BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 11, 419–444 (1990)

PHARMACOKINETICS OF MORPHINE AND ITS SURROGATES XI: EFFECT OF SIMULTANEOUSLY ADMINISTERED NALTREXONE AND MORPHINE ON THE PHARMACOKINETICS AND PHARMACODYNAMICS OF EACH IN THE DOG

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ABSTRACT

There were no dramatic modifications of the pharmacokinetics in the dog of i.v. bolus doses of 0·5, 2·7 and 5 mg kg^{-1} morphine by coadministering i.v. 5 mg kg^{-1} naltrexone as bolus injections over 15–20 s and 12·3 mg kg^{-1} by continuous infusion. Morphine's terminal half-life, clearances, apparent volumes of distribution (except for that of the central compartment), percentages of drug and conjugated metabolite excreted in urine and bile did not differ significantly by paired *t*-test (probability (p) > 0·05 for rejection of the null hypothesis of no difference) when naltrexone was coadministered. There were no statistically significant (by *t*-test) modifications of the plasma pharmacokinetics in the dog of i.v. bolus doses of 5 mg kg^{-1} naltrexone with and without morphine coadministration except for the coefficient of the second (or terminal) exponential of the sum that fitted the plasma concentration–time data of naltrexone. Although morphine coadministration did not significantly affect the terminal half-life of naltrexone, its clearances or apparent volumes of distribution by *t*-test of the differences between averages (with each dog equally weighted), drug coadministration did significantly (by *t*-test) affect the fraction of naltrexone dose secreted into bile as conjugate (f_B), the fraction of the dose excreted as conjugate in urine, and the fraction excreted elsewhere (f'_B). Although naltrexone reversed the central action of morphine in affecting monitored pupil diameters, it did not antagonize the peripheral effects of morphine in perturbing renal and biliary flow rates. This led to a larger fraction of the naltrexone dose being metabolized to conjugate on morphine coadministration. Since less naltrexone conjugate was renally and biliary excreted initially, due to morphine inhibition of the initial renal and biliary processes, naltrexone conjugate plasma concentrations were higher when morphine was coadministered.

KEY WORDS Morphine Naltrexone Pharmacokinetics Metabolism Interactions

INTRODUCTION

Narcotic antagonists, such as naltrexone or naloxone, have three main clinical applications: (1) diagnosis of narcotic addiction, (2) prophylactic treatment

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0142–2782/90/050419–26$13.00

Received 12 October 1989

of narcotic abuse, and (3) emergency treatment of narcotic overdosage. Each of these is based upon the belief that such compounds displace previously assimilated opiates from their receptor sites[1,2] and/or, 'if administered prior to narcotic intake, will preclude narcotic agonist activity at those sites'.[3]

Pharmacokinetic studies of morphine alone and naltrexone alone in various mammalian species have been published.[4–7] The principal metabolite in dogs was morphine-3-glucuronide.[8,9] In bile-cannulated dogs, 11–14 per cent of the dose was eliminated in the bile as conjugate.[10]

The metabolic routes of naltrexone elimination vary among species but only conjugates of naltrexone were major metabolites in the dog, rat and mouse.[11–16] A recent study by Garrett *et al.*[17] used HPLC with electrochemical detection to quantify naltrexone and its conjugates in dogs after i.v. bolus administration of 0·5 and 5 mg kg^{-1} naltrexone HCl.

Opioid agonists and antagonists are frequently administered together, e.g. for the treatment of narcotic overdosage[1,2] or to minimize the psychotropic effect of the narcotic.[18] Although pharmacokinetic interactions appear feasible due to the similar metabolic pathways of the components of such combinations, controlled pharmacokinetic studies to investigate the influence of opioid antagonists on the pharmacokinetics of agonists and vice versa are rare. Garrett *et al.*[19] studied the pharmacokinetics of naloxone and its conjugates and their effect on simultaneously administered morphine in dogs. Morphine total, renal, and biliary clearances were smaller at higher doses. Morphine coadministration lessened the clearances of naloxone. Plasma levels of naloxone and its conjugate were elevated with simultaneous morphine administration. Urinary flow rates were greatly lessened and initial renal shut-down was implied at the higher morphine dose with and without administered naloxone.[19]

This present study focuses on the question of whether similar pharmacokinetic interactions exist between morphine and naltrexone. Its purpose is to challenge whether common pharmacodynamic effects of morphine, such as inhibition of bile and urine flow and pupillary constriction, are modified on simultaneous naltrexone administration.

The pharmacokinetics of morphine and naltrexone given separately to larger groups of animals have been reported earlier.[10,17] In the present study a small group of dogs was used repetitively so that each dog could serve as its own control and biological, pharmacokinetic, and pharmacodynamic variability could be minimized.

EXPERIMENTAL

Analytical procedures

The materials and apparatus used were as stated in previous publications.[17,19] Except for a modified mobile phase of 0·05 M monobasic potassium phosphate pH 4·8: acetonitrile (95:5, v:v) with a flow rate of 1·5 ml/min^{-1}, and with electro-

Table 1. Pharmacokinetic studies of morphine sulfate and naltrexone hydrochloride in dogs

Study*	Weight (kg)	Dose (base)†		
		Morphine ($mg\ kg^{-1}$)	Naltexone ($mg\ kg^{-1}$)	Time when naltrexone given after morphine
A1M‡	23·8	4·7	–	–
A2MN§	22·3	4·7	5·0	32s
B1M	21·5	2·8	–	–
B2N	24·0	–	5·0	–
B3MN	21·8	4·8	5·0	50s
B4MN	22·8	2·4	5·1	30s
B5M	23·2	4·7	–	–
$B6MN_{INF}$§	27·2	3·8	12·3	(§)
C1M	26·7	0·4	–	–
C2N	26·0	–	4·6	–
C3MN	25·5	4·3	5·0	16s
C4M	25·4	4·6	–	–

*The study label consists of an initial letter identifying the dog (A, B or C) followed by the number identifying the study's position in the sequence of studies in that dog. The terminal letter(s) indicate the drugs, morphine (M) and/or naltrexone (N), used in that study. Each drug (except in study $B6MN_{INF}$) was injected in the jugular over 15–20 s. All drug amounts are given as base equivalents.

†Conversion factors from salt to base: for morphine sulfate, 0·85331; for naltrexone hydrochloride, 0·9035.

‡Dog A was bile cannulated.

§In this study, 82·5 mg (as base equivalent) of naltrexone was given as a bolus and then 252·5 mg were infused into the jugular for 293 min at a rate of $0{\cdot}862\ mg\ min^{-1}$ to achieve and maintain a steady state concentration. Morphine as bolus was injected at 125 min when a steady state plasma concentration was achieved.

chemical detection at an applied potential of +0·95 V, the HPLC conditions and extraction procedure for morphine and naltrexone from plasma and urine were the same as given previously.[19–21] Experimental conditions for the extraction of conjugates of morphine and morphine antagonists following acid hydrolysis were also described earlier.[17,19]

Pharmacokinetic studies in dogs

Three healthy mongrel dogs with average weights of 23·1 (23·8 and 22·3 kg) (A), 23·4 ± 2·1 (SD) $n=6$ (B), and 26·0 ± 0·6 (SD) kg, $n = 4$ (C) were used in these studies. The time between two consecutive experiments for the same dog was at least 4 weeks. The blood analyses of the dogs showed no pathogenic abnormality or presence of microfilaria. The procedures of fasting, water-loading, insertion of catheters in the jugular and brachialis veins, and dog handling have been given previously.[17,19]

Morphine sulfate and naltrexone hydrochloride were each dissolved in 10 ml of sterile 0·9 per cent NaCl solution and bolus doses were injected for most

studies separately into the jugular catheter over 10 s, followed by a flush of 10 ml of normal saline. Pharmacokinetic studies were conducted when morphine alone, naltrexone alone, and morphine with follow-up doses of naltrexone were administered as summarized as amounts of base equivalents in Table 1. The identifying label for each study consisted of an initial letter identifying the dog (A, B or C) followed by the number identifying the study's position in the sequence of studies in that dog. The terminal letter(s) indicate the dog, morphine (M) and/or naltrexone (N), used in that study. Naltrexone doses were *ca.* 5 mg kg^{-1} except for study B6MN$_{INF}$ when 252·5 mg of naltrexone was infused into the jugular catheter for 293 min at a rate of 0·862 mg min^{-1} after an initial loading dose of 82·5 mg of naltrexone. Morphine (3·85 mg kg^{-1}) was injected into the vena brachialis at 125 min at steady state naltrexone plasma concentrations. Blood samples were withdrawn at appropriate intervals from the same brachialis catheter in this study. Transient (< 30 s) sham or mock rage was exhibited immediately after morphine injection in all studies except study B4MN.

The purpose of the dual sampling from both the jugular and brachialis vein during the first 60 min post-injection was to confirm the drug had been equitably distributed (i.e. the plasma samples from both sources had the same concentration in the systemic circulation post-injection). Plasma and urine samples were obtained as detailed previously.[17,19] They were frozen immediately at −20°. All samples were assayed within 8 weeks after the study. The concentrations of morphine, naltrexone, and their conjugates in plasma and urine did not change significantly when stored under these conditions during an observation period of 8 weeks. Dog A underwent surgery to permit complete bile collection.[19] However, yellowish fluids were observed to have dripped from around the bile cannula onto the table. Thus the presumption of complete bile collection in studies 1 and 2 is unwarranted and these questionable biliary data are not presented.

The concentration–time data were fitted by nonlinear regression to a sum of exponentials

$$C = Ae^{-\alpha t} + BE^{-\beta t} + Ce^{-\gamma t} \quad (1)$$

after obtaining initial parameter estimates by the method of residuals using the computer program Rstrip.[22] Goodness of fit was supported by the values of the correlation coefficient, the sum of squares of the residuals, and the Akaike Information Criterion (AIC).[23]

The renal clearances were estimated by regression of the cumulative amount excreted in the urine (ΣU) and leaving the bladder via urinary catheter against the area under the plasma concentration–time curve AUC in accordance with:

$$\Sigma U = Cl_{ren}\,AUC + \text{Intercept} \quad (2)$$

Plasma concentrations of the conjugates were fitted to a sum of exponentials and could be generated by the 'integral method'.[24] In this method, the total

amount of hepatically formed metabolite, Σmet_{tot} in a first order process at a time t is calculated from $Cl_{met}AUC_{par}$ where AUC_{par} is the area under the plasma concentration–time curve of the parent compound up to that time t and Cl_{met} is the metabolic clearance. The formed conjugate is either in the body with a concentration of [met] in a volume of distribution $V_{d_{met}}$ (when a one compartment body model is assumed), or excreted into the urine (ΣU_{met}) or bile (ΣB_{met}), before enterohepatic recirculation. Thus,[10] before any enterohepatically recirculated material is returned to the systemic circulation,

$$\Sigma met_{tot} = Cl_{met}AUC_{par} = \Sigma U_{met} + \Sigma B_{met} + V_{d_{met}}[met] \quad (3)$$

If the amount of conjugate excreted in the bile is not known, a constant biliary clearance Cl_B of hepatically formed metabolite can be postulated and equation (3) can be modified to:

$$\Sigma met_{tot} = \Sigma U_{met} + Cl_B AUC_{par} + V_{d_{met}}[met] \quad (4)$$

Equation (4) can be solved for the Cl_{met} and $V_{d_{met}}$ parameters by multiple linear regression or obtained from the parameters of linear plots of the rearranged equations, such as:

$$\frac{\Sigma U_{met}}{[met]} = (Cl_{met} - Cl_B)\frac{AUC_{par}}{[met]} - V_{d_{met}} \quad (5)$$

Linear regression of plots of experimentally available quotients of the left-hand sides against the quotients on the right-hand sides permit the estimates of values for the differences between metabolic and biliary clearances ($Cl_{met} - Cl_B$) and the apparent volume of distribution of ($V_{d_{met}}$) of the metabolite. The validity of these estimates can be challenged by generating $[met]_{calc}$ from rearrangements of equation (5):

$$[met] = \frac{(Cl_{met} - Cl_B)AUC_{par} - \Sigma U_{met}}{V_{d_{met}}} \quad (6)$$

Biliary clearances in the normal dog can be estimated from the differences between Cl_{met} values and the ($Cl_{met} - Cl_B$) values obtained from appropriate plot in accordance with equation (5).

The biliary excretion of the hepatically formed metabolite ΣB_{calc} can be calculated in the normal animal from the determined biliary clearance Cl_B according to:[10]

$$\Sigma B_{calc} = Cl_B AUC_{par} \quad (7)$$

and expressed as a fraction, f_B, of the dose:

$$f_B = \Sigma B_{calc}/Dose = Cl_B AUC_{par}/Dose \quad (8)$$

under the assumptions of constant clearances and negligible direct biliary excretion of the metabolite circulating in the plasma. Thus, on the postulation of

stoichiometry being preserved, the actual fraction, f'_B, of the dose delivered to the feces at infinite time is the difference between the total amount of metabolite formed (equation (3)) and the amount of metabolite (ΣU_{met}) excreted in the urine at infinite time i.e:

$$f'_B = (Cl_{met}AUC_{par} - \Sigma U_{met})/Dose \quad (9)$$

The difference between the fraction biliary eliminated and the fraction delivered to the biliary system estimates the fraction of conjugate that has been enterohepatically reabsorbed,

$$f_{ent} = f_B - f'_B \quad (10)$$

Pharmacodynamic monitoring

In order to monitor the pharmacodynamic action of morphine and the influence of naltrexone on the CNS, the effect on the pupil diameter was quantified by measuring the diameter of the pupilla with a caliper under two conditions: (1) diameter under normal and constant illumination and (2) diameter during light stimulus.[25] Baseline pharmacodynamic values were obtained by measuring pupil diameters starting at 120–200 min prior to, and were continued up to 1400 min following, drug administration.

The inhibition of urinary flow induced by morphine was monitored.

RESULTS

All values given herein, unless specified differently are the averages of mean values from each dog. The ±SEM values following these averages, where each dog is equally weighted are the standard errors of the mean for these averages where $n = 3$ unless specifically stated differently.

Effect of morphine and naltrexone on urine flow

Representative plots typical of all studies, which show the effect of morphine, with and without naltrexone coadministration, on urine flow and its kinetics are shown in Figure 1. A large dose (4·7 mg kg^{-1}) of morphine caused complete cessation of urine flow (Figure 1(A)) which was *not* antagonized with naltrexone coadministration (Figure 1(B)). Apparently this is followed by compensatory polyuria. A low morphine dose (0·4 mg kg^{-1}) decreased urine flow immediately after injection into the water-loaded dog for a shorter interval but did not halt it completely (Figure 1(A)). Naltrexone alone had no effect on urinary flow. These phenomena occurred in all studies.

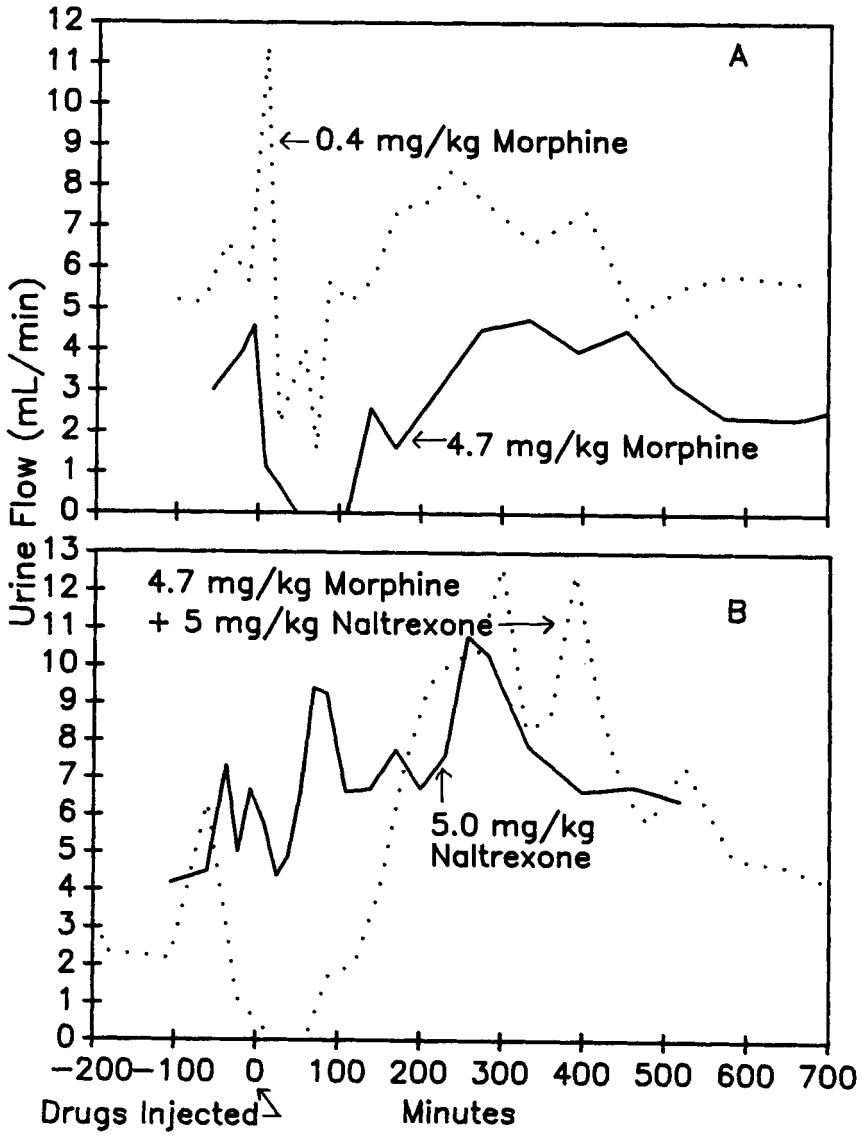

Figure 1. Typical variations of urine flow rates with time before and after morphine and naltrexone administration at 0 min. Panel A: morphine, 0·4 mg kg^{-1}, study C1M (....); morphine, 4·7 mg kg^{-1}, study A1M (____); panel B: morphine, 4·7 mg kg^{-1}, + naltrexone, 5·0 mg kg^{-1}, study A2MN (....); naltrexone, 5·0 mg kg^{-1}, study B2N (____)

When the duration of the cessation of urine flow was plotted against time, a linear relationship was obtained between the lag time (before urine flow recommences) and the morphine dose (Figure 2). Coadministered naltrexone

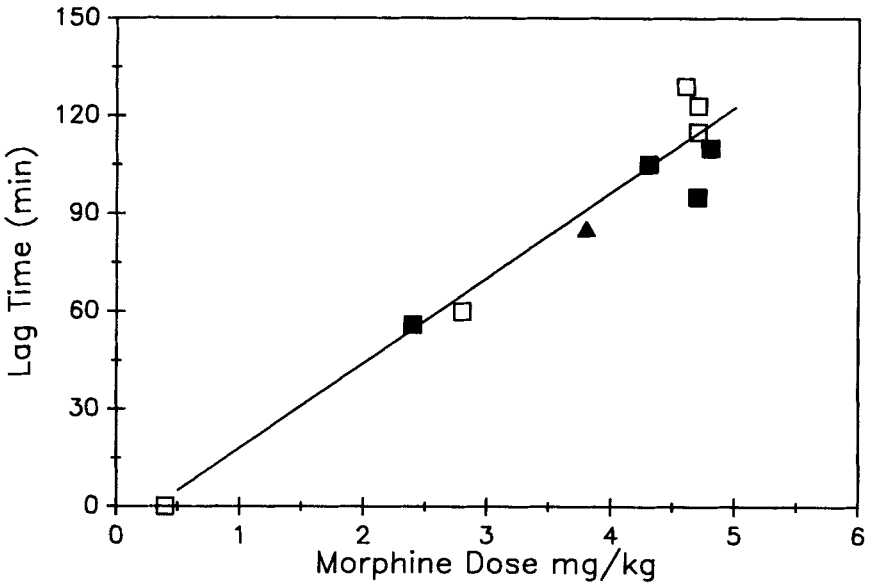

Figure 2. Effect of morphine dose on duration of initial cessation of urine flow (lagtime); ■ studies A2MN, B3MN, B4MN, C3MN, with morphine + naltrexone (5 mg kg^{-1}); ▲ study B6MN$_{INF}$, morphine + naltrexone (12·3 mg kg^{-1}); □ studies A1M, B1M, B5M, C1M, C4M, morphine alone

at two doses (5·0 mg kg^{-1} and 12·3 mg kg^{-1}) had no effect on urine flow inhibition by morphine and conformed to the same linear relationship (solid symbols, Figure 2). Coadministration of naltrexone did not reverse the action of morphine on urine flow (Figures 1 and 2).

Pupil response to morphine and naltrexone, alone and on coadministration

Typical plots of the effects of morphine on the time course of pupil size are given in Figure 3 for dog A and are typical for all the dog studies. Marked pupil constriction occurred shortly after morphine injection at 0 min and was maintained up to 1000 min after the injection. This effect did not correlate with morphine plasma concentrations which were below analytical sensitivity at 540 min in these studies. Similar pharmacodynamic effects persisted longer than assayable morphine plasma concentrations in studies with dogs B and C.

In order to quantify the magnitude and onset of the miotic effect of morphine and its dose dependency, the parameters AUC, R_{max} and t_{max} were estimated (Table 2). These values were zero when naltrexone alone was administered. The AUC is the area between the pupil diameter–time curve and the baseline as determined by the trapezoidal method; R_{max} is the maximum response of the pupil diameter expressed as per cent deviation from the baseline value

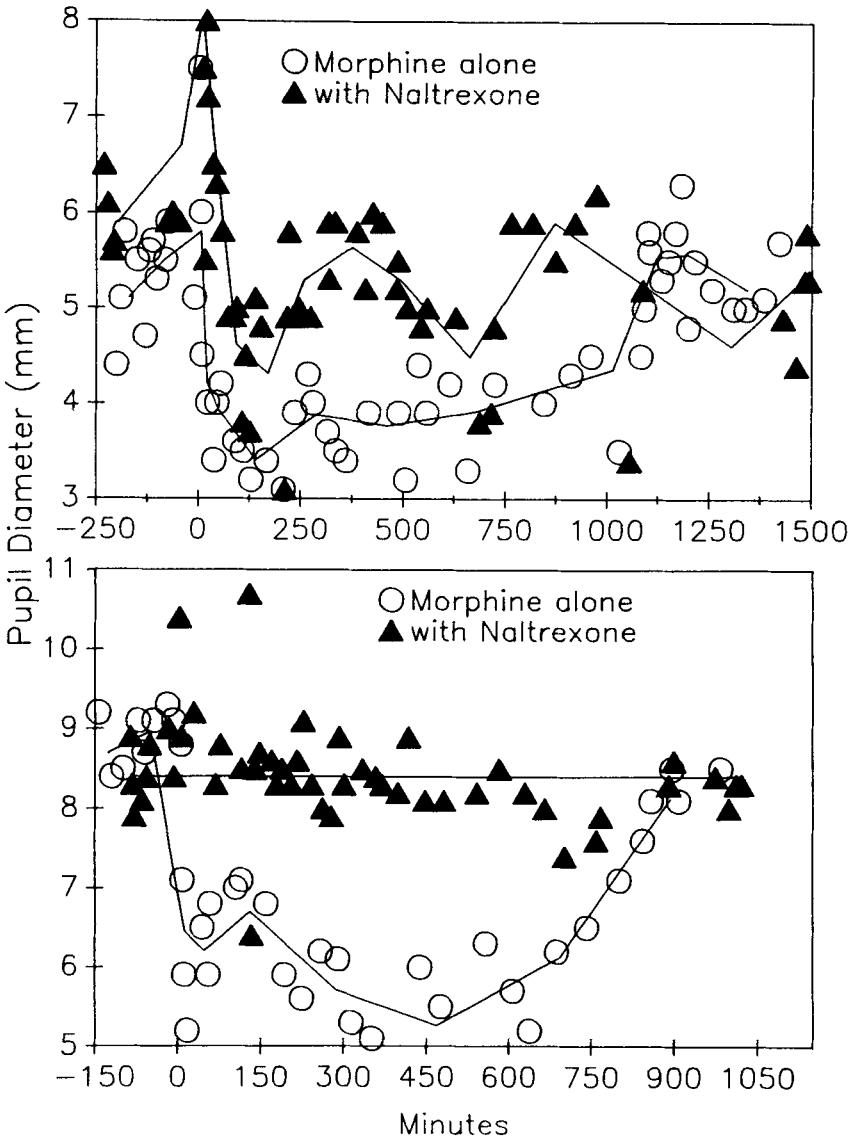

Figure 3. Representative plots of effects of 4·5 mg kg^{-1} of morphine alone (O) upper panel, study A1M; lower panel, study C4M); and of coadministered naltrexone (▲ upper panel study A2MN, 5·0 mg kg^{-1}; and lower panel, study B6MN$_{INF}$, 12·3 mg kg^{-1} naltrexone) on pupil diameter without previous light stimulation. The solid lines join the means of five sequential measurements

according to 100(B-R)/B, where B and R are the pupil size prior to and at maximum following drug administration, respectively. The t_{max} value is the time it takes to reach that maximum response. The average R_{max} value for

Table 2. Pupillometric responses* after morphine and with coadministered naltrexone injection in dogs

Drugs administered		Average** ± SEM: Morphine	Morphine + naltrexone	Paired t statistic[28]	Probability (p) of difference††	
AUC†	NL‡	2526 ± 940	1212 ± 639	4·04	0·10 > p > 0·05	NS
[(mm) × (min)]	L§	1387 ± 215	523 ± 187	113·2	0·01 > p > 0·001	S
t_{max}‖	NL‡	175 ± 104	370 ± 130	7·03	0·05 > p > 0·02	S
[min]	L§	275 ± 52	415 ± 120	1·93	0·2 > p > 0·1	NS
R_{max}¶	NL‡	51·1 ± 84·0	40·0 ± 6·6	2·08	0·2 > p > 0·1	NS
[%]	L§	44·1 ± 3·2	33·2 ± 6·8	1·39	0·4 > p > 0·3	NS

*Studies C1M (at the low morphine dose, 0·4 mg kg^{-1}), B6MN$_{INF}$ (when 3·8 mg kg^{-1} of morphine was injected at steady-state plasma concentrations of morphine) and naltrexone studies (B2N, C2N) are not included since no significant miosis was observed under the experimental conditions, i.e. all AUC, t_{max}, and R values were zero.

†Area by the trapezoidal rule between the pupil diameter-time curve and the baseline from time of injection up to time t where t is the time when pupil sizes returned to baseline levels.

‡Parameters obtained under constant illumination without previous light stimulation, i.e. no light (NL).

§Parameters obtained following light stimulation, i.e. with light (L).

‖Time after drug administration when maximum meiosis was observed.

¶Maximum response of pupil diameter expressed as per cent deviation from the baseline value according to 100(B − R)/B, where B and R are the pupil sizes prior to, and the maximum size following, drug administration, respectively.

**Each dog is equally weighted by averaging the mean values of studies for each of the 3 dogs.

††df = 2; $p \leq 0{\cdot}05$ is considered significant probabilities to reject the null hypothesis that the average value from ca 4·6 mg kg^{-1} of morphine administration alone is the same as the average value obtained on coadministration of 5 mg kg^{-1} of naltrexone. Values with significant differences by t-test are marked with S.

morphine given alone showed a 51·1 ± 1·8 per cent reduction in pupil diameter without, and a 44·1 ± 3·2 per cent reduction with, previous light stimulation (Table 2). The data for t_{max} were variable but averaged to 175 ± 104 min without, and 275 ± 52 min after, previous light stimulation.

Areas between baseline and drug-affected pupil diameters vs time appeared to be dose proportional (Figure 4). Naltrexone itself did not have any quantifiable effect on pupil diameter, however its continuous infusion completely blocked the miotic action of morphine (Figure 3, lower panel). For the studies when bolus morphine and bolus naltrexone were coadministered, the AUC due to morphine action was reduced by 52 per cent (no prior light stimulation, NL) and 62 per cent (prior light stimulation, L). Coadministered naltrexone significantly (by paired t-test,[26] see Table 2) decreased the AUC of morphine action when pupil diameter was challenged with prior light stimulation. The maximum responses were diminished by 22 per cent (NL) and 25 per cent (L). The t_{max} of morphine action without prior light stimulus was prolonged significantly from 175 ± 104 min to 370 ± 130 min on naltrexone coadministration with morphine (Table 2).

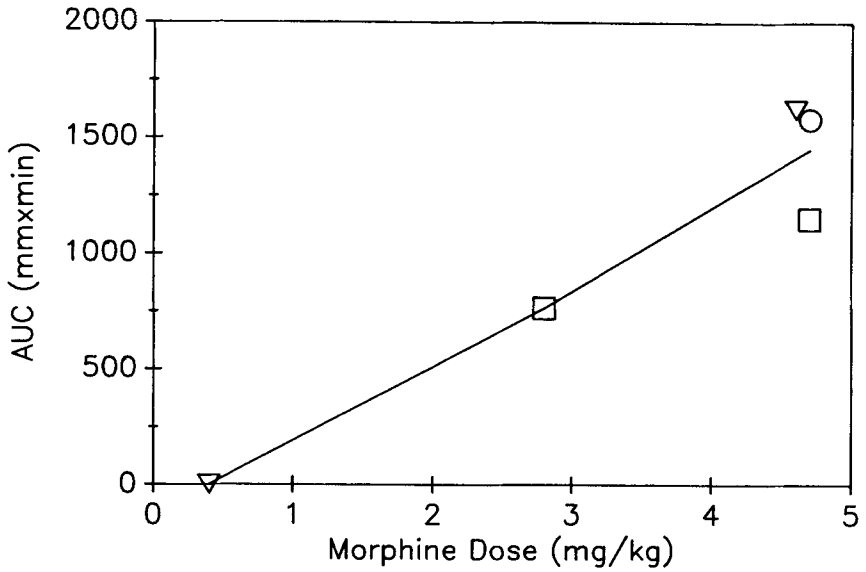

Figure 4. Morphine dose dependency of miotic response with previous light stimulation expressed by the integral of change of pupil diameter with time with respect to its baseline value. The area between baseline pupil diameters and drug-affected pupil diameters vs time, AUC, was calculated by the trapezoidal rule: O dog A, study A1M; □ dog B, studies B1M and B5M; ▽ dog C, studies C1M and C4M

Pharmacokinetics in plasma

The pharmacokinetic parameter values for morphine and naltrexone, dosed separately and coadministered, are listed in Table 3. Except for the listed averages the studies with naltrexone alone, where the values from previously published studies[17] are included, the values listed are the averages ± SEM of the means for each dog for the studies listed in Table 1. When mean values are available only from 2 dogs, these means for dogs B and C are separated by a comma and are given in the parenthesis after the average. When three studies were conducted in 1 dog, the mean ± SEM of these studies is given in the parentheses.

Values in Table 3 for morphine and naltrexone administered separately agreed with values obtained previously.[9,10,17,19] Except for three studies in dog B (studies B1M, B4MN, and $B6MN_{INF}$), with observed third exponential phases of respective terminal half-lives of 249, 296, and 169 min, the plots of plasma concentrations against time were best fitted (Figure 5) by the sum of two exponentials (equation (1)), characteristic of the two compartment body model. As previously reported,[10] an even slower terminal morphine elimination (γ-phase) with an average half-life of 1955 ± 576 min could be concluded from the fitting of appropriate urinary excretion plots viz. from slopes of the terminal data of $\ln \mid \Sigma U_\infty - \Sigma U \mid$ versus t plots where ΣU_∞ and ΣU are the cumulative

Table 3. Pharmacokinetic parameters of intravenous morphine and naltrexone averaged from the mean values obtained from dogs[a]

	Morphine (M) Values[a]			Naltrexone (N) Values[a]		
	When M dosed alone[a]	When M dosed with N[a]	Probability (p) of difference by t-test[p,q]	When N dosed alone[a]	When N dosed with M[a]	Probability (p) of no difference by t-test[q,s]
Plasma parameters[b]						
A(ng ml^{-1})/(mg kg^{-1})	1383 ± 180	1125 ± 458	$0{\cdot}6 > p > 0{\cdot}5$	681 ± 187 [1023]	584 (733, 434)	$0{\cdot}7 > p > 0{\cdot}6$
B(ng ml^{-1})/(mg kg^{-1})	234 ± 3	250 ± 25	$0{\cdot}6 > p > 0{\cdot}5$	195 ± 16 [188]	368 ± 128	$p < 0{\cdot}001$ S[t]
α, min^{-1}	0·22 ± 0·08	0·18 ± 0·13	$0{\cdot}8 > p > 0{\cdot}7$	0·28 ± 0·14 [0·52]	0·13 (0·088, 0·16)	$0{\cdot}6 > p > 0{\cdot}5$
$t^{\alpha}_{1/2}$, min	6·2 ± 2·0	12·1 ± 1·9	$0{\cdot}3 > p > 0{\cdot}2$	6·3 ± 1·5 [5·2]	6·3 (7·9, 4·6)	$p > 0{\cdot}9$
β, min^{-1}	0·11 ± 0·003	0·012 ± 0·0014	$0{\cdot}5 > p > 0{\cdot}4$	0·014 ± 0·001 [0·013]	0·0151 ± 0·0014	$0{\cdot}7 > p > 0{\cdot}6$
$t^{\beta}_{1/2}$, min	74·0 ± 4·5	62·2 ± 3·4	$0{\cdot}2 > p > 0{\cdot}1$	51·2 ± 4·2 [55]	46·7 ± 4·1	$0{\cdot}8 > p > 0{\cdot}7$
Clearances, ml min^{-1}						
Cl_{tot}[c]	750 ± 131	711 ± 91	$0{\cdot}9 > p > 0{\cdot}8$	1132 ± 107 [1388]	918 ± 182	$0{\cdot}4 > p > 0{\cdot}3$
Cl_{ren}[d]	239 ± 17	149 ± 30	$0{\cdot}2 > p > 0{\cdot}1$	73 ± 12 [72]	158 ± 53	$0{\cdot}1 > p > 0{\cdot}05$
Cl_{met}[e]	625 (474, 776)	599 (685 ± 59, 512)	$0{\cdot}9 > p > 0{\cdot}8$	1060 ± 105 [1317]	885 (1144 ± 185, 627)	$0{\cdot}3 > p > 0{\cdot}2$
$Cl_{met} - Cl_{bil}$[f]	377 (364, 389)	368 (490 ± 53,245)	$p > 0{\cdot}9$	273 ± 33 [334]	493 (703 ± 59, 283)	$0{\cdot}2 > p > 0{\cdot}1$
Cl_B[g,h]	248 (110, 387)	231 (195 ± 59, 267)	$0{\cdot}9 > p > 0{\cdot}8$	779 ± 107 [983]	393 (441 ± 191, 344)	$0{\cdot}1 > p > 0{\cdot}05$
$f_B^{(i,g)}$	0·29 (0·15, 0·42)	0·32 (0·21 ± 0·09, 0·42)	$p = 0{\cdot}5$	0·69 ± 0·03 [0·71]	0·41 (0·32 ± 0·14, 0·49)	$0{\cdot}02 > p > 0{\cdot}01$ S
$f_B^{(j,g)}$	0·21 (0·08, 0·33)	0·15 (0·11 ± 0·08, 0·18)	$0{\cdot}6 > p > 0{\cdot}5$	0·39 ± 0·05 [0·51]	0·19 (0·15 ± 0·18, 0·22)	$0{\cdot}05 > p > 0{\cdot}02$ S[u]
$f_{ent}^{(k,g)}$	0·09 (0·08, 0·10)	0·18 (0·11 ± 0·02, 0·24)	$0{\cdot}4 > p > 0{\cdot}3$	0·35 ± 0·11 [0·20]	0·21 (0·17 ± 0·08, 0·27)	$0{\cdot}5 > p > 0{\cdot}4$
Cl_{ren}[d] of conjugate	102 ± 17	148 ± 46	$0{\cdot}6 > p > 0{\cdot}5$	109 ± 19 [142]	174 ± 28	$0{\cdot}1 > p > 0{\cdot}05$
Volumes of distribution (l)						
v_c[l]	19·8 ± 1·1	25·9 ± 2·0	$0{\cdot}05 > p > 0{\cdot}02$ S	27 ± 4 [27]	35 ± 9	$0{\cdot}5 > p > 0{\cdot}4$
v_{pss}[m]	106·2 ± 29	109·1 ± 51	$p > 0{\cdot}9$	83 ± 10 [108]	63 ± 16	$0{\cdot}3 > p > 0{\cdot}2$
v_{ss}[m]	65 ± 17	65 ± 18	$p > 0{\cdot}9$	— [87]	48 ± 8	$0{\cdot}4 > p > 0{\cdot}3$[v]
$v_{d_{met}}$[o]	8·2 ± 0·3	11·4 ± 3·8	$0{\cdot}5 > p > 0{\cdot}4$	4·4 ± 1·2 [7·2]	15 ± 3	$0{\cdot}01 > p > 0{\cdot}001$ S
Per cent of dose in urine						
Drug	18·6 ± 4·0	13·1 ± 1·2	$0{\cdot}4 > p > 0{\cdot}3$	7·7 ± 0·9 [7·1]	4·6 ± 0·8	$0{\cdot}1 > p > 0{\cdot}05$
Drug conjugate	54 ± 11	68 ± 2	$0{\cdot}5 > p > 0{\cdot}4$	54 ± 5 [43]	75 ± 6	$0{\cdot}05 > p > 0{\cdot}02$ S

[a] Parameter values are the averages of the means obtained from studies performed (Table 1) in each dog. The averages of values from 3 dogs are given ± SEM, $n = 3$. When averages ($n = 2$) of 2 dogs are only available, the means for the individual dogs B and C, separated by a comma, are given in the parenthesis after the average. If three studies were conducted in 1 dog, the mean ± SEM is given in the parentheses. The square bracketted values in the naltrexone column (when dosed alone) are the averages from study B2N and C2N. The non-bracketted averages ± SEM ($n = 5$ or 6) include the values from these two studies and from the 5 mg kg^{-1} dose studies previously published.[17]

[b] Parameters estimated from best fit of naltrexone base (ng ml^{-1}) and morphine base (ng ml^{-1}) in plasma against time to $Ae^{-\alpha t} + Be^{-\beta t} + Ce^{-\gamma t}$. Only in one study of morphine administered alone (study B1M) and in two studies (B4MN and B6MN$_{INF}$) when naltrexone was coadministered did morphine plasma concentration exhibit a detectable third (γ) phase. The estimated values of $Ce^{-\gamma t}$ [C in (ng ml^{-1} mg^{-1} kg^{-1}) and γ in min^{-1}] of the terminal phase were B1M:$43{\cdot}6e^{-0{\cdot}00279t}$ ($t^{\gamma}_{½}$ = 249 min); B4MN:$15{\cdot}0e^{-0{\cdot}00235t}$ ($t^{\gamma}_{½}$ = 296 min); and B6MN$_{INF}$:$42{\cdot}0e^{-0{\cdot}00409t}$ ($t^{\gamma}_{½}$ = 169 min).

[c] Total clearance estimated from ratio of dose to total area under plasma versus time curve $D_0/AUC_{0\to\infty}$ where $AUC_{0\to\infty} = A/\alpha + B/\beta + C/\gamma$.

[d] Renal clearance estimated from the slope of cumulative amounts of drug (or conjugate) excreted into the urine, ΣU_t, against the area under the plasma concentration–time curve at that time of collection, AUC_t.

[e] Metabolic clearances of drugs to conjugates are estimated from the averages of $Cl_{tot} - Cl_{ren}$ data when bile was not collected.

[f] The apparent differences ($Cl_{met} - Cl_B$) between the metabolic clearance (Cl_{met}) of drug to conjugate and the clearance of drug conjugate into the bile (Cl_B) as estimated from appropriate plots of equation (5).

[g] Since dog A was bile cannulated, equation (5) is inoperative for dog A. Thus only the averages ($n = 2$) of the means of study values for dogs B and C are given to equally weight each dog in the overall average.

[h] Biliary clearance, Cl_B, was estimated from the difference between Cl_{met} and ($Cl_{met} - Cl_B$) values.

[i] $f_B = Cl_B AUC/Dose$, the theoretical fraction of the dose excreted as conjugate in the bile (equation (8)).

[j] $f'_B = (Cl_{met} AUC/Dose) - f_B$, the fraction of the dose conjugated and not excreted in the urine (equation (9)).

[k] $f_{ent} = f_B - f'_B$, the fraction of the dose that is enterohepatically recirculated (equation (10)). For derivations see section on Integral methods to determine biliary clearances and volumes of distribution of metabolites after administration of morphine and naltrexone.

[l] Apparent central compartment volume of distribution referenced to morphine (or naltrexone) concentration in plasma $V_c = D_0/(A + B)$.

[m] Apparent overall pseudo-steady state volume of distribution from the total clearance and the rate constant of the terminal plasma phase, β or γ; $V_{pss} = Cl_{tot}/\beta$ (or γ).

[n] Steady state volume of distribution obtained from i.v. dose × (AUMC)/(AUC)^2 where AUMC is the total area under the first moment curve.[27]

[o] $V_{d_{met}}$ is the apparent volume of distribution of conjugate metabolite on the premise of its production into a rapidly equilibrated one-compartment body model. It can be determined from the intercept of appropriate plots of equation (5).

[p] Unless footnoted differently, the probability (p) of no differences in these averages (between drug alone and when one drug is coadministered with the other) was determined by paired t-test among 3 dogs with df = 2. Unless footnoted differently the p values reported herein for the paired t-test were not widely different from t-tests of differences between averages when values from previous pharmacokinetic studies on *ca.* 4·7 mg kg^{-1} of morphine alone[19] were included in the obtained averages among dogs for single drug administration.

[q] $p \leqslant 0{\cdot}05$ is considered a significant probability to warrant rejection of the null hypothesis that there is no difference between the value from administration of one drug alone and the value from coadministration of both drugs. Values with significant differences by t-test are marked with S.

[r] Parameter values are the averages of the means obtained from the present studies B2N and C2N in dogs B and C plus results from the 5 mg kg^{-1} doses of naltrexone previously published.[17] The averages of $n = 5$ or 6 dogs are given ± SEM. The values in the squared brackets are the averages of the two values obtained in the present study of dogs B and C when each was administered 5 mg kg^{-1} doses of naltrexone alone.

[s] Values from previous studies[17] on administration of 5 mg kg^{-1} naltrexone were included so that df = 5–7 in applying the t-test to challenge the null hypothesis of no difference between averages of dogs administered naltrexone alone and averages of dogs coadministered naltrexone and morphine. Unless footnoted differently, paired t-tests and t-tests of averages of *all* studies with and without coadministered morphine showed similar p values for confidence in the null hypothesis of no difference.

[t] The paired t-test, df = 1, for the values obtained for the studies presented herein (Table 1) was also significant; df = 1, ($p < 0{\cdot}05$).

[u] The t-test (df = 10) with the probabilities ($p < 0{\cdot}05$) cited here rejected the null hypothesis for no difference between the averages of all studies with naltrexone alone and *all* studies with coadministered naltrexone and morphine (independent of which dog was studied). The t-test for rejection of the null hypothesis of no difference between the dog averages of means (with and without coadministered morphine) just missed statistical significance ($0{\cdot}1 > p > 0{\cdot}05$).

[v] By paired t-test, df = 1.

amounts of unchanged drug excreted into the urine at infinity and time t respectively.

Naltrexone plasma concentrations were fitted (equation (1)) by a sum of two exponentials (except for study $B6MN_{INF}$ where naltrexone was infused for 293 min and study C3MN where *no* α phase was detected). A third (γ) exponential phase was observed in naltrexone urinary data, $t_{½} = 808$ (330 and 1286) min. It was hypothesized in previous studies[10,17] that these (γ) phases were due to the recycling of conjugates secreted in the bile, subsequently gastrointestinally split, and reabsorbed as parent compound into the systemic circulation.

Effects of coadministered drugs on the plasma pharmacokinetics of morphine, naltrexone and their conjugates

The averages from the morphine pharmacokinetic studies in each dog for morphine administered alone and for naltrexone coadministered with morphine were challenged by paired t-test[26] and the probabilities of the null hypothesis of no difference are given in Table 3. Only one pharmacokinetic parameter, the apparent volume of distribution of the central compartment, showed a significant difference between the values averaged from morphine alone and when naltrexone was coadministered. In all other cases, it can be concluded that naltrexone coadministration had no significant effect on morphine plasma concentration–time parameters, clearances, and apparent volumes of distribution.

Plasma concentrations of morphine conjugates in four out of the five interaction studies (see representative plots in Figure 5) were reduced when naltrexone was coadministered.

Coadministered morphine did not significantly affect the plasma pharmacokinetics of naltrexone except for the coefficient (B) of the second exponential of equation (1). There were no significant differences by t-test of the differences (see Table 3) between the parameter averages, clearances or apparent volumes of distribution for naltrexone with or without coadministered morphine. Also, bolus i.v. morphine addition did not change the steady state plasma concentration of constant rate infused naltrexone in study $B6MN_{INF}$ (Figure 6).

Plasma concentrations of naltrexone conjugate increased for $>4{\cdot}3\,mg\,kg^{-1}$ morphine coadministered with $5\,mg\,kg^{-1}$ of naltrexone (studies B3MN and C3MN) over those when naltrexone was administered alone (studies B2N and C2N) in both dogs B and C, respectively (Figure 7). In the one instance when a lower dose of morphine (study B4MN; $2{\cdot}4\,mg\,kg^{-1}$) was coadministered with $5\,mg\,kg^{-1}$ of naltrexone, the naltrexone conjugate plasma concentrations did not exceed those observed when naltrexone was administered alone (B2N). Nevertheless, the average total area under the curve of naltrexone conjugate plasma concentration per $mg\,kg^{-1}$ of naltrexone dose vs time was significantly higher when morphine was coadministered ($126\,(\mu g\,ml^{-1}\,min^{-1})/(mg\,kg^{-1}) \pm 28$

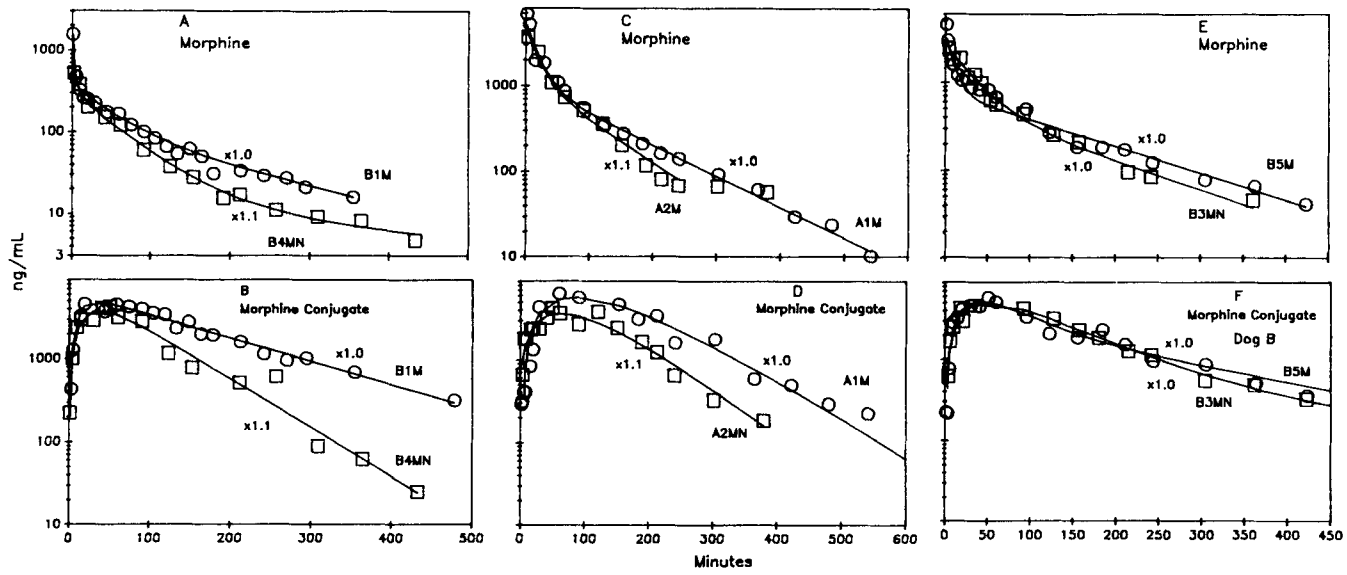

Figure 5. Representative semilogarithmic plots of plasma concentrations of morphine (panels A, C, E) and its conjugate (panels B, D, F) against time. The symbols are: for morphine administered alone O; with naltrexone □. Curves are labelled with study identifications (Table 1) and the multiplying values of dose ratios used to adjust the data to the same dose for comparative purposes

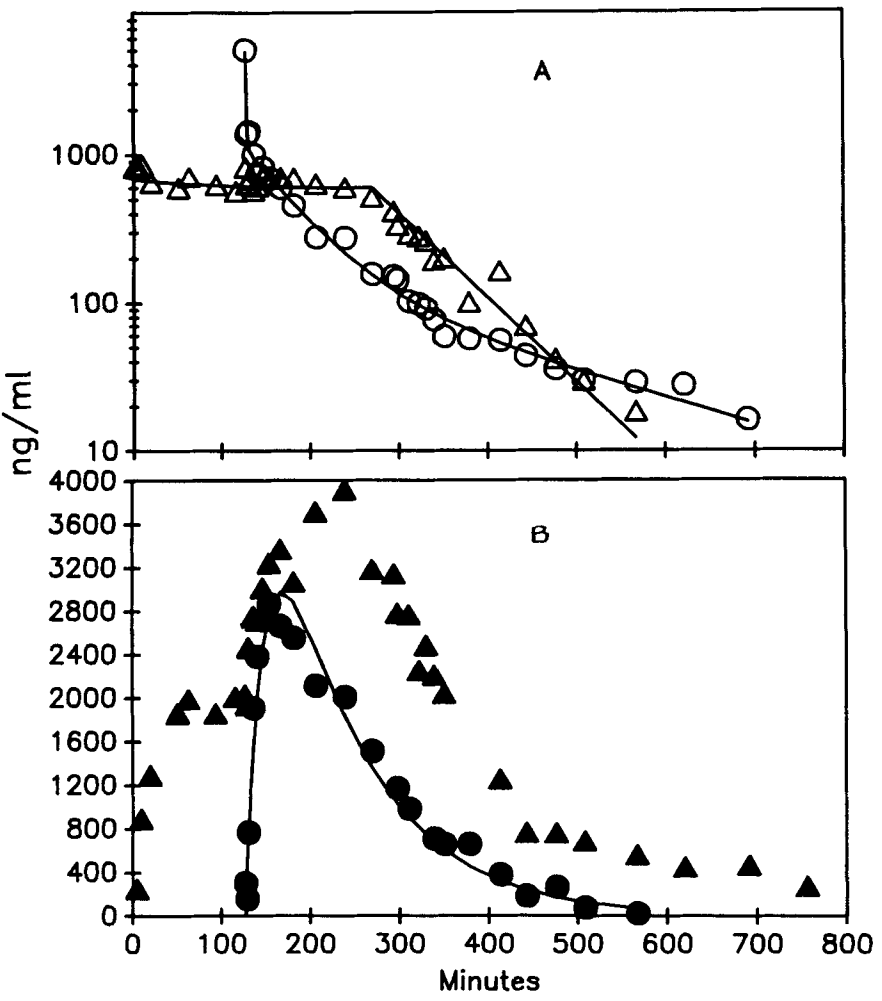

Figure 6. Plots of plasma concentration of morphine (○), its conjugate (●), naltrexone (△), and naltrexone conjugate (▲) against time when morphine is injected as a bolus during the steady state infusion of naltrexone. The data are taken from study $B6MN_{INF}$

($n = 5$, studies A2MN, B3MN, B4MN, $B6MN_{INF}$, and C3MN)) as compared to when naltrexone was administered alone (65(42,88) $\mu g\,ml^{-1}\,min^{-1}$ ($n = 2$, studies B2N and C2N)) This was confirmed by application of the Dixon-Hood nonparametric[28] test which demonstrated a significant difference at the 95 per cent confidence level.

Also, steady state naltrexone conjugate plasma levels increased sharply with the renal and biliary perturbation processes that undoubtedly resulted when morphine was injected (Figure 6). The perturbation of the renal process by

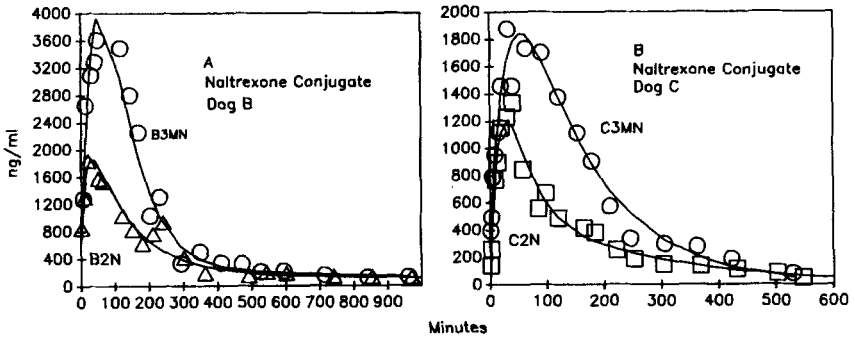

Figure 7. Plots of plasma concentrations of naltrexone conjugates against time. Studies B2N and C2N were without simultaneously administered morphine whereas Studies B3MN and C3MN were with coadministered morphine. Curves are labelled with study number

morphine resulted in the delay of drug and conjugate urinary excretion (Figure 8). Also, the apparent overall volume of distribution of the naltrexone conjugated metabolite ($V_{d_{met}}$ in Table 3) was significantly enhanced by morphine coadministration.

Total clearances and apparent volumes of distribution

The total clearance of morphine when administered alone to 21–27 kg dogs in this study averaged 750 ± 131 ml min^{-1} (Table 3). Previous studies[10] estimated total clearances of 340 ± 43 (SD) ml min^{-1} (range 290–370 ml min^{-1}) at 7·2–7·7 mg kg^{-1} and 701 ± 138 (SD) (range 554–886 ml min^{-1}) at doses below 0·5 mg kg^{-1} for dog weights between 11·0 and 16·0 kg. If clearances are standardized by the dog's weight, the previous studies 25·2 ± 3·1 ml min^{-1} kg^{-1} [10] and 23·6 (21·8 and 25·4)[19] are not inconsistent with our results (30·8 ± 4·3 ml min^{-1} kg^{-1}).

Naltrexone was cleared more rapidly; its total clearances averaged 1132 ± 107 ml min^{-1}, a value close to the 1388 average of the two naltrexone studies conducted herein.

Coadministration of morphine and naltrexone did not significantly affect (by *t*-test, Table 3) the clearances or apparent volumes of distribution (other than that of the central compartment for morphine) of either drug administered alone.

Renal clearance

Representative plots of urinary data of morphine and naltrexone (Table 3) according to equation (2) can be seen in Figure 8. The intercepts for such plots should be zero if there is no cessation of urine flow and/or no cessation of renal processes. This is true when naltrexone is given alone or morphine is given at the very low doses ($< 0{\cdot}4$ mg kg^{-1})[10] which do not affect renal function. As demonstrated previously,[10] increased morphine dose can decrease urine

flow (0·40–0·47 at mg kg^{-1} in the dog)[10] and/or renal processes (such as glomerular and tubular secretion at 7·2–7·7 mg kg^{-1} in the dog)[10] and increase time lags before renal excretion. Consequently, negative intercepts for both morphine and naltrexone clearance plots are apparent in Figure 8.

When naltrexone was given by continuous i.v. infusion, a constant renal clearance was observed prior to morphine injection of 3·8 mg kg^{-1} (Figure 9A and equation (2)). Thereafter, naltrexone urinary excretion was hindered by the cessation of urine flow. However, the drug was apparently still filtered by the glomerulus and stored in the lower urinary tract at this morphine dose since it was eliminated when urine flow was regained. This is apparent from the ΣU vs t plot (Figure 9(B)) where a constant renal clearance fits the amounts of naltrexone excreted before and after the cessation of urine flow. This also indicates that no alternative excretion pathways were favored during the times of urine flow inhibition at this morphine dose.

The fact that morphine inhibits its own and naltrexone's urinary elimination is illustrated in Figure 10. The cumulative amounts of morphine, naltrexone, and their glucuronides are plotted against time and fitted lines are drawn through the symbols in accordance with equation (2), using the calculated renal clearances and intercepts. In general, the calculated ΣU conformed to the experimentally obtained values showing that parent compound and metabolite clearances were constant as long as the renal function was operative and there was adequate urine flow. However, it can be seen that increasing doses of morphine inhibited its own and naltrexone's initial elimination due to dose-dependent periods of urine flow cessation.

When morphine alone was administered to these 22–27 kg dogs the renal clearances averaged 239 ± 17 ml min^{-1} (Table 3), considerably higher than the clearances reported earlier[10,19] (85 ± 9 ml min-1 for dogs with an average weight of 13·1 kg (11·0–16·0).[10] The discrepancy in clearances between these studies may be due to the differences in the weights of the dogs studied although it seems excessive. Since the glomerular filtration rate for a 20 kg dog has been claimed to be 40–130 ml min^{-1},[29] the previous suggestion[10] that morphine is filtered by the glomerulus and tubularly secreted is supported. The conjugate, with an estimated renal clearance of 102 ± 17 ml min^{-1}, can be eliminated solely by glomerular filtration or by glomerular filtration with accompanying tubular secretion and compensatory reabsorption. Renal clearances for parent compound and metabolite were independent of urinary flow and pH.

The renal clearances of naltrexone were independent of pH values and averaged 73 ± 12 ml min^{-1}, a value close to the 71 ± 11 reported by Garrett and El-Koussi.[17]

Renal disposition

Unchanged naltrexone and its conjugates excreted into the urine were $7·7 \pm 0·9$ per cent and 54 ± 5 per cent of the dose, respectively. When morphine

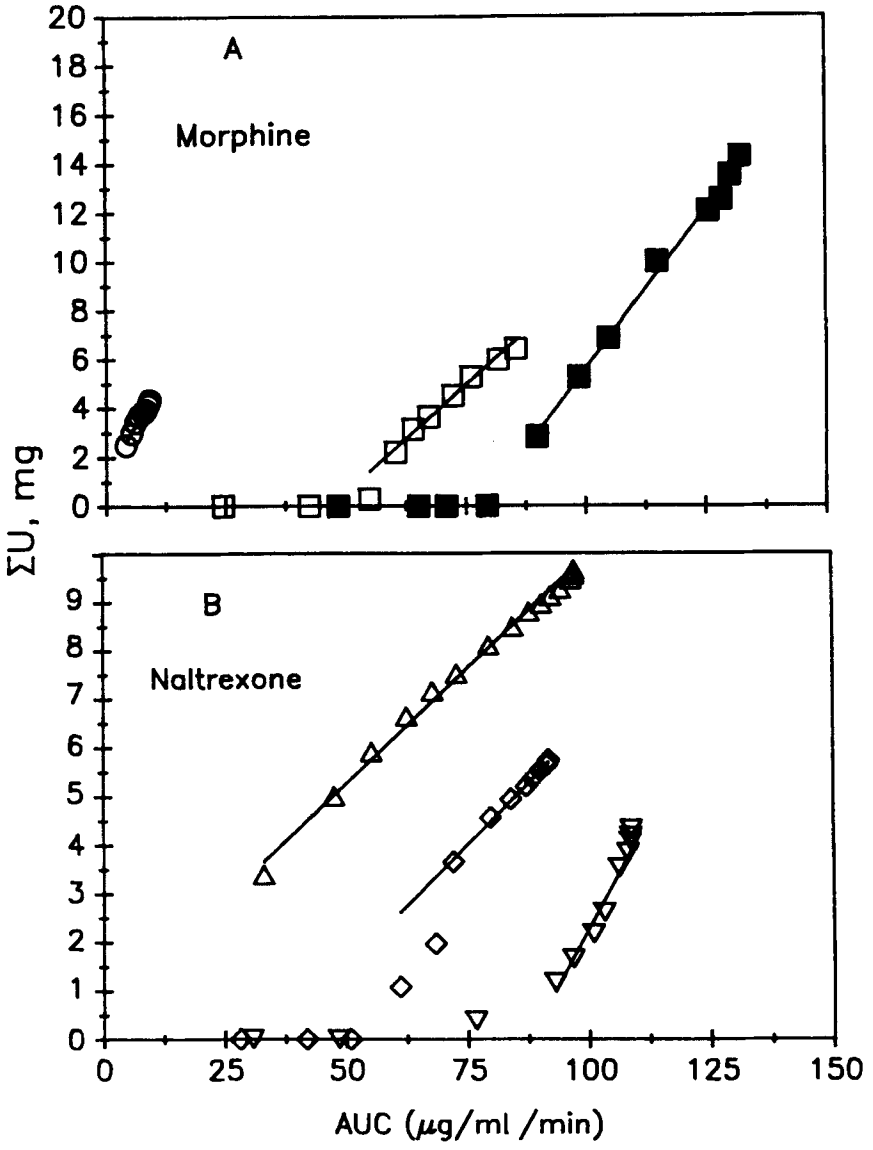

Figure 8. Representative plots of cumulative amounts excreted into the urine (ΣU) against the area under the plasma concentration time curve (AUC) for morphine (A) and naltrexone (B) fitted in accordance with $\Sigma U = Cl_{ren}AUC$ + intercept. The studies for low, medium, and high doses of morphine alone in panel A are: ○ study C1M, 0·4 mg/kg; □ study B1M, 2·8 mg/kg; ■ study B5M, 4·7 mg/kg, respectively. In panel B, study B2N (△) is for naltrexone dosed alone and studies B4MN (◇), and B3MN (▽) are for naltrexone dosed with medium (2·4 mg kg^{-1}) and high (4·8 mg kg^{-1}) doses of morphine, respectively

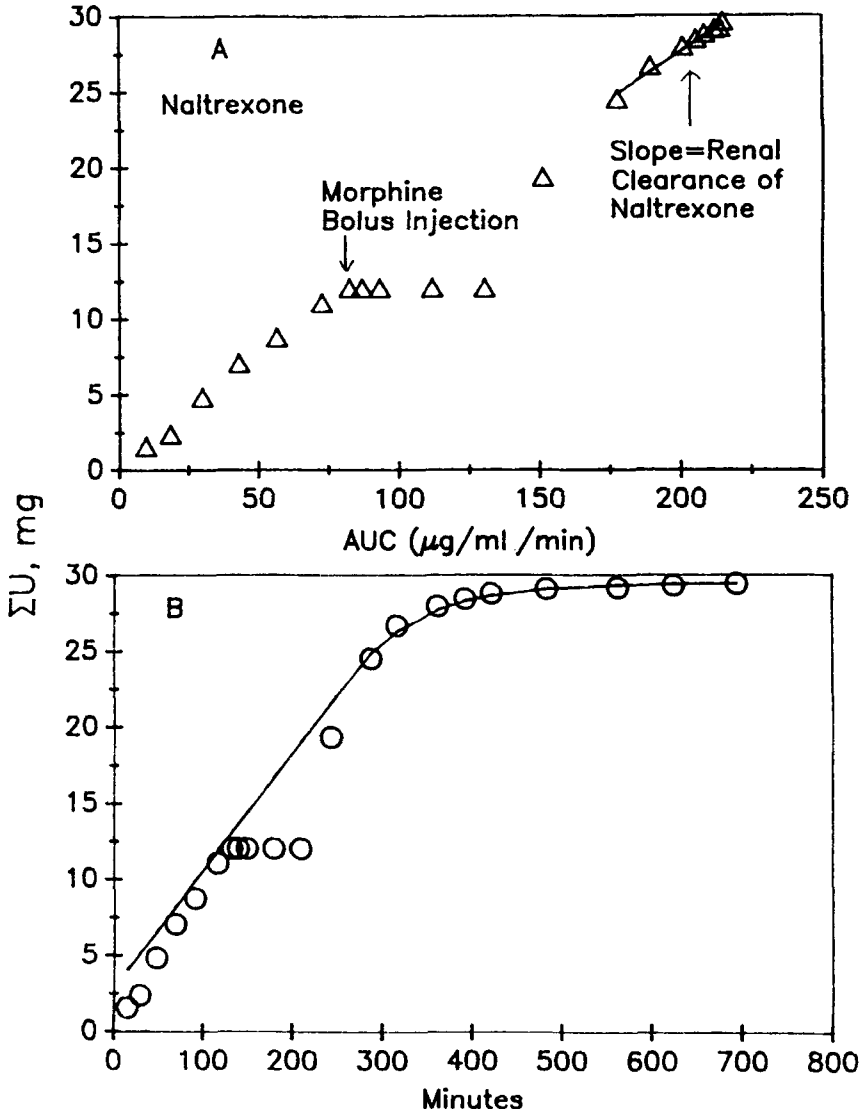

Figure 9. Plots of cumulative amounts of naltrexone excreted into the urine (ΣU) via urinary cathether against the AUC (panel A) and time (panel B) for study $B6MN_{INF}$. The line drawn through the experimental points in panel B is calculated ($\Sigma U = Cl_{ren}AUC$) from the renal clearance value obtained from panel A

was coadministered, the amount of naltrexone excreted unchanged did not change significantly (Table 3). However, the amount eliminated as conjugate significantly increased by *t*-test to 75 ± 6 per cent. The overall percentages of the dose excreted in the urine as unchanged morphine or as conjugate were not significantly different when morphine was given alone or with naltrexone.

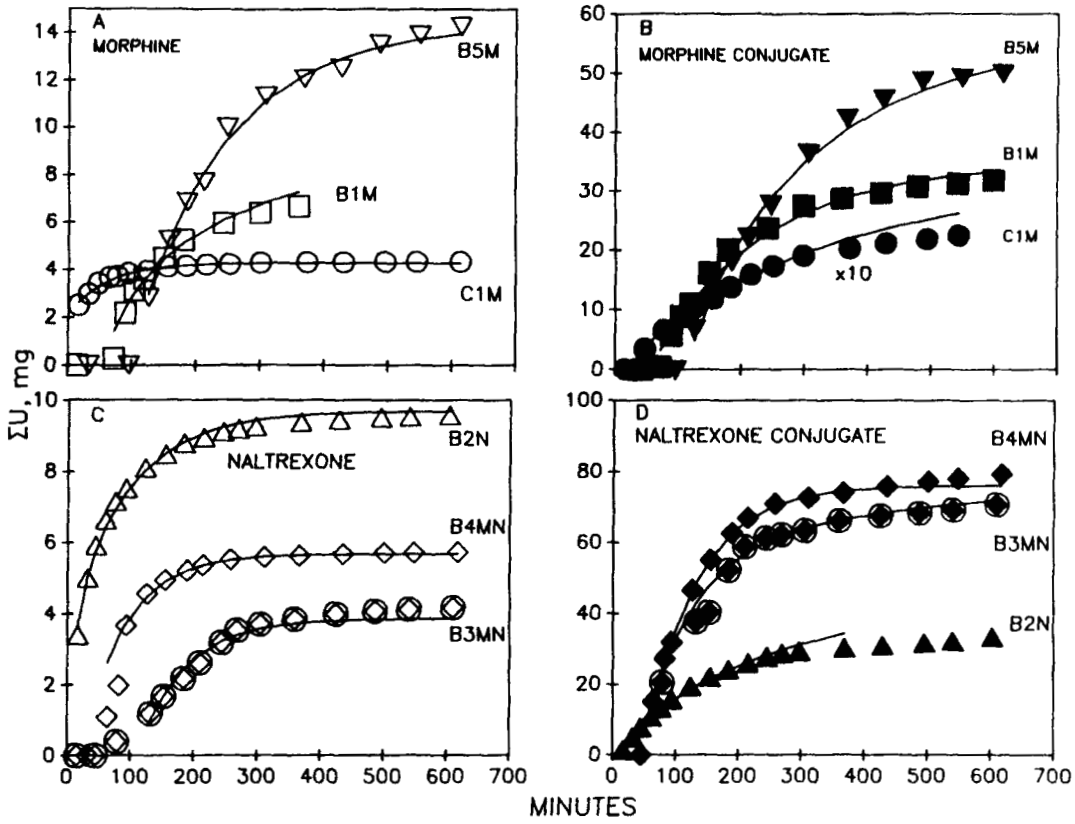

Figure 10. Representative plots of cumulative amounts (ΣU) of morphine (panel A), morphine conjugate (panel B), naltrexone (panel C), and naltrexone conjugate (panel D) excreted into the urine fitted in accordance with $\Sigma U = Cl_{ren}AUC$ + intercept. The symbols, study, and mg kg^{-1} morphine doses when only morphine is administered are: ○, ●, C1M, 0·4; □, ■, B1M, 2·8; ▽, ▼, B5M, 4·7. The symbols, study and mg kg^{-1} morphine doses when 5·0 mg kg^{-1} of naltrexone is coadministered are: △, ▲, B2N, 0·0; ◇, ◆, B4MN, 2·4; ◇, ◉, B3MN, 4·8

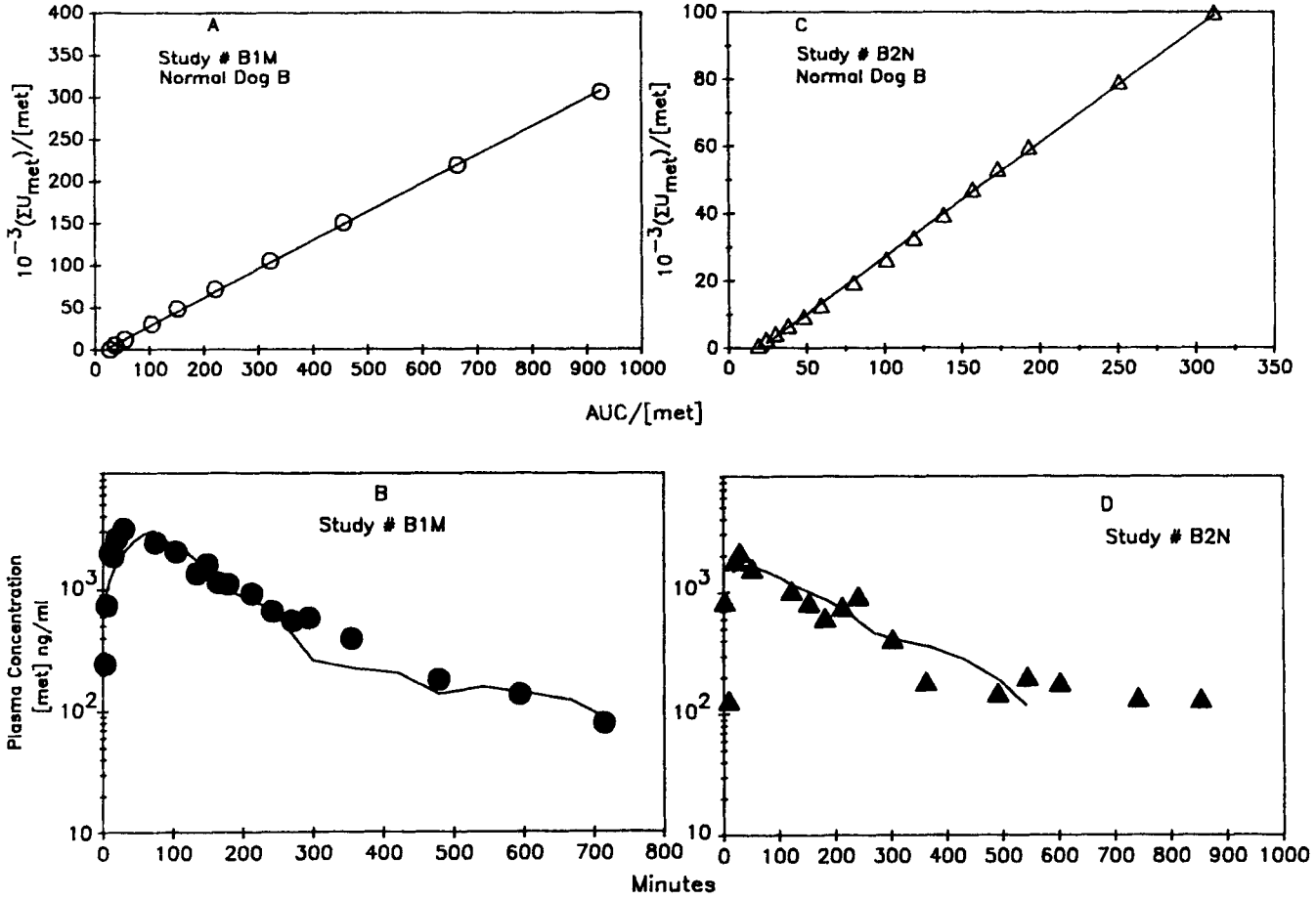

Figure 11. Examples of plots for morphine and naltrexone in accordance with equation (5) for the normal dog B of studies B1M and B2N (panels A and C). The fits of metabolite concentrations in plasma in accordance with equation (6) are given in respective panels B and D for the morphine and naltrexone studies, respectively

Fitting of plasma metabolite concentration by the 'integral method'

Examples of fitted metabolite concentrations are given in Figures 11(B) (for morphine) and 11(D) (for naltrexone). Direct plasma conjugate measurements were consistent with [met] calculated from equation (6) except for the terminal phase ($t > 500$ min) of Figure 11(D) where measured plasma concentrations of naltrexone conjugates exceeded the calculated levels. This elevation in plasma conjugates in the non-bile-cannulated dog can be assigned to material returned to the system by enterohepatic recirculation of the bile contents whereas equation (6) does not account for this enterohepatic conjugate return. Imperfections in the fit may be due to both normal statistical variation and the possibility of random acute gallbladder emptying. The initial plasma concentration of metabolite predicted from equation (6) may be less than those observed since complete equilibration in the body fluids may be time dependent. Thus the underlying postulate of equation (6) of a one compartment body model would not hold at early times. The estimated biliary clearances of morphine after morphine administration alone averaged 248 ml min^{-1} and were not significantly different from those after coadministration with naltrexone (231 ml min^{-1}). The biliary clearances for naltrexone administered alone averaged 779 ± 107 ml min^{-1} which was greater (but not at the $p < 0{\cdot}5$ level of significance) than the 393 ml min^{-1} when morphine was coadministered (Table 3). Thus it appears that although coadministration of morphine could inhibit the biliary excretion of naltrexone conjugate at the doses studies, naltrexone did not affect the biliary excretion of morphine.

It can be estimated (Table 3) that 0·285 (f_B) of the total dose of morphine is secreted into the bile (equation (8) as conjugates in the non-bile cannulated animal, a value not significantly changed by naltrexone coadministration.

The estimated biliary secretion of naltrexone as conjugate averaged 69 ± 3 per cent of the dose (Table 3). However, when morphine was coadministered with naltrexone, the estimated biliary secretion of naltrexone conjugate dropped to 41 per cent, a significant decrease by t-test (Table 3, f_B values).

DISCUSSION

Coadministration in the dog of i.v. bolus 5 mg kg^{-1} of the opioid antagonist naltrexone did not affect significantly (by t-test) i.v. bolus 0·5, 2·7, and 5 mg kg^{-1} morphine's plasma half-lives, clearances (total, metabolic, renal, and biliary), apparent overall volumes of distribution (steady state and pseudosteady state), time lags in recommencement of urine flow, and the per cents (of dose) of unchanged morphine and morphine conjugate renally and biliary excreted. Similarly, coadministered morphine did not affect the pharmacokinetics of naltrexone except for significantly enhancing the conjugate excreted into urine. The apparent overall volume of distribution of naltrexone conjugate was significantly increased with the coadministration of morphine.

In contrast to naltrexone coadministration lessening the plasma concentration of morphine conjugate in four out of five instances, the naltrexone conjugate plasma concentrations were significantly enhanced on the coadministration of morphine since metabolic processes still proceed during periods when elimination is not operational.

A possible explanation of the former could be that, since both drugs are enterohepatically recirculated, hydrolysis of morphine conjugate in the gut, before reabsorption and first pass reconjugation, may be competively inhibited by the presence of large amounts of naltrexone conjugate, or of derived naltrexone. The latter phenomenon could be readily explained by the well-documented[10–19] perturbation of renal and biliary pathways by morphine, with and without coadministered naltrexone.

Morphine decreases urine flow since it causes the release of antidiuretic hormone (ADH) from the neurohypophysis and also spastic contractions of the smooth muscle (detrusor and sphincter) in the urinary tract.[30,31] Pressure in the biliary tract is also increased due to constriction of the sphincter of Oddi.[32] Although naltrexone administered alone did not inhibit bile[17] and urine flow (Figures 8 and 9), its coadministration did not affect the time lag in urine flow (Figure 2) and bile flow[10] initiated by morphine. Consequently, morphine coadministration could produce the increased plasma concentration of naltrexone conjugate (Figure 7). This increase would not translate into increased biliary elimination (f_B in Table 3 significantly decreased by t-test) since only hepatically formed conjugates of opiods appear to be secreted into bile.[10] Although this increased amount of naltrexone conjugate in the systemic circulation suffers a delay in its urinary excretion, it must eventually be eliminated by this route and thus urinary excretion of naltrexone conjugate is enhanced by morphine coadministration. The fact that there was no significant difference in the amount of unchanged morphine or its conjugate excreted in the urine when naltrexone was not administered indicates that morphine perturbation of renal processes was the same with and without naltrexone coadministration. Thus, the fact that the per cent of the dose urinary excreted as naltrexone conjugate when drugs are coadministered (75 ± 6 per cent) is statistically significantly (Table 3) larger than when naltrexone alone is administered (54 ± 5 per cent) is readily explained. Thus it can be concluded that morphine coadministration significantly affects naltrexone's disposition by its perturbation of renal and biliary processes.

Since the miotic effect of morphine is a specific opioid receptor mediated effect,[33] this action should be reversed by opioid antagonists. In contrast to naltrexone's lack of effects on morphine's pharmacokinetics, disposition, and perturbations of renal and biliary flow rates, coadministered naltrexone did significantly reverse morphine's central action in affecting monitored pupil diameters (Figure 3 and Table 2). Morphine induces miosis in the human, dog, and rabbit which is thought to be mediated through the central nervous system.[33,34] Theories have been advanced suggesting that morphine produces

its effect by direct stimulation of the Edinger-Westphal nucleus[22] which is part of the nuclei of the oculomotor nerve. However, the significance of opioid-induced pupil effects as a measure of analgesia remains unclear although it has been argued that correlations exist between miosis and analgesia.[34]

The fact that marked pupil constriction up to 1000 min did not correlate with and significantly outlasted the analytical sensitivity (up to 540 min) of plasma concentration of morphine, suggests a 'deep compartment' or a prolonged receptor half-life of morphine at its site of action. Another possible explanation is an indirect relationship between plasma morphine concentration and response intensity that is mediated by endogenous substances. The slow achievement of a maximum response (t_{max} in Table 2) also implies that the site of pharmacodynamic action (receptor drug-interaction) has the characteristics of a deep compartment. A reviewer of this manuscript prefers to assign these phenomena to the slow return of morphine glucuronide from the brain.

ACKNOWLEDGEMENTS

This study was supported by a grant from the scientific committee of NATO and the DAAD and in part by grant DABB 5R01 DA00743–15 from the National Institute of Drug Abuse.

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