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Bioavailabilities of rectal and oral methadone in healthy subjects

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Aims
Rectal administration of methadone may be an alternative to intravenous and oral dosing in cancer pain, but the bioavailability of the rectal route is not known. The aim of this study was to compare the absolute rectal bioavailability of methadone with its oral bioavailability in healthy humans.

Methods
Seven healthy subjects (six males, one female, aged 20–39 years) received 10 mg d_5-methadone-HCl rectally (5 ml in 20% glycofurol) together with either d_0-methadone intravenously (5 mg) or orally (10 mg) on two separate occasions. Blood samples for the LC-MS analyses of methadone and it's metabolite EDDP were drawn for up to 96 h. Noninvasive infrared pupillometry was peformed at the same time as blood sampling.

Results
The mean absolute rectal bioavalability of methadone was 0.76 (0.7, 0.81), compared to 0.86 (0.75, 0.97) for oral administration (mean (95% CI)). Rectal absorption of methadone was more rapid than after oral dosing with Tmax values of 1.4 (0.9, 1.8) *vs.* 2.8 (1.6, 4.0) h. The extent of formation of the metabolite EDDP did not differ between routes of administration. Single doses of methadone had a duration of action of at least 10 h and were well tolerated.

Conclusions
Rectal administration of methadone results in rapid absorption, a high bioavailability and long duration of action. No evidence of presystemic elimination was seen. Rectal methadone has characteristics that make it a potential alternative to intravenous and oral administration, particularly in cancer pain and palliative care.

Introduction

Oral opioids are the mainstay of chronic cancer pain therapy, and >50% of patients have severe pain requiring opioids classified as Step 3 [1]. Morphine is the WHO opioid of choice for Step 3 therapy [1]. However, methadone has attracted an increasing interest in palliative care [2–10]. The usefulness of the latter for patients that are not properly managed with morphine, either due to adverse effect or inadequate pain relief, is documented in several reports underlining the pharmacological differences between the two opioids [9–15].

Most patients with moderate to severe cancer pain can be managed by oral opioids, but 50–70% will require alternative routes of administration during their clinical history, particularly during their last months of life [16]. In many countries only oral and intravenous

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formulations of methadone are available. Subcutaneous infusion has been discontinued due to local toxicity [17]. Nasal administration results in rapid absorption and high bioavailability, but also causes local irritation [18].

Rectal administration of opioids may be an alternative to (a) the oral route in cancer pain patients with nausea and vomiting, or (b) to repeated parenteral injections in patients with immunological deficiencies and bleeding disorders, or (c) when infusion pumps may not be available [19–22].

Only a few studies have reported on the pharmacokinetics and clinical effects of rectal methadone. Moolenaar *et al.* [23, 24] compared aqueous solutions and fatty suppositories for rectal and oral dosing of 10 mg methadone in healthy subjects. The bioavailability and AUC of the rectal solution were lower than after oral dosing, and those of the suppositories were even lower. Ripamonti [2] studied the clinical effects and pharmacokinetics of rectal methadone in 6 opioid-naïve cancer patients with pain. Analgesia was significant at 30 min and lasted for at least 8 h**.** Rectal methadone was shown to be an acceptable alternative to oral hydromorphone or morphine in patients requiring high dose opioids [3, 4, 25, 26].

Relatively little is known about the pharmacokinetics of rectal methadone, and its absolute rectal bioavailibility has not been determined. The aim of this study was thus to compare the pharmacokinetics of oral, rectal and intravenous methadone in healthy subjects.

Methods

This study was conducted according to the guidelines of the Helsinki declaration and approved by the Institutional Review Board at the University of Washington. Informed, written consent was obtained from all subjects before inclusion.

Subjects

Subjects with a history of liver disease, those taking any medications metabolized by or affecting CYP3A, having local anal/rectal disease, with a history of drug allergies, or a history of drug abuse were excluded from the study, as were pregnant women. Nine subjects (8 male, 1 female; aged 20–39 years) entered the study. One subject withdrew after one session due to schedule constraints, and one subject received incorrect drug doses. Seven subjects completed the study. Safety data are reported for all subjects**.** For the seven subjects who completed the study, weight and height (mean, min-max) of the males were 84 (70–93) kg and 177 (170–185) cm, respectively, and the corresponding values for the female were 47 kg and 167 cm.

Setting and study design

This randomised two-way crossover study was conducted at the General Clinical Research Center (GCRC) at the University of Washington Medical Center. Subjects received deuterated rac-(d_5) methadone rectally at each session, together with rac-(d_0) intravenous or rac-(d_0) oral methadone. Each phase separated by at least one week, consisted of a 13 h stay followed by daily visits for 4 additional days.

Drug doses and administration

Ring-deuterated rac-d_5-methadone-HCl was synthesized in our laboratory as described previously [27]. Rac-methadone-HCl (d_0) was obtained from Roxane Laboratories, INC (Columbus, Ohio). The rectal formulation was produced by the Hospital Pharmacy, whereas commercially obtained solutions were used for intravenous and oral administration. Methadone d_0/d_5 was dosed simultaneously either by the intravenous and rectal routes (*IV-rectal*) or by the oral and rectal routes (*oral-rectal*). Rectal methadone-d_5 (10 mg) was given in an aqueous solution (5 ml) containing 20% glycofurol at a concentration of 2 mg ml^{-1} delivered by a syringe with a rectal tip. Intravenous d_0-methadone-HCl was given in a dose of 5 mg, while d_0-oral methadone was given as a 5-ml solution containing 10 mg. Ten mg of methadone-HCl corresponds to 8.94 mg free base.

Protocol

Volunteers were asked to ingest no alcohol, grapefruit, grapefruit juice, caffeine or drug medication for 12 h prior to and during each study period (6 days). Subjects were asked to abstain from food and liquids after midnight prior to the day of methadone administration.

Two 20 g peripheral intravenous catheters were inserted in a hand or arm vein for drug administration and blood sampling. The blood pressure and oxygen saturation of the subjects were monitored for 2 h. Oxygen was administered if oxygen saturation decreased below 94%.

Venous blood samples (5 ml) were drawn at 0, 2, 5, 15 and 30 min and 1, 1.5, 2, 4, 6, 8, 10, and 12 h after drug administration. Subjects were fed a standard breakfast 2 h after receiving methadone, and had free access to food thereafter. Subjects were advised not to drive, operate machinery or engage in other activities with similar risk for the remainder of the day. Subjects

returned once daily for additional blood samples at 24, 48, 72, and 96 h after drug administration. Dark-adapted pupil diameter was assessed by noninvasive infrared pupilometry (Pupilscan-model 2.1 (Fairville Medical Optics, Inc, UK), except at 12 h, under constant lighting intensity [18].

Drug analysis

Plasma concentrations of methadone and its metabolites 2-ethyl-1,5-dimethyl-3,3-diphenylpyrrolinium (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP) were determined by HPLC-positive electrospray mass spectrometry (Agilent 1100 MSD). The internal standard (7-dimethylamino-5,5-diphenyl-4-octanone, 2.5 ng) was added to plasma (0.5 ml), which was acidified and processed by solid phase extraction (Oasis MCX cartridges, Waters Corp, Massachusetts USA) according to the manufacturers instructions. Eluants were evaporated to dryness under nitrogen, reconstituted in 50 µl of 30% methanol and 12 µl was injected onto the HPLC. Compounds were eluted from a Zorbax Eclipse XDB-C18 column (2.1 × 50 mm × 5 µm, with guard column) using an isocratic mobile phase of 55% methanol in 0.05% TFA (pH 3.6) at 0.25 ml min^{-1}, and detected by selected ion monitoring (methadone *m/z* 310.1, EDDP *m/z* 278.1, EMDP *m/z* 264.1, and internal standard *m/z* 324.1). Standard curves were prepared using blank plasma and were linear over the range 0.5–200 ng ml^{-1} for methadone and 0.5–10 ng ml^{-1} for metabolites. The lower limit of determination was defined by the lowest calibration sample. Interday coefficients of variation were 12, 12 and 9% for 1, 15 and 100 ng ml^{-1} methadone and 18% (1 and 5 ng ml^{-1}) for EDDP. EMDP was not detected in plasma. Concentrations can be converted from ng/ml to nmol/l by multiplying by 3.12 and 3.08 for methadone-d_0 and methadone-d_5, respectively. The corresponding conversion factors are 3.62 and 3.54 for EDDP-d_0 and EDDP-d_5, respectively.

Plasma concentration data were analysed by noncompartmental techniques. Pharmacokinetic parameters (Table 1) were calculated by computerized curve fitting using Win-Nonlin Standard 4.0.1 (Pharsight Corporation, Mountain View, California). Bioavailabilities were estimated from $(F_x) = (AUC_x \cdot dose_y)/(AUC_y \cdot dose_x)$ where x denotes rectal or oral AUC and dose, and y denotes the corresponding parameters for intravenous administration. Results are reported for the four different datasets, namely *IV* (intravenous), *oral* (oral), *rectal* (*IV*) (rectal given with IV methadone) and *rectal* (*oral*) (rectal given with oral methadone).

Statistics

Data are reported as mean or median with 95% CI, s.d. or range as appropriate. The nonparametric Mann–Whitney *U*-test was used for the comparison or t_{max}, as normality could not be assumed. Ninety-three percent CIs were calculated for the median difference regarding Tmax (StatExact®, Cytel corp.), as 95% intervals were noninformative due to the low sample size. Dynamic measures were compared by repeated measures ANOVA. Post-hoc testing was performed using the Student-Newman-Keuls Method.

Results

The time course of the plasma concentrations of methadone are displayed in Figures 1 and 2 and the pharmacokinetic measurements are shown in Table 1. Times to maximum plasma methadone concentration (Tmax) were 0.04 (estimated from the first sample), 2.8, 1.3 and 1.4 hs for IV, oral, rectal (IV) and rectal (oral), respectively. The corresponding maximum concentrations (Cmax) were 93, 31, 32 and 26 ng/ml. Mean terminal half-lives of 31–35 hs and clearances (Cl or Cl/F) of 8.3–11 l/h were observed for the four administrations. The absorption of rectally administered methadone was faster than after oral administration. Thus, a mean plasma concentration of about 10 ng ml^{-1} was reached 10–15 min after rectal administration, while this concentration took 60 min to achieve after oral dosing. The lag time observed after oral methadone did not occur with rectal methadone. The best estimate of rectal t_{max} was considered to be the mean value of the two mea-

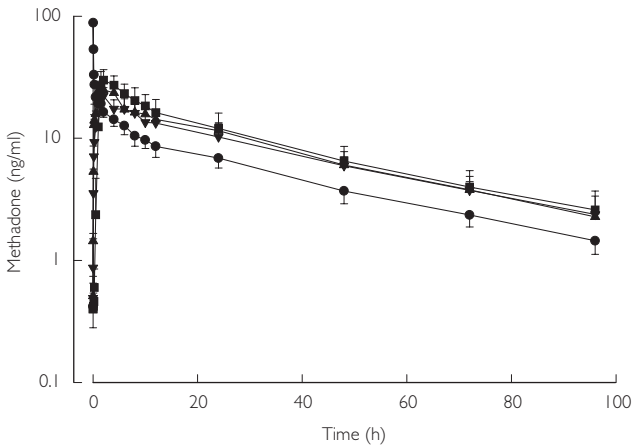

Figure 1

The time course (0–96 h) of plasma concentrations of methadone (mean (s.d.)) in seven healthy subjects after IV-rectal, and oral-rectal administration of methadone-HCl (5 mg IV, 10 mg rectally (deuterated methadone) and orally). IV (●); rectal (IV) (▲); oral (■); rectal (oral) (▼)

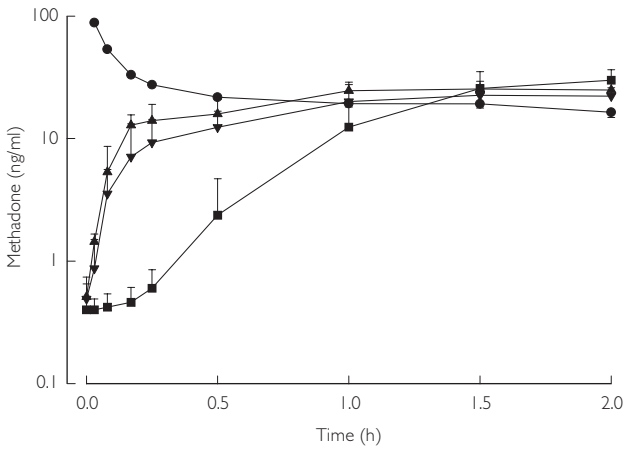

Figure 2
The time course (0–2 h) of plasma concentrations of methadone (mean (s.d.)) in seven healthy subjects after IV-rectal, and oral-rectal administration of methadone-HCl (5 mg IV, 10 mg rectally (deuterated methadone) and orally). IV (●); rectal (IV) (▲); oral (■); rectal (oral) (▼)

surements in each subject. The median difference between rectal and oral Tmax was 1,75 h (93% CI 0,5–4,25), $P = 0.0625$ (Mann-Whitney). No statistically significant differences were observed for the mean clearances and terminal half-lives between the three routes of administration. The mean rectal and oral bioavailability were 0.76 and 0.86 respectively (Table 2), (mean difference [95% CI] = –0.1 [–0.24; +0.04]). The mean relative rectal/oral bioavailabilites were 0.90 and 0.88 for the two rectal studies.

Plasma concentrations of EDDP showed significant inter individual variation, and were much lower than those of methadone (Figure 3). None of the pharmacokinetic parameters for EDDP, especially the AUC EDDP/AUC methadone ratios, differed between routes of administration (Table 3), although concentrations after oral methadone appeared somewhat higher.

The time-course (mean and s.d.) of dark-adapted pupil diameter after IV-rectal and oral-rectal methadone administration for the first 24 h is shown in Figure 4.

Table 1
Pharmacokinetic variables (mean, 95% CI) for methadone after IV (5 mg methadone-HCl) and oral and rectal (10 mg methadone HCl) in 7 human subjects

Route	Tmax (h)	C_{max} (ng/ml)	T1/2 (h)	AUClast (hr*ng/ml)	AUCinf (h*ng/ml)	Vz (obs)(l)	Cl (obs) or Cl/F (l/h)
IV	0.04	93	32	517	587	375	8.3
	0.02, 0.06	58 129	27, 37	356, 678	388, 786	229, 470	6.2, 10.5
Oral*	2.8	30	31	866	980	430	9.8
	1.3, 4.3	25, 36	26, 35	648, 1083	720, 1240	398, 562	7.2,12.3
Rectal	1.3	32	32	793	901	502	11.2
(IV)	0.83, 1.9	20, 43	27, 37	480, 1105	520, 1281	358, 648	8.0, 14.4
Rectal	1.4	26	35	737	861	552	11.2
(oral)	0.83, 2.0	20, 31	28, 41	565, 909	638, 1083	380, 724	8.0, 14.4

**The estimated median difference between rectal (mean of rectal (IV) and rectal (oral))and oral T_{max} was 1.75 h (93% CI 0.5–4.25), P = 0.0625 (Mann -Whitney).*

Table 2
Rectal, oral and relative rectal/oral bioavailabilities* (mean, 95% CI, and 90%CI #) for methadone after IV (5 mg methadone-HCl) and oral and rectal (10 mg methadone HCl) in 7 human subjects

Rectal	Oral	Rectal (IV)/oral	Rectal (oral)/oral
0.76 (0.69, 0.82)	0.86 (0.72,0.99)	0.90 (0.76–1.04)	0.88 (0.83–0.93)
(0.70, 0.81)#	(0.75,0.97)#	(0.78–1.01)#	(0.84–0.92)#

**The mean (95%) CI for the difference between oral and rectal bioavailabilities was –0.1 (–0.24–0.04.) #, 90%CI.*

Table 3
Pharmacokinetic variables (mean, 95% CI) for EDDP after IV (5 mg) and oral and rectal (10 mg) administration of methadone in 7 human subjects

Route	Tmax (h)	C_{max} (ng/ml)	T1/2 (h)	AUClast (h*ng/ml)	Ratio AUClast (EDDP/Methadone)
IV	5.6	2.0	46	86	0.18
	–0.2, 13.5	1.5, 2.5	22, 69	51, 121	0.10, 0.27
Oral	2.1	6.7	29	203	0.25
	1.3, 2.9	4.9, 8.6	23, 35	139, 268	0.15, 0.36
Rectal (IV)	2.0	4.4	38	129	0.18
	1.1, 2.9	2.4, 6.4	24, 51	71, 187	0.08, 0.28
Rectal	1.5	5.2	33	155	0.23
(Oral)	1.2, 1.8	3.6, 6 .7	23, 42	104, 206	0.12, 0.35

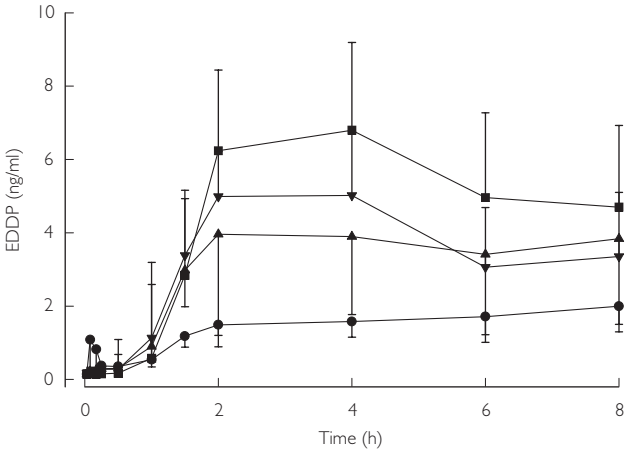

Figure 3
The time course (0–8 h) of plasma concentrations of the methadone metabolite EDDP (mean (s.d.)) in seven healthy subjects after IV-rectal, and oral-rectal administration of methadone-HCl (5 mg IV, 10 mg rectally (deuterated methadone) and orally). Note the linear scale on the ordinate. IV (●); rectal (IV) (▲); oral (■); rectal (oral) (▼)

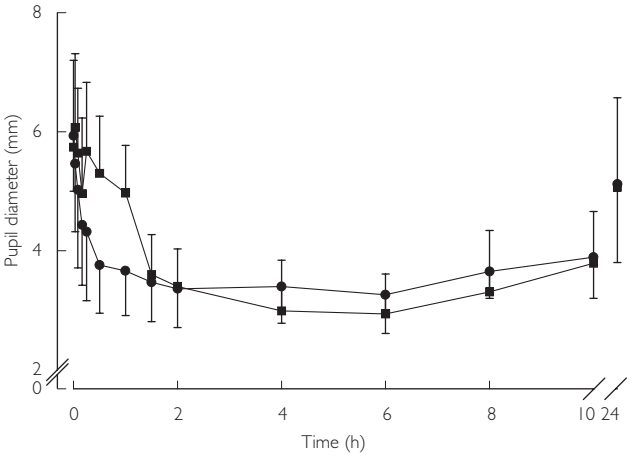

Figure 4
The time course (0–24 h) of resting pupil diameter (mean (s.d.)) in seven healthy subjects after IV-rectal, and oral-rectal administration of methadone-HCl (5 mg IV, 10 mg rectally and orally)[pp] For the IV-rectal administration dark-adapted pupil diameters were statistically significant different (two-way, repeated measures ANOVA, $P < 0.001$) from prestudy diameter in the period 0.167–10 h. The same was true for the oral-rectal administration between 2 and 10 h. Oral-rectal (■); IV-rectal (●)

There was considerable inter-individual variation in pupil diameters, but no differences in the areas under the curves were observed for the different routes. The oral-rectal combination had a slower onset of action than the IV-rectal route which, consistent with the lower initial plasma concentrations. However, the same maximum effect as the IV-rectal combination was achieved at about 2 h. For the IV-rectal administration, dark-adapted pupil diameters were statistically different from the prestudy values over the period 0.2–10 h. The same was true for the oral-rectal administration between 2 and 10 h.

Nine subjects were enrolled in the study and received methadone at least once. One subject withdrew after the oral-rectal phase. No severe adverse effects occurred. The one female subject was significantly sedated and nauseated (with emesis) during the oral-rectal phase, and was treated with droperidol. The episode resolved before discharge from the study unit. This subject experienced no problems during the IV-rectal phase.

Discussion

The major findings of this study are that rectal absorption of methadone is rapid and the bioavailability of the drug given by this route is 76%, only slightly lower than

reported by us for oral and nasal administration [18]. No evidence of presystemic metabolism was found. Pupillometry confirmed that the duration of action of a single dose of methadone given by this route was at least 10 h. There was no loss of drug after rectal dosing, indicating that bioavailability was accurately determined, and that the formulation and route were well tolerated.

We employed a formulation described by Moolenaar et al. [23, 24], due to its favourable absorption pattern. Our findings confirm their claim that the difference in the oral and rectal bioavailability of methadone is small. It is a common view that rectal uptake is highly variable and erratic [21]. However, in our study rectal and oral variabilities with pharmacokinetics of methadone were low and essentially the same. These and earlier findings suggest that methadone can be rotated safely between the various routes of administration without substantial change in dose. However, the results should be confirmed in patients.

Methadone is usually given as a racemic mixture. Studies in chronic pain and opioid replacement patients have shown different pharmacokinetic characteristics of the enantiomers. However, the bioavailabilities and AUCs of the latter did not differ in any of these studies [28, 29]. Thus, our data on racemic bioavailability probably reflects those of the respective enantiomers.

Absorption of rectal methadone was significantly more rapid than oral methadone, for which there may be several reasons. First, rectal uptake takes place at the site of administration, whereas oral absorption requires gastric emptying into the intestine. Second, the absorption of methadone across mucosal membranes is rapid, as demonstrated previously for nasal administration [18]. Third, the rectal mucosa provides a larger surface area for absorption compared to the nasal route [21, 30]. Fourth, we used a volume that the rectum can easily accommodate [21], Fifth, we used a solution formulated with the absorption enhancer glycofurol [23]. Sixth, rectal contents are usually alkaline, favouring uptake of alkaline drugs such as methadone [21]. Last, there is minimal, presystemic elimination of rectal methadone.

There are several reasons for employing rectal administration of opioids in palliative care [21, 22, 31]. Alternatives to oral dosing, other than parenteral administration, may be required in patients with altered mental status, neuromuscular dysfunction, nausea, vomiting, dysphagia, bowel obstruction or malabsorption. Rectal dosing may also be an alternative to repeated parenteral injections in patients with immunological deficiencies and bleeding disorders, or when infusions systems may not be available or in home health care settings [19, 20, 20]. Rectal administration is efficacious, technically easy for patients and caregivers to administer, and economical. It is considered safe, and adverse effects are usually reversible [21], but some patients may dislike the rectal route due to concerns of modesty [32].

There is an increasing interest in the use of methadone in palliative care, particularly in the context of opioid rotation [9, 10, 26]. Methadone has favourable characteristics, both with respect to pharmacodynamics (faster onset of effect, long duration of action, incomplete cross tolerance towards morphine, and possible effects on NMDA receptors) and pharmacokinetics (faster absorption, long half-life, no active or toxic metabolites and little dependence on metabolite renal excretion) compared to morphine [9]. Methadone is therefore often preferred when morphine fails, either due to lack of adequate analgesia or intolerable side-effects. For patients converted to methadone or on methadone for other reasons, intravenous administration has been the only alternative to oral medication, since subcutaneous infusion is unfavourable due to local irritation, and nasal methadone awaits the development of formulations that also do not cause local irritation [17, 18]. Thus patients not able to take methadone orally may require prolonged hospitalization or more intensive home health care to enable intravenous dosing. Thus, rectal methadone would be a less invasive and less expensive, and an effective alternative to intravenous methadone [26].

In conclusion, we have shown that methadone has good rectal bioavailability in healthy subjects, and only slightly lower than that of the oral route. Furthermore, the absorption of rectal methadone was significantly more rapid than that of oral drug. Pupillometry confirmed the long duration of action of a single dose of rectal methadone.

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