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Research Article

Altered Pharmacokinetics and Dynamics of Apomorphine in the Malnourished Rat: Modeling of the Composed Relationship Between Concentration and Heart-Rate Response

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The impact of malnutrition on the pharmacokinetics and pharmacodynamics (change in heart rate) of apomorphine was studied in the rat. One group of rats received a low-protein diet (0.5%) *ad libitum* to produce prekwashiorkor. The control group received commercial food pellets. In the first experiment, the two groups received a 2 mg/kg iv bolus dose of apomorphine to determine any differences in the basic pharmacokinetic parameters. The pharmacodynamic characteristics in each group were studied at different steady-state plasma levels, achieved by iv infusions with continuous measurements of the heart rate. There was an almost twofold decrease in the plasma clearance in the malnourished rats compared with controls. A pronounced change in the pharmacodynamic response was also observed in the malnourished group. In the control group, apomorphine produced bradycardia at low concentrations and tachycardia at high concentrations, while only bradycardia was registered in the malnourished group, with maximum effects at steady-state plasma concentrations of 50 ng/ml and a return to baseline at higher concentrations. The effects in control and malnourished rats were fitted simultaneously to the sum of two Hill equations with a nonlinear regression program, and the fits were compared by means of an F test. The maximum pure tachycardia obtainable differed significantly in the prekwashiorkor group compared to the control group. These results suggest a selective down regulation/desensitization only of the receptors responsible for the tachycardia produced by apomorphine during malnutrition.

KEY WORDS: apomorphine; pharmacokinetics; pharmacodynamics; heart rate; rat; malnutrition.

INTRODUCTION

Various diseases and pathophysiological states can alter the pharmacokinetic properties of drugs (1,2). However, it has been reported that pathophysiological conditions can also change the pharmacodynamics of drugs (3,4). To understand fully the impact of a disease and accordingly adjust dosage regimens, it is thus necessary to understand the alterations in both the pharmacokinetics and the pharmacodynamics. Apomorphine is a widely used tool for studying the dopaminergic system. It exhibits contrasting effects on motor activity (5), stereotyped behavior (6), and pain (7), where low doses cause decreased activity and increased pain reaction, while higher doses cause the opposite effects. The dual effects can be due either to stimulation of auto-receptors at low concentrations (8,9) or to stimulation of D_1 and D_2 receptors at high and low concentrations, respectively. D_1 is known to stimulate cyclic AMP, and D_2 to either inhibit it or to be unassociated with cAMP (10,11). The effect of apomorphine on the heart rate in rat is also bidirectional: low doses (50 μg/kg sc) cause bradycardia, while higher doses (5 mg/kg sc) first cause tachycardia and, later, as the apomorphine concentration decreases, bradycardia (12).

The two opposing effects of apomorphine might be affected differently by a disease. We chose to address this question with malnourished animals since there is an adequate animal model reproducing the effects seen in humans with the kwashiorkor syndrome (13). Malnutrition is a worldwide problem and it is known to cause different pathophysiological changes likely to alter the pharmacokinetics of drugs, e.g., changes in body composition, plasma and tissue proteins, and hepatic, renal, and cardiac function (14). The kinetic behavior of several drugs is changed in malnutrition; e.g., chloroquine shows a decreased absorption (15), procainamid a decreased clearance (16), and salicylic acid an increase in the free fraction of drug in plasma (17). It seems quite clear that malnutrition will influence the pharmacokinetics of drugs. However, the pharmacological response may also change. The neurotransmitters acetylcholine, dopamine, serotonin, and norepinephrine are changed in early undernutrition (18) and thereby may affect their respective receptors. In pharmacodynamic studies, ideally one should measure the effect in the disease state and in the control situation at the same concentration at the effect site. One can approximate this condition by comparing the effects at the same free steady-state plasma concentrations, which

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may equal the concentration at the effect site. However, if protein binding is linear over the concentration range used in the pharmacodynamic study, the total plasma concentration at steady state will be proportional to the concentration at the effect site and could also be used. To investigate the pharmacodynamics of apomorphine, the effect on heart rate under steady-state conditions was compared in control and malnourished rats. To obtain comparable concentrations in both groups, the total plasma clearance in each group was determined following an iv bolus dose. The degree of protein binding was determined *in vitro* by ultrafiltration.

MATERIALS AND METHODS

Animals

Male albino Sprague–Dawley rats (ALAB, Sollentuna, Sweden) were used throughout the study. The animals were housed under standardized environmental conditions and the study was approved of by the ethical committee of Uppsala University. The control rats (170–230 g) had free access to commercial food pellets (22% protein, 52% carbohydrates, 5% crude fat). The malnourished rats weighed 100 g before the initiation of a special diet (Table I) containing 0.5% protein for 6–7 weeks, by which time they weighed 65–75 g. The ages of the rats were then about 7 weeks in the control group and 10 weeks in the malnourished group. Pathophysiologically, they were then characterized as being prekwashiorkor with the characteristic signs of edema, hair loss, and extensive weight loss (13). Food was removed 12 hr before starting the experiment but water was freely available. One week of acclimatization was allowed for the control rats before entering the study.

Drugs and Chemicals

Apomorphine HCl (Sigma; optical rotation, −47.6 at concn. of 1.2 in DH20 at 25°C) was dissolved in 0.9% NaCl (saline) and stabilized with 0.1% ascorbic acid. The internal standard, (−)-*n*-propyl-norapomorphine HCl, was obtained from Research Biochemical Inc., Natick, MA. All other chemicals used were of analytical grade.

Pharmacokinetic Study

Both control (n = 17) and malnourished (n = 28) animals had silicon-rubber (Silastic) catheters implanted in their jugular veins, under ether anesthesia. The catheters were passed, subcutaneously, to the back of the neck and exteriorized. During the experiments the rats were conscious and unrestrained. The pharmacokinetic experiment was performed the day after surgery.

Table I. Experimental Diet (%, w/w) to Produce Rats with Prekwashiorkor Syndrome

Dextrin	56%
Sucrose	28%
Lactalbumin	0.5%
Salt mix[a]	5%
Vitamin mix[b]	0.5%
Choline	0.02%
Fat[c]	10%

[a] Salt mix 900 (Ewos AB, Södertälje, Sweden).
[b] Vitamin premix (Ewos AB, Södertälje, Sweden).
[c] Refined soybean oil (Karlshamns Oljefabriker, Sweden).

Apomorphine HCl was administered as an iv bolus dose (2 mg/kg) in one catheter and blood samples were withdrawn from the other. It was not feasible to sample frequently enough to describe the plasma concentration–time profile in each rat, because of the risk of blood depletion. The volume withdrawn ranged from 100 μl blood at early time points to 600 μl at later time points, except for the last sample. Hence, the sample selection was randomized and blood was taken at the following time points: 2.5, 5, 10, 15, 20, 30, 45, 60, and 90 min (controls) and 2.5, 5, 10, 15, 20, 25, 30, 45, 60, 75, and 120 min (malnourished) after the injection. Each sample was replaced by an equal volume of saline, and with the exception of the last sample, the maximum cumulative sample volume never exceeded 10% of the total blood volume. After centrifugation, the plasma samples were stabilized by the addition of EDTA and ascorbic acid. The internal standard (*n*-propyl-norapomorphine) was added (50 ng in 100 μl), and the samples were immediately frozen pending analysis.

Pharmacodynamic Study

A polyethylene catheter (PE50) was inserted into the left carotid artery and a silicon rubber catheter (Silastic) was inserted into the right jugular vein under ether anesthesia and the catheters were exteriorized at the back of the neck. The animals were allowed to recover from the anesthesia and then placed in restraining cages to avoid apomorphine-induced rotational behavior disturbing the pulse signal.

The arterial catheter was connected to a pressure transducer (Statham P23 DC writing on a Grass Model 7 Polygraph). The heart rate was triggered from the blood-pressure pulse wave by means of a Grass Tachygraph (7P4DE).

Before starting the intravenous infusion of apomorphine, the basal values of arterial blood pressure and heart rate were recorded for at least 30 min. The effects of apomorphine were then determined as the change in heart rate from the baseline value for each rat. The venous catheter was connected to an infusion pump and the rate of infusion (R_{inf}) was calculated as

$$R_{inf} = CL \times C_{SS}$$

using the average value of clearance (CL) for each group of rats obtained from the iv bolus experiments. Each rat received three consecutive rates of infusion, aiming at three different steady-state concentrations (C_{ss}) in each rat (2, 10, 50, 200, 500, and 2000 ng/ml). The order of established steady-state concentrations in plasma was always from the lowest to the highest concentration. Each infusion continued until steady state was reached. Based on the pharmacokinetic parameters calculated from the iv study, each infusion rate was maintained for 60 min in the control rats and 90 min in the malnourished rats. The total volume infused never exceeded 5 ml during the 3–4 hr of infusion. When at steady state, a blood sample was withdrawn from the arterial catheter to validate the steady-state plasma concentration. The change in heart rate in rats receiving saline only was investigated in six rats from each group. The blood volume with-

drawn never exceeded 10% of the total blood volume, and the blood samples were treated as described above.

Protein Binding

The binding of apomorphine to plasma proteins was determined by ultrafiltration, at concentrations of 50, 250, 500, and 2000 ng/ml. Plasma was obtained from both control and malnourished rats undergoing the same surgical procedure as in the pharmacodynamic experiment, including the time spent in the restraining cages. The plasma from 8 control and 16 malnourished rats was then pooled and kept frozen until the ultrafiltration procedure. The plasma was adjusted to pH 7.4 with 0.1 *M* HCl and spiked with known amounts of apomorphine. After 15 min of equilibration, 0.5 ml of plasma was transferred to each ultrafiltration tube (AMICON Micropartition system MPS-1) and then centrifuged at 1000*g* through a membrane (YMT, 14 mm) for 7 min, yielding a filtrate volume of 150 μl. The free fraction (f_u) was determined as the ratio of the concentration in the filtrate to the total concentration (C_{tot}), corrected for the fraction of the plasma occupied by plasma water according to

$$f_u = C_{filtrate} \times 0.93/C_{tot}$$

Assay of Apomorphine

Apomorphine plasma concentrations were determined using a high-performance liquid chromatographic method (12). Apomorphine was accordingly chromatographed as an ion pair with heptan sulfonate and detected with a fluorescence detector (Shoeffel FS 970; excitation, 280 nm; emission, 360-nm cutoff filter). The coefficient of variation was 10% for the lowest standard and the recovery of apomorphine from plasma was 80 ± 8%. The limit of determination was 3 ng.

Data Analysis

Pharmacokinetic Data

Mono- and biexponential equations were fitted to the mean plasma concentration data after administration of the iv bolus dose by the nonlinear regression program PCNONLIN (19) according to Eq. (1).

$$C_p = \text{dose}/V_c \sum_{i=1}^{2} C'_i \times e^{-\lambda_i \times t} \quad (1)$$

In Eq. (1), C_p represents apomorphine plasma concentration at time t, C'_i is the fraction of the intercept from the ith exponential term, λ_i is the exponent of the ith term, and V_c is the volume of the central compartment. The number of exponential terms needed to describe the data was determined using an F test (20).

C'_i, λ_i, and V_c were estimated by the program as primary parameters and the clearance (CL) and volume of distribution at steady state (V_{ss}) were estimated by the program as secondary parameters by the following equations:

$$CL = \text{dose}/AUC \quad (2)$$

$$V_{SS} = \text{dose} \times AUMC/AUC^2 \quad (3)$$

$$AUC = \text{dose}/V_c \times (C'_1/\lambda_1 + C'_2/\lambda_2) \quad (4)$$

$$AUMC = \text{dose}/V_c \times (C'_1/\lambda_1^2 + C'_2/\lambda_2^2) \quad (5)$$

In the biexponential fit C'_2 was expressed as $1 - C'_1$.

The data points were given weights according to $n/(C_{calc} \times CV)^2$, where CV is the coefficient of variation of the measured concentration in each data point, C_{calc} is the estimated concentration, and n is the number of data points at each time point. Differences in CL and V_{ss} between the groups of rats were tested with a t test (20).

Pharmacodynamic Data

Apomorphine elicits different effects on the heart rate depending on the concentration in the biophase, thereby producing a biphasic concentration–response curve, where low concentrations produce bradycardia and higher concentrations tachycardia (12). Accordingly, the observed effect, E, is composed of two separate effects, E_1 (tachycardia) and E_2 (bradycardia). Each of these two effects can be described by the Hill model, and the net effect, E, is the sum of these functions according to

$$E = \frac{E_{max}(1) \times C_{SS}^{N1}}{EC_{50}(1)^{N1} + C_{SS}^{N1}} + \frac{-E_{max}(2) \times C_{SS}^{N2}}{EC_{50}(2)^{N2} + C_{SS}^{N2}} \quad (6)$$

where C_{ss} is the concentration of apomorphine at steady state, and $EC_{50}(1)$ and $EC_{50}(2)$ are the concentrations producing half-maximum tachycardia and bradycardia, respectively. $E_{max}(1)$ and $E_{max}(2)$ are the maximum effects for tachycardia and bradycardia, respectively, and $N1$ and $N2$ are the slope factors of the respective curve. Since the number of parameters is fairly large, simultaneous fitting of the two groups of animals would appreciably confine the parameter values. The fit would, however, benefit only as long as the parameters are the same for the two groups, which can be tested by an F test, where the number of parameters needed in relation to the WSS (weighted sum of squares) of the fit is determined.

To detect any differences in parameter values between the groups, the following procedure was applied. If there is no change in the pharmacodynamics in the prekwashiorkor group compared with controls, all six parameters in Eq. (6) should be equal for the two groups. On the other hand, if a change has occurred in one of the parameters, it should be different in the prekwashiorkor group and the other parameters the same in the control and malnourished rats. To test for differences in the parameters, Eq. (6) was fitted to all the effect–concentration data points for both control and malnourished rats simultaneously with PCNONLIN. By doing this test systematically, three different situations arise: (i) the 6 parameters are completely different for both groups, thus 12 parameters are needed in the fit; (ii) the 6 parameters are equal for both groups; and (iii) 1, 2, 3, 4, or 5 parameters are equal, resulting in 11, 10, 9, 8, or 7 parameters. The last situation yielded many different combinations of parameters. The number of parameters required was determined by comparing the sums of squares in each fit by an F test (20).

RESULTS

Pharmacokinetic Data

The plasma concentration–time profiles for apomor-

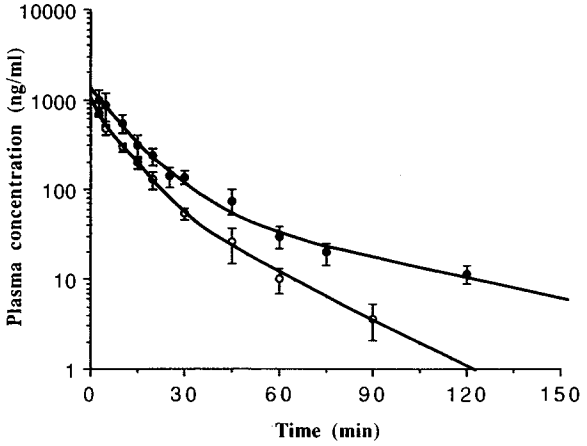

Fig. 1. Plasma concentration–time profiles in control (○) and prekwashiorkor (●) rats. Each point is the mean ± SD. The solid lines represent the concentrations predicted from the data fit to Eq. (1).

phine in the malnourished and control rats are shown in Fig. 1. A biexponential equation gave the best fit to the data and the estimated pharmacokinetic parameters of apomorphine are shown in Table II. There was a significant decrease in the plasma clearance in malnourished rats compared with control animals. No significant difference was found in V_{ss}, but V_c was significantly smaller in the malnourished rats. The distribution and elimination half-lives, $t_{1/2}\lambda_1$ and $t_{1/2}\lambda_2$, were also longer in the malnourished rats, although not statistically significant.

Protein Binding

The free fraction in the control rats was 9.7 ± 1.5% (mean ± SD; n = 16) and linear over the concentration range observed. The malnourished rats showed about the same degree of binding up to 500 ng/ml (8.8 ± 1.0%; n = 15). However, at the highest concentration, 2000 ng/ml, the free fraction was significantly elevated, to 15.3 ± 1.2% (n = 8, P < 0.001) (Table III).

Table II. Pharmacokinetic Parameters After Bolus Injection of Apomorphine HCl (2 mg/kg)

	Control		Malnourished	
	Estimate	(% CV)[a]	Estimate	(% CV)[a]
C'_1	0.86	(7.9)	0.93	(3.6)
C'_2	0.14[b]		0.08[b]	
CL (ml/min × kg)	196	(2.7)	106**	(5.6)
V_{ss} (L/kg)	2.7	(5.6)	2.6	(17)
V_c (L/kg)	2.0	(6.6)	1.5*	(12)
$t_{1/2}\lambda_1$ (min)	5.4	(14)	7.5	(12)
$t_{1/2}\lambda_2$ (min)	17.1	(19)	40.5	(33)

[a] Calculated as parameter SE/parameter estimate, where SE is the standard error of the estimate.
[b] Obtained as $1 - C'_1$.
* $P < 0.05$.
** $P < 0.001$.

Table III. Free Fraction (%) of Apomorphine in Plasma in Control and Prekwashiorkor Rats

	Total concentration (ng/ml)			
	50	250	500	2000
Control				
Mean	10.6	9.7	8.3	10.8
SD	—	0.5	0.5	1.6
n	1	4	5	6
Prekwashiorkor				
Mean	9.9	8.5	8.8	15.3
SD	1.3	1.1	0.7	1.2
n	2	5	8	8

Effect of Apomorphine on Heart Rate

The basal mean arterial blood pressure for the 22 control rats was 112 ± 12 mm Hg and the basal heart rate was 408 ± 30 beats/min. The corresponding values for the 22 malnourished rats were 96 ± 13 mm Hg and 424 ± 41 beats/min. The mean arterial blood pressure was significantly lower (P < 0.001) in the malnourished group, but the difference in heart rate was not significant. The results from the rats receiving only saline are presented in Fig. 2. There is a slight, but not significant, decrease in heart rate with time. After apomorphine infusions to different steady-state concentrations a biphasic concentration–response relationship was found for both groups of rats (Figs. 3A and B). The data from both groups of rats were adequately described by Eq. (6), thus, as the sum of the two opposing effects, bradycardia and tachycardia (Fig. 3C). It is obvious from the data presented here that there is a difference in the response to apomorphine. In control rats, low concentrations of apomorphine, about 2–70 ng/ml, produced a bradycardia and higher concentrations caused an increasing tachycardia (Fig. 3A). In the malnourished rats, however, all concentrations produced bradycardia, with a maximum occurring at about 50 ng/ml. With higher concentrations of apomorphine, the response shifted to less bradycardia, approaching the baseline (Fig. 3B). The results from the pharmacodynamic modeling of observed effects are presented in Table IV and Table V. After testing systematically for possible significant differences by com-

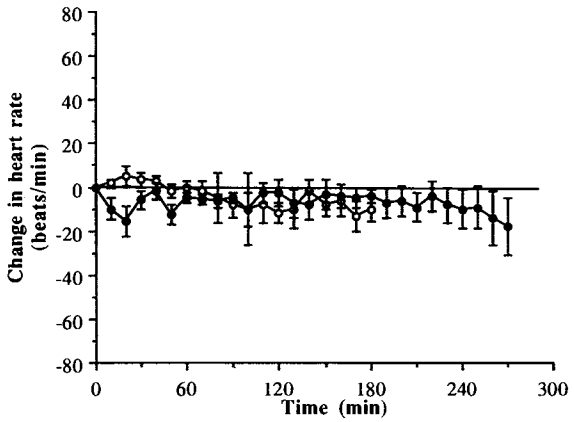

Fig. 2. Change in heart rate vs time for control and prekwashiorkor rats infused with saline for 180 min (control, ○) and 270 min (prekwashiorkor, ●).

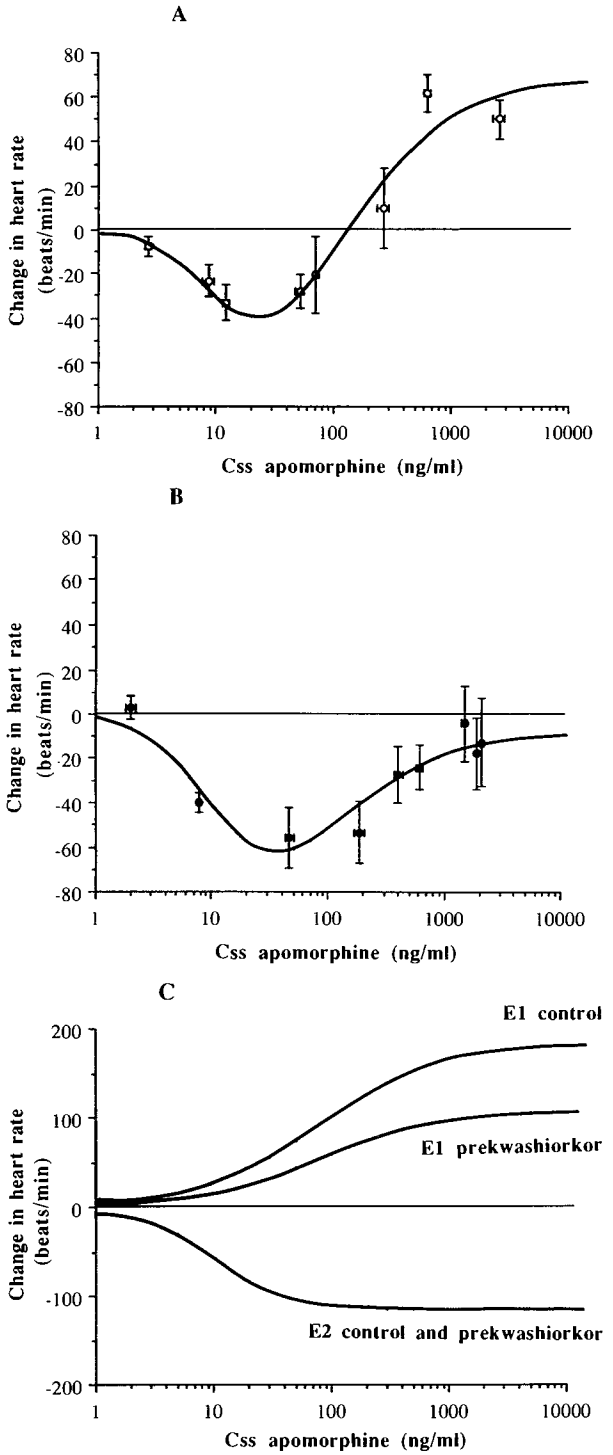

Fig. 3. Effect–concentration profiles for the control rats, n = 6–7 (A), and prekwashiorkor rats, n = 4–6 (B). The symbols represent the mean ± SE, for effect as well as concentration. The solid lines represent the computer-estimated curve from Eq. (6). In C are the computer-calculated effect curves for tachycardia (E1) and bradycardia (E2).

paring the weighted sum of squares (WSS) from the different fits by means of an F test, this study shows that a change in the $E_{max}(1)$ parameter is most likely ($P < 0.01$). Since this maximal pure tachycardia was substantially decreased in the malnourished rats, no net tachycardia was observed in this group. The observed bradycardia, however, returned from its lowest value to the baseline value because of an underlying tachycardia yielding the U-shaped concentration–response relationship seen in Fig. 3B.

Table IV. Pharmacodynamic Parameters for the Heart-Rate Effect of Apomorphine

	Estimate (% CV)[b]	
Tachycardia		
E_{max} (1), control (beats/min)	184	(42)
E_{max} (1), malnourished (beats/min)	108	(78)
$EC_{50}(1)$[a] (ng/ml)	88	(73)
$N1$	0.86	(34)
Bradycardia		
E_{max} (2)[a] (beats/min)	115	(70)
$EC_{50}(2)$[a] (ng/ml)	11.5	(63)
$N2$	1.41	(47)

[a] These parameters were set equal for the two groups.
[b] Calculated as SE/parameter estimate, where SE is the standard error of the estimate.

It cannot be ruled out that a change in the effect is caused by a change in $E_{max}(2)$. The WSS obtained from the computer fit do, however, suggest that it is more likely that a change in $E_{max}(1)$ has occurred.

DISCUSSION

The present study shows that the pharmacokinetics as well as the pharmacodynamics of apomorphine are altered in rats classified as prekwashiorkor. The plasma clearance was significantly decreased, from 196 ml/min × kg in the control group to 106 ml/min × kg in the malnourished group. Since the hematocrit has been reported to be 35 ± 2.5% in prekwashiorkor, compared with 46 ± 1.6% in control rats from our laboratory (21), the difference in blood clearance is even greater, since $CL_B = CL_P \times C_P/C_B$, assuming that the partitioning into red blood cells is unchanged in the malnourished rats.

The decreased plasma clearance, observed in the prekwashiorkor group, can be due to either an increase in binding to plasma proteins, decreased enzyme capacity, or decreased blood flow. According to the literature, the extraction ratio of apomorphine in the liver is about 0.9 (22) and hepatic blood flow in the rat is 80 ml/min × kg (23), which

Table V. The Best Data Fit for Each Number of Parameters

Number of parameters	WSS[a]	DF[b]
6	125,745	96
7	72,629	95
8	72,015	94
9	69,418	93
10	66,435	92
11	65,529	91
12	64,224	90

[a] Weighted sum of squares.
[b] Degrees of freedom.

gives a hepatic blood clearance of 72 ml/min × kg. Since the measured plasma clearance is 196 ml/min × kg, hepatic clearance is only about 35% of total clearance, unless apomorphine is extensively distributed to red blood cells.

The major metabolic steps of apomorphine are glucuronidation and *O*-methylation by COMT (catechol-*O*-methyl-transferase) (24,25). The fraction of apomorphine excreted unchanged in the urine is less than 5% (26). Thus, apomorphine is probably metabolized to a large extent outside the liver. Since COMT is found in many different tissues, including red blood cells, *O*-methylation is probably an important extrahepatic metabolic pathway and the activity of this enzyme might be decreased in malnutrition. A plausible explanation for the decreased clearance, however, might also be a decrease in cardiac output, which is reported in malnourished children (27), thereby reducing the blood supply to all eliminating organs. The liver blood flow is probably also reduced in kwashiorkor, due to the fatty infiltration that often occurs (14,28).

Protein binding seems to be unrelated to the altered clearance since there was no difference in the free fraction between control and prekwashiorkor rats over the concentration range obtained following the bolus dose. The binding was 9.7% in the control and 8.8% in the malnourished group, which is in good agreement with the previously reported 9.1% (29). It was not significantly different in the malnourished group at low concentrations but showed a nonlinear increase at higher concentrations, with a free fraction of 15.3% at 2000 ng/ml. Apomorphine binds to both albumin and α_1-acid glycoprotein (29). Since the binding was the same in both groups over the linear range, but saturated only in the prekwashiorkor group, the binding to one of the proteins can be reduced and the other one increased in the prekwashiorkor group. This result can be explained by changes in both albumin and α_1-acid-glycoprotein. Hypoalbuminia is reported in kwashiorkor, together with an increase in free fatty acids; these are highly bound to albumin (30) and therefore can compete with apomorphine for the albumin binding sites, thereby increasing the free fraction at higher concentrations of apomorphine. Together, the reduced concentration of albumin and the elevated concentrations of free fatty acids might explain the saturation of binding seen between 500 and 2000 ng/ml. However, there has to be a drastic change in albumin binding capacity to explain the saturation, since the molar concentration of apomorphine (6 μM) is far from the albumin concentration in control rats (600 μM). Since α_1-acid-glycoprotein is known to increase in different diseases (31), it is possible that the binding to this protein is increased in prekwashiorkor.

It was found in this study that there was no change in the bradycardia induced by low apomorphine concentrations, suggesting that the high-affinity receptor is preserved in malnutrition. However, there was a decrease in the maximal tachycardia effect [$E_{max}(1)$]. The nonlinearity in protein binding cannot account for this observation since the observed heart rate was returned to baseline values in the range above 500 ng/ml in the kwashiorkor rats and did not change with increasing concentration (Fig. 3B). Malnutrition has earlier been shown to diminish the stereotyped behavior produced by apomorphine in normal rats (32). The authors suggested that this effect might be due to elevated dopamine levels causing receptor adaptation to dopaminergic stimulation. This conclusion was later supported by a study where a decrease in the number of dopamine receptors was found in undernourished animals (33). Our study cannot reveal the mechanisms of the decrease in $E_{max}(1)$, but the findings are consistent with a decrease in receptor number.

The rather complex pharmacodynamic model in Eq. (2) is preferable over a nonparametric model, since it is based upon physiological and pharmacodynamic principles and the parameters describe both potency and efficacy. Because of the number of parameters in the model, the standard error of the estimates obtained from the computer fit is fairly large (Table IV). Thus, the numerical values of the parameters should be treated with caution. However, it is of greater interest whether there is a significant difference between the two groups of rats in their response to apomorphine and, if so, in what way they differ.

This study shows that two closely related pharmacological systems do not change in the same manner in malnutrition, which implies that pharmacological effects and side effects do not necessarily change in the same way. Further, when designing dosage regimens for patients who deviate from the average population, changes in both pharmacokinetic and pharmacodynamic properties of the drug are to be considered.

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