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Medical Therapy of Malignant Nerve Pain. A Randomised Double-blind Explanatory Trial With Naproxen Versus Slow-release Morphine

P.L.I. Dellemijn, H.B.C. Verbiest, J.J. van Vliet, P.J. Roos and C.J. Vecht

It is uncertain whether there exists a nociceptive component in malignant nerve pain responsive to NSAIDs and opioids. 20 patients with malignant nerve pain were randomly assigned to treatment with naproxen 1500 mg versus slow-release morphine 60 mg daily during 1 week, followed by cross-over medication during the second week in a double-blind, double-dummy protocol. In the 16 evaluable patients, a significant ($P < 0.05$) reduction of 26% (S.E. ± 7.9) in pain intensity was reached at day 7, compared to baseline pain. At day 7, significant pain relief of 32% ($P < 0.05$) was observed in the naproxen group, but not in the morphine group (21%, $P = 0.14$). Patients using morphine needed approximately twice as much paracetamol rescue than patients using naproxen. Additional pain relief could be observed in 4/9 patients with cross-over medication. These data support the concept of a nociceptive component in malignant nerve pain responding to NSAIDs and opioids, and favour the combination of both an anti-inflammatory drug and an opioid for symptomatic pain relief.

Key words: malignant nerve pain, nociceptive nerve pain, neuropathic pain, opioids, non-steroidal anti-inflammatory drugs naproxen, morphine
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INTRODUCTION

NEUROPATHIC pain in cancer is usually severe, but unfortunately, response to treatment is often poor. Asbury and Fields have introduced the existence of two types of neuropathic pain: one nociceptive or inflammatory type of pain, which they designated as nerve trunk pain and one non-nociceptive type of pain designated as dysesthetic pain or deafferentation pain [1]. The concept of a nociceptive type of nerve pain is based on the assumption of an inflammatory reaction sensitising C-fibers travelling in the nerve trunk as induced by cancer or any other source of local ongoing tissue damage [2–5]. The dysesthetic type of nerve pain is associated with a previous nerve injury in the absence of ongoing tissue damage.

The clinical importance of distinguishing these two types of neuropathic pain is that their symptomatic treatment could be different. Deafferentation pain seems less responsive to anti-inflammatory drugs (NSAIDs) and opioids than nociceptive pain [6–10].

If the concept of nociceptive or inflammatory nerve pain holds true, one could expect that conventional analgesic drugs known to be effective for nociceptive pain, such as NSAIDs and opioids, may also produce relief of nociceptive nerve pain in cancer. Based on the positive results of a pilot study [11], we conducted a double-blind, double-dummy randomised explanatory trial in

Correspondence to P.L.I. Dellemijn.
P.L.I. Dellemijn, H.B.C. Verbiest, J.J. van Vliet and C.J. Vecht are at the Department of Neuro-Oncology and Pain Clinic; P.J. Roos is at the Department of Pharmacy, Dr Daniel den Hoed Cancer Center and University Hospital Rotterdam, P.O. Box 5201, 3008 AE Rotterdam, The Netherlands.
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which the effect of the NSAID naproxen (N) was compared to slow-release morphine (S) in a series of patients with severe pain caused by radiculopathy or plexopathy due to compression or infiltration by cancer.

PATIENTS AND METHODS

The study was designed as a 2-week double-blind, double-dummy randomised trial with a parallel-group comparison during the first week, followed by cross-over treatment during the second week.

Subjects

Patients were recruited from the Neurology Clinic and Pain Clinic in the Daniel Den Hoed Cancer Centre in between August 1990 and December 1991. In this period, 238 new patients with radicular or plexus pain and cancer were seen at our neurological consultation service and pain clinic. Of these, only 20 patients (8.4%) fulfilled all criteria of eligibility for this trial.

Inclusion criteria

The presence of malignant nerve pain caused by tumour involvement of the nerve root(s) or plexus, fulfilling the following criteria were included in the study: radicular pain or plexus pain for less than 4 weeks radiating along the proximal course of one or more nerve roots or parts of the brachial or lumbosacral plexus with a corresponding sensory deficit, but without allodynia, hyperesthesia or hyperpathia; radiographic proof of metastasis or tumour at the involved site corresponding to the clinically affected nerve-root(s) or plexus by means of X-rays, CT scan or myelography; the patient was known to have histologically verified cancer; a pain-score of 40 or more at the start of the study, on numerical rating scale for pain intensity; the patient was physically and mentally able to keep a pain diary; informed consent given; the patient was willing to stop other pain medications prior to the start of the study during a wash-out period of 6 h [12].

Exclusion criteria

The following criteria excluded patients for the study: contra-indications for the use of NSAIDs including history of stomach or duodenal ulcer, stomach pain induced by previous analgesic medications or other known adverse effects to NSAIDs; use of anti-coagulants; contra-indications for morphine or its derivatives or known intolerance for morphine; use of corticosteroids during the last 4 weeks prior to the study; known history of drug abuse; diabetes mellitus; associated other pains; change in hormonal therapy or chemotherapy during the last 6 weeks prior to the start of the study; prior or ongoing radiotherapy to the area encompassing the involved nerve root(s) or plexus, although patients were allowed to change or start new anti-tumour therapy during the second week of the study. If anti-tumour therapy was started during the second week, patients were only evaluable for the first week of the trial.

Conduct of the trial

The study was conducted as a randomised double-blind double-dummy parallel-group comparison of N (Naprosyne®) 500 mg three times a day, orally versus S (MS-Contin®) 30 mg, twice daily, orally during 1 week; thereafter both groups received the other arm of the medication during the second week. A double-dummy design was used by giving placebo N or placebo S together with true S or true N, respectively, rendering tablets provided in the first or second week indistinguishable from each other. Patients who started using N during the first week followed by using S in the second week, belonged to the N/S arm. Patients who started with S followed by N belonged to the S/N arm. Patients were stratified according to previous opioid use.

Because an acute radiculopathy or plexopathy usually causes severe pain and all patients had a pain score of 40 or more, it is practically impossible to maintain wash-out periods of analgesics for periods longer than 6 h in cancer patients with severe pain [12]. For reasons of convenience and reliability, patients were allowed to take their usual analgesic at bedtime the night before day 1 of the study.

Patients were provided with paracetamol tablets and were allowed to use paracetamol tablets 500 mg up to eight times a day, if they felt insufficient pain relief. In case of nausea or vomiting, patients were allowed to use domperidon 60 mg suppositoria up to four times a day. In case of obstipation, they were provided with sachets of psyllium seeds.

Pain evaluation

Pain assessment was performed by the patient recording his or her pain on a 101-point numerical rating scale [13, 14]. The baseline pain assessment was the maximal pain score of three assessments 24 h prior to taking the study medication. Treatment efficacy was based on maximal pain score at the last day of each treatment period. We chose the maximal pain score, since this is the most relevant pain score for the patient. Ratings were recorded in a pain diary three times daily just prior to taking study medication.

At the end of each treatment period, the patient scored his pain relief on a six-point scale, rating his response as either complete (5), considerable (4), moderate (3), slight (2) or no pain relief (1) and pain worse (0) [15]. We defined responders as having either complete, considerable or moderate pain relief, and non-responders as having either slight or no pain relief or worse pain.

Patients were asked to give an overall evaluation of the drug at the end of each treatment period, using a four-point scale for the degree of side-effects. These effects were scored as either very well tolerated (no side effects) (1), well tolerated (mild side-effects) (2), badly tolerated (troublesome side-effects) (3), or not tolerated (serious side-effects) (4).

At the end of the second week, patients were asked whether they preferred overall either the first or second drug for their pain when considering both the analgesic and side-effects of the painkiller.

The numbers of paracetamol tablets, domperidon suppositoria and psyllium seeds used were recorded daily in the diary.

Statistical analysis

Results are presented as means ± S.E. Parametric data were analysed with a two-tailed t-test for numerical variables, and χ^2 test for categorical variables. For non-parametric data, Wilcoxon signed rank test, Mann–Whitney U-test, Friedman test and one sample sign test were used, where appropriate.

Side-effects were analysed on a four-point scale and, in addition, by comparing the number of domperidon suppositoria and the number of psyllium seeds in both treatment regimens.

The study was approved by the Protocol Review Board and the Medical Ethical Committee of the Daniel den Hoed Cancer Center.

RESULTS

20 patients entered the study and were randomly assigned to the N/S or the S/N arm. Baseline characteristics of the patients are shown in Table 1. Treatment arms were comparable regarding age (N/S arm: 59 ± 3 years versus S/N arm: 63 ± 5 years), sex (N/S arm: 3 males versus: S/N arm: 6 males), baseline pain (N/S arm: 83 ± 5 versus S/N arm: 82 ± 7), and neurological diagnosis (plexopathy: N/S arm: 7 versus S/N arm: 4; radiculopathy: N/S arm: 3 versus S/N arm: 6).

4 patients, 2 of each arm, were considered as non-evaluable: 1 patient (no. 9) was lost to follow up; a second patient received radiotherapy (no. 17), a third patient received chemotherapy during the first week (no. 16), and a fourth patient did not complete the pain diary (no. 19).

Pain evaluation with parallel group comparison during the first week

For the whole group, a significant pain reduction of 26% (±7.9, $P < 0.01$) was reached at day 7, compared to baseline pain. Pain reduction with N administered in the first week (N/S arm: 32% ± 11.0) was significantly different from baseline pain ($P < 0.05$); pain reduction with S administered in the first week was not significant after 1 week of treatment (S/N arm: 21% ± 11.8; $P = 0.14$; Figure 1 and Table 2).

4 patients, 2 from the N/S arm and 2 from the S/N arm, used opioids before entry: no. 8 (10 mg S twice daily), no. 10 (20 mg S twice daily), no. 14 (0.2 mg buprenorphin subcutaneously three times daily) and no. 18 (50 mg pentazocine three times daily). If these previous opioid users were excluded from the analysis, pain reduction for the whole group was more pronounced: 32% ±8, $P < 0.01$. In the N/S arm, the average pain score was 82 (±6.0) at baseline, and decreased to 50 (±9.3) at day 7, a reduction of 39% (±11.0, $P < 0.05$). In the S/N arm, the average pain score was 89 (±5.5) at baseline and decreased to 67 (±11.7) at day 7, a reduction of 25% (±12.7, $P < 0.05$).

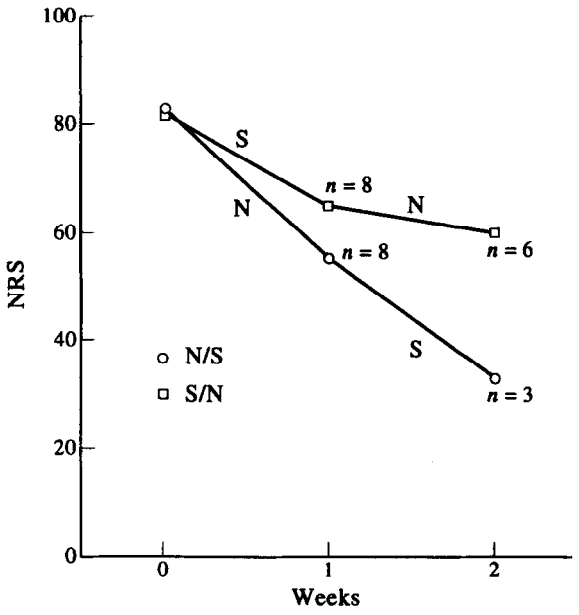

Figure 1. Plot of maximal pain intensity on numerical rating scale (NRS) after 1 and 2 weeks of treatment. N, Naproxen; S, slow-release morphine; *n*, number of evaluable patients.

Patients were classified as responders based on the rating of their pain relief. There were 5/8 responders in the N/S arm, and 4/8 responders in the S/N arm after the first week. Excluding patients who used opioids before entry, 5/6 patients using N and 3/6 patients using S showed a treatment response during the first week.

The number of paracetamol rescue tablets taken was scored daily in the pain diary. The total of paracetamol tablets taken was 71, with an average of 9 tablets/patient/week in the N/S arm.

Table 1. Characteristics of patients with malignant nerve pain

Patient number	Age/sex	Primary tumour	Site of disease	Neurological diagnosis	Previous anti-tumour therapy
01	81 F	Oesophagus	Epidural	Radiculopathy C7 + C8	RT
02	65 F	Mammary	Infraclavicular	Brachial plexopathy	Surgery, RT
03	58 M	Mesothelioma	Apex lung	Brachial plexopathy	VP-16, RT
04	58 F	Mammary	Epidural	Radiculopathy L5	CMF, RT
05	80 F	Mammary	Epidural	Radiculopathy C5	Surgery, RT, tamoxifen
06	68 F	Melanoma	Paravertebral	Lumbar plexopathy	Surgery, Il-2 + α-interferon
07	53 F	Mammary	Infraclavicular	Brachial plexopathy	Surgery, RT
08	59 M	Rectal	Presacral	Lumbosacral plexopathy	Surgery, RT + 5-FU
09	70 M	Mesothelioma	Apex lung	Brachial plexopathy	IL-2 + CDDP, surgery
10	58 M	Renal	Epidural	Radiculopathy C8	Surgery
11	52 F	Cervix	Presacral	Lumbosacral plexopathy	RT, CDDP and IFOS
12	74 M	Lung	Epidural	Radiculopathy T3	RT
13	60 F	Mammary	Epidural	Radiculopathy T5	Surgery, RT, tamoxifen
14	44 M	Lung	Epidural	Radiculopathy T4	RT
15	42 M	Adrenal gland	Paravertebral	Lumbar plexopathy	Suramine, RT
16	43 F	Mammary	Epidural	Radiculopathy T2	Surgery, RT
17	58 M	Rectal	Presacral	Lumbar plexopathy	Surgery
18	69 M	Prostate	Epidural	Radiculopathy L4 + L5	Surgery, RT, orchidectomy
19	66 M	Rectal	Para-aortal	Lumbar plexopathy	Surgery
20	44 F	Mammary	Infraclavicular	Brachial plexopathy	CMF

F, female; M, male; RT, radiotherapy; CDDP, cisplatinum; IFOS, ifosfamide; IL-2, interleukin-2; CMF, cyclofosfamide, methotrexate, 5-fluorouracil; VP-16, etoposide.

Table 2. Pain ratings during first week

Patient number	Pain at baseline	Pain at day 7	Pain reduction (%)*	Pain-relief rating	Responder†	Tablets paracetamol used
N/S arm						
02	70	20	71	Moderate	R	3
03	70	50	29	Moderate	R	7
06	70	70	0	Slight	NR	14
08	100	55	45	Slight	NR	10
10	75	90	−20	Slight	NR	8
11	80	30	63	Moderate	R	4
13	100	50	50	Moderate	R	12
20	100	80	20	Moderate	R	13
Mean	83	56‡	32‡		5/8R	9§
S.E.	5	8	11			1
S/N arm						
01	100	100	0	Worse	NR	37
04	100	70	30	Moderate	R	7
05	90	90	0	None	NR	40
07	100	50	50	Considerable	R	0
12	70	70	0	Slight	NR	20
14	70	90	−29	Worse	NR	27
15	75	20	73	Moderate	R	2
18	50	30	40	Considerable	R	23
Mean	82	65	21		4/8R	20
S.E.	7	10	12			5

*Negative percentages denote an increase in pain. †R indicates responder, NR, non-responder. ‡Significantly different from pain at baseline ($P < 0.05$). §Significantly different from S/N arm ($P < 0.01$).

In the S/N arm, the total of tablets paracetamol taken was 156 with an average of 20 tablets/patient/week (Table 2). Thus, patients receiving S in the first week needed twice as much paracetamol rescue than patients receiving N ($P < 0.01$).

There was good correlation between the several measures used for assessment of pain relief. Percentage of pain reduction correlated well with pain relief score ($r = 0.71$), and pain relief correlated similarly with paracetamol rescue ($r = -0.70$), $P < 0.0005$.

Pain evaluation with cross-over comparison of both weeks

After the first week, 2 patients discontinued the study. One patient from the N/S arm (no. 11) developed renal insufficiency and could neither complete her pain diary nor visit our clinic. Another patient from the S/N arm (no. 14), already used opioids before entry and, experiencing more pain, did not wish to proceed. Thus, a total of 14 patients entered the second week of the study. One patient (no. 3) died because of tumour progression during this week. 4 other patients (nos. 6, 10, 13 and 15) received radiotherapy in the second week and were, therefore, also ineligible for pain assessment and side-effects in the second period.

At day 14, maximal pain was reduced by 37% (±12, $P < 0.05$) compared to maximal baseline pain at day 0 in the remaining 9 patients. When maximal pain intensity scores at days 0, 7 and 14 were compared, there was a significant pain reduction after each week of treatment (χ^2 6.1, $P < 0.05$). After a sharp initial decrease in pain intensity during the first 3 days of the first week, both arms showed an increase in pain relief during the first few days after cross-over (Figure 2).

At the end of the two study periods, the 9 patients who had used both drugs indicated that the best pain relief was produced by N in 3 cases (nos. 2, 5, 7), and by S in 4 cases (nos. 4, 8, 18, 20). 2 patients (nos. 1 and 12), non-responders for both drugs, had experienced no difference in pain relief with either regimen (Table 3).

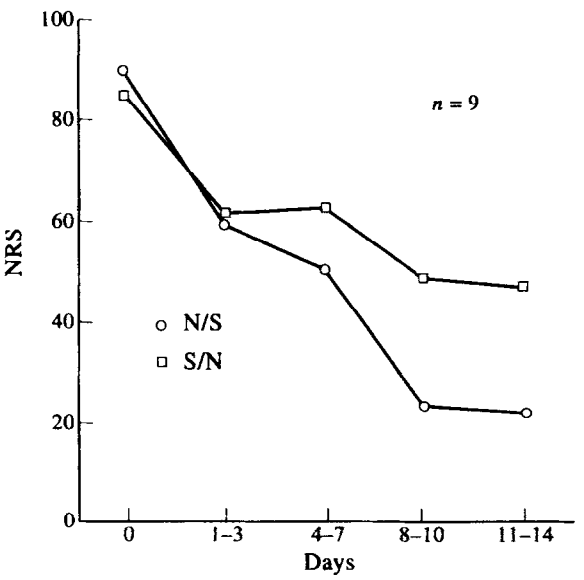

Figure 2. Plot of the maximal pain intensity on numerical rating scale (NRS) in the first and second part of each treatment period.

Side-effects

The mean score of side-effects was significantly higher during the S treatment periods than during N treatment periods (2.8 ± 0.4 versus 1.4 ± 0.1, $P < 0.05$). This difference was mainly caused by complaints of nausea and vomiting due to use of S. With N treatment, less domperidon was used than during S treatment (30 ± 15 versus 140 ± 49 mg domperidon/patient/week, $P < 0.05$). There was no difference between the use of psyllium seeds: 3.3 ± 1.6 in N treatment periods and 2.7 ± 1.5 in the S treatment periods ($P = 0.6$).

The 9 patients who completed the cross-over part of the study were asked which of the two analgesics was best tolerated according to side-effects. 7 (nos. 2, 4, 5, 7, 8, 18, 20) of the 9 patients reported that N had less side-effects. Patients who had used both drugs were asked which drug they preferred overall, considering both painkilling effects and side-effects: 5 patients (nos. 2, 5, 7, 8, 20) preferred N and 3 patients (nos. 1, 4, 18) S; 1 patient (no. 12) had no preference.

DISCUSSION

Neuropathic pain is the second most frequent cause of pain in cancer patients following bone metastases. Neuropathic pain is usually difficult to treat, and reasons for this may include that the applied treatment is not appropriate for the mechanism generating the pain. It has been proposed that nerve pain may be differentiated into two general types: nerve trunk pain or nociceptive nerve pain and deafferentation (dysesthetic) pain or non-nociceptive nerve pain [1]. The concept of deafferentation pain is well established, and there seems to be a growing consensus as to its mechanism, syndrome types and therapy [6, 16–19]. Well-known clinical examples include postherpetic neuralgia, post-dissection pain in patients with cancer, stump pain and phantom pain [19–21]. Double-blind studies have shown that the anti-depressants, amitriptyline and desipramine, probably constitute the therapy of first choice for this type of pain [6, 15, 22, 23]. A more controversial issue is whether deafferentation pain also responds to opioids [7–10].

Mechanism, clinical picture and symptomatic treatment of nociceptive nerve pain are less clear. One explanation is stimulation of free nerve endings (*'nervi nervorum'*) present in the surrounding epi- and perineurium of a nerve root or plexus induced by an inflammatory reaction associated with cancer or other causes of ongoing tissue damage [2, 3]. Alternatively, sensitisation of C-fiber axons may be induced by release of eicosanoids by the action of an inflammatory response caused by the presence of malignant tumour or metastasis [5]. Over the last few years, more evidence for this type of nerve pain has been presented, both experimentally and in the clinical situation [4, 21, 24]. One justification for distinguishing two types of neuropathic pain is that, if true, different therapies for symptomatic relief should be applied.

Common examples of nociceptive nerve pain are compression or infiltration of a nerve root or plexus by tumour or metastasis, or compression of a nerve root by a herniated disc [25–27]. In a pilot study in patients with nociceptive nerve pain with compression of the nerve root or plexus by tumour or vertebral metastasis, we studied the effect of the NSAID N 1500 mg per day. A significant pain reduction of 31% was observed after 1 week of treatment [11]. We have now studied the analgesic effect of 1500 mg N versus 60 mg S in a double-blind double-dummy fashion with a parallel-group comparison during 1 week of treatment followed by cross-over analysis after 2 weeks.

We established that 1500 mg N is at least as effective as 60 mg S. After 1 week of treatment, the group receiving N showed a significant pain reduction in contrast to the group receiving S and needed less paracetamol rescue tablets.

We used a wash-out period of only 6 h. We think that this shortcoming is inevitable as the baseline pain score of our patients was more than 80 on a numerical rating scale. With such severity of pain, patients cannot be expected to tolerate longer periods of time without using effective pain killers. In a similar study with N for severe pain due to bone metastsis, a baseline period of 6 h was also used [12]. Because of a short baseline period, the results of our study are possibly mitigated. The maximal pain rating before entry is scheduled at a time when wash-out may not yet be completed and the observed analgesic effects might have been stronger if we could have been able to use a longer medication-free period.

As all patients had severe pain, we could not afford to use a control group receiving only placebo without active treatment.

Table 3. Pain ratings during second week

Patient number	Pain at day 7	Pain at day 14	Pain reduction (%)*	Pain-relief rating	Responder†	Tablets paracetamol used
N/S arm						
02	20	50	29	Worse	NR	1
08	55	40	60	Considerable	R	0
20	80	10	90	Considerable	R	1
S/N arm						
01	100	100	0	None	NR	33
04	70	80	20	None	NR	9
05	90	50	44	Moderate	R	8
07	50	10	90	Complete	R	0
12	70	70	0	None	NR	26
18	30	50	0	Slight	NR	10
Mean	63	51‡	37‡		4/9R	10
S.E.	9	10	12			4

See legend of Table 2.

It might be argued that similar results as we established could have been obtained from a placebo response. However, several observations contradict this: in the first week N produced a significant pain relief in the contrast to S. Ongoing administration of placebo is unlikely to yield a gradual increase of pain relief as we observed in both study arms, especially in cancer where pain intensity over time usually becomes stronger. We observed high correlations between measures of pain intensity, pain relief and paracetamol rescue. Therefore, the lower use of paracetamol rescue in the group receiving N is another argument of the true analgesic action of N. Furthermore, an increase in pain relief could be observed during the first few days after cross-over. It would be unlikely that such a carry-over effect would be observed in both treatment arms without at least one of the drugs having an analgesic effect.

The observed pain relief in this study was not complete. We found a pain reduction of 26% after 1 week and of 37% after 2 weeks of treatment. This degree of improvement corresponds to figures from studies on nerve pain in which pain relief varied between 30 and 37% [15, 23, 28], and between 0 and 65% in cancer pain [12, 26, 29]. The number of 16 evaluable patients in this explanatory trial clearly restricts the statistical power of the study, although this sample size is similar to other recent double-blind trials studying pharmacological effects on nerve pain [9, 10, 28]. The high number of drop-outs during the second week illustrates the difficulties in carrying out double-blind studies in patients with severe pain and progressive disease. This, of course, limits the statistical power for the cross-over part of this study.

The substantial number of new patients (238) with radicular or plexus pain caused by cancer illustrates the high incidence of malignant nerve pain. Of course, many patients suffered from concomitant pains elsewhere or had recently changed their anti-tumour therapy. This explains the low frequency (8.4%) of patients fulfilling all criteria of eligibility for this trial.

With opioid therapy, individual dose titration is important in obtaining maximal pain relief [8]. The fixed dose of 60 mg S, as used in this study, is probably not adequate for most patients to obtain maximal pain relief. Alternatively, a high incidence of side-effects due to use of S is probably related to a starting dose of 60 mg of S. However, step-wise increasing doses of opioids would not have been compatible with a double-blind, double-dummy design. Although it is often advisable to initiate S by 60 mg day, as we did here, our data indicate that it is probably better to start with 10 or 20 mg twice daily and gradually increase the dose as needed.

For clinical practice, two factors may help to differentiate between nociceptive nerve pain and deafferentation pain. In nociceptive nerve pain, ongoing tissue damage is present as caused by tumour, trauma, ischaemia or inflammation. In deafferentation pain, there is no indication of active tissue damage, and essentially only scar tissue is left. The second factor is time. In nociceptive nerve pain, the pain starts simultaneously with the process of tissue damage. In deafferentation pain, usually a latent period of only days or weeks, after the onset of damage, is present [20, 21]. Possibly, this period reflects the time necessary to develop the underlying mechanism related to this type of pain [18, 30].

Our observations on the effect of a NSAID and an opioid on malignant nerve pain are clinically important for three reasons. First, they show that there exists a nociceptive component of neuropathic pain responding to conventional analgesics. Considering this study as an explanatory trial, our results support evidence for the concept of nociceptive nerve pain. Second, the response to both an NSAID and opioid provides a good rationale for combining both drugs in clinical practice. The step-wise application of a non-opioid drug first, followed if necessary, by an opioid drug for the treatment of pain in cancer is known as the stepladder of the WHO (World Health Organization). The results of our study lend support to application of this ladder for nociceptive nerve pain in patients with cancer. It may also help to argue that in using step 3 of this ladder, a strong opioid should not be used alone, but rather in combination with an anti-inflammatory drug.

To conclude, distinguishing between two types of neuropathic pain seems useful in applying the appropriate treatment. Deafferentation (non-nociceptive) pain seems primarily responsive to certain anti-depressants [15, 22, 23]. Nociceptive nerve pain should mainly be treated as any other nociceptive pain.

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Treatment of Advanced Colorectal Cancer With Folinic Acid and 5-Fluorouracil in Combination With Cisplatinum

P. Sagaster, R. Essl, G. Teich, E. Fritz, M. Wasilewski, H. Umek, E. Dünser, H. Mascher and M. Micksche

51 patients with metastatic colorectal cancer (stage Dukes D) were treated with intravenous (i.v.) infusion on days 1, 3, 5, 8 and 16 with folinic acid (200 mg/m²) and 5-fluorouracil (600 mg/m²), and on days 1, 8 and 16 with cisplatinum (25 mg/m² i.v.); cycles were repeated every 4 weeks. All 51 patients were evaluable for toxicity and response criteria. 26 patients had objective responses (3 complete responses, 5.9%; 23 partial responses, 45.1%), relative risk 51% (95% confidence intervals 36.7–65.0%). Response duration ranged from 4 to 28.0 months (median 16.8). Overall median survival of all patients included was 14.7 months (range 3.0–33.0). Toxicity of WHO grade III, requiring dose reduction, occurred in 9 (18%) patients. The regimen described here appears to be active, safe and well tolerated for treatment of patients with advanced colorectal cancer.

Key words: colorectal cancer Dukes D, chemotherapy, folinic acid, 5-fluorouracil, cisplatinum, objective response rate, survival time, toxicity
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INTRODUCTION

TREATMENT OF advanced colorectal cancer is still considered a major problem in oncology. For more than 30 years 5-fluorouracil (5-FU) monotherapy was generally accepted as an active agent for treatment of metastatic disease, despite the fact that response rates in the range of only 10–20% have been achieved [1].

In recent years, several attempts have been made to improve treatment results by combining 5-FU with other agents. One of these treatment approaches is the use of 5-FU together with folinic acid (FA) [2, 3]. This treatment regimen is based on *in vitro* studies which have shown an increased tumour cell kill [4]. The mechanism underlying the increased anti-tumoral activity of 5-FU and FA is probably a pharmacological manipulation of the intracellular pathway of 5-FU [5].

Several randomised trials, comparing 5-FU with 5-FU plus FA, have demonstrated two to four times higher response rates with the combination in metastatic colorectal cancer. Despite these higher response rates, survival improvement appears to be modest at best, not exceeding more than a few months [6].

Further attempts to increase the therapeutic potential of 5-FU have been made by combinations with cis-platinum (CDDP).