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Transdermal administration of morphine to healthy subjects

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1 Twelve healthy subjects received 10 mg morphine HCl delivered transdermally from an occlusive reservoir applied to a small area of skin, painlessly de-epithelialised by vacuum suction. On a separate occasion, 10 mg morphine HCl was given as an i.v. infusion over 20 min.

2 Venous blood samples were collected serially for 72 h and assayed for morphine, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G) by h.p.l.c. Pupil size, salivation, and central nervous effects (nausea, fatigue, headache, feeling of heaviness and dysphoria/euphoria) were also measured.

3 After transdermal application morphine was absorbed by a first-order process to produce relatively constant plasma drug concentrations over 11 h. The absolute bioavailability of transdermal morphine was 75% (65–85%; 95% CI). The plasma concentrations of both M6G and M3G were lower after transdermal administration than after i.v. infusion, and a considerable delay (of up to 1 h) was observed before the metabolites were detectable. AUC ratios for M3G and M6G relative to morphine were similar after both modes of administration.

4 Non-analgesic effects were less pronounced at the lower plasma drug and metabolite concentrations observed after transdermal delivery than after the i.v. infusion of morphine.

5 Transdermal administration of morphine warrants investigation as an alternative route of morphine delivery.

Keywords morphine metabolites transdermal administration bioavailability non-analgesic effects

Introduction

Morphine is the drug of choice for the treatment of severe postoperative pain and chronic pain associated with advanced cancer. Oral administration of morphine is highly effective and convenient, but for immediate postoperative care and in cases of terminal malignant disease when drug absorption is impaired or the oral route cannot be used, treatment with parenteral morphine is necessary. Continuous subcutaneous infusions of opioids administered by a PCA (patient controlled analgesia) technique with a portable pump may be satisfactory for many patients. However, subcutaneous injections may cause discomfort, local irritation and infection, and portable pumps are expensive and require skilled attention. Transdermal administration may be an alternative route to obtain sustained plasma concentrations of drugs when oral administration is not posssible. A transdermal system for the delivery of fentanyl through intact skin has been used [1], but requires large covered areas (10–40 cm^2) and the analgesic effect is delayed in onset owing to slow drug penetration of the epidermis. However, the epidermis can be removed painlessly by vacuum suction on a small area (diameter 5 mm) of skin and drugs can be given by this route. The absorption of a synthetic vasopressin analogue, desmopressin, has been studied after application of an improvised occlusive reservoir to the exposed dermis [2]. The absorption of desmopressin using this method of administration was sufficient to produce clinical effects of the drug.

We now report the plasma concentrations of morphine and its main metabolites, morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G), and the bioavailability of morphine following topical administration of morphine from an occlusive reservoir. Non-analgesic effects of morphine, often

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encountered as side effects during morphine therapy, namely dryness of the mouth, miosis, fatigue, nausea, euphoria/dysphoria, headache and a feeling of heaviness, were also assessed.

Methods

Subjects

The study was approved by the Ethics committee of the University of Lund and by the Swedish Medical Products Agency.

Twelve male volunteers aged 22–29 years and with a mean weight of 76.7 ± 7.4 (s.d.) kg participated after giving their written informed consent. The subjects were all healthy by clinical examination and had blood and urine chemistry values within normal ranges.

Procedure

All subjects received two treatments, I and II, in random order. The study was open-labelled, of a complete cross-over design and there was at least 1 week between the treatments.

The subjects had a light lunch 4 h after drug administration, dinner after 8 h and a light meal after 12 h.

Treatment I After an overnight fast, the subjects received an intravenous infusion of 10 mg morphine HCl (26.6 μmol morphine as 25 ml Morfin Epidural 0.4 mg ml^{-1}, Kabi Pharmacia, Sweden) over 20 min in an antecubital vein. A motor driven syringe (Terumo syringe pump STC-521) was used to deliver the dose.

Venous blood samples were drawn from a short indwelling catheter in a contralateral arm vein before the infusion and at 5, 10, 20, 25, 30, 45, 60, 80,100 min, 2.17, 3.17, 4.17, 5.17, 6.17, 8.17, 11.17, 14.17, 24.17, 30.17, 48.17 and 72.17 h after the start of the infusion.

Treatment II On the afternoon before the treatment, the volar side of the forearm was cleansed with ethyl alcohol, and the suctioning device was applied to the skin. A suction cup (diameter 5 mm) was sealed to the skin and a vacuum of 200 mm Hg below atmospheric pressure was applied. A blister with a diameter of approximately 5 mm was formed gradually and painlessly over 2.5 h, and the blister fluid was then removed with a hypodermic needle and syringe. The blister was covered by an adhesive protective polyurethane film (Tegaderm®, 3M, USA) made non-adhesive in the centre.

On the following day the roof of the blister was removed painlessly and the dermal surface was exposed. An open plastic chamber (diameter 6 mm) was placed around the de-epithelialised lesion and was sealed to the skin with polyurethane film. A piece of gauze (5 × 5 mm) was placed in the chamber, and 10 mg morphine HCl (26.6 μmol morphine as 0.5 ml Morfin Epidural 20 mg ml^{-1}, Apoteksbolaget, Umeå, Sweden) was injected into it. The chamber was then covered with polyurethane film. The chamber was removed after 24 h and the skin lesion was covered with polyurethane film for protection. The amount of morphine in the remaining gauze was measured.

Blood samples were drawn from a short indwelling catheter in a vein in the contralateral arm before drug administration, and at 5, 10, 20, 25, 30, 45, 60, 80, 100 min, 2, 3, 4, 5, 6, 8, 11, 14, 24, 30, 48 and 72 h after morphine was injected into the chamber.

After both treatments, oxygen saturation was recorded and salivation was measured at the same time as the blood samples were drawn up to 14 h after morphine was given. Fatigue, euphoria, dysphoria, headache, nausea and feeling of heaviness were evaluated using category ratio scales [3, 4] at the same time as the blood samples were drawn up to 30 h after drug administration.

Pupil size was measured before the infusion and at 26, 51, 66, 86, 106 min, 2.27, 3.27, 4.27, 5.27, 6.27, 8.27, 11.27 and 14.27 h after the start of the infusion (treatment I) and before and at 26, 51, 66, 86, 106 min, 2.08, 3.08, 4.08, 5.08, 6.08, 8.08, 11.08 and 14.08 h after morphine was given (treatment II).

Measurements Blood samples were drawn into heparinized glass vacuum tubes (Vacutainer®), which were placed in icewater and subsequently centrifuged at +4° C and 1500 *g*, for 10 min. The plasma was then separated and frozen.

The plasma samples were assayed for morphine, M3G and M6G by h.p.l.c. using electrochemical (EC) and ultraviolet (UV) detection [5]. The lower limits of quantification were 2, 5 and 20 nmol l^{-1} for morphine, M6G and M3G, respectively. Inter-assay coefficients of variation for concentrations of 4–200 nmol l^{-1} morphine, 40–250 nmol l^{-1} M3G and 10–50 nmol l^{-1} M6G were 3.8–10.0% (n = 30), and intra-assay coefficients of variation were 0.8–6.4% (n = 6).

Values of C_{max} and t_{max} were noted directly from the data.

Values of clearance, mean residence time and the terminal elimination half-life were calculated by standard methods.

The transdermal absorption rate was calculated using the Loo-Riegelman method [9].

Plots of fraction of dose absorbed over time were fitted by both zero order and first-order functions and a combination thereof using the SAS procedure NLIN [10]. The results are generally presented as mean ± s.d. or 95% confidence intervals. A two-tailed t-test for paired samples was used for comparisons between the two treatments and the level of significance was set at 5%.

Results

The subjects tolerated the two treatments well and oxygen saturation remained normal throughout the procedure. When morphine was injected into the

gauze and reached the dermis the subjects felt a weak smarting sensation of short duration. A discrete, localised flush was seen in the skin around the chamber. The flush disappeared after approximately 45 min.

The de-epithelialised skin lesion healed without leaving a scar in less than 1 week in all of the subjects.

In one of the subjects (subject 10), interfering peaks in the chromatogram prevented the measurement of plasma morphine in samples from the i.v. study. Analysis of M3G and M6G was unaffected. The results are therefore given for eleven subjects unless specified otherwise.

In subject 1, there was a small leakage of the morphine solution from the chamber immediately after the application of the drug. Additional polyurethane film was used to cover the chamber. The bioavailability of morphine in this subject was 83%, and 1.5 mg morphine remained in the gauze on removal of the delivery system after 24 h.

Mean plasma concentrations (± s.d.) of morphine, M6G and M3G after the two treatments are shown in Figure 1.

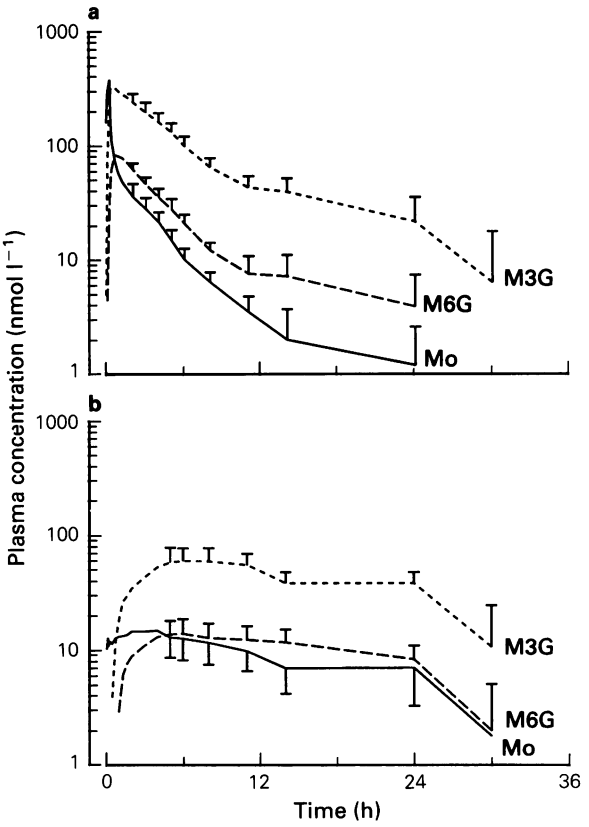

Figure 1 a) Mean plasma concentrations (± s.d.) of morphine (Mo), M6G and M3G after i.v. infusion of 10 mg morphine HCl over 20 min (n = 11). b) Mean plasma concentrations (± s.d.) of morphine (Mo), M6G and M3G after transdermal administration of 10 mg morphine HCl for 24 h (n = 11).

I.v. infusion of morphine

At the end of infusion, the mean morphine concentration was 410 ± 77 nmol l^{-1}. The value of t_{max} for M6G ranged from 0.5 to 1.33 h with a median value of 0.75 h, and the t_{max} for M3G ranged from 0.42 to 1 h (median 0.5 h). Mean C_{max} values of M6G and M3G were 85 ± 17 and 336 ± 69 nmol l^{-1}, respectively. M3G was detected in the plasma of two subjects at 30 h. At this time, morphine was detected in one subject and M6G was not detectable in any subjects. The mean terminal elimination half-life of morphine after i.v. infusion was 2.3 ± 0.5 h and its systemic clearance was 1.29 ± 0.25 l min^{-1}.

Transdermal administration of morphine

Transdermal administration of morphine was associated with a mean C_{max} of 18 ± 4 nmol l^{-1} and a t_{max} of 0.08 to 24 h (median 1.0 h). The plasma concentrations of morphine were relatively constant for 8 h (Figure 1). At 24 h the mean plasma drug concentration was 7 ± 4 nmol l^{-1} and all subjects had measurable concentrations at this time. At 30 h after administration, morphine was detectable in plasma from four subjects.

Mean C_{max} values of M6G and M3G were 15 ± 4 and 68 ± 18 nmol l^{-1}, respectively. The t_{max} of M6G ranged from 3 to 14 h (median 6 h) and that of M3G from 5 to 14 h (median 11 h). At 30 h, M6G was detected in plasma from four subjects and M3G was present in the plasma of five subjects. Neither morphine, nor metabolites were detected in plasma at 48 or 72 h.

The absolute bioavailability of transdermal morphine was 75 ± 15% with a 95% confidence interval of 65–85%. The mean recovery of morphine in the

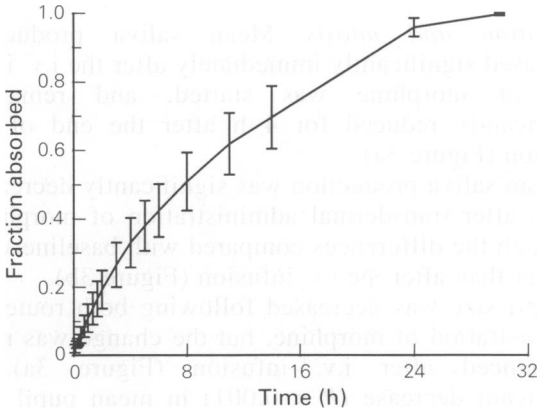

Figure 2 Mean cumulative absorption (± s.d.) of morphine after transdermal administration of 10 mg morphine HCl.

gauze on removing the delivery device was 1.45 ± 0.31 mg (range 1.0–2.1 mg).

The mean fraction of morphine absorbed as a function of time after transdermal administration is shown in Figure 2. The absorption was described better by a first-order rather than a zero-order process as judged by the Akaike information criterion [11].

The mean absorption rate constant, k_a, was 0.09 ± 0.026 h^{-1} (range 0.063–0.152) corresponding to a

Table 1 Plasma AUC ratios of M3G and M6G to morphine (Mo) and M3G to M6G after i.v. and transdermal (tr) administration of 10 mg morphine HCl. The absolute bioavailability (*F*, %) after transdermal administration and the amount remaining in the gauze 24 h after application (gauze, mg) are also indicated

	M6G/Mo		*M3G/Mo*		*M3G/M6G*			
Subject	*i.v.*	*tr*	*i.v.*	*tr*	*i.v.*	*tr*	F (%)	*Gauze (mg)*
1	0.71	0.82	3.88	3.62	5.47	4.42	82.9	1.5
2	1.09	0.94	5.88	4.74	5.39	5.07	70.4	1.5
3	1.24	0.91	6.63	6	5.34	6.56	78.1	1.4
4	1.67	0.86	6.69	3.75	4.01	4.37	80.2	1.0
5	1.11	1.62	4.22	6.87	3.79	4.25	82.4	1.4
6	1.25	1.29	4.42	4.34	3.53	3.36	88.9	1.5
7	1.03	1.33	5.71	6.45	5.55	4.86	55.9	2.1
8	1.41	0.90	5.9	3.96	4.19	4.42	85.8	1.8
9	1.8	1.61	9.16	7.34	5.09	4.56	84.9	1.2
11	1.33	1.09	7.59	5.23	5.69	4.79	75.2	1.0
12	0.86	1.22	3.31	4.72	3.85	3.86	38.6	1.5
Mean	1.23	1.14	5.76	5.18	4.71	4.59	74.9	1.45
s.d.	0.32	0.29	1.74	1.30	0.83	0.81	15.1	0.32
95% CI								
lower	1.01	0.95	4.60	4.31	4.16	4.05	64.7	1.23
upper	1.44	1.34	6.93	6.06	5.28	5.13	85.0	1.66

mean absorption half-life of 7.5 ± 1.95 h and a mean absorption time of 10.9 ± 2.8 h.

The mean residence time of morphine after i.v. infusion was 3.4 ± 1.1 h and after transdermal administration it was 12.0 ± 1.8 h.

The plasma AUC ratios for M3G, M6G and morphine were similar after i.v. and transdermal administration of morphine (Table 1).

Non-analgesic effects

Salivation and miosis Mean saliva production decreased significantly immediately after the i.v. infusion of morphine was started, and remained significantly reduced for 4 h after the end of the infusion (Figure 3a).

Mean saliva production was significantly decreased 1–4 h after transdermal administration of morphine, although the differences compared with baseline were smaller than after the i.v. infusion (Figure 3b).

Pupil size was decreased following both routes of administration of morphine, but the change was most pronounced after i.v. infusion (Figure 3a). A significant decrease ($P < 0.001$) in mean pupil size was observed from the first photograph, taken 26 min after the start of morphine infusion. Mean pupil size was reduced significantly for 8 h after the i.v. infusion of morphine. A small, but significant decrease ($P < 0.02$) of mean pupil diameter was measured 0.45 h after transdermal administration of morphine. Mean pupil size decreased significantly ($P < 0.02$) compared with baseline from 1.1 h until 14.1 h ($P < 0.002$) after transdermal administration of morphine (Figure 3b).

CNS effects Mean ratings of dysphoria/euphoria, fatigue, headache, nausea and heaviness are shown for both treatments in Figure 3a,b.

Nausea occurred in six subjects during treatment I and in one subject during treatment II. Nausea was experienced for short periods of time, up to 2 h, and none of the subjects vomited. One subject reported nausea 10 min after the i.v. infusion was started, continuing for 2 h.

Dysphoria was reported by four subjects during treatment I and by one subject during treatment II. Dysphoria was experienced in short episodes during or immediately after the i.v. infusion of morphine. Euphoria was more common than dysphoria and was felt by eight subjects during treatment I and by seven subjects during treatment II.

Fatigue was reported by all subjects in both treatments. Most subjects reported slight fatigue in the pre-drug assessment. After the administration of morphine the ratings of fatigue were increased.

A feeling of heaviness was experienced by all subjects during treatment I and started during or immediately after the infusion of morphine and continued for up to 5 h (Figure 3a). The mean ratings of heaviness were significantly higher ($P < 0.05$) at 0.08–3.17 h after the start of the i.v. infusion compared with baseline. During treatment II, feelings of heaviness were reported by 10 subjects, but started later and were of shorter duration and were less intense than after the i.v. infusion (Figure 3b). The mean ratings of heaviness after transdermal administration of morphine were significantly higher ($P < 0.05$) at 0.25 and 1 h after dose than baseline ratings.

Headache was reported by nine subjects following the i.v. infusion, and occurred either during the infusion or developed 4–6 h after the end of the infusion. Headache was experienced by eight subjects during treatment II. In two subjects, headache was of short duration (less than 1 h) with an early onset. In the other subjects, slight to moderate headache developed 2–3 h after transdermal administration of morphine and persisted for a few hours.

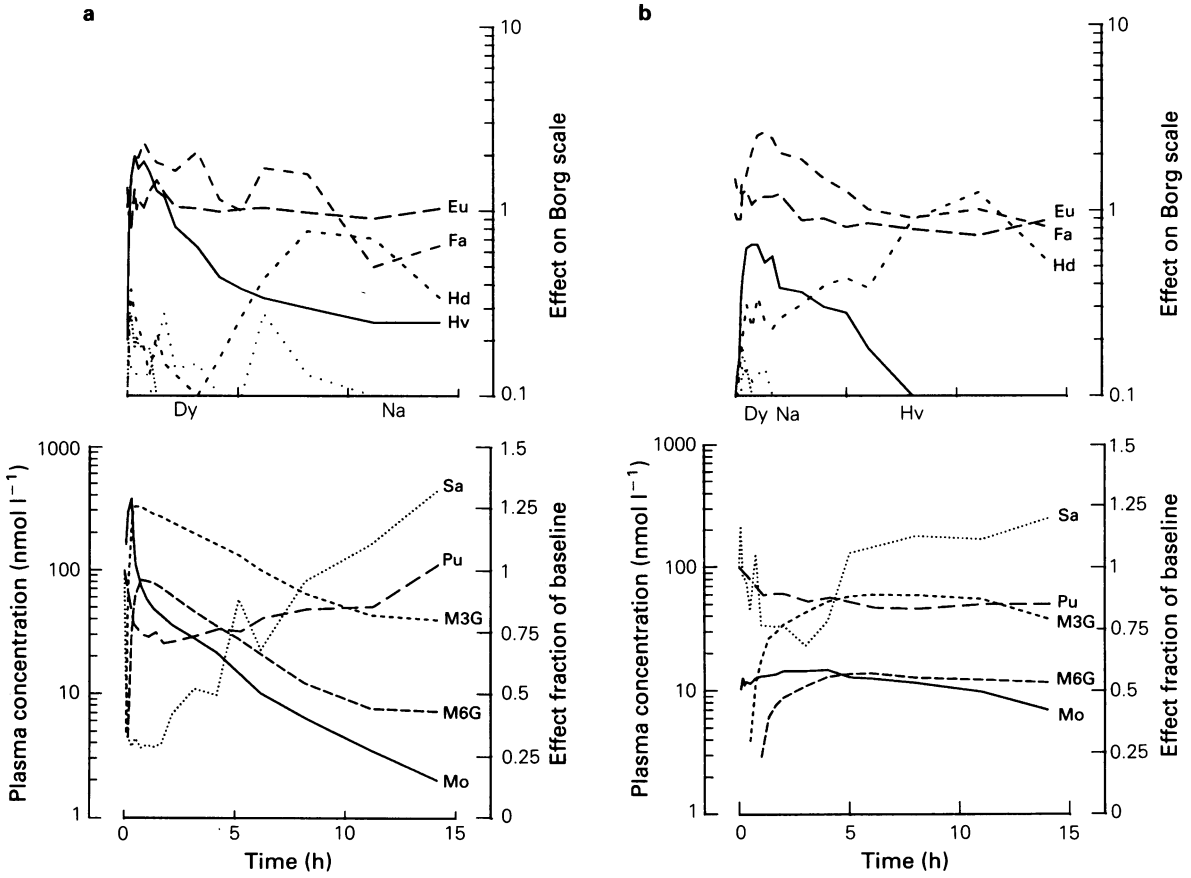

Figure 3 a) Upper panel. Mean ratings of dysphoria (Dy), euphoria (Eu), fatigue (Fa), headache (Hd), nausea (Na) and feeling of heaviness (Hv) during and after i.v. infusion of 10 mg morphine HCl over 20 min (n = 11). Lower panel. Mean change in salivation (Sa) and pupil size (Pu) as fraction of baseline values, and concomitant mean plasma concentrations of morphine (Mo), M6G and M3G during and after i.v. infusion of 10 mg morphine HCl over 20 min (n = 11).

b) Upper panel. Mean ratings of dysphoria (Dy), euphoria (Eu), fatigue (Fa), headache (Hd), nausea (Na) and feeling of heaviness (Hv) after transdermal administration of 10 mg morphine HCl (n = 11, except pupil size, where n = 8). Lower panel. Mean change in salivation (Sa) and pupillary size (Pu), fraction of baseline values, and concomitant plasma concentrations of morphine (Mo), M6G and M3G after transdermal administration of 10 mg morphine HCl (n = 11, except pupil size, where n = 8).

Discussion

The transdermal administration of fentanyl [12, 13] is associated with sustained plasma drug concentrations and effective pain relief in the treatment of chronic pain of malignant origin [1]. A 12–24 h delay is observed before therapeutic plasma concentrations are obtained which reduces the usefulness of the method for relief of postoperative pain relief. Morphine is highly polar [14, 15] and *in vitro* studies have indicated that it does not penetrate human skin [16, 17]. To circumvent this problem we have used an occlusive reservoir applied to a small area of skin, painlessly de-epithelialised by vacuum suction. The mean absolute bioavailability was high, 75%, which should be compared with an oral bioavailability of morphine reported to range between 20 and 40% [18, 19, 20]. Sustained plasma concentrations of morphine were obtained for up to 11 h following transdermal administration. The concentrations of morphine were in the lower range of those observed during PCA (9–39 ng l^{-1}) when a mean morphine dose rate of 2.6 mg h^{-1} (range 1.1–4.0 mg h^{-1}) was self-administered i.v. by postoperative patients [21].

The rate of absorption exhibited first-order kinetics, indicating that the absorption process was not saturated and that uptake of drug may be increased after a higher dose of morphine. The plasma concentrations of M3G and M6G were initially considerably lower and were detected later after transdermal administration than after i.v. infusion of morphine. However, the AUC ratios with reference to parent drug were similar, indicating that the metabolites were formed in the same proportion during both treatments.

Dryness of the mouth is common during morphine therapy [22]. The mechanism by which morphine reduces production of saliva is unknown, but both central and peripheral opioid receptors [23] may be involved. In our study, the reduction of saliva production occurred before the central nervous effects, indicating that at least part of the effect may be the result of interaction at peripheral opioid receptors. Unstimulated salivation was reduced significantly after the administration of morphine in combination with some restrictions in fluid intake.

Miosis is a well-known side effect of opioid therapy and is considered to be caused by cut-off cortical inhibition of the Edinger-Westphal nuclei, although morphine may also have a direct stimulating action on the sphincter nucleus [24]. These effects are reported to be caused by stimulation of μ and κ opioid receptors, since both μ and κ opioid agonists cause miosis [25]. Miller *et al.* [26] studied pupil size after i.v. premedication with morphine and alfentanil and found that the main changes in pupil diameter occurred within a few minutes after i.v. bolus injection of either of the drugs. In the present study, a significant reduction of the pupil size was measured after the administration of morphine and the pupils remained constricted for up to 8 h after i.v. infusion.

Side-effects encountered during morphine therapy may complicate an otherwise effective pain treatment. Non-analgesic effects may be caused not only by morphine but also by its metabolites. In the present study in healthy subjects, the analgesic effects of morphine were not investigated. Instead, we focussed our interest on non-analgesic effects, which were less pronounced after transdermal administration of morphine than after i.v. infusion of the drug. Transdermal administration of morphine seems promising as an alternative route of morphine delivery.

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