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SHORT COMMUNIATION

Adjunct dipyrone in association with oral morphine for cancer-related pain: the sooner the better

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Abstract
Introduction Adjunct nonopioid analgesics may improve pain control in patients with cancer needing morphine or its derivates. Dypirone is a cheap nonopioid analgesic widely used in many countries.
Objective The objective of the study was to evaluate, whenever morphine was started, if associating dipyrone with it would improve pain control and if this effect was time dependent.
Materials and methods This is a double-blind placebo-controlled randomized crossover study. Thirty-four ambulatory cancer patients experiencing cancer-related pain for which oral morphine was to be started at the dose of 10 mg orally (PO) every 4 h were randomized to take either dipyrone 500 mg PO every 6 h or placebo. After 48 h, patients would be switched from dipyrone to placebo and vice versa. Pain was the primary outcome and was measured using a visual analogue scale before starting medications, at 48 and 96 h.
Results We randomized 16 patients to start with placebo (group 1) and 18 with dipyrone (group 2). Pain scores for groups 1 and 2 were at baseline: 7.31±0.29 vs 6.88±0.28 (p=0.3), at 48 h: 7.06±0.32 vs 5.5±0.31 (p=0.001), and at 96 h: 3.18±0.39 vs 1.94±0.37 (p=0.03). Both groups had significant improvements in pain scores after introducing dipyrone (p<0.001, for both). Main toxicities were nausea, vomiting, epigastric pain, and myalgias. Twenty-eight patients chose dipyrone, four placebo, and two were indifferent.
Conclusions We conclude that dipyrone adds significantly to the analgesic effect of morphine and, when given at the time of starting morphine, results in better pain scores even after dipyrone is discontinued.

Keywords Dipyrone · Double-blind method · Drug administration schedule · Morphine · Neoplasms · Pain · Pain measurement

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Introduction

Cancer is one of the leading causes of mortality in both developed and underdeveloped countries [1]. Unfortunately, most of these otherwise incurable cancer patients may, at some time in their life, experience pain because of their disease. Therefore, adequate pain control emerges as a very important target to preserve a good quality of life for these patients [2].

Opiates such as morphine are the mainstay for severe cancer-related pain not usually amenable to be controlled with less potent analgesics [2]. Weaker analgesics currently used for to treat cancer-related pain include nonsteroidal anti-inflammatory agents (NSAIDs) and combinations containing low dose of opioids such as codeine with paracetamol [2]. Pain control after starting strong opioids such as morphine, methadone, or fentanyl may take some time to be achieved during which patients may experience unnecessary suffering.

Dipyrone belongs to the pyrazolone [3] group of analgesics and constitutes a cheap and often used NSAID in many countries including Austria, Belgium, France, Germany, Italy, The Netherlands, Spain, Switzerland, South Africa, Latin America (including Brazil), Russia, Israel, and India [4]. Other countries such as the USA and UK restricted its use because of several reports in the literature of agranulocytosis linked to its utilization [5, 6]. The real epidemiologic risk of agranulocytosis associated with dipyrone is still unknown and probably small, as judged by the scarcity of reports in view of its wide use for so many patients [7–9]. Other common side effects of dipyrone are somnolence, epigastric pain, and nausea [4]; however, in contrast to other NSAIDs, the incidence of upper gastrointestinal bleeding associated with dipyrone is not increased [10].

It is interesting to note that although weaker nonopioid analgesics seem to be ineffective once strong opioids are started, Stockler et al. [11] demonstrated that paracetamol, when added to morphine or hydromorphone, improved pain and well-being in 30 patients with cancer-related pain. We decided then to test if adding a weak analgesic such as dipyrone could shorten the time needed to stabilize analgesia and improve the pain control in patients with cancer-related pain about to be started on morphine. We also evaluated if dipyrone's effect would be time dependent.

Materials and methods

After approval by our Institutional Ethics Committee, we enrolled 34 patients recruited from Mario Covas Hospital from ABC Foundation School of Medicine who agreed to take part in this study and signed informed conset forms. Eligibility criteria included a proven histological diagnosis of cancer and the presence of cancer pain associated, for which analgesia with morphine was indicated. Patients with neuropathic pain were not included. No patient had additional analgesic medication such as NSAIDs or corticosteroids prescribed together with morphine, nor were patients allowed to participate if they were already using dipyrone. Patients were excluded if they had known renal or hepatic failure or any degree of jaundice.

This study was a double-blind randomized trial with crossover in which all patients were started on morphine 10 mg orally (PO) at every 4 h and randomized to receive either placebo (group 1) or dipyrone at a dose of 500 mg PO at every 6 h (group 2; Fig. 1). After 48 h, patients switched from placebo to dipyrone and vice versa, while still on the same dose of morphine. We interviewed patients personally at entry into the study and by phone after 48 and 96 h thereafter. We oriented patients when they entered the study to evaluate their pain with a visual analogue pain

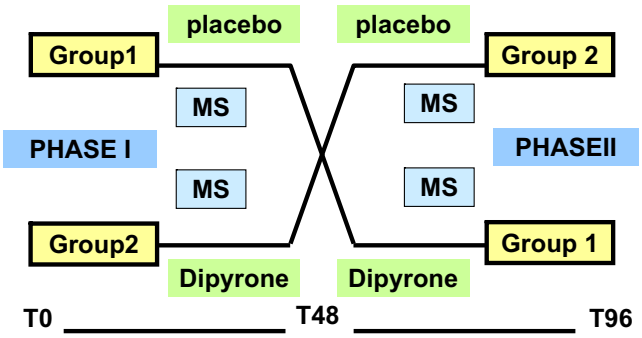

Fig. 1 Experimental design of the study. *MS* Oral morphine, *T0* time at study entry, *T48* 48 h into the study; *T96* 96 h into the study. Patients were crossed over to the other experimental arm at 48 h

scale from 0 (absence of pain) to 10 (most intense pain ever felt). At every interview, patients were asked to rate their pain at that moment and also to report any adverse effect. At the end of the study, we also asked patients which study phase they preferred to ascertain, after unblinding, if they would have chosen placebo, dipyrone, or if they would be indifferent. One patient who was also taking paracetamol plus codeine combination (Tylex®) before enrollment did not stop this medication, which was continued throughout the study. This patient was randomized to group 2, and we did not exclude him so that we could analyze results by the intent to treat principle.

We compared pain scores within the same group by the paired analysis of variance (ANOVA) test and from different groups at each time point with the ANOVA test. We employed Chi-squared and Fisher exact tests to evaluate for significant correlations between categorical variables. We employed the NCSS statistical package for statistical calculations (Kaysville, UT; www.ncss.com).

Results

We enrolled 34 patients in the study. Sixteen patients were randomized to start with placebo (group 1) and 18 with dipyrone (group 2). Clinical characteristics of the patients are shown in Table 1. Median age was 57 years in both groups, all patients had metastatic disease, and the most common tumors were colorectal, prostate, lung, and breast carcinomas. Groups 1 and 2 were comparable except for larger number of patients who had not yet receive oncological treatment in group 2 ($p=0.04$), a higher proportion of visceral pain in group 1, and of bone pain in group 2 ($p=0.02$). Most patients had severe pain at baseline.

Pain scores for groups 1 and 2 were at baseline: 7.31±0.29 vs 6.88±0.28 ($p=0.3$), at 48 h: 7.06±0.32 vs 5.5±0.31 ($p=0.001$), and at 96 h: 3.18±0.39 vs 1.94±0.37 ($p=0.03$). Significant improvements in pain scores were observed in

Table 1 Clinical characteristics of the patients included in the study according to the group they were randomized to

	Arm 1 (n=16), number of patients	Percent	Arm 2 (n=18), number of patients	Percent	Overall (n=34), number of patients	Percent
Age (years)						
Median	57		57		57	
Range	24–76		35–78		24–76	
Sex						
Female	6	37	9	50	15	44
Male	10	63	9	50	19	56
Primary site						
Prostate	2	12	3	17	5	15
Lung	3	19	7	40	10	29
Colorectal	6	37	2	11	8	23
Breast	2	12	5	28	7	20
Other	3	19	1	5	4	12
Metastatic	16	100	18	100	34	100
Previous treatment						
Chemotherapy	5	31	3	17	8	23
Chemoradiotherapy	3	19	1	5	4	12
At diagnosis	3	19	10	55	13	38
Surgery	3	19	3	17	6	18
Radiotherapy	2	12	1	5	3	9
Palliative care	0	0	0	0	0	0
Current treatment						
Chemotherapy	11	69	13	72	24	70
Chemoradiotherapy	2	12	1	5	3	9
Surgery	0	0	0	0	0	0
Hormonetherapy	2	12	3	17	5	15
Radiotherapy	0	0	1	5	1	3
Palliative care	1	6	0	0	1	3
Daily morphine dose (mg)	60		60		60	
Pain sites						
Back	0	0	2	11	2	6
Pelvis	4	25	2	11	6	18
Abdomen	6	37	1	5	7	20
Chest	3	19	10	55	13	38
Others	3	19	3	17	6	18
Source of pain						
Bone	4	25	12	67	16	47
Soft tissue, lymph nodes, skin	4	25	4	22	8	23
Visceral	8	50	2	11	10	29

Group 1: satrted with placebo; group 2: started with dipyrone

both groups 1 and 2 after introducing dipyrone ($p<0.001$ for both; Fig. 2).

The toxicities that we observed are depicted in Table 2. At time 0, we reported the symptoms patients experienced before study entry. There was no significant differences regarding the toxicities observed between groups 1 and 2 throughout the study. We had no known instances of agranulocytosis seen in our patients.

Twenty-eight patients (85%) reported that they would prefer dipyrone, four placebo, and two had no preference for any of the experimental arms ($p<0.001$).

Discussion

Despite of the reported risks of agranulocytosis [5–7], dipyrone is frequently used as an over-the-counter medication by millions of patients all over the world. Many cancer patients also employ this medication in countries where it is approved for use [12, 13]. In fact, Rodriguez et al. [13] evaluated 121 patients with cancer-related pain in a double-blind, randomized, and parallel clinical trial in which two oral doses of dipyrone (1 and 2 g) administered every 8 h (3 and 6 g/day) were compared to 10 mg of oral morphine given every 4 h

(60 mg/day). The authors reported the analgesic effect of dipyrone, 2 g every 8 h, was similar to that of morphine. We could thus speculate, based on the data presented by Rodriguez et al. [13], that the dose of dipyrone we used in our study (i.e., 500 mg four times a day) correspond to about one third of the dose that was found to be equivalent to the 60 mg/day of morphine also employed in our patients.

In our study, we did not evaluate dipyrone as a single medication as Rodriguez et al. [13] did but as an adjunct to morphine. Our data clearly show, similarly with the results reported by Stockler et al. [11] with paracetamol added to opioids, that for patients with cancer-related pain, dipyrone improves the efficacy of morphine for pain control. This result is further corroborated by the striking proportion of patients (85%) who preferred dipyrone.

It is interesting to note that the additive analgesic effect of dipyrone observed in our study seems to be time dependent, as pain control was still improved at 96 h, even after the switch from dipyrone to placebo after the first 48 h. This is a unexpected result, as the biological half-life of the dipyrone metabolites, some of which are similar to those of aminopyrine, is of 2 to 3 h [3]. It would then be expected that at 96 h, no more dipyrone metabolites will be detectable and will account for the observed improved analgesia in patients taking dipyrone for the first 48 h and then placebo for the next 48 h (group 2 in our study). It is possible that achieving adequate pain control earlier may translate into a superior analgesia latter. These findings corroborate the use of weaker analgesics together with opioids whenever these stronger analgesics are to be started, to shorten the time needed for these medications to produce adequate analgesia.

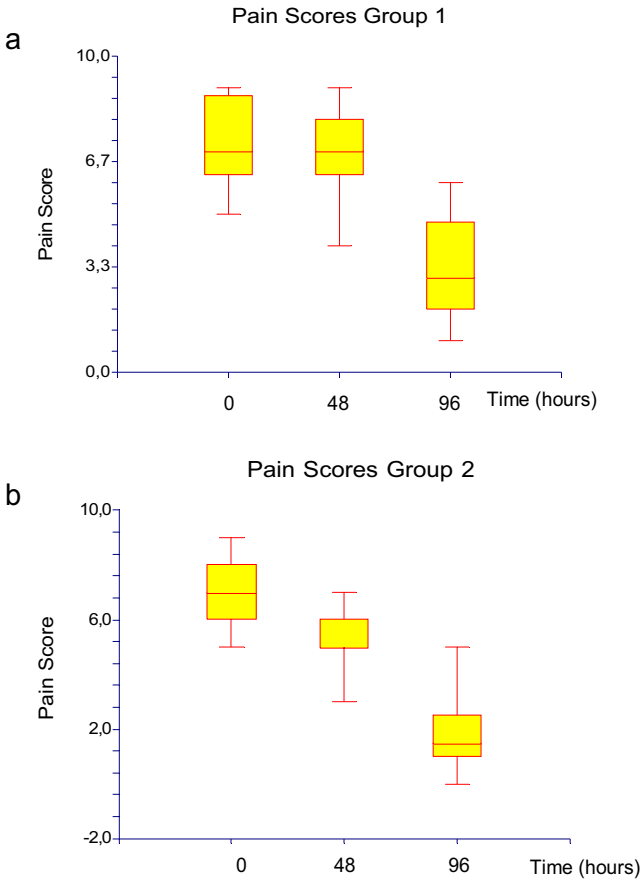

Fig. 2 Box plots of pain scores at times 0, 48, and 96 h for groups 1 (first placebo and then dipyrone) and 2 (first dipyrone and then placebo)

Table 2 Toxicities reported by patients randomized to groups 1 and 2 at 0 (before entry into the study), 48, and 96 h

	Group 1			Group 2		
	0 h, *n* (%)	48 h, *n* (%)	96 h, *n* (%)	0 h, *n* (%)	48 h, *n* (%)	96 h, *n* (%)
Side effects	2 (12.5)	9 (56.2)	15 (93.7)	0	7 (38.9)	16 (88.9)
Vomiting	0	2 (12.5)	0	0	0	0
Nausea	2 (12.5)	2 (12.5)	0	5 (27.8)	4 (22.2)	0
Myalgias	5 (31.2)	2 (12.4)	0	6 (33.3)	5 (27.7)	2 (11.0)
Leg cramps	1 (6.2)	0	0	1 (5.5)	0	0
Anorexia	2 (12.5)	0	0	1 (5.5)	1 (5.5)	0
Epigastric pain	0	0	0	2 (11.1)	1 (5.5)	0
Back pain	0	0	0	2 (11.1)	0	0
Headache	0	0	0	0	0	0
Constipation	1 (6.2)	0	0	0	0	0
Abdominal pain	2 (12.5)	1 (6.2)	1 (6.2)	0	0	0

The double-blind randomized crossover design of our study lessens several biases that could confound our results. There were, however, imbalances in some clinical characteristics of patients randomized to the two experimental arms. Nevertheless, the mean pain intensity reported by patients from both groups before starting the study were similar, so we do not believe that these imbalances may have affected our results. Furthermore, the small sample size of this study may decrease the power to detect other smaller but clinically important differences.

In terms of the toxicities reported, we saw no instances of agranulocytosis in our patients. We observed 22% incidence of nausea in the group initially treated with dipyrone as compared to 12.5% in the group that received placebo (p=0.6). Although this difference was not statistically significant, as nausea can be triggered by both medications [4], it is possible that the association of both drugs may need the support of prophylactic antiemetics for some patients. There is, however, an important limitation to

our study in terms of assessment of adverse effects as we interviewed patients over the telephone and did not use specific validated instruments to evaluate symptoms such as nausea, vomiting, and constipation.

We conclude that dipyrone adds to the efficacy of morphine for pain control, and if started as soon as morphine is prescribed, it results in earlier and longer lasting analgesia even after the dipyrone is discontinued. Further studies should assess if these effects can be reproduced with other weak analgesics such as acetaminophen so these results could benefit patients in countries where dipyrone is not available.

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