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EFFECTS OF AZAPERONE ON CARDIOVASCULAR AND RESPIRATORY FUNCTIONS IN THE HORSE

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1 The butyrophenone tranquillizer, azaperone, was administered intramuscularly, at dose levels of 0.4 and 0.8 mg/kg, to ponies and its effects on cardiovascular and respiratory functions assessed.

2 Arterial blood pH, CO_2 tension ($PaCO_2$) and O_2 tension (PaO_2) remained relatively constant throughout the course of action of azaperone.

3 Azaperone did not modify plasma protein concentration but venous blood packed cell volume and haemoglobin concentration were reduced by 5 to 10% for at least 4 hours. These changes were probably caused by uptake of erythrocytes into the splenic reservoir.

4 Small increases in heart rate occurred for up to 60 min after administration of the drug, and this was followed by a slight bradycardia in some ponies.

5 Azaperone reduced mean arterial blood pressure (MAP) for at least 4 h, by which time its ataractic action was generally no longer apparent. The hypotension was caused, during the early phase of action at least, by a reduction in peripheral resistance, since cardiac output was increased slightly 20 min after its administration. Possible mechanisms underlying the cardiovascular changes are discussed.

6 In spite of reductions in arterial blood O_2 content and MAP produced by azaperone, it is likely that tissue oxygenation was adequate, since arterial blood lactate concentrations were not increased.

Introduction

In veterinary medicine tranquillizers are used extensively to quieten, calm and pre-medicate animals which, because of their individual or species temperament, may be less amenable to approach and handling than other animals or man. Drugs of the phenothiazine and butyrophenone groups, having proved particularly useful, have now largely superseded traditional sedatives, such as chloral hydrate, for use in many species. For example, azaperone is a relatively new butyrophenone derivative, which has been used in recent years in porcine (Marsboom & Symoens, 1968; Clarke, 1969; Symoens & van den Brande, 1969; Lang, 1970; Callear & van Gestel, 1971; Nienaber, 1972) and in equine (Roztočil, Něměcek & Pavlica, 1971; Aitken & Sanford, 1972a,b; Ehmke, 1972; de Leglise, 1973; Serrano & Lees, 1976) medicine.

Previous reports on the actions of azaperone have been concerned primarily with its general properties and clinical efficacy. The present paper complements these studies by describing the pharmacological actions of azaperone on cardiovascular and respiratory functions in the horse. Possible mechanisms underlying the most profound action of azaperone, a moderate, long-lasting degree of hypotension, are considered.

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Methods

Drugs, animals and experimental protocols

The drugs used were azaperone (Suicalm, Crown Chemical Co.) and heparin (Pularin, Evans Medical Co.).

The actions of azaperone were investigated in four series of experiments, using Welsh Mountain ponies of either sex, ranging in age from 3 to 5 years and in weight from 202 to 300 kg. No animal was used in more than three of the four series, and at least 10 weeks elapsed between each series. The sedative action of azaperone was assessed by means that have been described elsewhere (Serrano & Lees, 1976).

Both carotid arteries of each pony had been transposed to subcutaneous positions in the neck at leasf 6 months before the experiments (Tavernor, 1969). This facilitated cardiovascular measurements and the collection of samples of arterial blood. The ponies were trained to accept the recording

procedures, and it is assumed, therefore, that all values were obtained from non-stressed animals unless otherwise stated.

In the first experimental series, changes in heart rate were recorded in seven ponies before and at predetermined times after injecting azaperone, at a dose rate of 0.4 mg/kg, into the gluteal muscle. In the second series, intramuscular injections of azaperone were given to the same animals at the higher dose rate of 0.8 mg/kg and changes in heart rate again recorded. This dose level of azaperone always produced a satisfactory degree of ataraxy and it was used, therefore, in all subsequent experiments. In the third experimental series, six ponies each received an intramuscular injection of azaperone and the following variables were measured before and at predetermined times after its administration: arterial blood pH, CO_2 tension ($PaCO_2$), O_2 tension (PaO_2), lactate concentration and pyruvate concentration; venous blood haemoglobin (Hb) concentration and packed cell volume (p.c.v.) and venous plasma protein concentration; heart rate and mean arterial blood pressure (MAP).

In the fourth series of experiments six ponies each received an intramuscular injection of azaperone on three occasions at six-week intervals. Arterial blood pH, $PaCO_2$, PaO_2, MAP and cardiac output were measured both before and 20 min after injection, and further indices of cardiovascular function were derived from these measurements.

Cardiovascular measurements

Heart rate (beats/min) was measured from one of the standard limb leads of the ECG, recorded on a Devices M2 two-channel recorder. The rate was derived from the distance between ten consecutive QRS-complexes, using a chart speed of 10 or 25 mm/second. Arterial blood pressure was recorded from a carotid artery, into which a Braunula Number 1 catheter (Armour Pharmaceutical Co. Ltd.) had been inserted at least 1 h before the start of the experiment. The catheter was connected by a polythene tube containing heparinized saline (25 u/ml) to a Bell and Howell pressure transducer (type 4/327/L221). Recordings were made on the second channel of the Devices recorder. The transducer was placed 50 mm above the point of the shoulder in all ponies, because radiographic studies (Bell, Beltran & Price, personal communication) have demonstrated that the position of the right atrium is, on average, at this level in ponies of similar size to those used in this study. Mean values of systolic and diastolic pressure were derived from ten consecutive systoles and diastoles. MAP was calculated from the formula:

$$MAP = Pd + \frac{Ps - Pd}{3},$$

where Pd = mean diastolic pressure and Ps = mean systolic pressure (Folkow & Neil, 1971). Results are expressed in mmHg.

Cardiac output (CO) was determined by a dye dilution technique using indocyanine green dye (Cardiogreen; Hynson, Westcott and Dunning, Inc.) as described previously (Hillidge & Lees, 1975). Values are expressed in litres/minute. Left ventricular stroke volume (LVSV) was calculated by dividing CO by the simultaneously recorded heart rate. Left ventricular stroke work (LVSW) was determined as the product of MAP and LVSV, and expressed in kp m. Total peripheral resistance (TPR) was calculated from the formula:

$$TPR = \frac{MAP \times 1{,}334 \times 60}{CO \times 1{,}000}$$

Values of TPR are approximate, since the formula assumes that left ventricular end-diastolic pressure equals zero. The values are expressed as dyn s cm^{-5}.

Respiratory measurements

Samples of arterial blood for determining pH, PaO_2 and $PaCO_2$ were obtained from the Braunula catheter in the carotid artery. Each sample was collected anaerobically in a heparinized 10 ml glass syringe (5,000 u/ml). The Clark O_2 electrode (Radiometer type E 5046) and Severinghaus CO_2 electrode (Radiometer type E 5036) were mounted in thermostatted cells. Values of PaO_2 and $PaCO_2$, expressed in mmHg, were read on a pH meter (Radiometer pH 27) linked to a gas monitor (Radiometer pH A 927). Arterial blood pH was determined with the Radiometer pH meter 27 in conjunction with a microelectrode system (Radiometer type E 5021). Blood samples were either analysed immediately or stored on ice and read within 45 min of collection. Measurements were made at a known, constant electrode temperature within the range of 37 to 38°C. All readings were later corrected to the animal's rectal temperature at the time of sampling using a blood gas calculator (Severinghaus, 1966).

Analytical procedures

Samples of arterial blood for measurement of lactate and pyruvate concentrations (Hillidge & Lees, 1974) were obtained from the Braunula catheter in the carotid artery. Venous blood samples for duplicate determinations of p.c.v., Hb concentration and plasma total protein concentration were collected from a Braunula Number 2 catheter, which had been filled with heparin solution (5,000 u/ml) and inserted in a jugular vein on the day preceding the experiment. The samples were collected in 10 ml glass syringes, lubricated with heparin solution (5,000 u/ml).

Estimations of p.c.v. were made using a capillary tube microhaematocrit method (Hawksley and Sons

Ltd.). Blood Hb concentrations were measured by the cyanmethaemoglobin method of Drabkin with a Pye Unicam SP 600 spectrophotometer at a wavelength of 540 nm. Twenty mm^3 of well-mixed blood was added to 4 ml Drabkin's solution, mixed and allowed to stand at room temperature for at least 15 min before reading. Commercial cyanmethaemoglobin solutions (Diagnostic Reagents Ltd.) containing 3.0 and 18.0 g/100 ml were used as standards. Total protein concentrations in plasma were measured by the biuret method of Reinhold (1953), using an SP 600 spectrophotometer at a wavelength of 555 nm.

Statistical analyses

The significance of differences between mean values was assessed by the paired *t*-test at two levels, $P < 0.05$ and $P < 0.01$. Values quoted in the text are means together with s.e. means.

Results

Tranquillizing action of azaperone

The tranquillizing effect of azaperone was assessed in the first three series of experiments. In the first series, doses of 0.4 mg/kg produced levels of tranquillization that were classified as good or excellent in five of seven ponies, and as fair and slight, respectively, in the sixth and seventh animals. The degree of ataraxy was generally similar in the second and third series, when the higher dose level of 0.8 mg/kg was used, but a good or excellent response was obtained more consistently (twelve of thirteen instances). The onset of action was usually apparent within 10 min, becoming maximal after 10 to 70 minutes. The effects had always decreased by 2 h and usually were no longer apparent after 4 hours.

Heart rate

Azaperone produced small increases in heart rate for up to 60 min (Figure 1). The smallest degree of tachycardia occurred in response to a dose level of 0.4 mg/kg; at no time did the response reach significant levels. After 2 h, however, a significant degree of bradycardia was recorded ($P < 0.05$). In the second and third series of experiments a higher dose rate of azaperone (0.8 mg/kg) produced significant increases in heart rate (Figure 1), the greatest response occurring after 20 min and involving changes of 17% ($P < 0.05$) and 24% ($P < 0.01$), respectively, from the control levels. After the first hour, heart rate was reduced slightly below initial levels. At 4 h, for example, decreases of 11 and 10% were recorded in the second and third series, respectively, but these changes were not significantly different from the controls.

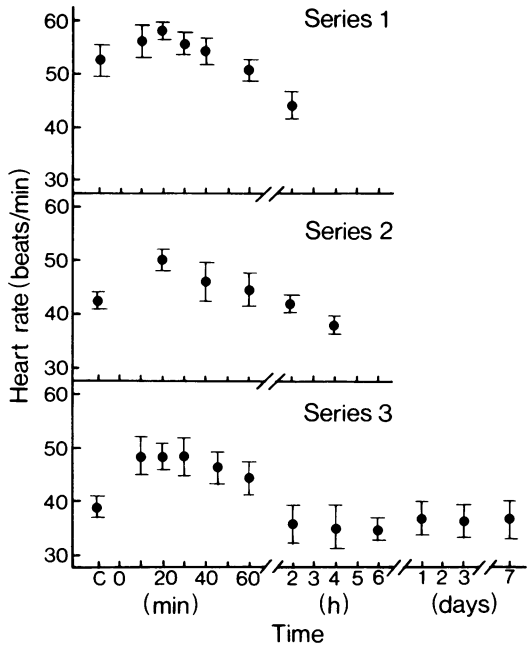

Figure 1 Effect of azaperone injected intramuscularly at zero time on heart rate of ponies. C = control heart rates measured 5 to 15 min before administration of azaperone. Each point represents the mean value for: seven animals each receiving 0.4 mg/kg (series 1); seven animals each receiving 0.8 mg/kg (series 2); and six animals each receiving 0.8 mg/kg (series 3). Vertical bars indicate s.e. mean.

Mean arterial blood pressure

MAP was reduced following the administration of azaperone at a dose rate of 0.8 mg/kg (Figure 2). Pressures were reduced by 30 to 38% from the control level for up to 4 h ($P < 0.01$ at all times), the greatest decrease being recorded at one hour. After the first hour MAP increased slightly from the minimal level, but even after 4 h the pressure was still 35 mmHg less than the control value.

Cardiac output and total peripheral resistance

Since the degree of hypotension produced by azaperone was relatively constant between 10 and 120 min, while the tachycardia was maximal at 20 min, measurements of CO, MAP and TPR were obtained before and 20 min after injecting azaperone (0.8 mg/kg) in the next series of experiments. Azaperone was administered to each of six ponies on three occasions to provide average results from eighteen estimations. The mean control value of CO for the eighteen determinations was 23.1 ± 1.4

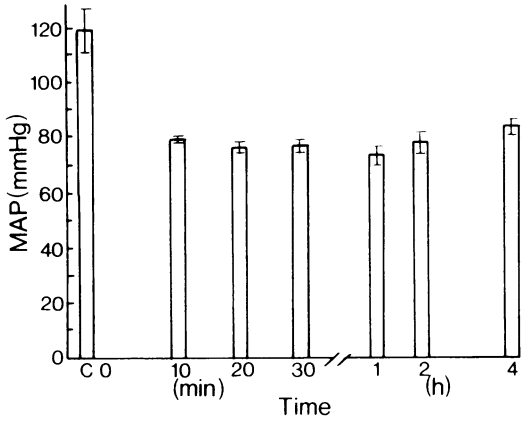

Figure 2 Effect of azaperone (0.8 mg/kg) injected intramuscularly at zero time on mean arterial blood pressure (MAP). C = control pressure recorded 5 to 15 min before administration of azaperone. Each column represents the mean value for five animals. Vertical bars indicate s.e. mean.

1 min^{-1}, corresponding to 88.3 ± 4.0 ml kg^{-1} min^{-1}. Twenty minutes after injecting azaperone the mean CO was increased by 4% to 23.9 ± 1.8 l min^{-1} (91.9 ± 6.1 ml kg^{-1} min^{-1}). This change was not significant. Since MAP was decreased to a moderate extent, while CO was almost unchanged, TPR was reduced by 30% from 457 ± 34 to 319 ± 24 dyn s cm^{-5}. Further calculations revealed that LVSV and LVSW were also reduced, from 0.52 ± 0.03 to 0.39 ± 0.04 l/beat and from 0.86 ± 0.05 to 0.54 ± 0.05 kp m, respectively.

Arterial blood pH, $PaCO_2$ and PaO_2

The slight changes in pH and $PaCO_2$ recorded up to 4 h after azaperone administration (0.8 mg/kg) were not statistically significant (Figure 3). The greatest changes in $PaCO_2$ comprised a slight increase of 2.4% at 30 min and a small decrease of 4.6% 4 h after administering the drug. In the fourth series of experiments azaperone (0.8 mg/kg) was administered to each of six ponies on three occasions. For these eighteen measurements the mean $PaCO_2$ was 47.8 ± 0.9 before and 47.3 ± 0.8 mmHg 20 min after the injection, a difference that was also insignificant.

In the third experimental series values of PaO_2 tended to fall after injecting azaperone but the changes were small and insignificant (Figure 3). Likewise, for the eighteen experiments in the fourth series, PaO_2 decreased from a mean control level of 98.5 ± 1.3 to 95.0 ± 2.3 mmHg in samples collected 20 min after azaperone administration. This small change was also insignificant.

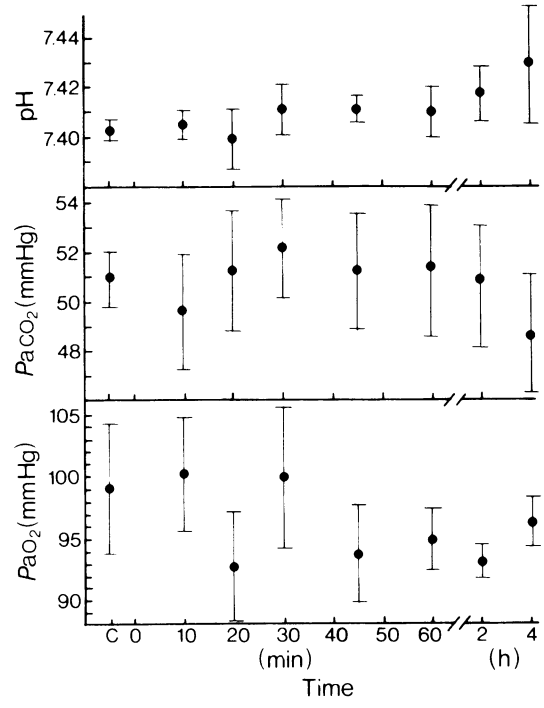

Figure 3 Effect of azaperone (0.8 mg/kg) injected intramuscularly at zero time on arterial blood pH, $PaCO_2$ and PaO_2. C = control values obtained 5 to 15 min before administration of azaperone. Each point represents the mean value for five animals. Vertical bars indicate s.e. mean.

Venous blood packed cell volume and haemoglobin concentration

Mean control values of p.c.v. and Hb concentration for six ponies were 30.3 ± 1.3 and 10.9 ± 0.5, respectively. Small reductions in both variables occurred (Figure 4) in response to injections of azaperone (0.8 mg/kg). At each time interval the changes in the two variables were proportionally similar, so that mean corpuscular Hb concentration was almost unchanged. The decreases in p.c.v. and Hb concentration were apparent 10 min after injecting azaperone and maximal after 2 h, at which time both were reduced by 12% from the control levels. The absolute values at 10 min and 2 h, respectively, were 29.2 ± 1.0 and 26.8 ± 1.3 (p.c.v.) and 10.5 ± 0.4 and 9.7 ± 0.5 (Hb concentration). All values recorded between 30 min and 4 h were 8 to 12% less than the controls. Small increases in both variables occurred at 24 h and 3 days but they had returned to normal levels again by 7 days.

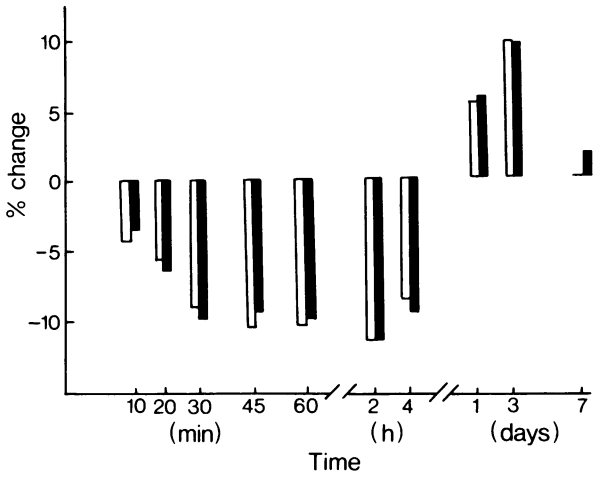

Figure 4 Percentage changes in jugular venous blood packed cell volume (closed columns) and haemoglobin concentration (open columns) following the intramuscular injection of azaperone (0.8 mg/kg) at zero time. Each column represents the mean change for six animals.

Plasma protein concentration

Plasma protein concentration was affected only slightly by the administration of doses of 0.8 mg/kg azaperone (Table 1). The greatest change occurred 2 h after its administration, when the mean concentration was reduced by 1.3%. However, this was not significant at the 95% probability level.

Blood lactate and pyruvate concentrations

Concentrations of lactate and pyruvate in arterial blood were measured in three ponies. Both values fell slightly following azaperone administration, although the changes were not statistically significant (Table 1).

Discussion

The effects of azaperone on respiratory function call for little comment, since the slight changes in $PaCO_2$, PaO_2 and arterial blood pH were not statistically significant. However, arterial blood O_2 content was decreased by approximately 10% because of a reduction of this magnitude in Hb concentration. Whole body tissue oxygenation was probably adequate nevertheless. When tissue glycolysis proceeds anaerobically, lactate production leads ultimately to rises in circulating lactate levels but arterial blood lactate concentrations were not altered in this study.

Azaperone produced several changes in cardiovascular function: p.c.v. and Hb concentration were reduced by 5 to 12% for at least 4 h; a small though significant degree of tachycardia occurred for approximately 60 min while a slight bradycardia was recorded between 2 and 6 h in some ponies; and blood pressure was reduced by 30 to 50 mmHg for at least 4 hours. The degree of hypotension was relatively constant between 10 min and 4 h, whereas the tachycardia was maximal after 20 minutes. It was of interest, therefore, to note that cardiac output was not significantly affected at this time, so that the fall in pressure was attributable entirely to a reduction in total peripheral resistance. The present experiments do not establish the cause of the latter effect. It could be due, in part, to a reduction in blood viscosity resulting from the fall in p.c.v. An approximate estimate of the contribution of the latter to the 30% fall in TPR occurring 20 min after azaperone administration was made; a figure of 7% was obtained, suggesting that the remaining 23% of the decrease at this time was produced by some other mechanism.

It is probable that a second cause of the decrease in TPR was a vasodilator action of azaperone and this could be mediated in several ways. Marsboom (1969, 1971) has described a protective effect of azaperone against lethal doses of noradrenaline in rats, and others have demonstrated postsynaptic α-receptor

Table 1 Effect of azaperone on venous plasma protein concentration and arterial blood lactate and pyruvate concentrations

	Control	*Time after injecting azaperone*						
		10	*20*	*30*	*45*	*60*	*2*	*4*
				min			*h*	
Protein (g/100 ml)	8.56 ± 0.37	8.57 ± 0.35	8.63 ± 0.38	8.66 ± 0.37	8.59 ± 0.43	8.66 ± 0.45	8.45 ± 0.31	8.62 ± 0.34
Lactate (mg/100 ml)	10.5 ± 3.3	8.9 ± 2.8	8.8 ± 2.1	9.3 ± 2.0	9.0 ± 2.1	9.6 ± 2.0	9.1 ± 2.1	10.5 ± 2.1
Pyruvate (mg/100 ml)	0.67 ± 0.15	0.63 ± 0.13	0.58 ± 0.11	0.53 ± 0.14	0.58 ± 0.13	0.60 ± 0.14	0.55 ± 0.10	0.53 ± 0.08

Each value is the mean with s.e. mean for six animals (protein concentration) and for three animals (lactate and pyruvate concentrations). No significant changes from control values occurred.

blocking activity of the butyrophenone on isolated tissues (Hapke & Prigge, 1972; Niemegeers, van Neuten & Janssen, personal communication) and reversal of the pressor action of adrenaline by azaperone in dogs and cats (Hapke & Prigge, 1972). Moreover, unpublished findings from this laboratory indicate that similar doses of azaperone to those used in this study partially antagonize several effects of adrenaline in ponies (rise in MAP, hyperkalaemia and increases in p.c.v. and Hb concentration), mediated at least partially by α-adrenoceptors. From this evidence it seems possible that the hypotensive action of azaperone may be attributable in part to blockade of vascular α-receptors and a consequent reduction in vasomotor tone. However, this action of azaperone may not account wholly for its vasodepressor effect because a study of the actions in ponies of acepromazine (0.1 mg/kg), another tranquillizer with α-receptor blocking properties (Marsboom, 1971), indicates that while it is somewhat more effective than azaperone (0.8 mg/kg) in suppressing the pressor effect of adrenaline it is less effective as a hypotensive agent (Serrano & Lees, 1976). It is clear that further investigations are needed to establish the cause of azaperone-induced hypotension.

An α-adrenoceptor blocking action of azaperone could also explain the reductions in p.c.v. and Hb concentration reported in this study. Other tranquillizers, including chlorpromazine, propriopromazine and promethazine, with known α-receptor blocking properties, decrease p.c.v. in sheep (Turner & Hodgetts, 1960a,b), dogs (Collette & Meriwether, 1965) and horses (de Moor & van den Hende, 1968). This action has been attributed to relaxation of the splenic capsule, the consequent enlargement of the spleen leading to uptake of erythrocytes from the circulation. However, there is some doubt concerning this hypothesis, since it depends on the presence of a tonically active sympathetic discharge to the capsule of the spleen, and Shepherd (1968) has claimed that little or no such activity exists. Another possible explanation for the reductions in p.c.v. and Hb concentration is a haemodilutant effect arising from an altered pre/post-capillary resistance ratio and a net transfer of interstitial fluid into the vascular compartment. Such an action has been reported in man for drugs, including guanethidine and phenoxybenzamine, which act in different ways to depress vasomotor tone (Weil & Chissey, 1968). However, this mechanism probably does not account for the present findings. This is indicated by the absence of significant changes in plasma protein concentration throughout the course of action of azaperone, when proportionally similar changes in p.c.v. and protein concentration would have been predicted by this hypothesis.

The findings of Roztočil *et al.* (1971) differed from those of the present investigation, these authors reporting an absence of significant changes in heart rate in horses receiving doses of 1 mg/kg azaperone intramuscularly. The small though significant degree of tachycardia produced by azaperone (0.8 mg/kg) in this study may have resulted indirectly from the hypotensive action of the drug through decreased sinus and aortic baroreceptor stimulation and a consequent change in the balance of sympathetic and parasympathetic nervous control of heart rate. However, the hypotension lasted for at least 4 h, whereas the tachycardia was usually no longer apparent after 1 h, suggesting that the reflex effect is overridden by some direct or indirect action to reduce heart rate. The mechanism of the secondary bradycardia which sometimes occurred is unclear. In any event it is of doubtful importance, since it attained a significant level only in the first series of experiments. This series was the only one to be carried out in an environment to which the ponies were unaccustomed. The mild apprehension that this might have caused could explain both the relatively high control heart rate (52 ± 2.7 beats/min) and the reduction in rate following azaperone administration.

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