 8 h. Differences in pain intensity between days 2, 3 and 4 were statistically significant ($P < 0.01$) when groups 1 and 2 were compared, but not between dipyrone 2 g and morphine-treated patients.

The percentage of patients with pain improvement by 50% or more at each day was significantly higher (χ^2 test, $P < 0.05$) in both groups 2 and 3 at days 3 and 5 as compared with group 1 (day 3: group 1, 5%; group 2, 25%; group 3, 8%; day 5: group 1, 12%; group 2, 39%; group 3, 48%).

There were no significant differences in the number of patients that decided to increase the dose of the analgesic drug on day 4; 17/31 patients in group 1 (55%), 12/35 in group 2 (34%) and 11/27 in group 3 (41%). Rescue treatment had to be given to 52 patients, 17 in the group given dipyrone 1 g every 8 h, 14 in those receiving morphine, and 21 in the group of dipyrone 2 g every 8 h.

A total of 207 side-effects were recorded in 86 patients: group 1, 52 side-effects in 27 patients; group 2, 92 side-effects in 34 patients; and group 3, 63 side-effects in 25 patients (Table 3). The incidence of side-effects was lower in groups 1 and 3, but differences were not statistically significant. Although morphine-treated patients experienced severe side-effects more commonly than dipyrone-treated patients, withdrawal of treatment was not required.

Results of routine laboratory tests at the end of the study were within normal limits.

On day 7, the overall efficacy of analgesic treatment graded as excellent/good by patients in the three treatment groups corresponded with the findings of the observers (group 1, 38 versus 39%; group 2, 46 versus 47%; group 3, 46 versus 47%). Tolerance was also graded as excellent/good by 77% of patients and 77% observers for group 1, 49% of patients and 54% of observers for group 2, and 62% of patients and observers for group 3.

Table 3. Self-reported side-effects recorded in the studied patients

	Group 1			Group 2			Group 3		
	A	B	C	A	B	C	A	B	C
Nausea	6	4	4	8	7	4	9	1	3
Pyrosis	9	2	2	6	3	0	8	6	3
Constipation	6	3	0	2	8	6	3	2	3
Sedation	2	2	0	7	6	5	6	2	1
Euphoria	1	1	0	2	4	0	3	0	0
Dizziness	1	1	1	1	4	3	4	1	3
Skin rash	2	0	0	5	0	0	1	0	0
Diarrhoea	2	0	0	0	0	0	1	0	0
Meteorism	0	0	0	0	0	0	0	1	0
Diaphoresis	0	0	0	0	0	1	0	0	0
Gastric discomfort	0	0	0	0	0	1	0	0	1
Anorexia	0	0	0	0	0	1	0	0	0
Bad taste	0	0	0	0	1	0	1	0	0
Disorientation	0	0	0	1	1	0	0	0	0
Fever	0	0	0	0	1	0	0	0	0
Ageusia	1	0	0	0	0	0	0	0	0
Respiratory allergy	1	0	0	3	1	0	0	0	0
Migraine	1	0	0	0	0	0	0	0	0
Subtotal	32	13	7	35	36	21	36	13	14
Total		52			92			63	

A, mild; B, moderate; C, severe.

DISCUSSION

The measurement of pain relief by means of the visual analogue scale from baseline to day 7 showed no statistically significant differences in the analgesic efficacy of the schedule of dipyrone 2 g every 8 h and morphine 10 mg every 4 h. However, significant differences were found between the analgesic efficacy of both morphine and dipyrone 2 g regimens as compared with the administration of dipyrone 1 g every 8 h. These findings were also evident when the mean percentage of pain decrease on day 7 as compared to baseline, differences in pain intensity between day 1 and day 7, and the percentage of patients with pain improvement by 50% or more at each day were analysed.

The number of patients requiring rescue treatment was similar in all groups and differences were not significant. The analysis of subjective impressions by patients and observers with regard to the efficacy of analgesic drugs showed no significant differences. However, more patients rated the tolerance of dipyrone regimens as excellent/good than that of morphine.

The occurrence and severity of side-effects were lower in patients receiving dipyrone, although statistical significance was not reached. The most frequently recorded side-effects consisted of pyrosis and nausea in patients receiving dipyrone, and nausea, sedation and constipation in patients treated with morphine.

We conclude that the analgesic efficacy of dipyrone 2 g every 8 h for the treatment of cancer pain is similar to that of 10 mg of morphine every 4 h. The efficacy of dipyrone, 1 g every 8 h is lower than that of dipyrone 2 g every 8 h. However, dipyrone at either 1 or 2 g doses tended to be better tolerated than morphine, although the differences were not statistically significant.

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Acknowledgements—We are indebted to Ricardo Kuhlmann, M.D. for critical review of the manuscript, to Manuela Enríquez, M.D. and Mr Pedro Bravo for technical help, to Mr. Antonio Arjona for secretarial assistance and to Marta Pulido, M.D. for the scientific editing of the manuscript.

Pergamon

European Journal of Cancer Vol. 30A, No. 5, pp. 587–590, 1994

0959–8049/94 $7.00 + 0.00

0959-8049(93)E0073-4

Cisplatin–Fotemustine Combination in Inoperable Non-small Cell Lung Cancer: Preliminary Report of a French Multicentre Phase II Trial

A. Rivière, A. Le Cesne, J. Berille, S. Baio and T. Le Chevalier

Fotemustine is a new nitrosourea derivative whose activity has been demonstrated on metastatic melanoma with specific activity on brain metastases and also on poor prognosis lung cancers. Results of *in vitro* studies of a cisplatin–fotemustine combination seem promising. In order to evaluate the efficacy and safety of this combination, we performed two trials. 6 patients entered a preliminary study whose schedule was cisplatin 120 mg/m² on day 1 and fotemustine 100 mg/m² on days 1 and 8. 22 patients were enrolled in a second study which added 120 mg/m² cisplatin on day 22 followed by a 4-week rest period. In both trials, maintenance therapy consisted of cisplatin 100 mg/m² and fotemustine 100 mg/m² every 3 weeks until progression. Despite the poor prognostic factors which characterised our population (metastatic disease 86%, brain metastases 59%, ≤ 80% performance status 45%), the results remain attractive with a 23% partial response rate (29% in non-pretreated patients). Moreover, 3 out of 8 patients with evaluable cerebral metastases achieved a partial response (37.5%). Toxicity was mild and related to the cumulative dose of cisplatin (peripheral neuropathy and renal toxicity). We concluded that these results need to be confirmed in a randomised trial.
Eur J Cancer, Vol. 30A, No. 5, pp. 587–590, 1994

INTRODUCTION

THE CONSISTENTLY poor prognosis of advanced non-small cell lung cancer (NSCLC) calls for new drugs or drug combinations to be tested such as the combination of fotemustine and cisplatin. Fotemustine is a new nitrosourea derivative with proven efficacy against metastatic melanoma [1], and specific activity on brain metastases [2]. Recent phase II studies showed that fotemustine was a potent drug when used alone in the treatment of NSCLC [3, 4]. Cisplatin is one of the most active single agents in NSCLC treatment. Its activity has also been observed in combination with other drugs and particularly with vinca alkaloids [5, 6]. *In vitro* studies of cisplatin–fotemustine combination in melanoma cell lines found this association to be more effective than fotemustine alone [7]. Moreover, both drugs cross the blood–brain barrier [2, 8].

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Revised 9 Aug. 1993; accepted 6 Oct. 1993.

MATERIALS AND METHODS

From February 1989 to December 1990, two trials were performed in order to define the efficacy and safety of a cisplatin–fotemustine combination in NSCLC and, more specifically, in brain metastases.

6 patients were initially included in a preliminary study (Trial A). They received cisplatin 120 mg/m² on day 1 and fotemustine 100 mg/m² on days 1 and 8. As no major toxicity occurred, a second study (Trial B) was initiated which added to the first schedule a 120 mg/m² cisplatin administration on day 22 followed by a 4-week rest period. 22 patients entered this second study. In both trials, patients achieving a response or stabilisation received maintenance therapy consisting of cisplatin 100 mg/m² and fotemustine 100 mg/m² every 3 weeks until progression.

Eligibility criteria were histological evidence of NSCLC with