European Journal of Pain (2001) **5**: 443–447
doi:10.1053/eujp.2001.0267, available online at http://www.idealibrary.com on IDEAL®

Driving and intrathecal morphine administration

G. Van den Bosch[a], M. De Doncker[a], P. Vercruysse[b], J. Maeyaert[c], K. Vissers[d] and H. Neels[a]

[a]*Laboratory of Medical Biochemistry and Toxicology, Algemeen Centrumziekenhuis Antwerpen, Campus Stuivenberg, Lange Beeldekensstraat 267, 2020 Antwerp, Belgium,* [b]*Painclinic Anaesthesiology Department, Algemeen Ziekenhuis Sint Jan, Ruddershove 10, 8000 Brugge, Belgium,* [c]*Painclinic Anaesthesiology Department, Heilig Hartziekenhuis, Moeie 18, 9900 Eeklo, Belgium,* [d]*Painclinic Anaesthesiology Department, Ziekenhuizen Oost-Limburg, Campus Andre Dumont, Stalenstraat 2, 3600 Genk, Belgium*

Since Belgian law recently set a limit to morphine concentration detectable in blood and urine while driving a vehicle, questions arose about the implications for the medical use of opiates. We determined morphine concentrations in whole blood and urine by gas chromatography–mass spectrometry in 15 patients on continuous intrathecal morphine administration. Effects on blood and urine concentration after water intake and the correlation with the intrathecal morphine daily dose were also evaluated. Our results confirm that, in all patients examined, the legally determined maximum blood morphine concentration of 20 ng/ml was never exceeded. Even patients on high intrathecal morphine dose schedules did never reach the maximum legal blood concentration. However, morphine concentration in urine reached levels which exceeded by far the legally determined maximum concentration of 300 ng/ml. Although legal actions against driving under the influence of morphine can only be taken after a positive urine and a subsequent positive blood sample, drivers on intrathecal opiates must be aware of the possibility of a positive roadside drug test.

KEYWORDS: intrathecal opioids, chronic pain, legal issues, morphine concentration.

INTRODUCTION

Several studies both retrospective and prospective have shown that excellent pain management can be achieved through intrathecal opiate administration. Therefore treatment of chronic pain of malignant and non-malignant aetiology by means of intrathecal catheter implant systems has become a valuable alternative to oral opiate therapy in cases where oral administration of opioid analgesics fails to provide adequate pain relief or where such high doses are needed that severe opioid side-effects occur (Anderson and Burchiel, 1999; Angel *et al*., 1998; Likar *et al*., 1999; Valentino *et al*., 1998). Cancer pain, chronic leg and low back pain, axial somatic pain and pain caused by complex regional pain syndrome (CRPS) type I and II, peripheral neuropathy, arachnoiditis and chronic pancreatitis can be considered as a possible indication for the implantation of an intraspinal drug delivery system (Maeyaert and Kupers, 1996).

According to the Wolschrijn categorization system of drugs that may influence driving performance, morphine is in Belgium ranked as a category III drug (severe impairment) (Wolschrijn

Paper received 28 February 2001 and accepted in revised form 9 July 2001.
Correspondence to: Hugo Neels PhD, Laboratory of Medical Biochemistry and Toxicology, Algemeen Centrumziekenhuis Antwerpen, Campus Stuivenberg, Lange Beeldekensstraat 267, 2060 Antwerp, Belgium.
Tel: +32-3-217-78-01; Fax: +32-3-217-78-00;
E-mail: hugo.neels@ocmw.antwerpen.be

1090-3801/01/040443 + 05 $35.00/0

et al., 1991). A similar ranking was found in literature data from the Netherlands, Italy, Norway, Finland, Iceland and Sweden. In the Netherlands, France and the Nordic countries the package of morphine containing drugs carries a warning label, although this is not always mandatory by law. The Wolschrijn classification of morphine, however, relates to oral administration and does not take into consideration the dose and route of administration. Although there is a general acceptance that certain drugs can impair driving ability, legal requirements for police powers to execute testing vary between European countries. The legal authority to carry out a urine test exists in Denmark, Italy, Belgium and the Netherlands, while in Spain, Germany and the UK it is also allowed to carry out a blood test. However, to authorize a blood test in Belgium, Spain and Ireland, police need to have evidence of infringement of the law. In Denmark, Germany and the UK there has to be suspicion of some agent other than alcohol. A more uniform legislation for all European countries as worked on by the European Transport Safety Council may level the differences between the legal aspects of driving under the influence of drugs.

In Belgium a roadside drug test on the urine of a driver of a vehicle may be performed if there are external signs of the use of impairing substances present. In the case of a positive result a blood sample is taken for further analysis. Recently a maximum blood and urine concentration for several drugs that may impair driving ability was determined. For morphine maximum blood concentration determined by means of a gas chromatography–mass spectrometry (GC–MS) method with deuterized internal standards was set to a limit of 20 ng/ml (free morphine). This cut-off value was taken from the experience of German laboratories with drug testing in blood. For morphine urine concentration a limit of 300 ng/ml (total morphine) was set as a maximum (as recommended by the Substance Abuse and Mental Health Services Administration). Although these measures were taken to detect the use of heroin while driving, this legislation may also effect patients on morphine pain therapy. To evaluate whether this decision had any impact on patients receiving intrathecal morphine, we determined morphine concentration in blood and urine of 15 patients on continuous intrathecal morphine administration. Furthermore, we also evaluated the effect of various morphine dosing schedules.

PATIENTS AND METHODS

Fifteen patients on intrathecal opiates were included in this study from three different hospitals. Dose and start date of the intrathecal morphine treatment were noted. To explain possible confounding effects of oral opiate intake, patients were also asked to give information about the use of oral co-medication. All patients had been implanted with an intrathecal catheter connected to a programmable implantable pump (SynchroMed®, Medtronic, Inc.) placed subcutaneously in the abdominal cavity, at least 4 months before onset of the study (range: 4 months–10 years). Age of selected patients ranged from 34 to 77 years (median: 51 years). Morphine hydrochloride dose varied between 1.6 and 11 mg/24 h. A first peripheral blood and urine sample was obtained after overnight fasting, a second one after intake of 0.5 l water (within 10 min after the first sampling). This was done to see whether endogeneous dilution of the urine had any effect on the morphine concentration. Blood was collected into glass tubes containing lithium heparin. All patients were informed about the study protocol procedures and gave written consent.

Free morphine detection in whole blood was done by GC–MS analysis after a solid phase extraction method and subsequent derivatization with *N*,*O*-bis(trimethylsilyl)trifluoroacetamide as described by Gaillard *et al.* (1996). Extraction from blood was performed with reversed phase C18 cartridges (Bakerbond, Phillipsburg, USA). Deuterized morphine was used as an internal standard. For total morphine detection in urine a similar method was applied except from the hydrolysation with β-glucuronidase prior to solid phase extraction and the use of nalorphine as internal standard (Huang *et al.*, 1992). A Bond Certify column (Varian, Harbor City, USA) using cation exchange and non-polar mechanisms was used for extraction of morphine in urine instead of the C18 cartridge.

RESULTS

Blood and urine morphine concentrations after overnight fasting and water intake are shown in Table 1. All blood morphine concentrations of the 15 patients stayed below the maximum legal concentration of 20 ng/ml. In urine morphine concentrations reached levels as high as 2877 ng/ml in the first sample (patient 7), and as high as 4276 ng/ml in the second sample (patient 10). This patient, however, was also on oral morphine medication (morphine sulphate 100 mg daily in a slow release formulation). Although changes in the urine morphine concentration were observed in some patients after intake of 0.5 l water, statistical analysis showed no significant effect of water intake (Wilcoxon signed rank test, $p > 0.20$). Generally an increase of the intrathecal morphine dose led to higher urine concentrations. The correlation between the intrathecal morphine dose and the urine concentration, however, appeared weak and was not statistically significant after overnight fasting (Spearman's coefficient of rank correlation, 0.522; $p = 0.051$) or after drinking water (Spearman's coefficient of rank correlation, 0.412; $p = 0.124$).

DISCUSSION

Side-effects of morphine that may have a detrimental impact on road user performance are sedation, impairment of cognitive functions, mood changes, impairment of psychomotor functions and pupil restriction. Sedation and cognition impairment seem important in the beginning of treatment but tend to wear off in most patients after some days or weeks. A survey among patients on oral morphine medication found that absolute unfitness exists at onset of the treatment, when important changes in drug dose are introduced and when other central nervous system depressants or alcohol are coingested. In long-term stabilized oral opioid therapy with unchanged doses no impairment of driving behaviour was observed (Lakemeyer *et al.*, 1998). In an experimental study by Strumpf *et al.* (1997), patients on oral morphine medication showed no impairment of psychomotoric functions when compared to a control group, while the patient group on benzodiazepines showed significant impairment. Since experimental studies on cancer patients have demonstrated that long-term oral morphine treatment does not increase the risk of

TABLE 1. Urine and blood morphine concentrations after intrathecal morphine administration.

Patient	Morphine dose (mg/kg per 24 h)	Blood sample 1 (ng/ml)	Blood Sample 2 (ng/ml)	Urine sample 1 (ng/ml)	Urine sample 2 (ng/ml)	Oral opioid co-medication
1	0.02875	< 2	< 2	848	914	None
2	0.08182	2.2	2.2	1420	1931	None
3	0.02195	< 2	< 2	254	183	None
4	0.05128	< 2	< 2	1215	1243	None
5	0.05743	< 2	< 2	786	753	None
6	0.15534	< 2	< 2	854	654	None
7	0.07675	< 2	< 2	2877	1230	None
8	0.14118	< 2	< 2	178	285	None
9	0.03448	< 2	< 2	275	704	None
10	0.17460	3.9	3.7	1954	4276	Morphine sulphate 100 mg daily
11	0.07639	< 2	< 2	1310	1415	Codeine (dosis unknown)
12	0.07639	< 2	< 2	340	285	None
13	0.05368	< 2	< 2	448	579	None
14	0.01500	< 2	< 2	74	78	None
15	0.01758	< 2	< 2	213	341	None

Sample 1: sample obtained after overnight fasting. Sample 2: sample obtained after drinking 0.5 l water, preferably within 10 min after first sampling. Detection limit for detection of morphine in blood: 2 ng/ml. In blood free morphine was measured, while in urine total morphine concentrations were determined after hydrolysation of morphine glucuronides.

road accidents, intrathecal morphine administration may be considered as a safe treatment option in patients who take part in public traffic (Bruera *et al.*, 1989; Vainio *et al.*, 1995). Further investigation on this subject, however, may be needed to confirm these findings finally with intrathecal administration of opiates.

Our results show that intrathecal morphine administration can lead to high urine morphine concentrations, which exceed the legally determined maximum concentration of 300 ng/ml. The lowest intrathecal dose that gave a urine morphine concentration higher than this limit was 2.3 mg/24 h. We also observed a urine morphine concentration below this value with a dose regimen as high as 12 mg/24 h. The weak dose–concentration correlations found may be due to the limited number of patients or due to the fact that morphine urine determinations were not performed on a 24 h urine collection.

The legally determined maximum blood morphine concentration of 20 ng/ml was never exceeded in the 15 selected patients. Oral opiate co-medication did not have any influence on this finding. The low blood morphine concentrations we observed after intrathecal administration are in agreement with earlier findings (Chauvin *et al.*, 1981; Kotob *et al.*, 1986). In conclusion, it may be clear that further research on the relation between intrathecal opiate administration and driving ability is still needed to determine whether adjustment of the law is appropriate for patients using medical opiates. Currently the absolute prohibition on driving for patients requiring chronic alleviation of severe pain with intrathecal morphine may needlessly restrict patients' mobility, despite the scientific evidence that taking part in traffic is possible when patients are on long-term stable doses of oral morphine. Our experiments show that urine morphine concentrations may exceed maximum levels as determined by Belgian law, while blood morphine concentrations of patients on intrathecal morphine remain under detection levels. Since roadside drug testing by the authority has to be legally performed first on urine, these patients may test positive when halted for a roadside drug screening. Therefore, patients on intrathecal morphine still should be made aware of the fact that they might be violating the law by driving a vehicle while under the influence of driving capacity impairing drugs.

ACKNOWLEDGEMENTS

We are grateful to Dr Ann Ver Donck (Pain Clinic AZ Sint Jan, Brugge, Belgium) for her assistance in conducting this study. We also would like to express our appreciation for the support we received from Kathleen Castelein and Suzy Van Dun (Medtronic Belgium) on all aspects of the study.

REFERENCES

Anderson VC, Burchiel KJ. A prospective study of long-term intrathecal morphine in the management of chronic nonmalignant pain. *Neurosurgery* 1999; **44**: 289–301.

Angel IA, Gould HJ, Carey ME. Intrathecal morphine pump as a treatment option in chronic pain of non-malignant origin. *Surg Neurol* 1998; **49**: 92–99.

Bruera E, Macmillan K, Hanson J, MacDonald RN. The cognitive effects on the administration of narcotic analgesics in patients with cancer pain. *Pain* 1989; **39**: 13–16.

Chauvin M, Samii K, Schermann JM, Sandouk P, Bourdon R, Viars P. Plasma concentration of morphine after i.m., extradural and intrathecal administration. *Br J Anaesth* 1981; **53**: 911–913.

Gaillard Y, Pepin G, Marquet P, Kintz P, Deveaux M, Mura P. Identification and quantification of benzoylecgonine, cocaine, methylecgonine-ester, codeine, morphine and 6-acetylmorphine in whole blood. *Toxicorama* 1996; **8**: 17–22.

Huang W, Andollo W, Hearn WL. A solid phase extraction technique for the isolation and identification of opiates in urine. *J Anal Toxicol* 1992; **16**: 307–310.

Kotob HIM, Hand CW, Moore RA, Evans PJD, Wells J, Rubin AP, McQuay HJ. Intrathecal morphine and heroin in humans: six-hour drug levels in spinal fluid and plasma. *Anesth Analg* 1986; **65**: 718–722.

Lakemeyer M. Opiathaltige Schmerzmittel und Verkehrssicherheit. Berichte der Bundesanstalt für Strassenwesen. Mensch und Sicherheit M 86. Bergisch Gladbach 1998.

Likar R, Spendel MC, Amberger W, Kepplinger B, Supanz S, Sadjak A. Long-term intraspinal infusions of opioids with a new implantable medication pump. *Drug Res* 1999; **49**: 489–493.

Maeyaert J, Kupers RC. Long-term intrathecal drug administration in the treatment of persistent noncancer pain: a 3-year experience. In: Waldham SD, Winnie AP. *Interventional Pain Management*. Philadelphia, PA: WB Saunders, 1996: 447–456.

Strumpf M., Kohler A, Zenz M, Willweber-Strumpf A, Derwinkel R, Donner B. Opioide und Fahrtüchtigkeit. *Schmerz* 1997; **11**: 233–240.

Vainio A, Ollila J, Matikainen E, Rosenberg P, Kalso E. Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet* 1995; **346**: 667–670.

Valentino L, Pillay KV, Walker J. Managing chronic non-malignant pain with continuous intrathecal morphine. *J Neurosci Nurs* 1998; **30**: 233–244.

Wolschrijn H, de Gier J, de Smet P. Drugs and driving: a new categorization system for drugs affecting psychomotor performance. Maastricht: Institute for Drugs, Safety and Behaviour, University of Limburg, IVGV, 1991.