J. Pharm. Pharmacol. 1986, 38: 28–34
Received June 11, 1985

Concentration-response relations for apomorphine effects on heart rate in conscious rats*

LENNART K. PAALZOW† AND GUDRUN H. M. PAALZOW

Department of Biopharmaceutics and Pharmacokinetics, University of Uppsala, Box 580, S-751 23 Uppsala and Department of Pharmacology, Central Laboratory, Apoteksbolaget AB, Box 3045, S-171 03 Solna 3, Sweden

The pharmacokinetics of apomorphine in plasma and brain tissue have been studied in relation to the time courses of effects on heart rate in conscious rats. The kinetic behaviour was investigated after 2 mg kg^{-1} i.v. and 5 mg kg^{-1} s.c., respectively. Apomorphine showed a high total plasma clearance (165–207 ml min^{-1} kg^{-1}) and, despite a relatively large volume of distribution (3·4–4·1 litre kg^{-1}), a biological half-life of about 14 min was obtained irrespective of route of administration. The kinetics in whole brain were identical with those in plasma. Apomorphine produced biphasic effects on the heart rate during the time courses of subcutaneous single doses: a low dose (50 μg kg^{-1}) induced pure bradycardia while the doses of 100 μg kg^{-1} and 5 mg kg^{-1} produced responses oscillating between bradycardia and tachycardia. When we evaluated the relation between apomorphine concentrations and effects on the heart frequency with a composed sigmoid E_{max} model, apomorphine exhibited a U-shaped steady-state plasma concentration-response curve. Bradycardia appeared after low concentrations, reached a maximum and then decreased with increasing concentrations. A further augmentation of apomorphine concentration resulted in the opposite effect, i.e. tachycardia. Separate concentration-response curves for bradycardia and tachycardia were calculated. The changes in biophase concentration that occur during the absorption and disposition may thus cause the fluctuations between contrasting effects seen during the time course of a single dose.

Apomorphine is widely used to evaluate the role of dopamine in functional and biochemical models (for review see: Di Chiara & Gessa 1978). Small doses in animals cause a decrease in dopamine neurotransmission and function, presumably due to activation of inhibitory dopamine autoreceptors (Carlsson 1975). Larger doses cause direct stimulation of post-synaptic dopamine receptors, resulting in an increase in the functional activity of dopamine (Ernst 1967). Thus, depending upon the concentration in the biophase, apomorphine is capable of interacting with different functional systems or receptors and thereby producing different or opposing pharmacodynamic effects. It follows that any factor influencing the biophase concentration of the drug is critical for its pharmacodynamic response as fluctuations in the concentration reaching the effector cells may cause not only a variable degree of response but may also change the nature of the effect (Paalzow et al 1985). Owing to concentration changes during the absorption and disposition processes, oscillations between contrasting effects in the temporal response to a single extravascularly administered dose of apomorphine might be seen, as previously observed with (Paalzow & Paalzow 1983), the yawning effect (Protais et al 1983) and on motor activity (Montanaro et al 1983).

We have therefore examined the pharmacokinetic behaviour in rats of apomorphine in plasma and brain tissues in relation to the time course of the effect on heart rate which, after subcutaneous administration, fluctuates between bradycardia and tachycardia (Paalzow et al 1985). In addition, we have evaluated the steady state plasma concentration-response relation for apomorphine effects on heart frequency.

MATERIALS AND METHODS

Animals

White male Sprague-Dawley rats (Anticimex, Sollentuna, Sweden), 180–200 g, were used in standardized environmental conditions. Studies were performed between 1300 and 1700 h. Food and water were freely available. One week of acclimatization was allowed before the rats were used.

Haemodynamic measurements

Under light ether anaesthesia, a polyethylene catheter (PE50) was inserted into the left carotid artery as described by Henning (1969). The free end was exteriorized to the back of the neck and

* Results of this investigation were presented at the workshop 'Variability in Drug Therapy', Rome 1984.

† Correspondence.

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 Tachograph (7P4 DE). The mean arterial blood pressure and the heart rate were recorded in the conscious unrestrained rat which was placed in a separate cage. Before administration of the drug, the basal values of the mean arterial blood pressure and heart rate were recorded for 30 min to ensure that they were normal and stable. Mean basal arterial blood pressure ± s.e. from 10 rats was 118 ± 3 mmHg and heart rate ± s.e. was 404 ± 5 beats min^{-1}. These values are in accordance with those reported by Henning (1969) and Trolin Georgsson (1975), respectively, in conscious rats. Drug effects were expressed as changes from the initial basal values of the heart rate and mean arterial blood pressure in the individual rat.

Pharmacokinetic experiments

The rats were implanted with silicon rubber catheters (Silastic) in the jugular veins under light ether anaesthesia. The free ends of the catheters were passed subcutaneously to the back of the neck and exteriorized. The intravenous administration of the drug was into one of the venous catheters and blood was serially sampled from the other. Each sample was replaced by an equal volume of saline and with the exception of the last sample, the maximum cumulative blood volume withdrawn from any rat never exceeded 10% of the total blood volume. During the experiments the rats were conscious and unrestrained.

Apomorphine HCl was given as a bolus dose of 2 mg kg^{-1} i.v. or 5 mg kg^{-1} s.c. in the neck, and blood samples (0·25–2·1 ml), were withdrawn 2·5, 5, 10, 15, 20, 30, 60, 90, 120, 150, 180 min later. After centrifugation, plasma samples were stabilized by addition of 2·2 mM EDTA and 5·7 mM ascorbic acid. The internal standard (n-propylnorapomorphine) was added and the samples were immediately frozen at −70 °C until analysed.

In another series of experiments, 5 mg kg^{-1} of apomorphine HCl was given subcutaneously and the rats were decapitated at different times during 135 min. Brains were immediately removed, placed on an ice-cold dissection plate and rapidly freed from blood vessels as much as possible. The pineal gland and the cerebellum were discarded and the remainder was weighed and frozen in methanol at −70 °C followed by homogenization in ice-cold 0·1 M hydrochloric acid with addition of EDTA, ascorbic acid and internal standard. After centrifugation the supernatants were stored at −70 °C until analysed.

Assay of apomorphine

Apomorphine concentrations in brain tissue and plasma were determined by high-performance liquid chromatography (Eriksson et al 1979) with modifications using (−)-*N*-n-propylnorapomorphine HCl as internal standard. Samples were usually analysed within 24 h. Plasma and brain samples were extracted at pH 7·6 with ethyl acetate followed by back-extraction into 0·005 M sulphuric acid. The sulphuric acid phase from brain supernatant was directly injected into the chromatograph. After pH adjustment, the sulphuric acid phase from plasma samples was extracted with dichloromethane, evaporated and dissolved in mobile phase (0·005 M heptane sulphonic acid in acetic acid–methanol–water (2 : 40 : 58)) before injection into the chromatograph which was equipped with an ODS-reversed phase column. Apomorphine was chromatographed as ion pair with heptansulphonate on a μBondapak C18 column and detected with a fluorescence detector. The recovery of apomorphine from plasma was 82 ± 6% with a s.d. of 1% for the peak height ratio. The detection limit was 0·4 ng ml^{-1} with a sample volume of 1 ml.

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) immediately before administration. The internal standard (−)-*N*-n-propylnorapomorphine HCl was obtained from Research Biochemical Inc, Wayland, USA.

Data analysis

Effect-concentration relation

Depending upon the dose, apomorphine produced dual effects on heart rate and exhibited a U-shaped dose-response curve. If we assume that the observed net effect (E) is composed of the sum of (at least) two separate effects, E_1 (tachycardia) and E_2 (bradycardia), and describe each of these by the Hill equation, the effect (E) may be expressed in the following manner:

$$E = \frac{E_{1\,max} \times C^{S_1}}{C^{S_1} + C(50)_1{}^{S_1}} + \frac{-E_{2\,max} \times C^{S_2}}{C^{S_2} + C(50)_2{}^{S_2}} \qquad (1)$$

($E = E_1 + E_2$) where C is the biophase concentration of drug, $C(50)_1$ and $C(50)_2$ are the concentrations producing half maximum tachycardia and bradycardia, respectively. E_{1max} and E_{2max} are the maxi-

mum effects. S_1 and S_2 are constants that create sigmoidicity and exert an influence on the slope of the concentration-response curves.

By recording the effects over time after different subcutaneous doses of apomorphine and fitting equation 1 to these effects, the unknown parameters (S_1; S_2; $C(50)_1$; $C(50)_2$; E_{1max} and E_{2max}) can be calculated with their standard deviations, since the change of drug level with time is known. Equation 1 was fitted to the observed effects over time by the NONLIN program (Metzler et al 1974). Several runs with different initial estimates were performed to avoid local minima in the sum of squares of surface. The best fit was based on the sum of squares, correlation coefficient (r), coefficient of determination (r^2) and standard deviations of parameters.

Pharmacokinetic data

The multi-exponential equations were fitted to the plasma and brain concentration-time data by the NONLIN program (Metzler et al 1974). The formulase given by Rowland & Tozer (1980) were used to calculate the primary pharmacokinetic parameters volume of distribution and total plasma clearance from the coefficients and exponents of the exponential functions obtained.

RESULTS

Pharmacokinetics of apomorphine

The time course of apomorphine concentration in plasma after i.v. administration of 2 mg kg^{-1} is shown in Fig. 1. A biexponential equation gave the best fit to the plasma data. The coefficients and exponents of this equation are shown in Table 1. In spite of a large apparent volume of distribution (4·1 litre kg^{-1}), the terminal half-life of apomorphine was short (13·8 ± 2·0 min) owing to a high total plasma clearance (206·9 ml min^{-1} kg^{-1}) (Table 1).

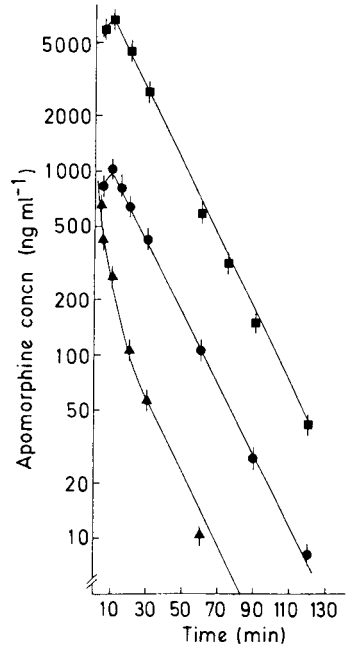

FIG. 1. Plasma and brain concentrations of apomorphine after intraveneous and subcutaneous administration of 2 mg kg^{-1} and 5 mg kg^{-1}, respectively. Each point represents the mean ± s.e. from 7–9 rats. The solid lines represent the fit according to biexponential equations. ▲—▲ Plasma 2 mg kg^{-1} i.v. ●—● Plasma 5 mg kg^{-1} s.c. ■—■ Brain 5 mg kg^{-1} s.c.

The plasma concentrations obtained after s.c. administration of 5 mg kg^{-1} of apomorphine HCl are also shown in Fig. 1 and the calculated parameters are presented in Table 1. Apomorphine exhibited a rapid absorption (absorption half-life was about 2 min) and maximum drug levels were reached at about 5–10 min. The terminal half-life was equal to that after i.v. administration.

Table 1. Pharmacokinetic parameters of apomorphine in plasma and brain tissues.

Treatment	Tissue	A ± s.d. (ng ml^{-1})	B ± s.d. ng ml^{-1}	α ± s.d. min^{-1}	β ± s.d. min^{-1}	$t_{\frac{1}{2}}\beta$ ± s.d. min	Vd_β[1] l kg^{-1}	Total[2] plasma clearance ml min^{-1} kg^{-1}	k_a ± s.d. min^{-1}	$t_{\frac{1}{2}}k_a$ ± s.d. min
Apomorphine HCL 2 mg kg^{-1} i.v.	Plasma (n = 21)	752·7± 61·4	273·2±27·4	0·24±0·02	0·050±0·007	13·8±2·0	4·10	206·9	—	—
Apomorphine HCl 5 mg kg^{-1} s.c.	Plasma (n = 17)	1727·7±108·8	—	—	0·047±0·003	14·5±0·9	3·44	165·0	0·380±0·029	1·82±0·14
	Brain (n = 56)	11828·7±122·0	—	—	0·049±0·0004	14·0±0·1	—	—	0·195±0·003	3·56±0·06

Functions: $C = A \cdot \exp(-\alpha \cdot t) + B \cdot \exp(-\beta \cdot t)$ (i.v.) [1] $V_{d_\beta} = \frac{\text{Dose}}{\beta \cdot \text{AUC}}$

$C = A \cdot \exp(-\beta \cdot t) - A \cdot \exp(-k_a \cdot t)$ (s.c.) [2] $Cl = \frac{\text{Dose}}{\text{AUC}}$

n = number of animals.

A rapid uptake of apomorphine into the brain was observed after s.c. injection of 5 mg kg^{-1} (Fig. 1) and maximum levels were attained at the first measurement (5 min). The half-life of elimination from brain tissue equalled that in plasma (14·1 ± 0·1 min). As plasma and brain tissue showed similar distribution and elimination characteristics, the plasma concentration can be assumed to reflect the time course of drug levels also in the brain.

The effect of apomorphine HCl on the blood pressure

In conscious rats we were unable to record any biphasic effect of apomorphine in the doses studied on the mean arterial blood pressure. The only significant effect seen was hypertension induced by the high dose of 5 mg kg^{-1} s.c. (Fig. 2). This effect developed relatively slowly and reached its maximum at about 30 min after the administration.

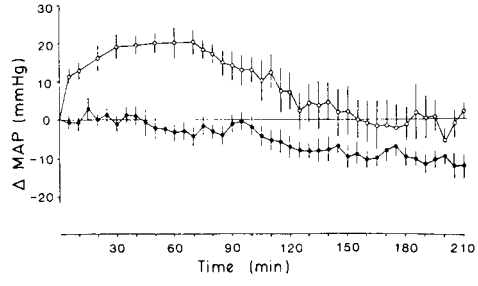

FIG. 2. The effects of apomorphine on the mean arterial blood pressure (MAP) after s.c. administration of 5 mg kg^{-1} (○—○) and the change of MAP during 3·5 h in s.c. saline-treated control animals (●—●). Each point represents the mean ± s.e. from 9–11 rats.

Saline-treated rats showed a slightly decreasing blood pressure with time during the experiment (Fig. 2).

The effects of apomorphine on the heart rate

Subcutaneous administration of 50 μg kg^{-1} of apomorphine HCl produced a pure bradycardia which lasted about 60 min (Fig. 3). A dose of 100 μg kg^{-1} s.c. induced an immediate onset of bradycardia in 8 out of 11 rats which reached maximum at 2–3 min. This was followed by brief tachycardia which peaked at 5–10 min and then turned into bradycardia which was at maximum at about 30–40 min, and the heart rate then returned to baseline level (Fig. 3). A dose of 5 mg kg^{-1} s.c. produced tachycardia followed by bradycardia (Fig. 3). The initial brief bradycardia observed after 100 μg kg^{-1} was only seen in 3 of 11 animals given 5 mg kg^{-1} s.c. Stereotyped behaviour appeared during the phases of tachycardia both for

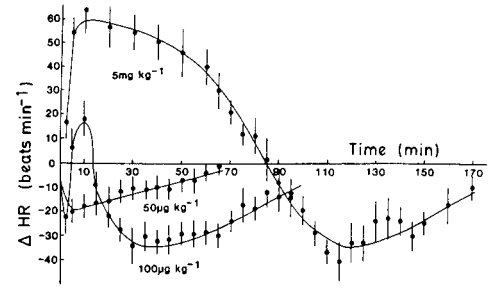

FIG. 3. The observed effects of apomorphine on heart rate (beats min^{-1}) after s.c. administration of 50 μg kg^{-1}, 100 μg kg^{-1} and 5 mg kg^{-1}, respectively during 170 min. Each point represents the mean ± s.e. from 9–11 rats. The solid lines represent the fit according to equation 1.

the doses of 100 μg kg^{-1} (repetitive licking and sniffing) and 5 mg kg^{-1} (sniffing and gnawing).

The basal values of the heart rate were followed after the subcutaneous administration of saline and were found to remain stable during 3·5 h following administration (Fig. 4).

Concentration-response relations

The observed effects on heart rate after the dose of 5 mg kg^{-1} s.c. were used as input in equation 1 to calculate the concentration-response relation for the two opposing responses, bradycardia and tachycardia. The parameters of the function describing the time course of apomorphine concentration were obtained from the plasma concentration (Cp) data (Table 1). Owing to the rapid absorption and distribution of apomorphine, we made the assumption that the plasma concentrations could be used to reflect the temporal changes of apomorphine levels in the biophase. As shown in Fig. 3, a good fit of equation 1 to the observed data was obtained and the

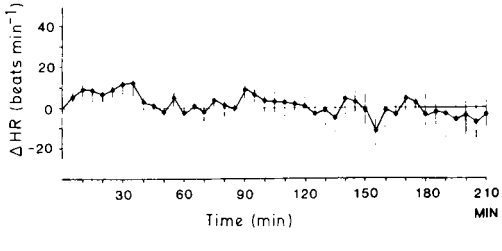

FIG. 4. The effects of saline s.c. on the heart rate (beats min^{-1}) during an experimental period of 3·5 h. Each point represents the mean ± s.e. from 10 rats.

parameters showed small standard deviations (S_1, S_2, $Cp(50)_1$, $Cp(50)_2$, E_{1max}, E_{2max}) and are given in Table 2. The Cp(50) values will be identical with the steady-state plasma concentration values ($Cp_{ss}(50)$).

Thus, to produce a pure bradycardia, a steady-state plasma concentration of $1{\cdot}2 \pm 0{\cdot}2$ ng ml^{-1} is needed for half of the maximum response ($E_{2max} = -50$ beats min^{-1}), while $35{\cdot}9 \pm 2{\cdot}3$ ng ml^{-1} is needed to elicit 50% of a pure maximal tachycardia ($E_{1max} = 110{\cdot}0$ beats min^{-1}). Equation 1 was also fitted to the effects on heart rate observed for 2 h after 100 μg kg^{-1} s.c. (Fig. 3). A good fit to the data was obtained for this dose also (Fig. 3), and the estimated parameters are given in Table 2. The Cp(50) for bradycardia was almost identical to that obtained after 5 mg kg^{-1} whereas the Cp(50) for the pure tachycardia was lower, $24{\cdot}4 \pm 2{\cdot}5$ ng ml^{-1}. The lowest dose (50 μg kg^{-1}) produced a pure decrease the heart rate and therefore the first term of equation 1 was omitted when fitted to the observed effect. The Cp(50) for bradycardia was then calculated to $2{\cdot}1 \pm 0{\cdot}5$ ng ml^{-1} (Table 2).

Table 2. Calculated parameters of equation 1 obtained from the fit of the time-courses of the effects of apomorphine after different s.c. doses.

Pharmacological effect	Dose apomorphine HCl s.c.	Plasma concn for 50% of maximal effect (Cp(50)) ng ml^{-1} ± s.d.	Slope factor ± s.d. (S)
Bradycardia	5·0 mg kg^{-1} (n = 11)	1·24 ± 0·18	1·12 ± 0·21
$E_{max} = -50{\cdot}0$	100 μg kg^{-1} (n = 9)	1 23 ± 0·34	0·88 ± 0·33
beats min^{-1}	50 μg kg^{-1} (n = 10)	2·12 ± 0·52	1·15 ± 0·58
Tachycardia	5·0 mg kg^{-1} (n = 11)	35·9 ± 2·3	1·32 ± 0·12
$E_{max} = 110$	100 μg kg^{-1} (n = 9)	24·4 ± 2·5	2·12 ± 0·78
beats min^{-1}			

n = number of animals.

Since the parameters of the plasma concentration-response curves of apomorphine for bradycardia and tachycardia were obtained (Table 2), these curves could be calculated and plotted separately, together with the composite effect (Fig. 5). The net effect on the heart rate in relation to its steady-state plasma concentration yielded a U-shaped curve. A maximum bradycardia should be observed at a plasma steady- state level of about 5 ng ml^{-1} and this effect will then decrease with increase in plasma concentration (Fig. 5). No effect on the heart rate should be produced at about 30 ng ml^{-1} and with further increase in plasma levels an increase in tachycardia will be achieved.

The U-shaped plasma concentration-response curve explains the fluctuations in the effect observed *over time* after subcutaneous administration of apomorphine. Pure bradycardia should be expected after small doses of apomorphine (Fig. 5) while doses of 100 μg and 5 mg kg^{-1} may produce bradycardia during the absorption phase when the drug level is rising and the concentration moves rightwards on the concentration axis in Fig. 4.

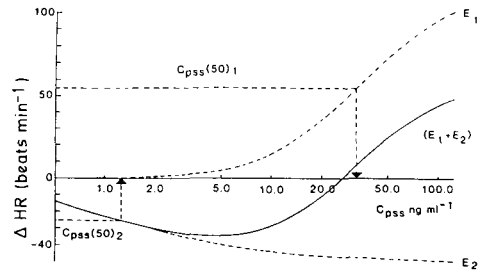

FIG. 5. The calculated relation between the steady-state plasma concentrations of apomorphine (Cp_{ss}) and its effect on the heart rate. The obtained relation between the net effect ($E_1 + E_2$) and Cp_{ss} was dissociated into two components: E_1 (tachycardia) and E_2 (bradycardia). The $Cp_{ss}(50)$ values for the pure effects are given.

As plasma levels exceed 30 ng ml^{-1} after the doses of 100 μg and 5 mg kg^{-1}, these doses also produce tachycardia (Fig. 3, Fig. 5). During the elimination-phase the plasma levels of apomorphine continuously decline and move leftwards along the concentration axis. Hence, the degree of tachycardia should decrease and shift into bradycardia, which should be maximal when the concentration reaches the minimum of the curve in Fig. 5. As a consequence, the magnitude of maximum bradycardia should be equal for the 100 μg and 5 mg kg^{-1} doses but this effect will appear at different times, as also was found and shown in Fig. 3. The lowest dose we used, 50 μg kg^{-1}, did not produce a maximal decrease in the heart rate, most probably because it did not produce the concentration that elicited maximum bradycardia in Fig. 5.

DISCUSSION

Apomorphine given intravenously or subcutaneously to rats had a high total plasma clearance (Table 1) which was about four to five-fold higher than the normal hepatic plasma flow (36 ml min^{-1} kg^{-1}) (Boxenbaum 1980). Since apomorphine is mainly cleared by metabolism in the liver (Kaul et al 1961; Campbell et al 1980), the high total plasma clearance we found indicates that extrahepatic metabolism also occurs. Besides glucuronidation, apomorphine is degraded in-vivo by catechol-*O*-

methyltransferase (COMT) (McKenzie & White 1973) and since this enzyme is present in significant amounts in various tissues, including red blood cells (Axelrod & Cohn 1971), extrahepatic metabolism by *O*-methylation could contribute to the high total clearance.

The apparent volume of distribution (V_d) was high (Table 1), indicating a pronounced tissue uptake. The brain levels of apomorphine were 6–7 times higher than those in plasma at post-distribution which is in accordance with the findings of Campbell et al (1980). The rate of uptake into, and disappearance from, the brain was rapid and the kinetics of apomorphine in the whole brain were almost identical to that found in plasma after subcutaneous administration of the drug. Butterworth & Barbeau (1975) and Kebabian (1978) found a fairly even distribution of apomorphine in different regions of the rat brain with levels similar to those found by us. However, Westerink & Horn (1979) reported lower apomorphine levels in the cerebellum than in other brain regions.

Owing to the high plasma clearance, the biological half-life in plasma was short after both intravenous (13·8 min) and subcutaneous (14·5 min) administration ($t_{\frac{1}{2}} = 0{\cdot}7 \times V_d$/clearance) and is in accordance with that previously reported in rats (Symes et al 1976; Melzacka et al 1979). The rate of absorption of apomorphine after subcutaneous administration of 5 mg kg^{-1} was rapid ($t_{\frac{1}{2}} = 1{\cdot}8$ min) and the extent of absorption (bioavailability) was complete ($AUC_{sc} \times Dose_{iv}/AUC_{iv} \times Dose_{sc} \geq 1{\cdot}0$). However, because of the high hepatic clearance, the bioavailability after the oral and the intraperitoneal routes will be low, as has been reported (Smith et al 1979; Campbell et al 1980).

Apomorphine produces variable effects on the cardiovascular system. In *anaesthetized* animals it produces hypotension in various species (Barnett & Fiore 1971; Finch & Haeusler 1973; Bogaert et al 1978) or high doses have a biphasic effect on blood pressure with an initial brief fall in systemic pressure followed by a hypertensive phase (Fadhel 1967; Barnett & Fiore 1971). In *conscious* dogs, Fadhel (1967) reported that apomorphine, in various doses, induced a pure hypertensive effect. In conscious rats, we found no significant hypotensive or biphasic effect on the systemic mean arterial blood pressure after 50 or 100 μg kg^{-1} of apomorphine subcutaneously, but at 5 mg kg^{-1} s.c., it induced a hypertensive response with a relatively slow onset. Thus it might be difficult to obtain small hypotensive effects in conscious animals, as Zandberg & De Jong (1977) found when they evaluated the blood pressure-lowering effects of clonidine.

In anaesthetized animals bradycardia has been shown to occur initially after apomorphine, but the whole time course of the dose has not been recorded (Finch & Haeusler 1973; Dutta et al 1975; De Meyer et al 1982). Although Dutta et al (1975) presented only data on bradycardia after low doses of apomorphine to anaesthetized cats, they mention that relatively high doses induced tachycardia. Moreover, dopamine alone given intracerebroventricularly to conscious cats, produced tachycardia followed by a phase of bradycardia (Day & Roach 1976).

Nevertheless, our present results show that in the unrestrained, conscious rat, apomorphine produced biphasic effects on the heart frequency so that a low dose (50 μg kg^{-1} s.c.) induced bradycardia while a high dose (5 mg kg^{-1} s.c.) exhibited a fluctuating response during the time course of its action, with tachycardia followed by bradycardia after which normal heart rate was regained (Fig. 3). A moderate dose (100 μg kg^{-1} s.c.) also caused a brief initial bradycardia (Fig. 3). These data suggest that apomorphine influences the heart frequency in two opposing ways depending on the concentration at the site of effect. Since we evaluated the time-course of apomorphine concentrations in plasma and brain tissue together with the continuous registration of the effects on cardiovascular parameters, we could calculate the concentration-response curves (Fig. 5) for the effects on heart rate.

Apomorphine exhibited a U-shaped concentration-response curve for the effects on the heart frequency with bradycardia appearing after low, steady-state plasma concentrations; this effect reached a maximum and then decreased with increasing concentrations (Fig. 5). A further increase of the concentration resulted in tachycardia. Steady-state plasma levels of apomorphine of about 5 ng ml^{-1} will produce a maximum bradycardia while above 30 ng ml^{-1}, tachycardia should appear (Fig. 5).

The high dose of 5 mg kg^{-1} of apomorphine is rapidly absorbed (Table 1) and in only 3 out of 11 rats was a decrease of the heart frequency seen during this phase. However, with the moderate dose 100 μg kg^{-1}, 8 out of 11 rats showed brief bradycardia 2–3 min after the subcutaneous administration (Fig. 3) explained by the slower rate of absorption with this lower amount (first order process). When drug levels exceed 30 ng ml^{-1}, brief (100 μg kg^{-1}) or sustained (5 mg kg^{-1}) tachycardia occurs (Fig. 5).

During the elimination, apomorphine is rapidly removed from the biophase (Table 1) and the degree of tachycardia will decrease and shift into bradycardia when the concentration has fallen below a critical level (Fig. 5). The temporal fluctuations between opposing effects seen here could thus be explained by the unique concentration-response features of apomorphine. Whether opposing dopamine functional systems are involved in the low- and high-concentration related effects on the heart rate has yet to be studied.

The appearance of active metabolites might explain the different effects seen with time after apomorphine administration or, similarly, the opposing responses could be derived from different effect compartments. However, a general objection to these suggestions is that, under the assumption made, we could fit the sum of two Hill equations to the observed time courses of effects after different doses and that these fits yielded small standard deviations of the estimated parameters which also coincided for all studied doses (Table 2). The calculated drug concentration response relation (equation 1), could, moreover, be used to fit the oscillating responses seen after 100 $\mu g\ kg^{-1}$ as well as after 5 $mg\ kg^{-1}$ (Fig. 3).

How factors related to bioavailability and thus to biophase concentration may change the response to apomorphine is further emphasized by the findings of Arnerić & Long (1983), who found that apomorphine produced hypermotility when given subcutaneously and hypomotility when given orally in the same dose. Not until very high doses of apomorphine were given orally did it mimic the hypermotility response produced by the subcutaneous administration.

The results of the present study probably have their equivalents within therapy where patients have long experienced on and off effects in motor performance occurring after dopaminomimetics in Parkinson's disease.

Acknowledgement

The authors wish to thank Miss Kerstin Frykman for her skilful technical assistance and Dr Per-Olof Edlund for the chemical analyses.

REFERENCES

Arnerić, S. P.., Long, J. P. (1983) Drug Development Research 3: 221–231

Axelrod, J., Cohn, C. K. (1971) J. Pharmacol. Exp. Ther. 176: 650–654

Barnett, A., Fiore, J. W. (1971) Eur. J. Pharmacol. 14: 206–208

Bogaert, M. G., Buylaert, W. A., Willems, J. L. (1978) Br. J. Pharmacol. 63: 481–484

Boxenbaum, H. (1980) J. Pharmacokinet. Biopharm. 8: 165–176

Butterworth, R., Barbeau, A. (1975) Can J. Biochem. 53: 308–311

Campbell, A., Kula, N. S., Jeppsson, B., Baldessarini, J. (1980) Eur. J. Pharmacol. 67: 139–142

Carlsson, A. (1975) in: Udsin, E., Bunney Jr, W. E. (eds) Pre- and postsynaptic receptors. New York, Marcel Dekker, p. 49

Day, M. D., Roach, A. G. (1976) Br. J. Pharmacol. 58: 505–515

De Meyer, J. M., Buylaert, W. A., Bogaert, M. G. (1982) Arch Int. Pharmacodyn. Ther. 256: 166–167

Di Chiara, G., Gessa, G. L. (1978) Adv. Pharmacol. Chemother. 15: 87–160

Dutta, S. N., Guha, D., Pradhan, N. (1975) Arch. Int. Pharmacodyn. Ther. 214: 259–265

Eriksson, B. M., Persson, B. A., Lindborg, M. (1979) J. Chrom. 185: 575–581

Ernst, A. M. (1967) Psychopharmacology 10: 316–323

Fadhel, N. (1967) Diss. Abstr. 28: 1632B

Finch, L., Haeusler, G. (1973) Eur. J. Pharmacol. 21: 264–270

Henning, M. (1969) Acta. Phsyiol. Scand. Suppl. 322

Kaul, P. N., Brochmann-Hanssen, E., Way, E. L. (1961) J. Pharm. Sci. 50: 248–251

Kebabian, J. W. (1978) J. Neurochem. 30: 1143–1148

McKenzie, G. M., White, H. L. (1973) Biochem. Pharmacol. 22: 2329–2336

Melzacka, M., Wiszniowska, G., Daniel, W., Vetulani, J. (1979) Pol. J. Pharmacol. Pharm. 31: 309–317

Metzler, C. M., Elfring, G. L., McEwan, A. J. (1974) Users Manual for NONLIN and Associated Programs, Upjohn Company, Kalamazoo, MI

Montanaro, N., Vaccheri, A., Dall'Olio, R., Gandolfi, O. (1983) Psychopharmacology 81: 214—219

Paalzow, G. H. M., Paalzow, L. K. (1983) Eur. J. Pharmacol. 88: 27–35

Paalzow, L. K., Paalzow, G. H. M., Tfelt-Hansen, P. (1985) in: Rowland, M., Sheiner, L. B., Steimer, J. L. (eds) Variability in Drug Therapy. Raven Press, New York

Protais, P., Dubuc, I., Costentin, J. (1983) Eur. J. Pharmacol. 94: 271–280

Rowland, M., Tozer, T. (1980) Clinical Pharmacokinetics. Lea and Febiger, Philadelphia

Smith, R. V., Wilcox, R. E., Soine, W. H., Riffee, W. H., Baldessarini, R. J., Kula, N. S. (1979) Res. Commun. Chem. Pathol. Pharmacol. 24: 483–499

Symes, A. L., Lal, S., Sourkes, T. L. (1976) Arch. Int. Pharmacodyn Ther. 223: 260–264

Trolin Georgsson, G. (1975) Acta Physiol. Scand. suppl. 430

Westerink, B. H. C., Horn, A. S. (1979) Eur. J. Pharmacol. 58: 39–48

Zandberg, F., De Jong, W. (1977) J. Pharm. Pharmacol. 29: 697–698