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## Pharmacokinetic Parameters of Morphine After Ocular Instillation Versus Intravenous Administration

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### Abstract

The route of administration of morphine, other than parenteral administration, may be promising in increasing the compliance in patients that continuously need morphine for its analgesic effect. Morphine systemic penetration was investigated after ocular instillation. Its pharmacokinetic parameters and its bioavailability after ocular instillation compared to its intravenous administration were determined in healthy New Zealand Albino rabbits. A cross over design was performed with an eight-days wash-out period between the ocular and intravenous administrations. After ocular instillation, morphine was rapidly absorbed and attained serum levels compatible with effective concentration for its analgesic effect. Ocular bioavailability of morphine was high, 66%. Ocular administration of morphine could provide prolonged high serum levels and prolonged systemic pharmacologic effect. Ocular administration of morphine should be considered for its systemic pharmacologic effect.

### Introduction

**PAIN** is one problem physicians face especially in caring for chronically ill terminal cancer patients. Morphine is a commonly used and useful medication in such cases. It elevates the threshold of pain and increases the patient's ability to tolerate it. Morphine alleviates the anxiety, fear, panic and suffering sensations that usually accompany pain [1].

Morphine is usually administered parenterally. There are also recently developed measures for morphine administration e.g. extradural or intrathecal injections. Parenteral routes are all painful and require special precautions and skill, which prevent good compliance to treatment [2]. Oral morphine is also used but its effectiveness is hindered by the high hepatic extraction rate and the extensive first pass metabolism [3].

Local ocular instillation of drugs is used for ophthalmic problems e.g. B-adrenergic blockers and pilocarpine in the treatment of glaucoma. Some of the drugs are associated with systemic side effects as a result of their systemic absorption [4]. In fact, topically applied ophthalmic medications can attain sufficient serum levels which can be linked to the intravenous rather the oral administration as they bypass the first pass metabolism [5, 6].

The present study aimed to evaluate morphine systemic penetration, by describing its pharmacokinetic parameters, after ocular instillation. The bioavailability of ocularly instilled morphine compared with intravenous administration was also investigated.

#### Material and Methods

##### *A-Materials Used:*

1- Morphine sulphate (Misr Company, Cairo-Egypt). As small volumes were used for ocular instillation, it was prepared in high concentration (20 mg/ml.)

2- Reagent Kits for Morphine Radio-Immuno-Assay (Diagnostic product Corporation "D.P.C.", California-U.S.A.).

##### *B- Study Design:*

Five healthy New Zealand Albino rabbits were used to determine the pharmacokinetic parameters and bioavailability of morphine after ocular instillation compared to intravenous administration. A cross-over design with eight-days wash-out period between the ocular and the intravenous administration of morphine was used.

##### *C- Experimental Procedures:*

Animals were placed, each, in a restraining cage un-anaesthetized as all manipulations were painless. The marginal

ear vein was cannulated for blood sampling, using an intravenous silicon catheter (Abboth) with a 22-gauge needle. Blood clotting inside the catheter was prevented by injecting sodium heparin (200 IU) into the catheter every hour. The other marginal vein was also cannulated for intravenous administration of morphine.

Morphine in a total dose of 1 mg/kg body weight was locally instilled in the cul-de-sac of both eyes of the animal by means of micro-pipette (Eppendorf). The intravenous administration of morphine was through the marginal ear vein in a dose of 1 mg/kg body weight. It was followed by injection of 2 ml saline.

Blood samples (2 ml) were collected at 0, 5, 10, 20, 40, 60, 90, 120, and 180 minutes after either intravenous or ocular administration. Blood samples were left to stand for 10 minutes at room temperature and then centrifuged for 10 minutes at 3000 rpm. Serum was collected and stored at -20°C until morphine concentration was determined.

##### *D-Assay Method:*

Serum concentration was determined by a solid phase  $^{125}$ I radio-immuno-assay using kits from Diagnostic Product Corporation (DPC). The intra and inter assay coefficient of variation were 3.5% and 5.2%, respectively.

##### *E-Pharmacokinetic Calculations:*

The plasma concentration-time data were investigated using a two compartment model with first order kinetics. All calculations of pharmacokinetic parameters were based according to "Manual of Pharmacologic Calculations with Computer Programs" [7].

For the pharmacokinetic purposes, a

first order reaction is simply described as follows; the morphine is in opposition to a system which can remove a definite proportion of it as substrate in unit time. It is assumed, thus, that morphine installed in the eye leaves the site at a rate proportional to its concentration there. The elimination equation would be as in equation (1).

$$\frac{\partial M}{\partial t} = k_{12}M \quad (1)$$

If we consider that  $M_0$  is the amount of morphine present at time  $t=0$  and it is equal to the dose administered  $D$ , then the equation is solved as equation (2).

$$M = M_0 e^{-k_{12}t} = D e^{-k_{12}t} \quad (2)$$

Equation 2 shows how much of the morphine has still not left the ocular site of instillation and so has not yet appeared in the blood. The quantity  $B$  which has already passed into the blood is given by equation (3).

$$B = M_0 - M = D - M = D(1 - e^{-k_{12}t}) \quad (3)$$

However, not all the morphine administered by ocular route is absorbed and this has to be accounted for in the calculations. If the fraction of the dose of morphine that is absorbed is  $F$  and the volume of distribution is  $V_d$ ; then the curve or equation of absorption which expresses concentration ( $C_t$ : the morphine serum concentration at time  $t$ ) is as in equation (4).

$$C_t = \frac{FD}{V_d} (1 - e^{-k_{12}t}) \quad (4)$$

Since elimination occurs the moment morphine reaches the blood, equation 4 alone can not describe the serum concentration of morphine. The rate of lost quantities  $M$  and  $B$  of the morphine from the blood compartments and the blood concen-

tration can be obtained by solving the following two differential equations (5, 6).

$$\frac{\partial M}{\partial t} = k_{12}M \quad (5)$$

$$\frac{\partial B}{\partial t} = +k_{12}M - K_{20}B \quad (6)$$

Solving equation 5 and 6 simultaneously, we obtain equation (7). ( $M_0 = FD/V_d$  and  $B_0 = 0$ ).

$$C_t = \frac{FD}{V_d} \cdot \frac{K_{12}}{K_{12} - K_{20}} \cdot (e^{-k_{20}t} - e^{-k_{12}t}) \quad (7)$$

This is called the Bateman Function.  $K_{12}$  is sometimes referred as  $K_a$  and is called the rate constant for absorption and  $K_{20}$  is sometimes referred to as  $K_e$  and is called rate constant for elimination.

Half-life (half-time) of elimination was calculated using equation (8) as follows:

$$t_{1/2} = \frac{\ln 2}{k_e} \quad (8)$$

Total plasma clearance ( $CL_p$ ) was calculated according to equation (9).

$$CL_p (ml \cdot min^{-1}) = k_e * V_d (ml) \quad (9)$$

Referring to equation 7, the concentration of a drug in the serum at any time appears to depend on at least four quantities. These are; the dose administered ( $D$ ), the size of the volume of distribution ( $V_d$ ), the rate constant of absorption ( $K_a$ ) and the rate constant of elimination ( $K_e$ ). The  $V_d$  and the  $K_e$  of a drug are standard biological quantities for the individual person and remain constant except for biological variations. Thus simplification of equation 7 can be made by calculating the Area Under Curve (AUC) mathematically as the integral between zero and infinity of equation 7. This results in the disappearance of the

indices associated with absorption as in equation (10).

$$AUC = \frac{FD}{V_d} \cdot \frac{1}{K_{20}} \quad (10)$$

It thus appears that the AUC is proportional to quantity of the substance with which the system is loaded (dose proportional). It is also independent of the time course of absorption of the dose which actually appears in the blood i.e. independent from the form and rate of administration. If the same drug is given on two separate occasions each time by a different route; as in the present study (intravenous, where absorption is by definition complete and ocular), then the agreement between the areas obtained is an index of the completeness of absorption by the one route to the other.

Thus the bioavailability of ocularly instilled morphine in relation to that intravenously administered (F) was calculated according to equation (11).

(N.B.: AUC is  $AUC_{0-\infty}$ ).

$$F = \frac{AUC_{ocular} * D_{iv}}{AUC_{iv} * D_{ocular}} * 100\% \quad (11)$$

If morphine exhibits a biphasic concentration-time curve corresponding to distribution and elimination periods, this can be expressed as the following model; equation (12).

$$C_t = A \cdot e^{-\alpha t} + B \cdot e^{-\beta t} \quad (12)$$

Where  $C_t$  is the morphine concentration in the serum at time  $t$ , A and B are zero intercepts of the data and  $\alpha$  and  $\beta$  are the fast and slow first order rate constants, respectively. These are used to calculate the Mean Residence Time (MRT) for the central compartment ( $MRT_c$ ). MRT for the body ( $MRT_b$ ) and Mean Absorption Time

(MAT) according to equations (13 and 14).

$$MRT_c = \frac{A/\alpha + B/\beta}{A+B} \quad (13)$$

The MAT is calculated as follows:

$$MAT = MRT_a - MRT_{iv} \quad (14)$$

MRT calculated after intravenous administration is the statistical moment analogue to the drug half-life. It provides a quantitative estimate of the persistence of a drug in the body. Comparison of the MRT after intravenous administration with MRT after ocular instillation provides information regarding the mean absorption time.

## Results

Marked sedation was observed early after morphine administration, both through the ocular and the intravenous routes, and was maintained throughout the experiment. No signs of local or systemic toxicity of morphine; such as ocular irritation or respiratory depression, were noticed during the observation time.

The serum concentration of morphine was measured following the administration through the ocular route and the results are shown in Figure 1-A. This serum concentration curve shows shouldering near 40 minutes after drug instillation in the eye. The mean serum concentration is shown in Fig. 1-B. These serum concentrations, when plotted on a semi-logarithmic plot was not a straight line. The curve is probably the result of interaction of more than one compartment as in the Bateman Function, where the rate of absorption and rate of elimination are superimposed. The combined effect of these two rates gave rise to a biphasic curve (Figs. 1-C and D); the first phase governed by both absorption,

distribution, elimination and the latter by the elimination which is the slower of these processes.

Pharmacokinetic parameters of morphine after ocular instillation are represented in Table (1).

Data after intravenous administration were available for only 4 rabbits. All intravenous data and those about bioavailability are the result of the 4 rabbits. Fig. 2 shows the plasma concentration of morphine after it is administered intravenously. Fig. 2-A shows the individual values for the four rabbits and Fig. 2-b shows the mean value of the plasma concentration. Using the log regression to plot the plasma values on a semi-logarithmic scale, the curve clearly shows to be biphasic representing the interaction of distribution and elimination, the latter being the slower process. Table 2 shows the pharmacokinetic

parameters of morphine after its intravenous administration.

The relative bioavailability of morphine after it is administered through the ocular route is expressed by the fraction absorbed relative to that administered intravenously. The intravenous route results in 100% bioavailability. Table 3 shows the F fraction for each rabbit and their mean and standard deviation. The first rabbit had no intravenous data and the F fraction could not be calculated.

Fig. 3 shows the mean plasma concentration of morphine after ocular and intravenous administration.

The Mean Residence Time and Mean Absorption Time are shown in Table 4. The values A, a, B and  $\beta$  are shown in the table. The means of  $MRT_b$ ,  $MRT_c$  and  $MRT_t$  were not calculated because they were not used in further calculations.

Table (1): Systemic Pharmacokinetics Data Obtained After Administration of 1 mg/kg of Morphine by the Ocular Route.

Parameter	Animal					Mean $\pm$ SD
	1	2	3	4	5	
$C_{max}$ ng. ml <sup>-1</sup>	120	92	100	140	175	125.4 $\pm$ 29.88
$t_{max}$ min	10	10	10	10	10	10
AUS ng. ml <sup>-1</sup> min	7909.5	6782.5	7240	7950	9015	7779.4 $\pm$ 755.98
AUS $0-a$ ng. ml <sup>-1</sup> min	11847.27	12385.95	9957.265	11261.11	13393.42	11769.01 $\pm$ 1145.94
$k_a$ min <sup>-1</sup>	.2071	.4299	.1871	.2084	.3657	.2796 $\pm$ .0989
$k_e$ min <sup>-1</sup>	.0063	.0045	.0072	.0069	.0059	.0062 $\pm$ .0009
$t_{1/2}$ min	109.18	155.36	96.59	99.79	116.73	115.53 $\pm$ 21.14
$V_d$ liters	28.31	38.38	28.53	27.83	27.65	30.14 $\pm$ 4.13
CLP ml. min <sup>-1</sup>	179.74	1717.25	204.77	193.30	164.21	182.65 $\pm$ 14.7

Table (2): Systemic Pharmacokinetics Data Obtained After Intravenous Administration of 2 mg/kg of Morphine by the Ocular Route.

Parameter	Animal				Mean $\pm$ SD
	2	3	4	5	
$C_{max}$ ng. ml <sup>-1</sup>	330	470	480	400	420 $\pm$ 60.42
$t_{max}$ min	5	5	5	5	5
AUS ng. ml <sup>-1</sup> min	8997.5	16708.131	17025.25	15207	14484.47 $\pm$ 3241.49
AUS <sub>0-a</sub> ng. ml <sup>-1</sup> min	1540.683	8310.681	20203.633	17819.225	17993.56 $\pm$ 1624.15
$k_a$ min <sup>-1</sup>					
$k_e$ min <sup>-1</sup>	.0041	.0125	.0091	.0100	.0089 $\pm$ 0031
$t_{1/2}$ min	170.54	55.54	75.97	69.64	92.92 $\pm$ 45.42
$V_d$ liters	36.64	12.20	14.59	15.76	19.8 $\pm$ 9.8
CLP ml. min <sup>-1</sup>	148.90	152.21	133.15	156.81	147.77 $\pm$ 8.89

Table (3): The Relative Bioavailability of Morphine when Administered Through Ocular Route Versus Intravenous Route (The Fraction of the Dose of Morphine Absorbed After Ocular Administration).

Parameter	Animal				Mean $\pm$ SD
	2	3	4	5	
Fraction absorbed by ocular administration (F)	79.19	54.38	55.74	75.16	66.12 $\pm$ 11.16

The mean residence time and mean absorption time are shown in tables 4 and 5. The values A,  $\alpha$ , B and  $\beta$  are shown in the tables. The means of the  $MRT_b$ ,  $MRI_c$  and  $MRT_t$  were not calculated because they were not used in further calculations.

Table (4): Mean Residence Time (MRT) Values for Morphine After Intravenous and Ocular Administration.

Parameter	Intravenous administration					Mean $\pm$ SD	Intravenous administration					Mean $\pm$ SD
	Animal				Mean $\pm$ SD		Animal				Mean $\pm$ SD	
	2	3	4	5			1	2	3	4		
A	253.73	510.60	536.31	422.96	430.9 $\pm 110.58$	131.29	103.49	114.35	161.98	193.47	140.92 $\pm 32.88$	
$\alpha$	.0476	.0316	.0384	.0279	.0364 $\pm .0075$	.0184	.0197	.0206	.0254	.0268	.0222 $\pm .0033$	
B	54.59	163.99	137.05	126.94	120.64 $\pm 40.47$	70.64	52.10	70.09	71.87	72.32	67.40 $\pm 7.69$	
$\beta$	.0041	.0125	.0091	.0099	.0089 $\pm .0030$	.0063	.0045	.0072	.0069	.0059	.0062 $\pm .009$	
MRT <sub>b</sub>	180.18	53.31	69.55	65.70		118.14	168.71	106.08	104.84	120.50		
MRT <sub>c</sub>	60.47	43.4	43.11	50.88		90.86	108.18	82.87	71.81	73.284		
MRT <sub>t</sub>	119.70	9.91	26.44	14.82		27.27	60.53	23.20	33.03	7.22		

MAT =  $34.57 \pm 9.74$

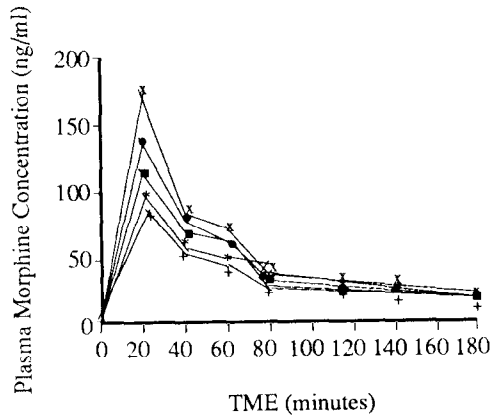


Fig. (1 A): Plots of morphine plasma concentration versus time after administration through ocular route.

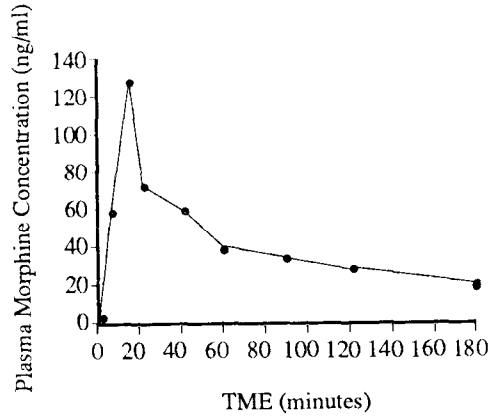


Fig. (1 B): Plots of morphine plasma concentration versus time after administration through ocular route.

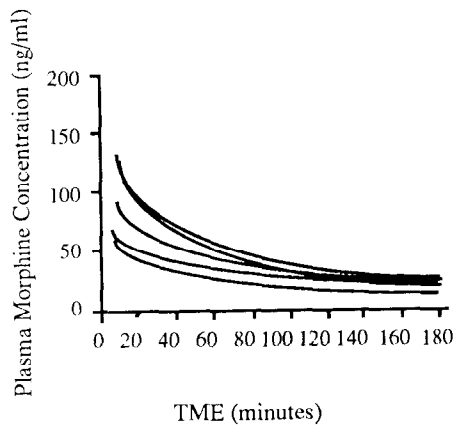


Fig. (1 C): Log regression of morphine plasma concentration versus time after administration through ocular route.

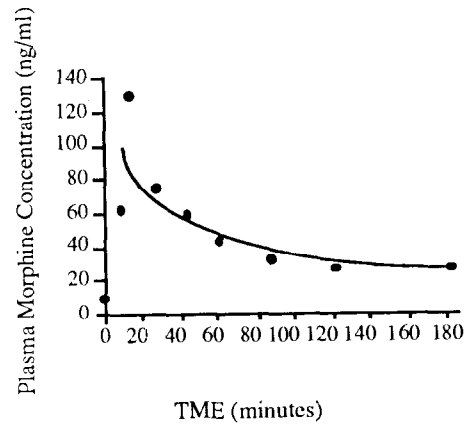


Fig. (1 D): Log regression of morphine plasma concentration versus time after administration through ocular route.



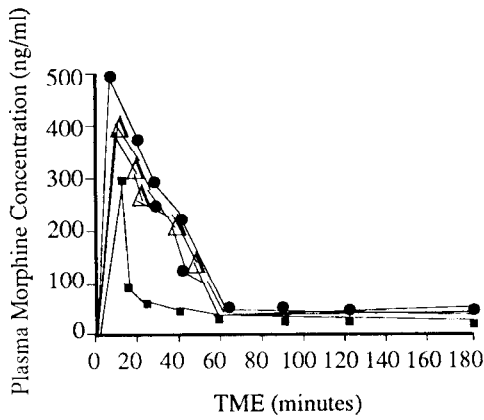


Fig. (2 A): Plots of morphine plasma concentration versus time after intravenous administration.

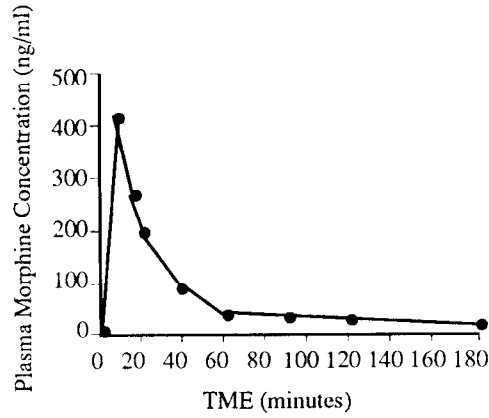


Fig. (2 B): Plots of morphine plasma concentration versus time after intravenous administration.

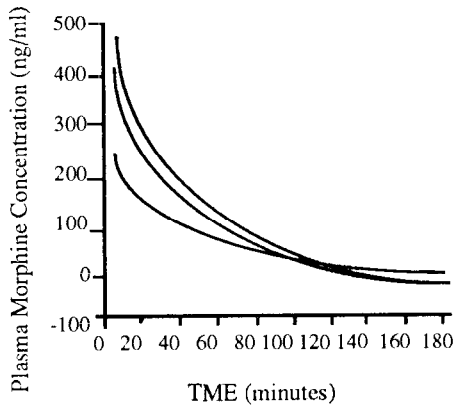


Fig. (2 C): Log regression of morphine plasma concentration versus time after intravenous administration.

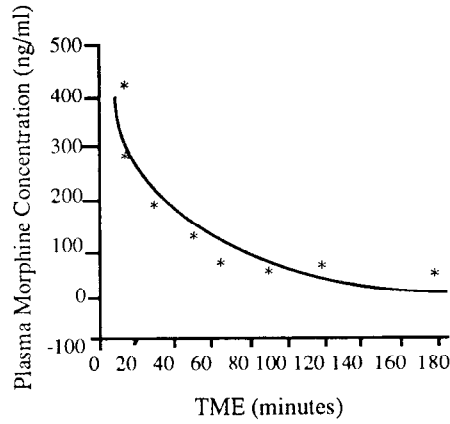


Fig. (2 D): Log regression of morphine plasma concentration versus time after intravenous administration.

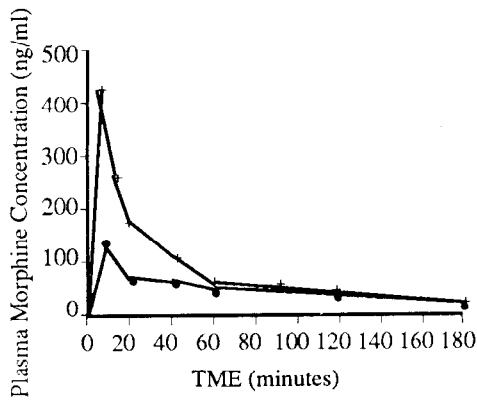


Fig. (3): Plot of mean morphine concentration versus time after ocular and intravenous administration.

### Discussion

Drugs are administered to the eye for their local effects, such as miosis, mydriasis, anaesthesia or reduction of intra-ocular pressure. Systemic effects have been observed with some medications [8]. On the other hand, the limitations associated with the parenteral and oral administration of morphine in patients who continuously need the medication lead to investigating other routes of administration. The present work reports on the pharmacokinetics profile and the bioavailability of morphine after ocular instillation in comparison with the intravenous (i.v.) route.

In this work, ocular instillation of morphine, in a dose of 1 mg/kg onto rabbits, was followed by a rapid absorption ( $t_{max}=10$  minutes), which was extensive ( $C_{max}=125.4\pm 29.88$  ng/ml). Comparing these findings with the corresponding values reported by Chast et al. [2] in rabbits, showed that their  $t_{max}$  ( $19.4\pm 1.7$  minutes) was delayed and  $C_{max}$  ( $94\pm 23$  ng/ml) was lower. However, both values appeared different from the corresponding results found in humans after intramuscular injection ( $t_{max}=15-30$  minutes and  $C_{max}=56-84$  ng/ml) [10]. Differences may be attributed to inter-species variability. In this work, serum morphine concentration ranged between 125 and 25 ng/ml after ocular instillation. At the same time, satisfactory analgesia in cancer patients has been associated with plasma concentration of morphine as low as 16 ng/ml [11]. This would explain the marked sedation seen in animals early after ocular instillation and continued all through the experimental time and would suggest an associated analgesic effect.

The pharmacokinetic profile showed shouldering of the concentration-time curve near 40 minutes after ocular instilla-

tion (Figs. 1-A and B). This could be explained by the multiple anatomical sites of absorption of morphine after ocular instillation. Gerber et al. [12] stated that any drug instilled into the eye will be distributed into three ways namely, the nasolacrimal apparatus, the systemic circulation through the conjunctival and lid vasculature and it may penetrate the cornea. Normally, nasolacrimal drainage accounts for most of the drug not absorbed by the cornea and it takes place through nasal, oropharyngeal and gastro-intestinal mucosal capillaries [5,12]. Although systemic absorption through conjunctival and lid vessels is quite small under normal conditions, yet it has been shown experimentally to account for 80% of the instilled drug when nasolacrimal drainage is blocked [13]. For a drug to penetrate the cornea, it must pass through its complex structure and must exhibit biphasic solubility [14]. Being an alkaloid, morphine might fulfill the concept of biphasic or differential solubility characteristics and penetrated easily the cornea like pilocarpine and homatropine [4]. Thereafter it is either be drained with the aqueous humour or absorbed through the uveal blood vessels [8].

The present results showed a biphasic nature of the serum-concentration curve after i.v. administration of morphine in a dose of 1 mg/ml (Figs. 2-C and D). This might suggest that morphine is distributed sufficiently slowly so that a significant fraction of the drug was eliminated before distribution equilibrium was achieved.

The volume of distribution of morphine after both ocular and i.v. administration was relatively large;  $30.14\pm 4.13$  and  $19.8\pm 9.8$  liters respectively. This large volume of distribution is an indication that morphine was extensively uptaken by the

animal's tissues. This coincides with the findings reported in humans by Stanski et al. [10].

The present study showed that, the half-life ( $t_{1/2}$ ) of ocularly instilled morphine was comparable to that after i.v. administration ( $115 \pm 21.14$  and  $92.92 \pm 45.42$  minutes respectively). These relatively long elimination half-lives might be due to the large volume of distribution, which means that the serum concentration is low relative to the total amount of the drug present in the body. These data were longer than those reported by Catlin [14] and Chast et al. [2]. The variability in results could be due to differences in liver blood flow, in the view of the limited elimination of morphine at non-hepatic sites [15].

As the bioavailability of a drug is a function of both rate and extent of absorption, rapid and complete absorption is an advantage for drugs used in acute and/or conditions such as severe pain. It will be particularly useful if self-administration is possible. In the present work, the eye was a suggested route of administration of morphine for systemic analgesic effect. The fraction of the dose of morphine that actually reached the blood after ocular instillation of 1 mg/kg was found to be 66% in comparison to 100% after i.v. administration of the same dose. On the other hand, value of 25% bioavailability of morphine after oral analgesic dose was previously reported [3].

The Mean Residence Time (MRT) after i.v. administration provides a useful estimate of the persistence of the drug in the body. The role of absorption of morphine after ocular instillation was estimated, based on difference in MRT after i.v. and ocular administration. The Mean Absorption Time (MAT) was found to be

$34.57 \pm 9.74$  minutes. This value suggested that ocular absorption of morphine seemed to be achieved more rapidly than after intramuscular injection estimated by Stanski et al. [10].

The MRT for the central compartment (MRT<sub>c</sub>) was longer after ocular instillation than after i.v. administration. This finding would suggest a prolonged higher serum concentration of morphine after ocular instillation. From the clinical point of view, this may suggest that the mean duration of the systemic pharmacologic effect of morphine is prolonged when given through the ocular route than if given i.v. These findings confirm those reported by Chast et al. [2].

On conclusion, morphine was rapidly absorbed after ocular instillation in rabbits. The estimated serum levels attained corresponded to those effective for its analgesic effect. Moreover, ocular instillation of morphine provided about 66% bioavailability with prolonged high serum concentrations and systemic pharmacologic effects. It might be suggested that morphine could be instilled ocularly for its analgesic effect and it would be a convenient route of administration rather than both parenteral and oral ones. To confirm these findings, further clinical studies on human subjects might be required.

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