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The cognitive effects of the administration of narcotic analgesics in patients with cancer pain

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Summary Forty patients with cancer pain receiving intermittent narcotics were admitted to a prospective study designed to assess the cognitive effects of narcotics. Twenty patients had undergone no change in narcotic dose or type $\geqslant 7$ days (stable dose, SD, group), and 20 patients had undergone an increase of $\geqslant 30\%$ in dose $\leqslant 3$ days before (increased dose, ID, group). Age, primary tumor, type, dose and route of narcotic were not different between the SD and ID group. Cognitive tests (finger tapping, FT, 10 and 30 sec, arithmetics, A, reverse memory of digits, RM, and visual memory, VM) were performed in all patients before and 45 min after their morning dose of narcotics for 2 consecutive days. Mean percentual change in FT 10 sec, FT 30 sec, A, RM, and VM after the narcotic dose were $97 \pm 9\%$, $100 \pm 14\%$, $100 \pm 13\%$, $100 \pm 15\%$, $98 \pm 19\%$, in the SD group, vs. $77 \pm 14\%$ ($P < 0.001$), $83 \pm 13\%$ ($P < 0.001$), $124 \pm 21\%$ ($P < 0.001$), $60 \pm 21\%$ ($P < 0.001$) and $68 \pm 21\%$ ($P < 0.001$) in the ID group, respectively. Our results suggest that patients who undergo a significant increase in the dose of intermittent narcotics experience significant cognitive impairment, that disappears after 1 week of the increase. More research is needed to better characterize the cognitive toxicity of intermittent narcotics, and to determine the cognitive effects of long acting narcotics, continuous infusions, or of the addition of amphetamines.

Key words: Narcotic analgesics; Cancer pain; Cognitive effects

Introduction

Cognitive disorders are among the most frequent psychiatric complications of advanced cancer [1,9,10]. They are frequently misdiagnosed as affective disorders, particularly depression [9,10], and the cause is unknown in the majority of patients [1,11]. Confusional syndromes occur most frequently in patients with terminal disease [1,11]. Seventy to 80% of these patients have cancer pain and receive narcotic analgesics [1,11,13]. Narcotics have been shown to decrease the performance in cognitive tests in single-dose studies [6]. The purpose of this prospective study was to assess the cognitive effects of the chronic administration of narcotics in patients with cancer.

Patients and methods

Forty consecutive patients with pain due to advanced cancer were admitted to this study. Patient characteristics are summarized in Table I. All patients were admitted to the hospital. None of the patients had brain metastasis, present or past history of neurological or psychiatric disease, sepsis, sodium, calcium, or renal function abnormalities. All patients had a minimum of grade 8 level education and good understanding of the English

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TABLE I

PATIENT CHARACTERISTICS

	Stable dose	Increased dose
Number	20	20
Age	56±8	54±8
Sex (female/male)	12/8	14/6
Primary tumor		
Breast	10	6
Gastrointestinal	2	4
Lung	1	1
Bladder	1	2
Prostate	1	3
Hematological	2	1
Ovarian	3	1
Sarcoma	0	2
Total	20	20
Mean equivalent dose (mg) of parenteral morphine	16.3±4	15.8±4
No. of patients receiving parenteral narcotics	6	8
Type of narcotic (no. of pts)		
Morphine	9	7
Hydromorphone	7	10
Oxycodone	3	1
Codeine	1	2
Total	20	20

language. Patients admitted to the study were receiving intermittent narcotics for the treatment of cancer pain. Patients receiving narcotics with very long half-life, such as long-acting morphine or levorphanol, or those receiving continuous infusion of narcotics were not admitted to this study. Patients were divided into 2 groups: (a) stable dose: patients who had undergone no change in type or dose of narcotics for seven days or more (n = 20); (b) increased dose: patients who had undergone an increase in the dose of narcotics of at least 30% less than 3 days before admission to the study (n = 20).

Patients who agreed to participate were assessed during 2 consecutive days in the morning. During each of the 2 days, patients were assessed twice, once immediately before their scheduled dose of analgesics, and once 45 min after the analgesic dose. No change in the dose or type of narcotic or any other medication was allowed during the 2 days of the study.

Each assessment included the following test:

(1) Visual analogue scales for pain, nausea, drowsiness, confusion, depression and activity (0 = worst possible; 100 = best possible).

(2) Tapping speed. This test consisted of 3 timed trials of 10 sec each, with a 15 sec interval between trials, and a 30 sec trial. The patient was instructed to tap a laboratory counter as rapidly as possible; taps were recorded automatically.

(3) Arithmetic test. A test of 20 problems (5 each in addition, subtraction, multiplication, and division) were used. This was scored for time and errors, with a total score equal to the time in seconds plus 10% of the time scored for each error. A different form of the test was employed at each of the 4 assessments with a constant order of tests for all patients.

(4) Memory for digits. A series of numbers of progressively increasing length (beginning with 3 digits) were read at the rate of 1 digit/sec, and the highest number of digits the patient could recall in reverse order was recorded. The test ended when the patient failed twice on a number of any given length. The patient received a score of 2 for each level at which no errors were made, a score of 1 if they missed the first trial but succeeded in the second trial, and a score of 0 if the patient missed both trials. Different lists were used for each of the 4 assessments with the order of the list constant for all patients.

(5) Visual memory. Before starting test no. 2, patients were shown a picture of 3 objects. After the completion of test no. 4, patients were asked to recall the 3 objects in reverse order. The patient received a score of 2 for each object recalled, a score of 1 if they missed the first trial but succeeded on the second, and a score of 0 if they missed both trials. Different objects were used at each of the 4 assessments, with the order of objects constant for all the patients.

Tests described in nos. 2, 3, 4 and 5 have been found to be reliable in the assessment in cognitive changes caused by barbiturates, amphetamines, and narcotics [4,6,7,14]. Results of the 2 assessments before the narcotic doses were averaged and

TABLE II

RESULTS AFTER THE COMPLETION OF THE STUDY *

Feature **	Stable dose group (n = 20)			Increased dose group (n = 20)		
	Before	After	*P* value	Before	After	*P* value
Pain (VAS 0–100)	38 ± 15	12 ± 10	0.000	42 ± 16	14 ± 9	0.000
Drowsiness (VAS)	8 ± 5	17 ± 10	0.001	14 ± 7	42 ± 13	0.000
Nausea (VAS)	14 ± 10	13 ± 8	0.392	10 ± 9	27 ± 12	0.000
Confusion (VAS)	8 ± 7	8 ± 7	0.826	7 ± 5	7 ± 5	0.449
Activity (VAS)	23 ± 11	23 ± 9	0.611	21 ± 8	20 ± 7	0.180
Tapping speed (10 sec)	38 ± 6	37 ± 7	0.132	37 ± 4	28 ± 5	0.000
Tapping speed (30 sec)	116 ± 12	116 ± 13	0.881	116 ± 10	96 ± 15	0.000
Arithmetic	78 ± 11	79 ± 12	0.516	77 ± 10	96 ± 12	0.000
Reverse digits	6 ± 2	6 ± 1	0.606	7 ± 1	4 ± 2	0.000
Serial memory	5 ± 1	5 ± 1	0.385	6 ± 1	4 ± 1	0.000

* Results expressed as mean ± S.D.
** See text for definition.

were compared with the 2 assessments after the narcotics.

Statistical analysis was performed using paired '*t*' test, unpaired '*t*' test and Chi-square test [12].

Results

All 40 patients were evaluable at the end of the study. Results are summarized in Tables II and III.

The study dose of narcotics was administered an average of 4.8 ± 1 and 4.9 ± 1.2 h after the previous narcotic dose in patients on stable and increased dose, respectively (*P*: NS). Within each of the 2 patient groups, no significant difference was found between the assessments made on day 1 and day 2.

Discussion

In this prospective study, we have assessed the cognitive effects of the intermittent administration of narcotics in patients with cancer pain. Both patient groups were similar in age, primary tumor, type, dose, and route of narcotic analgesics (Table I). Both groups were assessed before and after their morning dose of narcotics, and no change in medications was allowed during the 2 study days.

The cognitive tests we used have been found to be useful in the assessment of cognitive effects of drugs [4,7,14]. The fact that no significant difference was found between the assessment at day 1 and day 2 suggests that no 'training effect' occurred in our population.

Both groups showed the expected response to a dose of narcotics [3,5]: decreased pain and increased somnolence, with significantly more seda-

TABLE III

PERCENTUAL CHANGE IN DIFFERENT VARIABLES AFTER THE NARCOTIC DOSE

Variable	Stable dose group (n = 20)	Increased dose group (n = 20)	*P* value
Pain (VAS 0–100)	35 ± 32	35 ± 24	NS
Drowsiness (VAS)	156 ± 58	383 ± 284	0.002
Nausea (VAS)	112 ± 48	209 ± 191	0.04
Confusion (VAS)	99 ± 65	97 ± 34	NS
Activity (VAS)	103 ± 28	97 ± 30	NS
Tapping speed (10 sec)	97 ± 9	77 ± 14	< 0.001
Tapping speed (30 sec)	100 ± 14	83 ± 13	< 0.001
Arithmetic	100 ± 13	124 ± 21	< 0.001
Reverse digits	100 ± 15	60 ± 21	< 0.001
Visual memory	98 ± 19	68 ± 21	< 0.001

* Results expressed as mean ± S.D.
** See text for definition.

tion and nausea in the ID group as compared to the SD group. Our results suggest that patients experience significant cognitive impairment after a recent increase in the dose of narcotics. These cognitive effects have also been reported in single-dose studies of narcotics [6]. The fact that the SD group showed no evidence of cognitive impairment suggests that tolerance develops to the cognitive effects, as has also been shown for nausea or somnolence [3,5]. Because of its design, this study cannot establish the duration of cognitive impairment after each dose of narcotics. However, because of the need for administration of these drugs approximately every 4 h [3,5] cognitive impairment probably occurs 6 times/day after a change in dose. Amphetamine derivates have been shown to reverse somnolence in cancer patients [2], to increase arousal [14] and to reverse narcotic-induced cognitive failure in a single-dose study [6]. Future studies should better characterize the effects of amphetamines on narcotic-induced cognitive failure. The cognitive effects of long-acting narcotics such as slow-release morphine or methadone, or continuous infusions of morphine or hydromorphone, should also be established.

It is of interest that patients did not report increased confusion in the visual analogue scale after the dose of narcotics (Table III). This fact suggests that patients are less aware of cognitive impairment than of other narcotic-induced symptoms such as nausea or sedation (Table III).

Our results suggest that tests of automatic nature, such as finger tapping or simple arithmetics [8], were similarly affected as effortful tests such as reverse digits or visual memory [8]. More studies are needed to better characterize the type of cognitive impairment caused by narcotics. These results, if confirmed in other trials, will have significant impact on the consent for therapeutic or research procedures or counseling of cancer patients in areas such as driving, working or general decision making.

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