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Pharmacokinetic Modeling of M6G Formation after Oral Administration of Morphine in Healthy Volunteers

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Background: **Morphine is metabolized to two major metabolites, morphine-3-glucuronide and morphine-6-glucuronide (M6G). Under the conditions of long-term oral morphine administration, the accumulation of M6G may contribute to the analgesic effects, but it may also cause respiratory depression.**

Methods: **Five healthy male volunteers (ages 25–34 yr) received 90 mg MST (morphine sulfate $5H_2O$ sustained-released tablet, equivalent to 67.8 mg oral morphine). Multiple plasma and urine samples were taken for as long as 14 and 36 h, respectively. Individual pharmacokinetics after intravenous administration of morphine and M6G were available from a previous investigation. A new model that considers the M6G-plasma profile as a sum of the input from the first-pass metabolism of morphine and the input from systemically available morphine was applied to the plasma concentration *versus* time curves of M6G. The concentrations of M6G at the effect site after long-term morphine administration were simulated.**

Results: **The fraction of morphine absorbed from the gut was 82 ± 14%. Of this, 42 ± 8% passed through the liver, resulting in an oral bioavailability of morphine of 34 ± 9%. Of the total amount of M6G, 71 ± 7% was formed during the first-pass metabolism, and 29 ± 7% was formed by metabolism of systemic morphine. After 36 h, the amounts of M6G and morphine excreted in the urine were 92 ± 17% and 9 ± 3%, respectively. Simulation of effect-site concentrations of M6G indicated that after multiple oral dosing of morphine in patients with normal liver and renal function, M6G might reach concentrations two times greater than that of morphine.**

Conclusions: **M6G may contribute to the analgesic and side effects seen with long-term morphine treatment. The current model of morphine and M6G pharmacokinetics after oral administration of morphine may serve as a pharmacokinetic basis for experiments evaluating the analgesic contribution of M6G with long-term oral dosing of morphine. (Key words: First-pass metabolism; morphine-6-glucuronide.)**

THE contribution of morphine-6-β-glucuronide (M6G) to the analgesic and to the unwanted side effects produced by morphine is controversial. M6G is a potent opioid,[1] and there is strong evidence that it contributes to the clinical effects[2] of morphine in humans.[3] After intrathecal administration in humans, it produced analgesic effects with a potency approximately 2.6 times greater than that of morphine.[4] Although previous clinical investigations suggested analgesic effects after systemic administration,[5,6] we recently showed, in a study with placebo and positive (morphine) control, that M6G had neither clinical nor analgesic effects when administered as an intravenous bolus plus a 4-h intravenous infusion.[7] Retrospectively, our results were not surprising when recent reports of a slow distribution of M6G into the central nervous system are considered.[8] After short-term administration, M6G may not reach central nervous system concentrations great enough to produce central-nervous opioid effects. However, under conditions of long-term administration, central nervous system levels of M6G may become more relevant. This view is supported by the observation that after acute dosing, oral morphine is only 1:6 to 1:8 as potent as parenteral morphine, whereas with repeated oral administration this relation increases to 1:2 to 1:3.[9] The aim of the current investigation was to develop a pharmacokinetic model of M6G formation and disposition after oral administration of morphine. This model may serve as the

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basis for pharmacodynamic experiments; in addition, it can be used to interpret the clinical effects of morphine in different patient populations.

Methods

Study Design and Reference Compounds

The study was conducted according to the Declaration of Helsinki on Biomedical Research Involving Human Subjects (Somerset West amendment). The University of Erlangen-Nürnberg Ethics Review Committee approved the protocol. Each participant gave written informed consent. Five healthy male volunteers (ages 25 to 34 yr; mean body weight, 75.2 ± 6.9 kg) received 90 mg morphine orally (sustained-release tablets MST 30 and 60 [Mundipharma GmbH, Limburg/Lahn, Germany] containing 30 or 60 mg morphine sulfate $5H_2O$, equivalent to 22.6 mg and 45.2 mg morphine, respectively) together with 100 ml water. Only those persons were included who had already participated in a previous investigation of intravenous pharmacokinetics and pharmacodynamics of morphine and M6G; therefore, individual pharmacokinetic data after intravenous administration of morphine and preformed M6G were available for all participants.[7] The participants fasted overnight before drug administration. Eight hours after oral administration of morphine, the participants received a standard meal. At the beginning and at the end of the study, general clinical examination and routine clinical laboratory tests were performed, with special attention given to hepatic and renal function.

Plasma and Urine Concentrations of Morphine and M6G

Blood samples (4 ml) were collected in potassium EDTA tubes before drug administration (baseline) and then every 30 min for 8 h, and then at 9, 10, 11, 12, 13, 14, 24, and 36 h after drug administration. Plasma samples were obtained within 15 min of blood collection (centrifugation, 10 min at 3,500*g*) and immediately stored together with quality control samples at −25°C until analysis. Urine was sampled fractionally over 36 h. After the urine volume was measured, 20-ml aliquots were stored at −25°C until analysis.

Morphine, M6G, and morphine-3-glucuronide (M3G) concentrations were assayed using a high-performance liquid chromatography method previously described.[10,11] The reliable limit of quantification was 10 ng/ml for all analytes (35.05 nM and 22.45 nM for morphine and M6G, respectively). The coefficient of variation over the calibration range of 10 to 500 ng/ml was less than 10%.

Clinical Effects

Participants were supervised continuously during the study. Specifically, blood oxygen saturation and heart rate were monitored continuously using a pulse oximeter (Nellcor N-200 pulse oximeter, Nellcor, Haywood, CA). The presence or absence of physical and psychologic effects was recorded. In addition, in accordance with previous studies in our laboratory, the participants rated the intensity of "tiredness," "sickness," "vertigo," and "drowsiness" at the time of each blood sampling using visual analog scales (length, 100 mm), ranging from 0 ("no such symptom") to 100 ("symptom experienced at maximum").

Data Analysis

Plasma Concentration-over-Time Profiles of Morphine and M6G. The kinetics of metabolite (M6G) formation after oral administration of morphine were analyzed using data from the current oral administration of the parent compound (morphine) and the individual pharmacokinetic parameters obtained from previously published intravenous data.[12] The pharmacokinetic model is presented in detail in appendix 1 of this article. This section focuses on the principal ideas rather than the exact mathematical equations.

The pharmacokinetic model was developed to provide a flexible tool to predict plasma concentrations of M6G in various clinical situations and dosing regimens of morphine. The main principle of the modeling was as follows: Imagine that we give morphine in different ways, such as an intravenous bolus, an intravenous infusion, oral administration of fast-release tablets, or oral administration of slow-release tablets. Then the plasma concentration-over-time curves are determined by how the drug enters the systemic circulation, the input function I(t) (*i.e.*, intravenous infusion, absorption, and so on), and by how the body handles the drug, the disposition function $f_D(t)$, whereby the latter is given by the concentration–time curve after intravenous bolus injection, $f_D(t) = C_{iv}(t)/D_{iv}$ (fig. 1). Mathematically, this is a convolution of functions, which is noted with an asterisk:

$$C(t) = I(t) * f_D(t) \quad (1)$$

To describe the plasma concentration-over-time curves

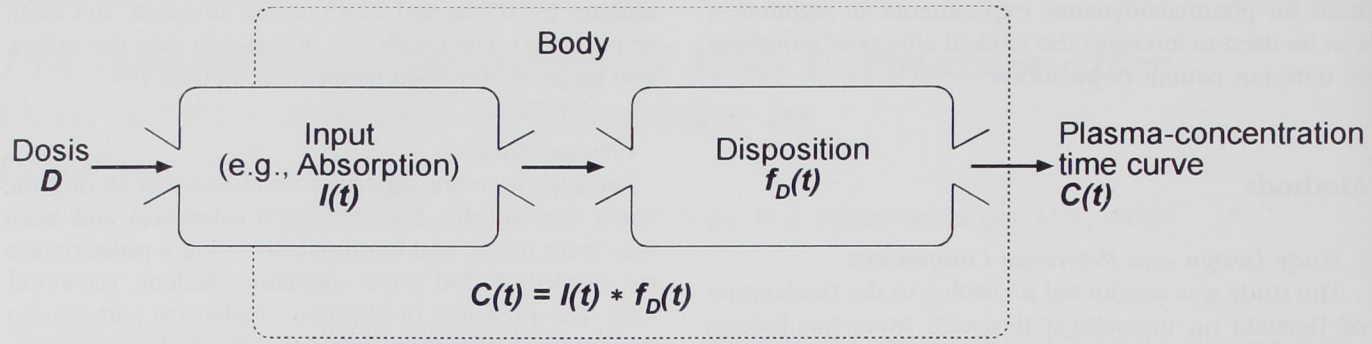

Fig. 1. The plasma concentration-over-time profile of a drug presented as a machine diagram. The input (*e.g.*, an absorption), an intravenous infusion, and the disposition function together determine the form of the plasma concentration-over-time profile of a drug. The plasma concentration-over-time curve C(t) thus is the result of a combination ("convolution") of an input function I(t) with the disposition function $f_D(t)$.

of M6G after oral administration of morphine, we need to know the input functions I(t) and disposition function $f_D(t)$ of M6G. Because with intravenous data the input function usually is known, the disposition function can be obtained from intravenous data using standard pharmacokinetic analysis tools (see also Glass *et al.*[13]). The disposition function is usually described as a sum of exponential decays $f_D(t) = \sum_{i=1}^{n} \alpha_i e^{-\lambda_i t}$ where n is the number of exponentials (*i.e.*, compartments; in the present case n = 2, table 1). Each exponential term is associated with a coefficient α and an exponent λ, which can be used to calculate the elimination rate constant (half-life = ln(2)/elimination rate constant), and the transfer constants between compartments (for details, see Wagner[14] and appendix 2 of this article).

After having determined the disposition functions $f_D(t)$ of morphine and M6G from the intravenous data (table 1),[12] the input function, I(t), of M6G after oral morphine was to be found. Because M6G is a metabolite of morphine, the first step is to model the absorption of morphine. We selected an inverse Gaussian density distribution to describe the absorption of morphine (*i.e.*, its input I(t)). The details of this function are described elsewhere[15] and in appendix 1 of this article (equation 16). Briefly, this function provides the right bell shape and asymptotic behavior for the time course of absorption. In addition, this function permits direct estimation of two parameters of interest: MAT, the mean absorption time, and its normalized variance $CV^2_{A,p}$, the shape factor of the absorption profile. The relation between morphine input, morphine plasma concentration, and the disposition of morphine can be expressed as a convolution of the same general form as equation 1:

$$C_{p,or}(t) = D_{or}F_p f_A(t) * f_{D,p}(t) \qquad (2)$$

where

$C_{p,or}(t)$ = plasma morphine concentrations over time

Table 1. Pharmacokinetic Parameters after Intravenous Administration of Either Morphine or M6G[12]

	Subject						
Parameter	1	2	3	4	5	Mean	SD
$\alpha_{1,p}[L^{-1}]$	0.018	0.074	0.085	0.009	0.105	0.058	0.042
$\alpha_{2,p}[L^{-1}]$	0.002	0.001	0.001	0.002	0.001	0.001	0.001
$\lambda_{1,p}[h^{-1}]$	9.668	25.385	17.033	6.543	25.077	16.741	8.636
$\lambda_{2,p}[h^{-1}]$	0.401	0.334	0.272	0.303	0.270	0.316	0.054
$\alpha_{1,m}[L^{-1}]$	0.109	0.079	0.114	0.049	0.061	0.082	0.029
$\alpha_{2,m}[L^{-1}]$	0.046	0.031	0.045	0.024	0.048	0.039	0.011
$\lambda_{1,m}[h^{-1}]$	6.664	3.466	5.168	2.204	3.842	4.269	1.706
$\lambda_{2,m}[h^{-1}]$	0.640	0.482	0.450	0.431	0.546	0.510	0.085
$CL_p[L^*h^{-1}]$	164.870	147.490	97.560	140.150	117.060	133.426	26.391
F_{mp}	0.078	0.097	0.080	0.128	0.071	0.091	0.023
$\lambda_{M,p}[h^{-1}]$	5.384	1.606	1.689	8.964	2.244	3.977	3.190

α_i and λ_i = parameters of the disposition functions of either morphine or M6G; CL_p = total body clearance of morphine; F_{mp} = fraction of morphine metabolized to M6G; λ_M = time constant of the metabolic transition from morphine to M6G.

D_{or} = oral dose of morphine
F_p = oral bioavailability of morphine
$f_A(t)$ = absorption function of morphine (the inverse Gaussian distribution function)
$f_{D,p}(t)$ = disposition function of morphine (known from previous intravenous studies[12]).

Only a fraction F_{mp} of the total clearance of morphine CL_p accounts for the formation of M6G, the rest being metabolized to other metabolites or excreted unchanged. Furthermore, the formation of the metabolite and its appearance in the plasma takes time, which can be seen as a delay between the plasma concentration-over-time curve of morphine and M6G. This delay was accounted for by introducing the metabolic transit time function of morphine to M6G, $f_{M,pm}(t)$ (for details, see equation 24 of appendix 1). Thus, after intravenous administration, the M6G input consists of the plasma concentration-over-time profile of morphine, the metabolic transit time, and the fraction of morphine that is metabolized to M6G. The relation between M6G input, M6G plasma concentration, and its disposition again can be expressed as a convolution of the same general form as equation 1:

$$C_{m,sys}(t) = F_{mp}CL_pC_{p,iv}(t) * f_{M,pm}(t) * f_{D,m}(t) \quad (3)$$

where

$C_{m,sys}(t)$ = the plasma concentrations over time of the M6G formed from systemic morphine; that is, from the morphine in the circulation
F_{mp} = the fraction of the total clearance of morphine that accounts for the formation of M6G (known from previous intravenous studies[12])
CL_p = the total clearance of morphine (known from previous intravenous studies[12])
$f_{M,pm}(t)$ = the metabolic transit time function, with time constant λ_M (known from intravenous studies[12])
$f_{D,p}(t)$ = the disposition function of M6G (known from previous intravenous studies[12]).

When morphine is administered parentally, equation 3 suffices as the description of the plasma concentration-over-time profile of M6G (equation 23 of appendix 1). However, when morphine is administered orally, the M6G formed during the first-pass liver metabolism of morphine adds to the M6G formed from the systemically available morphine. Only absorbed morphine is subjected to first-pass metabolism. The bioavailability, F, is the product of the fraction absorbed F_A and the fraction that passes unmetabolized through the liver $F_{H,p}$.[16] Thus,

$$F = F_A \cdot F_{H,p} \quad (4)$$

The fraction extracted by the liver, $E_{H,p}$, is 1 minus the fraction of the drug that passes unmetabolized through the liver:

$$E_{H,p} = 1 - F_{H,p} \quad (5)$$

The relation between M6G input from the first-pass metabolism of morphine, the M6G plasma concentration, and the disposition of M6G again can be expressed as a convolution of the same general form as equation 1:

$$C_{m,fp}(t) = D_{or}F_A(1 - F_{H,p})h_{mp}f_A(t) * f_{M,pm}(t) * f_{D,m}(t) \quad (6)$$

where

$C_{m,fp}(t)$ = the plasma concentrations over time of M6G from first-pass metabolism
D_{or} = the oral dose of morphine
F_A = the fraction absorbed of morphine
$F_{H,p}$ = the fraction of morphine that passes unmetabolized through the liver
h_{mp} = the fraction of hepatic morphine clearance $CL_{H,p}$ that forms M6G
$f_A(t)$ = the absorption function of morphine (the inverse Gaussian distribution function)
$f_{M,pm}(t)$ = the metabolic transit time function, with time constant λ_M (known from intravenous studies[12])
$f_{D,m}(t)$ = the disposition function of M6G (known from previous intravenous studies[12]).

Using the relation $h_{mp}CL_{H,p} = h_{mp}(1 - f_{eh})CL_p = F_{mp}CL_p$, where f_{eh} denotes the fraction of morphine eliminated extrahepatically, the unknown h_{mp} from equation 6 can be substituted by $F_{mp}/(1-f_{eh})$, and equation 6 can be rewritten as

$$C_{m,fp}(t) = D_{or}F_A(1 - F_{H,p})\frac{F_{mp}}{(1 - f_{eh})}f_A(t) * f_{M,pm}(t) * f_{D,m}(t) \quad (7)$$

The fraction of extrahepatic morphine elimination, f_{eh}, is the sum of the fraction of extrahepatically metabolized morphine and the fraction of morphine excreted unchanged in urine. The fraction of extrahepatically metabolized morphine was taken from the literature (38%).[17] The fraction of morphine excreted unchanged in urine, $F_{p,excr}$, was calculated from the amount of

morphine excreted in urine, $A_{p,e}$, and the amount of morphine that had entered the systemic circulation, given by $F_p \cdot D_{or}$. Together, the measured plasma concentration over time of M6G after oral administration of morphine could be obtained easily by adding $C_{m,sys}(t)$ to $C_{m,fp}(t)$, as given in equations 3 and 7:

$$C_m(t) = C_{m,sys}(t) + C_{m,fp}(t) \quad (8)$$

where

$C_m(t)$ = the plasma concentrations over time of total M6G
$C_{m,sys}(t)$ = the plasma concentrations over time of the M6G formed from systemic morphine (*i.e.*, from the morphine in the circulation)
$C_{m,fp}(t)$ = the plasma concentrations over time of M6G from first-pass metabolism.

The pharmacokinetic analysis was performed using the Scientist 2.01 computer software (MicroMath Inc., Salt Lake City, UT). Analysis of oral data began with fitting of the $C_{p,or}(t)$ curves observed after oral administration of morphine (p) (equation 21 of appendix 1) with fixed disposition parameters α_p and λ_p of morphine (from intravenous data[12]; table 1). After the morphine absorption parameters MAT_p, $CV^2_{A,p}$, and F_p were determined, they were used together with the disposition parameters of M6G (α_m and λ_m; table 1) and with the values of λ_M and F_{mp} to fit the plasma concentration-over-time profile of M6G after oral administration of morphine (equation 27 of appendix 1).

Urine Concentrations of Morphine and M6G. From the urine volumes and the urine concentrations of morphine and M6G, their cumulative amounts excreted in urine, $A_{e,p}$ and $A_{e,m}$, respectively, were calculated (equations 30 through 32 of appendix 1). The fraction of morphine eliminated unchanged in urine was obtained as the quotient of the amount of morphine excreted in urine and the amount of morphine that had entered the system:

$$F_{p,excr} = \frac{A_{e,p}}{F_p D_{or}} \quad (9)$$

where

$A_{e,p}$ = the amount of morphine excreted unchanged in urine
F_p = the oral bioavailability of morphine
D_{or} = the oral dose of morphine.

The fraction of M6G excreted in urine was calculated analogously; that is, from the amount of M6G excreted in urine divided by the total amount of M6G formed from morphine. The latter was given by the sum of the M6G formed from systemically available morphine and the amount of M6G formed during the first-pass liver metabolism of morphine (equations 30 and 31 of appendix 1, respectively).

Simulation of Plasma and Effect-Compartment Concentration–Time Profiles after Multiple Oral Dosing of Morphine. Considering the reported increase in the relative potency of oral morphine compared with parenteral morphine after multiple dosing,[9] we used the pharmacokinetic model to simulate the plasma concentration-over-time profiles of morphine and M6G after multiple oral dosing of morphine. Because we were interested in the effects rather than the plasma concentrations, we also simulated the concentrations at effect site. The concentration-over-time profile of a drug at effect site $C_{eff}(t)$ can be described using the principle of equation 1

$$C_{eff}(t) = C(t) * f_{D,eff}(t) \quad (10)$$

as a convolution of the input function C(t) (plasma concentration-over-time profile) of the drug and the transfer function $f_{D,eff}(t)$, which accounts for the time delay between $C_{eff}(t)$ and C(t). As in the case of the metabolic transit time, we assume a simple exponential density

$$f_{D,eff}(t) = k_{eO} e^{-k_{eO} t} \quad (11)$$

where k_{eO} is the rate constant for the transfer process.[18,19] Thus, by substituting equation 11 into equation 10, concentration-over-time profiles at effect site $C_{eff}(t)$ after oral drug administration were obtained by

$$C_{eff}(t) = k_{eO} e^{-k_{eO} t} * C_{p,or}(t) \quad (12)$$

where

$C_{eff}(t)$ = the drug concentration-over-time profiles at effect site
K_{eO} = the rate constant for the transfer from plasma to the site of drug effect
$C_{p,or}$ = the morphine plasma concentrations over time.

The effects site concentrations of M6G were calculated analogously. The k_{eO} values were taken from the literature[20] ($t_{1/2keO}$ = 16.7 min for morphine, and 20.3 h for M6G; $k_{eO} = \ln(2)/t_{1/2,keO}$). The simulation was performed

with N = 10 doses of 90 mg MST at an interval of τ = 12 h mimicking the clinical situation.

Because high M6G plasma concentrations have been related to side effects after morphine in patients with renal failure,[21] we also simulated M6G plasma and effect-compartment concentrations using a reduced plasma clearance of M6G of 10.6 ml/min as described for renal insufficiency[22] (compared with a clearance found in healthy persons of 162 ml/min[12] or 187 ml/min[23]). Reduced clearance translates into an altered disposition function $f_D(t)$. To obtain the altered disposition parameters (λ_{1b}; λ_{2b}, α_{1b}, α_{2b}), the disposition function was reparameterized as a two-compartment model in terms of volumes, clearances, and rate constants rather than α and λ, using standard equations (for details, see Wagner[14] and appendix 2 of this article). Then the compartmental parameters were replaced by values available in the literature from persons with renal failure,[22] and the disposition function was reparameterized back to α and λ, again using standard equations (for details, see Wagner[14] and appendix 2 of this article). The new values of λ_{1b} = 3.554 h^{-1}, λ_{2b} = 0.037 h^{-1}, α_{1b} = 0.063 l^{-1} (for comparison with the original values from healthy persons, see table 1) were used to simulate plasma concentrations of M6G in renal failure. The simulated plasma concentration-over-time profiles of morphine and M6G were used to predict the concentration–time profile at the effect site, using equation 12 (equation 33 in appendix 1).

Results

All participants completed the study. Side effects were generally mild to moderate and did not require medical assistance. During the first 8 h after dosing, the ratings of tiredness and drowsiness were elevated compared with baseline values; sickness and vertigo were mostly rated as "zero" (detailed data not given).

Fourteen hours after drug intake, plasma concentrations of both morphine and M6G were less than the lower limit of reliable quantification, and therefore sampling points of 24 and 36 h were discarded. M3G was the main metabolite of morphine that exceeded the concentrations of M6G by five to six times.

Plasma Concentration versus *Time Profiles of Morphine and M6G*

The plasma concentration–time data of morphine and M6G were well described by the pharmacokinetic model. Figure 2 shows individual plasma concentrations over time. The estimated bioavailability of morphine was 34.5 ± 8.7%, and the mean absorption time was 3.3 ± 0.9 h for this commercially available morphine formulation. The fact that in the case of the metabolite model a reasonable fit of the M6G data could be achieved using only one free parameter in the equation (*i.e.*, $F_{H,p}$) indicates the validity of the assumptions made. The total amount A_m of M6G formed from morphine was 25,532.7 ± 4,091 nmol, which is equivalent to 13 ± 3% of the amount of morphine absorbed. Of the total amount of M6G, 71 ± 7% were formed during the first-pass metabolism of morphine, and 29 ± 7% from systemically available morphine. The modeling of the metabolite kinetics of M6G also revealed a fraction of morphine absorbed F_A of 82.3 ± 13.7%, and a hepatosplanchnic availability of morphine ($F_{H,p}$) of 42 ± 8%. Thus, a first-pass liver extraction ratio of 58 ± 8% ($E_{H,p} = 1 - F_{H,p}$) was estimated. Table 2 shows individual and mean pharmacokinetic parameters.

Renal Excretion of Morphine and M6G

Most of the M6G was excreted in urine (92 ± 17%). In contrast, only 9 ± 3% of morphine was found as an unchanged substance in urine. Figure 3 shows the cumulative renal excretion of morphine and M6G.

Simulation of Plasma and Effect-Compartment Concentration–Time Profiles after Multiple Oral Dosing of Morphine

Figure 4 shows a prediction of plasma and effect-compartment concentrations of morphine and M6G after 10 doses of 90 mg MST at a 12-h interval, based on k_{eO} values published by Kramer *et al.*[20] According to this simulation, neither morphine nor M6G is expected to accumulate in the plasma of healthy persons (*i.e.*, in persons with normal renal function with this dosing regimen). In contrast, although there is no accumulation of morphine in the effect compartment under multiple dosing, the M6G concentration at the effect site increases progressively, reaching a steady state after approximately 80 to 100 h. Then concentrations of M6G were approximately two times higher than those of morphine. The simulation of M6G plasma and effect-compartment concentrations in patients with renal failure (fig. 4) shows that M6G is expected to accumulate in the plasma of those patients and, as a consequence, it may reach high and sustained concentrations at the effect site.

Discussion

This study characterized the pharmacokinetics of M6G formed from orally administered morphine in healthy

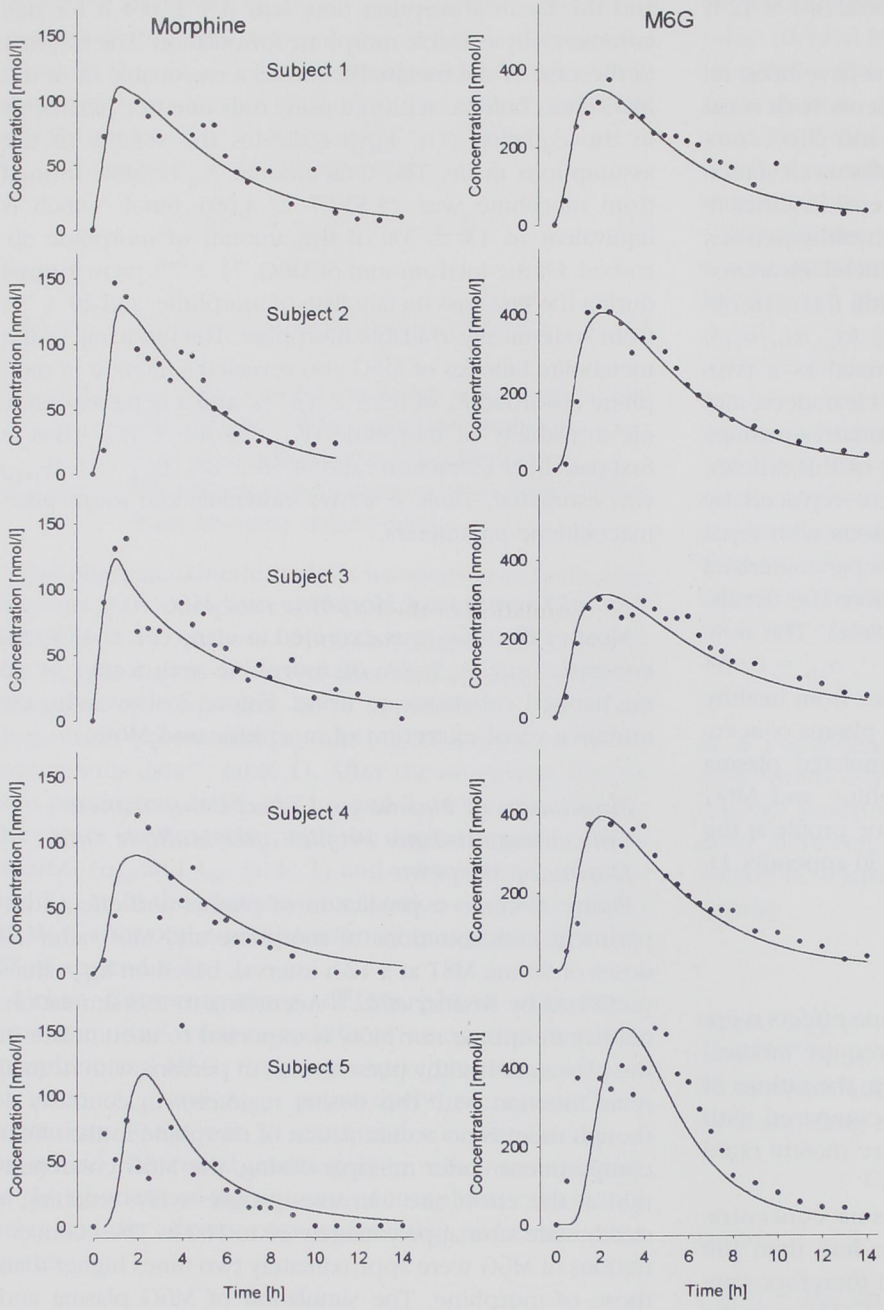

Fig. 2. Individual data (*dots*) and calculated plasma concentration over time profiles (*lines*) of morphine (*left*) and M6G (*right*) after oral administration of 90 mg morphine (MST) in five healthy persons.

volunteers. The pharmacokinetic model analysis was based on (1) the currently obtained data after oral administration of the parent compound (morphine), and (2) the individual data obtained after the intravenous administration of the parent compound and the preformed metabolite (M6G).[12] Thus, the current approach is an extension of previous results on M6G kinetics after intravenous administration of morphine. The effect of first-pass formation of M6G from morphine also has been described. The results can be regarded as an experimental validation of the underlying noncompartmental model of metabolite kinetics.[24] As shown earlier on the basis of the areas under the curves,[16] the assessment of metabolite kinetics enables us to distinguish between the fraction absorbed (F_A) and the first-pass extraction ($1 - F_{H,p}$) of the drug as determinants of its bioavailability. Thus, in addition to specific information on the time profile of the generated metabolite, useful information

Table 2. Pharmacokinetic Parameters after Oral Administration of Morphine[12]

Parameter	Subject 1	2	3	4	5	Mean	SD
MAT_p[h]	3.793 [2.138–5.446]	2.978 [1.765–4.281]	4.565 [1.994–7.136]	2.316 [1.564–3.069]	2.827 [2.532–3.122]	3.296	0.886
$CV^2_{A,p}$	1.680 [0.589–2.771]	0.962 [0.302–1.621]	1.971 [0.413–3.53]	0.666 [0.259–1.074]	0.221 [0.129–0.313]	1.100	0.720
F_p	0.467 [0.402–0.531]	0.395 [0.318–0.472]	0.290 [0.249–0.329]	0.323 [0.278–0.369]	0.248 [0.224–0.273]	0.345	0.087
$F_{A,p}$	0.980	0.891	0.671	0.687	0.887	0.823	0.137
$F_{H,p}$	0.476 [0.451–0.502]	0.443 [0.426–0.46]	0.431 [0.409–0.453]	0.471 [0.445–0.496]	0.280 [0.237–0.322]	0.420	0.081
$F_{excr,p}$	0.072	0.075	0.141	0.084	0.076	0.090	0.029

MAT = mean absorption time of morphine; CV^2_A = shape parameter of the inverse Gaussian density that was used as input function of morphine; F_p = bioavailability of morphine; F_A = fraction of morphine absorbed; $F_{H,p}$ = hepatic availability of morphine; $F_{excr,p}$ = fraction of morphine excreted unchanged in urine; 95% CI = 95% confidence interval on individual estimates given in brackets, where applicable.

on the pharmacokinetics of the precursor drug is obtained; this clearly exceeds information available from an analysis of the precursor kinetics alone. For drugs such as morphine in which a potential active metabolite is formed, this integrated mathematical model may enhance a differentiated approach to the pharmacokinetics and pharmacodynamics of the drug and its metabolite in specific clinical situations (*e.g.*, renal failure).

The pharmacokinetic model applied here provides a general approach to the metabolite kinetics of M6G. The only parameters specific to the administered formulation (*i.e.*, to MST) are the mean absorption time MAT (3.3 ± 0.9 h) and the normalized variance of its distribution CV^2_A (1.1 ± 0.7). The estimated absolute bioavailability of 34 ± 8% corresponds with that of 29 ± 7% or 32 ± 7% reported from other commercial oral morphine formulations.[25,26] In this respect, the results show the utility of the inverse Gaussian density (equation 16) as a flexible input function describing the absorption of MST sustained-release tablets. It is noteworthy that the observed relative dispersion CV^2_A of about 1 is characteristic of a nearly well-mixed system[27] and similar to the value estimated previously for a controlled-release formulation of another drug.[15] Furthermore, the liver extraction of 58% estimated in our five participants corresponds with that of 52% measured directly in eight healthy persons.[28]

The model that describes the kinetics of a metabolite formed from a parent compound by first-pass and systemic metabolism was developed on the basis of morphine and M6G; however, its application is not limited to these specific substances. It may even serve as the basis for appropriate experiments involving other substances with comparable pharmacokinetics, provided that intravenous data for both the parent compound and the preformed metabolite can be obtained.

The simulation of the time profiles of both plasma and effect-compartment concentrations indicated that in healthy volunteers neither morphine nor M6G are likely to accumulate in plasma after multiple administrations of morphine at a common dosing regimen. In contrast, the concentration of M6G but not that of morphine increases slowly at the effect site, reaching its steady state after four or five half-lives $t_{1/2,keO}$ of the transfer process ($t_{1/2,keO} = 0.693/k_{eO}$). This corresponds with the observation of Hanks *et al.*[9] that after acute dosing, the relative analgesic potency of oral to parenteral morphine is 1:8, whereas after long-term dosing this relation increases to 1:2. Thus, a fourfold increase in potency is observed after single compared with multiple dosing of oral morphine. Hanks *et al.*[9] explained their observation by the contribution of M6G to the analgesic effects. Our simulation shows that steady state concentrations of M6G at the effect site are approximately two times higher than that of morphine when renal function is not compromised. Thus, the twofold higher M6G levels produce a fourfold increase in potency. This gives a relative potency of M6G to morphine of 2:1, which is not far from the value of 2.6:1 that Hanna *et al.*[4] obtained after intrathecal administration of morphine and M6G in humans. According to Aasmundstad *et al.*,[29] the relative potency of M6G to morphine might be species specific. Thus, data obtained in animals showing a far higher relative potency of morphine (up to 650:1[1]) may not reflect the human situation.

Because M6G is excreted almost completely by the kidneys, it is expected to accumulate in plasma and the

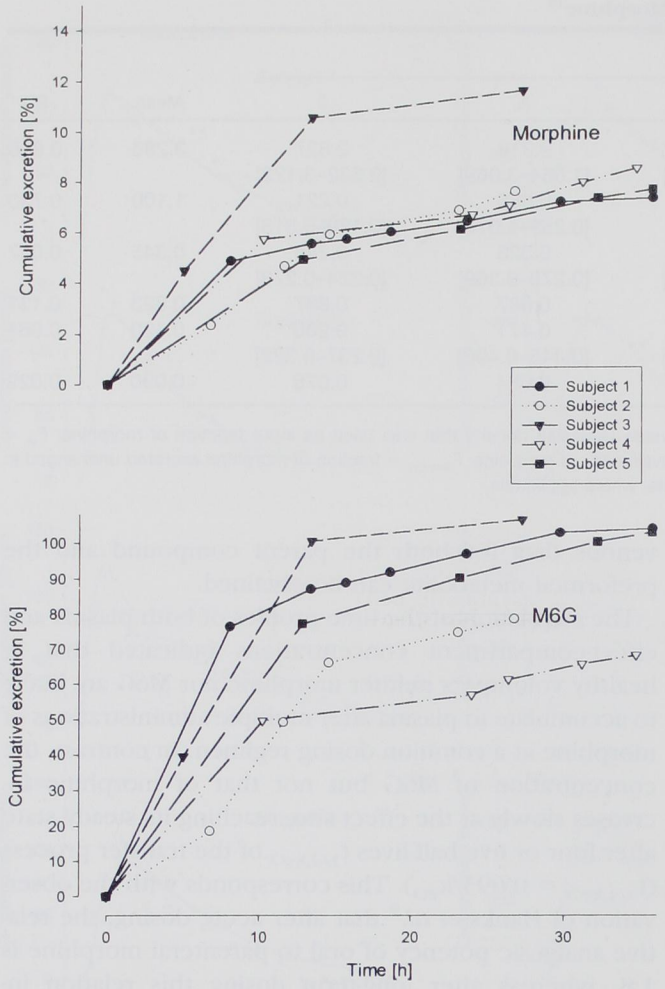

Fig. 3. The cumulative amount of morphine (*top*) and M6G (*bottom*) excreted unchanged in urine. Data are given as percentages of excretion, with 100% morphine resulting from $D_{or}F_p$ and 100% M6G calculated as $D_{or}F_AF_{mp}\cdot(1-F_{H,p}/1-f_{eh})+D_{or}F_pF_{mp}$ (for the M6G formed during the first pass and the M6G formed from systemically available morphine, respectively).

effect-compartment in patients with renal failure. The high steady state plasma concentrations that we predicted are in the range of those seen by Tiseo *et al.*[2] (approximately 4500 nM) in patients with renal dysfunction receiving long-term morphine treatment, indicating the relevance of our simulation. Patients with such elevated M6G concentrations had side effects after morphine therapy, specifically respiratory depression. Similar observations of an association of high M6G levels with opioid side effects have been reported by McQuay *et al.*[30] and Portenoy *et al.*[31]

The simulation of effect-compartment concentrations of M6G may provide an explanation for the lack of analgesic activity after short-term administration of M6G, which we reported recently.[7] The failure of M6G to produce analgesia in that study probably reflects a pharmacokinetic problem. Specifically, M6G seems to reach pharmacodynamically relevant concentrations at the effect site only after long-term administration. Thus, in the

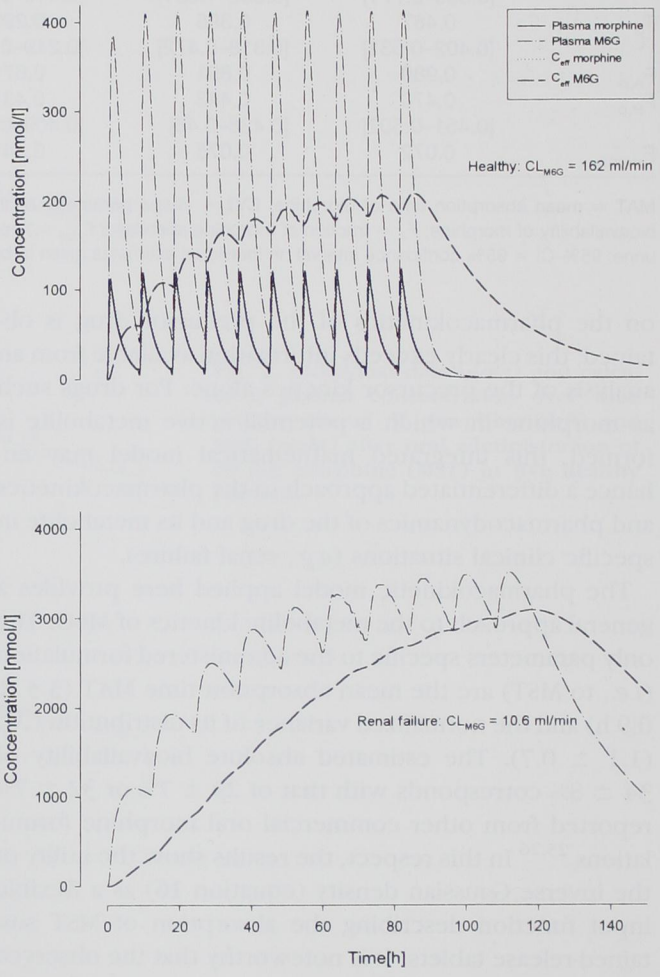

Fig. 4. A prediction of plasma and effect-compartment concentrations (C_{eff}) of morphine and M6G after 10 doses of 90 mg morphine at the 12-h interval, based on published k_{eO} values ($t_{1/2,keO}$ = 16.7 min for morphine, and 20.3 h for M6G; k_{eO} = $\ln(2)/t_{1/2,keO}$[20]). The predicted plasma and effect-compartment concentrations of M6G in healthy persons are shown at the top and those in patients with renal failure M6G clearance 10.6 ml/min[22] are shown at the bottom. Note the different scaling of the ordinates (factor 10). In healthy volunteers, neither morphine nor M6G are expected to accumulate in plasma. In contrast, M6G but not morphine is predicted to accumulate in the effect compartment. In patients with renal failure, the reduced M6G clearance leads to an accumulation of M6G in both plasma and the effect compartment. Because renal excretion plays a minor role for morphine clearance, plasma and effect-compartment concentrations of morphine probably will not be affected in renal failure.

time window of 4 h that was evaluated in that previous study, M6G probably did not reach effect-site concentrations high enough to produce clinical or analgesic effects. In contrast, under the conditions of long-term treatment, M6G might become an effective analgesic. Its possible therapeutic use should be evaluated under those long-term conditions. However, when considering the reports of increased toxicity of morphine in patients with renal impairment that has been attributed to increased levels of the predominantly renally eliminated M6G, the outcome of those studies regarding drug safety and toxicity, and thus the therapeutic index of M6G, is unpredictable.

The study focused on M6G because the clinical interest centered so far on this metabolite. The clinical importance of M3G, the primary metabolite of morphine, is difficult to estimate. There are several reports that M3G antagonizes the analgesic activity of both morphine and M6G and thus contributes to the development of tolerance to morphine.[32–35] This antagonism appears not to be mediated by opioid receptors.[36–40] Furthermore, a hyperglycemic effect of M3G by a nonopiate and nonhormonal mechanism has been shown.[41] On the other hand, several reports have questioned the hyperalgesic action of M3G.[42–46] Thus, the role of M3G in the effects of morphine remains unclear.

In conclusion, we have provided a detailed model of M6G metabolite kinetics that may serve as a pharmacokinetic basis for experiments evaluating the analgesic activity of M6G and may help to interpret the clinical effects of morphine in different patient populations.

Appendix 1: Pharmacokinetic Model

The approach was based on a general model of metabolite kinetics[24] that was developed as an extension of a previously described steady state (or area-under-the curve–based) model.[16] Application of the approach to the plasma concentration-over-time profiles of drug and metabolite as a consecutive representation of subsystems was simplified using the Laplace transform $\hat{f}(s)$ of a time function f(t) (analogous to the modeling of pharmacokinetics after oral administration[15]). The advantage of the Laplace transform results from the reduction of the mathematically relatively complicated convolution of functions to a simple multiplication. Thus, the plasma concentration time curve of a drug was considered as a result of the independent and consecutive input and disposition processes described by an input function $\hat{I}(s)$ and disposition function $\hat{f}_D(s)$:

$$\hat{C}(s) = \hat{I}(s)\hat{f}_D(s) \quad (13)$$

In the following outline of model equations applied in this study, the precursor morphine and its metabolite M6G are characterized by indexes p and m, respectively.

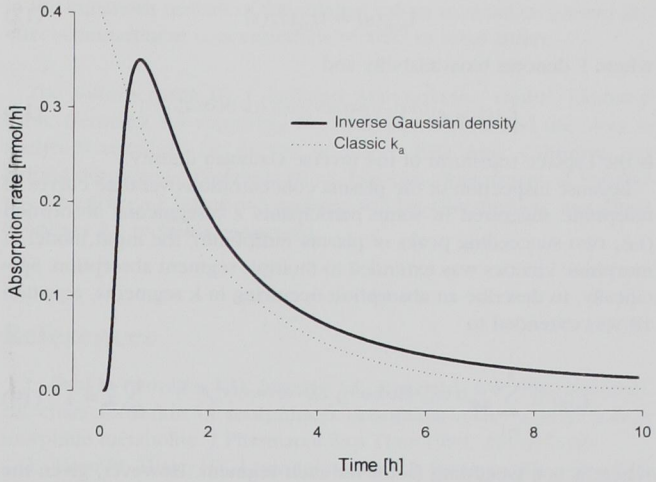

Fig. 5. The absorption function after oral administration of morphine: The inverse Gaussian density (equation 16, appendix 1) was chosen as an input function for the description of morphine absorption.[15] It provides flexibility and appropriate asymptotic behavior. The graph of the function $f_A(t)=\sqrt{MAT/2\pi CV_A^2 t^3}e^{[-(t-MAT)^2/2CV_A^2 MAT t]}$ is drawn using the original parameters of participant 1 (*i.e.*, MAT = 3.793 and CV_A^2 = 1.68 [*thick line*]). For comparison, the traditional approach to absorption is depicted as a dotted line. In the traditional approach, the rate of absorption dA/dt is given by the product of the absorption rate constant, k_a, and the amount remaining to be absorbed, A_a: $da/dt = k_a \cdot A_a$. The amount remaining to be absorbed is given by $A_a = F \cdot D_{or} \cdot e^{-k_a t}$. Thus, the rate of absorption over time is calculated as $d/dt = k_a \cdot D_{or} \cdot e^{-k_a t}$ (*dotted line*).

Whereas for intravenous administration of a bolus dose D_{iv}, the concentration time curve of morphine is completely determined by its disposition function

$$\hat{C}_{p,iv}(s) = D_{iv}\hat{f}_{D,p}(s) \quad (14)$$

for oral administration the input function $\hat{I}_{p,or}(s)$, which characterizes the absorption of a specific formulation (MST sustained-release tablets, Mundipharma GmbH, Limburg/Lahn, Germany), plays an important role

$$\hat{C}_{p,or}(s) = \hat{I}_{p,or}(s)\hat{f}_{D,p}(s) \quad (15)$$

The input function $\hat{I}_{p,or}(s)$ is determined by the processes of absorption and primary liver passage of the drug. The inverse Gaussian density was used as a model of the input time distribution

$$f_A(t) = \sqrt{\frac{MAT}{2\pi CV_A^2 t^3}}\, e^{[-(t-MAT)^2/2CV_A^2 MAT t]} \quad (16)$$

where MAT denotes the mean absorption time, and the normalized variance of the density function CV_A^2 is the shape parameter of the input function. Note that MAT includes the dissolution time of the pharmaceutical preparation. As shown recently, the inverse Gaussian density is a flexible input function with appropriate asymptotic behavior (fig. 5), with the advantage of reducing the effect of model misspecification in parameter estimation.[15]

Thus, the input can be written for a single oral dose D_{or} as

$$\hat{I}_{p,or}(s) = D_{or}F\hat{f}_A(s) \quad (17)$$

where F denotes bioavailability and

$$\hat{f}_A(s) = e^{\{1/CV_A^2 - [(MAT/(CV_A^2/2))(s+(1/2MATCV_A^2))]^{1/2}\}} \quad (18)$$

is the Laplace transform of the inverse Gaussian density.

Because inspection of the plasma concentration-over-time curves of morphine suggested in some participants a bisegmental absorption (*i.e.*, two succeeding peaks of plasma morphine), the input model of morphine kinetics was extended to multiple-segment absorption. Specifically, to describe an absorption occurring in k segments, equation 18 was extended to

$$\hat{f}_A(s) = \sum_{i=1}^{k} a_i e^{\{1/CV_{A,i}^2 - [(MAT_i/(CV_{A,i}^2/2))(s+(1/2MAT_iCV_{A,i}^2))]^{1/2}\}}, \quad \sum a_i = 1 \quad (19)$$

where a_i is a weighting factor for each segment. However, given the small number of persons tested, the subsequent calculations and predictions were based on a one-segment absorption to maintain their generality. Furthermore, introduction of a second segment of absorption improved the fit only slightly (data not given), and the model selection criterion[14] increased from 1.4 ± 0.4 to 1.5 ± 0.6.

Based on the general assumption that the disposition curves of morphine and the preformed metabolite can be described by a sum of exponentials, the Laplace transform of the unit impulse response (*i.e.*, the disposition functions) are given by

$$\hat{f}_{D,p}(s) = \sum_{i=1}^{np} \frac{\alpha_{p,i}}{s + \lambda_{p,i}} \quad (20)$$

for the precursor, and the same equation holds true for the metabolite with index m. Then it follows from equations 13 to 20 that the concentration–time curve of morphine after an oral dose can be described by

$$\hat{C}_{p,or}(s) = D_{or}F \cdot e^{\{1/CV_A^2 - [(MAT/(CV_A^2/2))(s+(1/2MATCV_A^2))]^{1/2}\}} \sum_{i=1}^{np} \frac{\alpha_{p,i}}{s + \lambda_{p,i}} \quad (21)$$

Note that $F = F_A F_{H,p}$ where F_A is the fraction absorbed and $F_{H,p}$ is the hepatosplanchnic availability of the drug (extraction ratio across the liver: $E_{H,p} = 1 - F_{H,p}$).

In the case of oral administration, the hepatic first-pass metabolism described by $\hat{I}_{m,sys}(s)$ must be considered, in addition to the metabolite formation $\hat{I}_{m,fp}(s)$ from plasma concentration $\hat{C}_{p,or}(s)$ (equation 21):

$$\hat{I}_{m,sys}(s) = D_{or}F_A\hat{f}_A(s)(1 - F_{H,p})h_{mp} \quad (22)$$

where $D_{or}F_A\hat{f}_A(s)$ describes the drug input to the liver, and $(1-F_{H,p})h_{mp}$ is the product of the extraction ratio and h_{mp}, the fraction of hepatic clearance $CL_{H,p}$ that forms the metabolite m. The input rate $\hat{I}_{m,fp}(s)$ of the metabolite (m) generated from the systemically available parent drug (p) is given by (analogous to intravenous administration)

$$\hat{I}_{m,fp}(s) = F_{mp}CL_p\hat{f}_{M,pm}(s)\hat{C}_{p,or}(s) \quad (23)$$

where CL_p is the total clearance of morphine, F_{mp} denotes the fraction of drug p metabolized to the primary metabolite m, and $\hat{f}_{M,pm}(s)$ denotes the transit time density across the site of metabolism corresponding to the systemic formation of m from drug p (analogous to intravenous administration). The transit time density is based on the well-stirred model as the simplest liver model:

$$\hat{f}_{M,pm}(s) = \frac{\lambda_M}{s + \lambda_M} \quad (24)$$

implying that the corresponding mean transit time across the site of metabolism is given by $MTT_M = 1/\lambda_M$. In the case of first-pass metabolism, this transit time is included implicitly in the parameter MAT. Note that

$$F_{mp} = h_{mp}(1 - f_{eh}) \quad (25)$$

where f_{eh} is the fraction of drug eliminated extrahepatically, because $h_{mp}CL_{H,p} = h_{mp}(1 - f_{eh})CL_p = F_{mp}CL_p$. The model takes into consideration that after oral administration of morphine, there are two inputs of M6G: One part of M6G is formed from systemically available morphine analogous to intravenous administration, and another part is formed during the first-pass metabolism of morphine. Because the total input function of metabolite (*i.e.*, the time course of metabolite generation) is the sum of $\hat{I}_{m,sys}(s)$ (equation 22) and $\hat{I}_{m,fp}(s)$ (equation 23), it follows analogously to equation 13:

$$\hat{C}_{mp,or}(s) = (\hat{I}_{m,sys}(s) + \hat{I}_{m,fp}(s))\hat{f}_{D,m}(s) \quad (26)$$

which finally leads to

$$\hat{C}_{mp,or}(s) = D_{or}F_AF_{mp} \cdot e^{\{1/CV_A^2 - [(MAT/(CV_A^2/2))(s+(1/2MATCV_A^2))]^{1/2}\}} \times \left[\frac{1 - F_{H,p}}{1 - f_{eh}} + F_{H,p}CL_p\frac{\lambda_M}{s + \lambda_M}\sum_{i=1}^{np}\frac{\alpha_{p,i}}{s + \lambda_{p,i}}\right] \cdot \sum_{i=1}^{nm}\frac{\alpha_{m,i}}{s + \lambda_{m,i}} \quad (27)$$

As shown in a previous application of this approach (intravenous data[12]), the disposition parameters of morphine ($\alpha_{p,i}$ and $\lambda_{p,i}$, i = 1,2) and metabolite ($\alpha_{m,i}$ and $\lambda_{m,i}$, i = 1,2) and the derived pharmacokinetic parameter, $CL_p = 1/\sum_{i=1}^{2}\alpha_{p,i}/\lambda_{p,i}$, can be estimated from C(t) data after intravenous administration of morphine and M6G, respectively, using

$$C_{iv}(t) = D_{iv}\sum_{i=1}^{n}\alpha_i e^{-\lambda_i t} \quad (28)$$

The parameters F_{mp} and λ_M are then obtained by fitting

$$\hat{C}_{mp,iv}(s) = D_{iv}F_{mp}CL_p\frac{\lambda_M}{s + \lambda_M}\sum_{i=1}^{np}\frac{\alpha_{p,i}}{s + \lambda_{p,i}}\sum_{i=1}^{nm}\frac{\alpha_{m,i}}{s + \lambda_{m,i}} \quad (29)$$

to the time course of M6G concentration generated after intravenous administration of morphine (*e.g.*, after a bolus dose D_{iv}). Because the parameters F, MAT, and CV_A^2 are estimated from the $C_{p,or}(t)$ data of morphine (equation 21), and $F_A = F/F_{H,p}$, the only parameter that remains to be estimated in equation 27 is $F_{H,p}$, the hepatosplanchnic availability of morphine.

The amount $A_{m,fp}$ of M6G formed during the first pass through the liver can be derived from the equation 22:

$$A_{m,fp} = D_{or}F_AF_{mp} \cdot \frac{1 - F_{H,p}}{1 - f_{eh}}, \quad (30)$$

and the amount $A_{m,sys}$ of M6G formed from systemically available morphine is given by

$$A_{m,sys} = D_{or}F_pF_{mp}. \quad (31)$$

The total amount of M6G A_m formed from morphine is then the sum of the amount of M6G formed during the first-pass metabolism, and the amount of M6G formed from systemically available morphine:

$$A_m = A_{m,fp} + A_{m,sys}. \quad (32)$$

The equations for multiple dosing can be formulated readily in the Laplace domain by substituting D_{or} with $D_{or}\sum_{i=1}^{N} e^{-(i-1)s\tau}$. To simulate concentrations at the effect site, an effect compartment with an equilibration time constant k_{eO} between plasma concentrations and effect was added to the pharmacokinetic model.[18,19] Thus, concentrations at effect site $\hat{C}_{eff}(s)$ can be obtained easily by

$$\hat{C}_{eff}(s) = \frac{k_{eO}}{s + k_{eO}} \cdot \hat{C}_{p,or}(s) \quad (33)$$

Appendix 2. Reparameterization to Simulate M6G Kinetics with Reduced Renal Clearance[14]

Disposition parameters of M6G were used to derive pharmacokinetic parameters V_1, k_{21}, k_{10}, and k_{12}, where V_1 denotes the volume of distribution of the central compartment, k_{10} denotes the elimination rate constant, and k_{12} and k_{21} denote the transfer constants between compartments[14]:

$$V_1 = \frac{1}{\alpha_1 + \alpha_2},$$

$$k_{21} = \frac{\alpha_1\lambda_2 + \alpha_2\lambda_1}{\alpha_1 + \alpha_2},$$

$$k_{10} = \frac{\lambda_1\lambda_2}{k_{21}}, \quad \text{and}$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{10}.$$

Clearance is given by $CL = k_{10} \cdot V_1$. To calculate the disposition parameters for reduced clearance, $CL_{reduced,\ k_{10}}$ was recalculated as $k_{10,reduced} = (CL_{reduced}/V_1)$, leaving V_1, k_{12}, and k_{21} unchanged and taking as $CL_{reduced}$ the value of 10.6 ml/min published by Hanna *et al.*[22] from patients with renal failure. Then new disposition parameters $\lambda_{1,reduced}$, $\lambda_{2,reduced}$, $\alpha_{1,reduced}$, and $\alpha_{2,reduced}$ were calculated as described by Wagner[14]

$$\lambda_{1,reduced} = 0.5[k_{12} + k_{21} + k_{10,reduced} + ((k_{12} + k_{21} + k_{10,reduced})^2 - 4k_{21}k_{10,reduced})^{1/2}],$$

$$\lambda_{2,reduced} = 0.5[k_{12} + k_{21} + k_{10,reduced} - ((k_{12} + k_{21} + k_{10,reduced})^2 - 4k_{21}k_{10,reduced})^{1/2}]$$

$$\alpha_{1,reduced} = \frac{(k_{21} - \lambda_1)}{V_1(\lambda_2 - \lambda_1)}, \quad \text{and} \quad \alpha_{2,reduced} = \frac{(k_{21} - \lambda_2)}{V_1(\lambda_1 - \lambda_2)}.$$

The new values of $\lambda_{1,reduced} = 3.554\ h^{-1}$, $\lambda_{2,reduced} = 0.037\ h^{-1}$, $\alpha_{1,reduced} = 0.063\ l^{-1}$, and $\alpha_{2,reduced} = 0.058\ l^{-1}$ (for comparison with the original values from healthy persons, see table 2) were introduced in the equations instead of the original values to simulate plasma and effect-compartment concentrations of M6G in renal failure.

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