PAPERS AND SHORT REPORTS

Patient-controlled dose regimen of methadone for chronic cancer pain

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Abstract

Fourteen patients with severe cancer pain participated in a trial of methadone given in a fixed dose (10 mg) but at intervals selected by the patients themselves during the loading phase. The aim was to achieve rapid pain relief while avoiding the risk of toxicity from accumulation of methadone. As expected, the dosage intervals increased gradually over the first few days of treatment, the daily dose decreasing from 30-80 mg on the first day to 10-40 mg at the end of the week. Plasma concentrations of methadone varied sevenfold after four to five days (0·24 to 1·75 μmol/l; 7·4 to 54·2 μg/100 ml). Eleven patients reported complete or almost complete pain relief and elected to continue with methadone after the study. In no case was treatment withdrawn because of intoxication.

From these findings a patient-controlled dosage regimen of oral methadone may be an effective and safe alternative to parenteral narcotic medication, adjusting both for individual variation in pain intensity and for pharmacokinetics.

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Introduction

In single doses methadone is reportedly a potent but fairly short-acting (four to six hours) narcotic analgesic.[1 2] For severe chronic pain repeated doses—say, every six to eight hours—may, however, lead to accumulation of methadone with attendant toxicity.[3 4] The most likely reason for these findings is that during single-dose studies patients obtain pain relief only during short absorption-distribution phases. Tissue concentrations in the true elimination phase after the first dose are insufficient for analgesia. The elimination half life of methadone is 13-58 hours.[5-7] Hence repeated dosing at *fixed* intervals—for example, thrice or four times daily—may lead to accumulation and toxicity.

These considerations of the pharmacokinetics of methadone and the need for a safe and more efficacious regimen for chronic severe pain in cancer led us to develop a protocol with a fixed dose but *flexible* and *patient-controlled* dosage intervals. We have evaluated this protocol in 14 patients and report here the results.

Patients and methods

We studied 14 patients (seven men and seven women) with incurable cancer (see table). The study was performed in the departments of surgery and gynaecology of a general hospital (cases 1-6) and in a university department of oncology (cases 7-14). All patients had severe pain and had been treated with narcotic analgesics other than methadone. They had been admitted to hospital for diagnostic procedures and adjuvant care, including treatment of pain. Three patients (cases 7, 12, and 13) were given palliative irradiation therapy. The patients were informed about the purpose and design of the study and their consent obtained.

Design—Methadone was given as 10 mg tablets of methadone hydrochloride (ACO Läkemedel AB, Stockholm). The principle of the dosage regimen was based on giving a fixed dose (10 mg) at flexible time intervals to suit each patient's need for pain relief. After the initial dose the patient was instructed to ask for another tablet as soon as the pain reappeared. Each patient thus controlled his own dosage and increased his body methadone concentration to a level consistent with his variation in pain intensity and opiate tolerance. After about one week the maintenance dose was set to fixed time intervals based on the patient's requirements. Also the six patients studied in the

departments of surgery and gynaecology had the treatment evaluated by questionnaire: items covered were pain intensity, sedation, anxiety, sleep, emotional contact, mood, global assessment of treatment, and side effects. Blood samples for methadone analysis were drawn immediately before giving the next dose. Blood samples were collected into Venoject tubes containing heparin. After centrifugation the plasma was separated and stored frozen at −20°C until analysis.

Analytical method—The plasma concentration of methadone was determined by mass fragmentography[8] with the following modifications. A 2 ml sample was analysed; extraction was made with N-hexane after adding 2 ml 0·05M NaOH. The analogue 2-dimethylamino-4, 4-diphenyl-5-octanonehydrochloride was used as internal standard. Gas chromatographic separation was accomplished with a 1 m silanised glass column packed with 3% SP-2250-DB on 100-120 mesh Supelcoport. The lower limit of detection with the method was 30 nmol/l (0·9 μg/100 ml). The coefficient of variation was 5·5% at 40 nmol/l (1·2 μg/100 ml; n=10).

Results

DOSE REQUIREMENTS

During the first day the methadone dose varied between 30 and 100 mg in all patients. During the first week the dose requirement decreased successively to a mean of 21·5 mg (fig 1). Accordingly the first dosage interval was short (three to seven hours), and increased to about 10 hours at the end of the week. After five to seven days the dosage intervals were set at eight or 12 hours, depending on the need of the patient. Individual doses varied between 10 and 15 mg and the daily dose between 10 and 40 mg.

PLASMA METHADONE CONCENTRATIONS

Plasma concentrations of methadone reached a plateau after two to three days. Considerable variations were found; fig 1 shows the concentrations before each dose in eight patients. After four to five days' treatment the concentrations ranged from 0·24 to 1·75 μmol/l (7·4 to 54·2 μg/100 ml).

Figure 2 shows a further example of the interindividual variation in the disposition of methadone. Despite a sevenfold difference in daily dose (per kg body weight) between the two patients (cases 5 and 6) the plasma concentrations were similar.

EFFECTS

Eleven of the 14 patients reported complete or almost complete analgesic effect. Of the six patients studied in the departments of gynaecology and surgery, four (cases 1, 2, 4, and 5) completed the evaluation questionnaire after one week of treatment. All reported a positive effect (global assessment) and decreased pain intensity, and two reported improved mood, sleep, capacity for emotional contact, and decreased anxiety; three reported increased sedation. Two patients (cases 2 and 4) considered all the effects advantageous. Of the remaining two patients, one (case 3) had rapidly progressive disease and was too ill to answer the questionnaire, and the other (case 6) did not continue treatment for the full week. This second patient, a 22-year-old woman with high tolerance for opiates (table), achieved relatively low plasma concentrations of methadone (fig 2). She preferred her previous treatment with 100 mg ketobemidone daily, administered intramuscularly in divided doses every one or two hours.

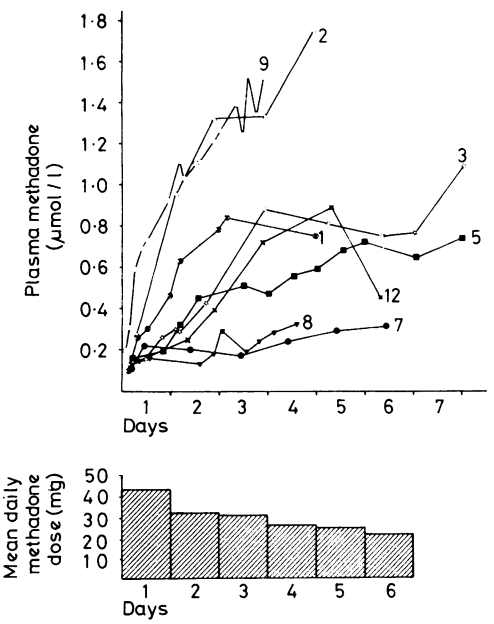


FIG 1—Mean daily methadone dose in all patients and plasma concentrations of methadone in eight of 11 patients who completed patient-controlled dose regimen for one week. Plasma concentrations in three patients not included because of incomplete blood sampling. (Figures on photo are case numbers.)

Conversion: SI to traditional units—Methadone: 1 μmol/l≈31 μg/100 ml.

One patient (case 14) stopped methadone at the beginning of the second day after a total of 70 mg because of continuing pain. Interestingly, her plasma concentration was only 0·18 μmol/l (5·6 μg/100 ml). Subsequently she was treated with parenteral morphine (30-40 mg), which also had a suboptimal effect.

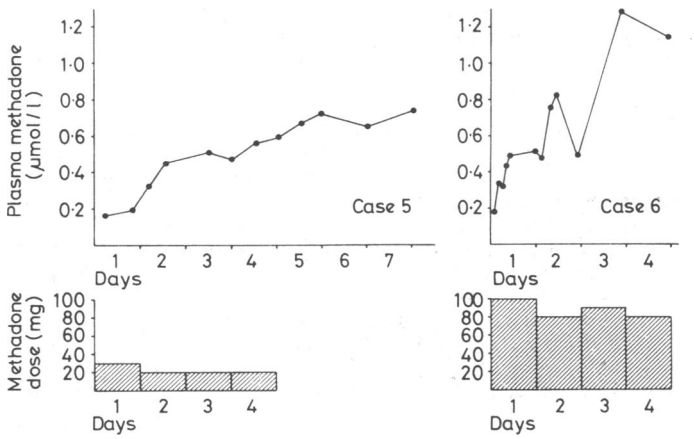
Treatment was therefore successful in 11 patients and failed in three. In two of the failures probably the dose was insufficient, owing to poor availability or rapid elimination, or both. The first doses of methadone caused mild sedation in some of the patients. These effects diminished with time and were absent after a few days. One

Clinical details of patients studied

Case No	Age and sex	Weight (kg)	Tumour site	Disease state*	Previous medication and daily dose	Total dose of methadone (mg)	
						Day 1	Day 6
1	75 M	73	Colon, hepatic metastases	70	Oxycodone 75 mg intramuscularly	50	20
2	75 M	70	Bladder, local growth	70	Oxycodone 200 mg intramuscularly	60	35
3	56 M	78	Bladder, multiple metastases; impaired liver and kidney function	40	Ketobemidone 40 mg by mouth, dextropropoxyphene, acetylsalicylic acid	40	20
4	49 F	50	Uterine, cervix, lung metastases	80	Ketobemidone 30 mg intramuscularly	50	20
5	69 M	75	Kidneys, lung and bone metastases	90	Pethidine hydrochloride 50 mg intramuscularly, paracetamol	30	20
6	22 F	50	Skeleton (sarcoma)	40	Ketobemidone 100 mg intramuscularly	100	
7	55 F	62	Rectal, local growth	70-80	Pentazocine 150 mg by mouth, dextropropoxyphene 200 mg	30	20
8	54 M	66	Testis	70-80		30	10
9	53 F	74	Sarcoma	70-80	Dextropropoxyphene 200 mg	80	40
10	43 F	43	Breasts, brain and lung metastases	40-50	Pentazocine 150 mg by mouth	50	
11	60 F	64	Breasts, bone metastases	60	Pentazocine 200 mg by mouth	30	20
12	66 M	53	Bladder, bone metastases	40	Paracetamol, chlormezanone	30	10
13	30 M	81	Malignant melanoma, brain metastases	80-90	Ketobemidone 30 mg by mouth, betamethasone	50	20
14	68 F	56	Haemangiopericytosarcoma	70	Ketobemidone intramuscularly, dextropropoxyphene, acetylsalicylic acid	60	

* 100-80: Able to carry on normal activity; no special care needed. 70-50: Unable to work; can live at home; can care for most personal needs; varying amount of help needed. 40-0: Cannot care for self; needs institutional or hospital care or equivalent; disease may be rapidly progressive. (Karnofsky.[12])

patient (case 10) stopped taking methadone after three days because of persistent vomiting. No severe side effects such as respiratory depression, somnolence, coma, or hallucinations were observed.



(FIG 2—Plasma methadone concentrations and daily dosage in cases 5 and 6 Methadone: 1 μmol/l≈31 μg/100 ml).

Discussion

The most important advantage of our patient-controlled methadone regimen was the rapid achievement of pain relief. The principle was similar to the patient-controlled schedule reported for post-operative pain.[9] Those patients established constant and analgesic plasma concentrations by self-adjustment of the dose. Our study also shows that a self-adjusted dosage regimen may be employed without overdosing or serious side effects.

As expected, the dosage intervals increased with the longer duration of analgesia after repeated doses of methadone. A decrease of the required daily dose over the first few days was also reported by Valentine *et al.*[2] On the sixth day the mean daily dose was only 21·5 mg.

The duration of analgesia after a single intramuscular dose of methadone in patients with cancer is reportedly four to six hours, which is similar to that of morphine.[1] The maximal effect occurs one to two hours after administration. On the other hand, the duration of other pharmacological effects of methadone have been reported to last longer. In healthy volunteers miosis appeared one to two hours after administration. The effect was maximal after three to four hours and lasted 31 to 47 hours.[10] The time course for respiratory depression resembled that of miosis. The diversity of time courses for the different effects and side effects may be explained by different locations (compartments) where these effects are exerted. Possibly equilibrium between each of these locations and plasma is established at different times.

The use of methadone for severe pain in cancer has been accompanied by reports of intoxication. Several cases of serious and sometimes fatal respiratory depression associated with somnolence or coma have been described.[3,4] In a study comparing methadone with diamorphine-cocaine, Twycross[11] found that the mortality was significantly higher in the methadone group. In that study most of the patients were dosed every four to six hours with 5 to 20 mg. The rationale for the frequent administration (high daily doses) of methadone, which is also recommended by the manufacturer, was the short duration of analgesia observed after a single oral dose. Possibly the regimen was based on single-dose studies not taking into account the pharmacokinetics and pharmacodynamics of methadone.[6,7,10] Frequent administration of 5-20 mg of methadone is therefore likely to lead to accumulation and toxicity in most patients.

The disposition of methadone is subject to large interindividual variation.[7] The terminal half life ranges from 13 to 58 hours,[5-7] and steady-state concentrations after a given dose may vary fourfold. In our patients there also appeared to be a pronounced interindividual variation in plasma concentration unrelated to dose. No clear-cut relation between the plasma concentrations and the analgesic effect could be established. This was, however, not expected, since the patients exhibited considerable variation in pain intensity and tolerance to narcotic analgesics. Thus the attained plateau concentrations of methadone may give only an indication of the minimum effective plasma concentration.

Our results indicate that the following dose regimen of oral methadone may be used in patients with cancer: 10 mg methadone as required but not more than every four hours during the first three to five days, followed by a fixed dose every eight to 12 hours based on the patient's requirements. During the dose-adjustment period the patient should be in hospital. Oral methadone given by this procedure affords safe and effective analgesia in most patients with cancer. It also allows the patient to spend more of his remaining life at home.

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MARIGOLDS are so plentiful in every garden, and so well known that they need no description. They flower all the Summer long, and sometimes in Winter, if it be mild.

It is an herb of the Sun, and under Leo. They strengthen the heart exceedingly, and are very expulsive, and a little less effectual in the smallpox and measles than saffron. The juice of Marigold leaves mixed with vinegar, and any hot swelling bathed with it, instantly gives ease, and assuages it. The flowers, either green or dried, are much used in possets, broths, and drink, as a comforter of the heart and spirits, and to expel any malignant or pestilential quality which might annoy them. A plaister made with the dry flowers in powder, hog's-grease, turpentine, and rosin, applied to the breast, strengthens and succours the heart infinitely in fevers, whether pestilential or not. (Nicholas Culpeper (1616-54) *The Complete Herbal*, 1850.)