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Driving ability in cancer patients receiving long-term morphine analgesia

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Summary

When given in single doses to healthy volunteers, opioid analgesics impair reaction time, muscle coordination, attention, and short-term memory sufficiently to affect driving and other skilled activities. Despite the increasing use of oral morphine daily, little is known about the effect of long-term opioid therapy on psychomotor performance. To examine the effects of continuous morphine medication, psychological and neurological tests originally designed for professional motor vehicle drivers were conducted in two groups of cancer patients who were similar apart from experience of pain. 24 were on continuous morphine (mean 209 mg oral morphine daily) for cancer pain; and 25 were pain-free without regular analgesics.

Though the results were a little worse in the patients taking morphine, there were no significant differences between the groups in intelligence, vigilance, concentration, fluency of motor reactions, or division of attention. Of the neural function tests, reaction times (auditory, visual, associative), thermal discrimination, and body sway with eyes open were similar in the two groups; only balancing ability with closed eyes was worse in the morphine group.

These results indicate that, in cancer patients receiving long-term morphine treatment with stable doses, morphine has only a slight and selective effect on functions related to driving.

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Introduction

When opioids are prescribed for severe cancer pain, good analgesia is often obtained at the expense of sedation, dizziness, and mental clouding.[1] These effects interfere with activities that demand alertness—especially driving. Drugs affecting the central nervous system are generally judged hazardous in motorists[2] and in many countries carry warning stickers.

In opioid-naive healthy volunteers, clinical doses of both sublingual and intramuscular buprenorphine are reported to impair reaction time, muscle coordination, attention, and short-term memory.[3,4] Likewise single oral doses of methadone increase reaction times and impair ocular coordination; yet in drug addicts receiving methadone maintenance, reaction times and overall cognitive functioning seem to be normal,[5,6] and the driving safety record of narcotic users is hardly worse than average, the relative risk of an accident being 1·1.[7]

What is known about morphine and its effects on complex tasks? Sjögren and Banning[8] measured simple reaction times to auditory stimuli in 14 cancer patients receiving constant doses (130–400 mg). When oral treatment was switched to epidural they were able to reduce median morphine dose from 210 mg to 80 mg; yet no significant differences were found in reaction times in the two treatment phases. Bruera and co-workers[9] used four simple bedside memory tests, before and 45 minutes after the morning dose, in 40 patients receiving long-term analgesia. In those with stable dosage morphine had no effect; but, in patients whose dose had been increased by 30% or more in the past two days, cognitive performance

	Morphine mean (SD)	Control mean (SD)
Morphine dose mg/day	209 (221)	0 (0)
Female/male	12/12	15/10
Age	53 (9·4)	51 (11·2)
Primary site of cancer		
Breast	7	10
Lung	3	3
Gastrointestinal	5	6
Urogenital	7	3
Other	2	3
Karnofsky grade (100–0)	80 (8·5)	80 (6·8)
Duration of disease (weeks)	31 (33)	53 (71)
Time on morphine (days)	96 (137)	0 (0)
Education		
Basic	11	12
Trade school	5	5
Intermediate	4	5
University	3	3

None of the differences were significant.

Table 1: **Characteristics of morphine and control groups**

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Test	Items measured	Morphine group (SD)	Control group (SD)	p
M 30: matrices test for nonverbal basic intelligence	No of correct answers	14·2 (4·6)	14·2 (5·0)	0·956
	No of wrong answers	13·0 (6·0)	11·1 (5·4)	0·245
Q1: test of capacity for attention	Fluctuation (SD) in items processed during 14 periods of 30 s	4·2 (1·9)	3·8 (1·6)	0·417
LL5: concentration and structuring ability	Items processed out of 45	18·8 (5·7)	21·3 (6·2)	0·186
	No of errors	1·7 (1·9)	1·5 (1·7)	0·711
SET 3: fluency of motor reactions	Time used (s)	432 (299)	369 (102)	0·343
	No of errors	17 5 (31)	10 2 (7·7)	0·285
PVT: peripheral vision test	"Time out of road" (s)	5·2 (7 1)	5·1 (4·2)	0·902
Division of attention	"Time out of road" when disturbed (s)	7·0 (9·8)	6·5 (5·4)	0·817
Coordination and peripheral vision	Peripheral reaction time (s)	2·8 (1·3)	2·4 (1·1)	0·328

Table 2: **Performance in "driving simulator" tests**

worsened significantly. Kerr and co-workers[10] used an ingenious intravenous system to achieve predetermined target concentrations of morphine in healthy opioid-naive volunteers. Plasma concentrations in the usual therapeutic range for analgesia impaired some but not all elements of cognitive and motor function.

Our clinical impression has been that, in cancer patients who are in good physical condition and who receive stable doses of opioids, chronic morphine treatment does not greatly affect psychomotor function. We now have investigated the matter with psychological and neurological tests relevant to driving ability.

Methods

Patients

The investigation was approved by the institutional ethics committee. 49 ambulatory cancer patients (22 male, 27 female) of the Helsinki University Central Hospital gave their informed consent to the study. The morphine group consisted of 24 consecutive cancer patients under treatment at the pain relief unit of the hospital. Their pain was controlled with slow-release morphine tablets (Dolcontin, Pharmacia) in a mean daily dose of 209 mg (range 60–1100 mg); the dose had been stable for at least two weeks. The patients took their morphine tablets twice a day. On the study day they were asked to take the morning dose at 0700 h.

The control group consisted of 25 cancer patients who had no pain and who did not take any regular analgesics. We selected them simultaneously from patients treated in the department of radiotherapy and oncology at the same hospital. For inclusion, patients had to have a Karnofsky physical performance grade of at least 70 (70=cares for himself/herself; unable to carry on normal activity or to do active work),[11] and were not to be receiving any oncological treatment that could interfere with the tests. Exclusion factors were current treatment with psychotropic drugs, metabolic disturbances, and suspected cerebral metastasis or other neurological dysfunction. 5 patients in the morphine group and two in the control group were on low-dose haloperidol or metotrimeptazine to control nausea; 2 in the control group and 1 in the morphine group were receiving small doses of corticosteroids. No instructions were given concerning coffee intake in the morning, but the patients were not served any coffee during the tests. The two groups were similar in age and sex, educational background, duration of illness, and physical performance capacity (table 1).

Performance tests and personality assessment

The tests started at 0830 h. After completing a questionnaire concerning demographic data, medical history, and educational background patients underwent a computerised test battery, consisting of five psychomotor tests, designed for professional drivers and industrial operators (details are available from the authors). The testing equipment (ART-90, Austria) has been developed and validated by the Austrian Road Safety Board.[12] Instructions appeared on screen and were amplified verbally by the psychologist or assistant. Patients were allowed to practice the tests until they mastered the procedure; all patients were tested by the same persons, who did not know whether the patient was taking morphine or not.

The psychomotor tests were followed by the Wartegg personality test,[13] as developed by Gardziella.[14] This describes the psychological state of the subject in terms of such variables as attitude, sense of reality, control, and initiative.

Neurological tests

Neurological assessment began at 1230 h, after a lunch break at noon. Simple reaction times for auditory, visual, and associative stimuli and finger tapping speeds were measured with a Hewlett Packard 9000/20 laboratory computer and proprietary program. The stimuli were given after varying delays and the subject responded by pressing a separate button. A mean of 20 attempts in each test was used for analysis.

Posture control was measured by means of the force platform technique.[15] The patient stood on a stable platform 40 cm×40 cm. The ground reaction forces were recorded by strain gauges placed in each corner, and the movement of the centre of gravity was calculated. Patients were tested twice, first with eyes open and then with eyes closed, each measurement lasting 60 seconds.

Thermal discrimination on the skin was studied by the Middlesex method.[16]

The tests, which altogether took about 6 h, were performed at the Finnish Institute of Occupational Health. 7 patients did not complete the whole set because of fatigue or equipment failure.

Plasma opioid concentrations

To confirm patient compliance and normal metabolism of morphine, plasma concentrations of morphine, morphine-6-glucuronide, and morphine-3-glucuronide were measured in 15 patients in the morphine group. The blood samples were drawn

Variable	Morphine group mean (SD)*	Control group mean (SD)†	p
Attitude	12·2 (1·8)	12·9 (1·9)	0·266
Sense of reality	18·3 (5·6)	20·5 (7·4)	0·268
Control	2·8 (0 7)	2·7 (0·6)	0·459
Uniformity	3·3 (0·9)	3·3 (0·7)	0·906
Opposition	0·66 (2·0)	1·09 (2·2)	0·512
Initiative	12·0 (2·3)	12·3 (1·9)	0·637

*n=21; †n=23.

Table 3: **Results of Wartegg personality test**

Test	Morphine group mean (SD)	Control group mean (SD)	p
Body sway (cm)			
Eyes open	134 (51)	113 (42)	0·178
Eyes closed	263 (136)	184 (82)	0·028
Finger tapping/15 s	76 (12)	69 (10)	0·023
Reaction time (ms)			
Auditive	187 (97)	163 (48)	0·289
Visual	291 (64)	277 (72)	0·497
Associative	869 (171)	874 (220)	0·930
Warm test °C	1·1 (0·5)	1·0 (0·7)	0·751
Cool test °C	0·8 (0·7)	0·5 (0·3)	0·05

Table 4: **Neural function tests**

	Plasma morphine	Plasma morphine-3-glucuronide	Plasma morphine-6-glucuronide
Q1 test	n=13 r=0·74 p<0·005	n=13 r=0·61 p<0·05	n=13 r=0·75 p<0·005
LL5 errors	n=10 r=0·85 p<0·005	n=10 r=0·93 p<0·001	n=10 r=0·87 p<0·001

Table 5: **Relations between plasma concentrations of morphine and its metabolites and the results of the Q1 and LL5 tests**

at noon. The assay was performed by reversed phase ion-pair high performance liquid chromatography.[17] Morphine and morphine-6-glucuronide were quantified electrochemically and morphine-3-glucuronide by fluorescence. The lower limit of detection for all substances was about 2 ng/mL.

Statistical analysis

For assessment of differences between the morphine and the control groups we used Student's *t*-test, the Wilcoxon 2-sample test, and the Kruskal-Wallis chi-square approximation. Simple linear correlation (Pearson *r*) was used for calculation of correlations. $p<0·05$ was taken as statistically significant.

Results

In the psychomotor tests measuring non-verbal basic intelligence, ability to maintain vigilance in monotonous circumstances, concentration and structuring ability, fluency of motor reactions, and division of attention there were no significant differences between the groups, though the patients on morphine did tend to perform less well: they were slower and made more errors (table 2). As judged by the Wartegg drawing test, the psychological state of the patients was similar in the two groups (table 3).

Again, neural functions were not grossly worse in those taking morphine: auditory, visual, and associative reaction times, thermal discrimination, and posture control with open eyes were about the same (table 4). However, balance with closed eyes was distinctly worse in the morphine group ($p<0·05$); finger-tapping with the preferred hand was better ($p<0·05$).

The mean plasma concentration of morphine measured in 15 of the morphine group was 66 (range 4·5–337, SD 79) ng/mL. The mean morphine-6-glucuronide and morphine-3-glucuronide concentrations were 258 (range 20–1014, SD 252) ng/mL, and 1639 (range 139–4857, SD 1361) ng/mL. There was a significant correlation between plasma concentrations of morphine and its metabolites and poor performance in two of the psychomotor tests—namely, Q1 (attention capacity) and LL5 (concentration and structuring ability) (table 5).

Examination for interactions revealed only the known age sensitivity of posture control. Karnofsky grade and educational background did not influence the results.

Discussion

What do these results tell us about driving ability (and other activities demanding intact psychomotor function) in patients receiving long-term opioids for cancer pain? The relation between laboratory test results and actual performance at the wheel is far from clear, and accident proneness is strongly determined by personality.[18] In a study of 13 568 traffic accidents the leading causes included improper look-out, excessive speed, inattention, and incorrect evasive action.[19] Alcohol seems to predispose specifically to speeding, running off the road, and failure to negotiate curves. Athough we know the target sites for some drugs in the brain, their influence on real-life skills remains to be determined.[20]

The psychological tests used in the present study give information about arousal and vigilance, about the ability to concentrate on a task, about the ability to divide attention, about the fluency of motor sequences, about the coordination of perception and movements, about motor performance, and about the distraction of performance under demanding circumstances. These tests are known to discriminate between different types of driver personality.[12] The results suggest no important differences in most of the psychomotor performance tests between cancer patients on chronic treatment with oral morphine and control cancer patients at a similar stage of the disease but not requiring analgesics. However, we cannot ignore the tendency of the morphine group to show slower reactions, make more mistakes, and process visual information and perform the motor sequences more slowly than the control group. This was not a matter of their attitude to the tests: all patients were well motivated and performed the tasks scrupulously. The present results in the LL5 test were compared with those of a group of 118 non-professional drivers who were over 45 years of age.[21] The performance of both cancer patient groups was comparable with that of the healthy volunteers, whose mean values for items processed out of 45 was 20·0 (SD 5·6) and for the number of errors was 1·7 (SD 2·0).

What is the relevance of the impaired balance control seen in morphine recipients with their eyes closed? In their work with tailored infusions, Kerr et al[10] found that morphine adversely affected force tasks that required precise motor control, and that the defects were greater when the subjects could not rely on vision. With our own observations, this finding suggests that vision provides important clues when other sources of information become unreliable through an adverse effect of morphine on proprioceptive feedback. The volunteers in the study by Kerr et al performed well in the visual perception tests and the letter identification tasks. However, an increase in reading time under morphine infusion suggested impairment of their ability to take in and process information. Their immediate memory and comprehension were as accurate as under saline, but their later recall of textual information was subnormal. The present study showed a similar slowing in the processing of information in the morphine group, though without significant deterioration in performance.

Kerr et al found little deterioration in performance at morphine concentrations of 20 and 40 ng/mL. Reading latency slowed at the mean target concentration of 40 ng/mL, and significant defects of motor-control appeared only at the highest target concentration of 80 ng/mL. The concentrations were chosen to correspond to those required for postoperative pain relief,[22] and the highest was just under that which causes obvious ventilatory depression. The mean plasma concentrations of morphine of 66 ng/mL (4·5–337 ng/mL) in our study corresponded well to the levels chosen by Kerr and co-workers, although there was large inter-individual variation in our patients. We also found a positive correlation between the plasma concentrations of morphine and its glucuronide metabolites and the deterioration in the Q1 and LL5 tests. LL5 especially demands great powers of concentration and good ocular muscle coordination.

The study by Kerr et al is one of the first attempts to differentiate and specify the effects of morphine on motor and cognitive functions. However, laboratory experiments in healthy volunteers may tell us little about effects of long-term morphine in patients with chronic pain. Pain itself is likely to have an arousal effect; on the other hand, severe pain may well lessen the ability to concentrate. In addition, studies with opioid-naive volunteers do not take into account the effect of morphine tolerance. Our patients in the morphine group had been on stable doses for at least two weeks, and this may explain why they performed nearly as well as the controls. Tolerance is a widely accepted explanation for the normal psychomotor performance of drug addicts taking methadone.[23] In Germany, an expert group has recently suggested a reevaluation of the notion that methadone addicts on maintenance programmes are unfit to drive a motor vehicle.[24] The results of Bruera et al[9] suggest that, in the treatment of chronic cancer pain with opioids, a 30% increase in dose is needed to cancel out the effect of habituation.

In conclusion, long-term analgesic medication with stable doses of morphine does not have psychomotor effects of a kind that would be clearly hazardous in traffic. Our main observation relevant to driving was a slight dose-dependent effect on the performance of tasks demanding special concentration.

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