The pharmacology and pharmacokinetics of high-dose methocarbamol in horses

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Summary

The haemodynamic, respiratory and behavioural effects and pharmacokinetics of methocarbamol were studied in eight healthy, adult horses after intravenous (iv) and oral administration of large dosages. Heart rate, cardiac output, mean pulmonary arterial blood pressure, systolic, diastolic and mean aortic blood pressure, respiratory rate and arterial blood gases did not change after either iv (30 mg/kg bodyweight [bwt]) or oral (50 and 100 mg/kg bwt) dosages of methocarbamol. Mild to moderate depression was observed in five of eight horses administered iv methocarbamol, and in all horses administered oral methocarbamol. Plasma methocarbamol concentration declined very rapidly during the initial or rapid disposition phase after iv administration; the terminal elimination half-life ranged from 59 to 90 mins. Peak plasma methocarbamol concentrations following oral administration occurred within 15 to 45 mins and oral bioavailability ranged from 50.7 to 124 per cent.

Introduction

METHOCARBAMOL, a skeletal muscle relaxant, is used in horses as therapy for painful musculo/skeletal conditions, muscle spasticity, exertion myopathy, pressure myopathy and tetanus (Mayhew and MacKay 1982, Booth 1988). Methocarbamol also protects against the development of convulsions induced by electro-shock, strychnine and pentylenetetrazole (Esplin 1970). The mechanism of action of methocarbamol is not known, although preferential block of spinal polysynaptic reflexes and decreases in nerve transmission in spinal and supra-spinal polysynaptic pathways are produced (Bianchine 1980). Studies in rats and mice suggest that methocarbamol increases suppressed responding in a conflict procedure and produces some sedative effects when dosages between three and six times the therapeutic recommendations are administered (Bennett and Amrick 1986). We have reported previously the haemodynamic, respiratory and behavioural effects, as well as the pharmacokinetic properties of methocarbamol in horses administered intravenous (iv) doses up to 17.6 mg/kg bodyweight (bwt) (Muir, Sams and Ashcraft 1984). Methocarbamol did not produce cardiorespiratory or behavioural changes in these studies.

Methocarbamol disposition appeared dose dependent; the total body clearance and steady-state volume of distribution decreased as the dose increased. Plasma concentrations of guaifenesin, a metabolite of methocarbamol, were not greater than 0.5 per cent of the plasma methocarbamol concentration (Muir, *et al* 1984). The current study was prompted by 1) our original data suggesting that the disposition of methocarbamol may be dose dependent and 2) continued reports that large oral doses of methocarbamol have been used in an attempt to modify behaviour in performance horses. The purpose of the present study was to investigate further the haemodynamic, respiratory and behavioural effects and the pharmacokinetic properties of large iv and oral dosages of methocarbamol.

*Reprint requests

Materials and methods

Haemodynamic and behavioural studies

Eight normal, clinically healthy, adult horses aged 4 to 15 years and weighing 452-521 kg were used in this study (six mares and two geldings). Health was assessed by physical examination, complete blood count and electrocardiography. All eight horses had their left carotid artery relocated to a subcutaneous position at least two months prior to the experiments to facilitate arterial catheter placement and withdrawal of arterial blood samples. The horses were familiarised with the experimental environment for at least one month prior to the experiments. Food, but not water, was withheld for at least 8 h before each experimental trial. The experiments were performed in accordance with *The Guiding Principles and The Care and Use of Animals of the American Physiological Society* and the *Regulations of the Institutional Animal Care and Use Committee of The Ohio State University.*

Animal preparation

The eight horses underwent identical preparation for the experiments: Both the right and left jugular furrows were clipped and surgically prepared for the placement of intravascular catheters after injecting approximately 1 to 2 ml of 2 per cent lidocaine subcutaneously. Number 8 French catheter introducers were placed transcutaneously in the right and left jugular veins to facilitate positioning of 1) a specialised balloon-tipped catheter with a thermistor located at its distal end in the pulmonary artery and 2) a PE 240, 90 cm catheter in the right atrium. Either a 17 or 19 gauge, 30 cm catheter was placed by percutaneous puncture into the previously relocated left carotid artery. Catheter postions were verified by observing the correct pressure values and pressure waveforms. The scapulohumeral joint was used as the zero pressure reference point. Dependent variables recorded included heart rate, cardiac output, mean systemic arterial blood pressure, mean pulmonary arterial blood pressure and mean right atrial pressure, respiratory rate and arterial and venous blood gases.

The bladder of each mare was catheterised 2 h before methocarbamol administration. A urine sample was collected and the bladder emptied immediately before methocarbamol administration. Urine samples were then collected every hour for 8 h following methocarbamol administration.

Drug dosage trials

All eight horses were given three different dosages of methocarbamol and a saline solution (placebo) according to a

blinded randomised procedure. The dosages of methocarbamol were 30 mg/kg bwt iv and 50 and 100 mg/kg orally. Not less than 10 days elapsed between experiments.

Haemodynamic data and blood samples for arterial pH and blood gas tensions (PaO_2 and $PaCO_2$) were obtained at 60 and 30 mins and immediately before drug administration, and at 15, 30, 60, 90, 120, 150, 180, 210 and 240 mins after drug administration. Data collected before drug administration were averaged and used as baseline data. Changes in behaviour or behavioural pattern were assessed subjectively by three independent observers who were not involved in drug or placebo administration. Behavioural changes were simply categorised as no change (1), increased locomotor activity (2), decreased locomotor activity, indifference or signs of sedation (lowered head, sawhorse stance, depression) (3).

Plasma methocarbamol and guaifenesin concentrations

Plasma methocarbamol and guaifenesin concentrations were determined by minor modification of a high-performance liquid chromatographic method described previously (Muir *et al* 1984; PPICO Muir and Sams 1980). The method was modified by substituting florfenicol (Batch No 14620-035A, Schering Pharmaceutical, Allentown, New Jersey) for chloramphenicol for use as the internal standard. Working stock solutions of florfenicol in methanol were prepared at concentrations of 20 g/litre and 0.10 g/litre. The limits of detection of methocarbamol and guaifenesin were 0.025 µg/ml of plasma.

Urinary methocarbamol concentrations

Urinary methocarbamol concentrations were determined by the same procedure as described above for plasma samples with the exception that 0.10 ml urine sample aliquots were used (Muir *et al* 1984; Kohn and Strasser 1986). Two sets of methocarbamol-supplemented urine samples were used to construct standard curves for quantitation. One set was prepared at concentrations of 5 to 50 µg/ml and used for determining the concentration of methocarbamol in samples containing less than 50 µg/ml. The other set was prepared at concentrations of 50 to 500 µg/ml and used for samples containing more than 50 µg/ml.

Pharmacokinetic calculations

Intravenous plasma methocarbamol concentration vs time data were analysed by non-linear least squares regression, using a computer programme for non-linear regression analysis with equal weighting of the data. Pharmacokinetic values were calculated from the coefficients (C_1, C_2) and exponential terms λ_1,λ_2) of the bi-exponential equation best describing the data for each horse (Jusko 1980). The area under the iv plasma concentration-time curve (AUC_{iv}) was calculated from:

$$AUC_{iv} = (C_1/\lambda_1) + (C_2/\lambda_2)$$

The total plasma clearance of methocarbamol (CL_p) was calculated from:

$$CL_p = dose/AUC_{iv}$$

The volume of distribution at steady-state ($V_{d[ss]}$) was calculated from:

$$V_{d(ss)} = dose\ (AUMC)\ (AUC_{iv})^2$$

Where AUMC is the first moment of the concentration-time curve, ie, $\int C_p\ t\ dt$, and was calculated from:

$$AUMC = (C_1/\lambda_1^2) + (C_2/\lambda_2^2)$$

The volumes of distribution, $V_{d(area)}$ and V_c, were calculated from:

$$V_{d(area)} = CL_p/\lambda_2$$
$$V_c = dose/(C_1 + C_2)$$

The half-life ($t_{1/2}$) of methocarbamol was calculated from λ_2:

$$t_{1/2} = 0.693/\lambda_2$$

Oral plasma methocarbamol concentration vs time data were analysed by a polyexponential curve fitting computer programme (RSTRIP, MicroMath Scientific Software, Salt Lake City, Utah). The bioavailability (F) of methocarbamol after oral administration was calculated from:

$$F = (AUC_{po}/AUC_{iv})\ (dose_{iv})/dose_{po})$$

Where AUC_{po} was calculated from the coefficients and rate constants of the polyexponential equation best describing the data for each horse.

Data analysis

All data were subjected to analysis of variance for multiple groups and repeated measures to compare differences due to time and treatment. Appropriate post tests were performed to determine differences due to treatment (Dunnett's *t* test) and differences due to drug treatment group (Student-Newman-Keul's multiple comparison method). A paired *t* test was performed when appropriate. $P < 0.05$ was considered significant.

Results

Cardiopulmonary effects

We did not observe significant changes in heart rate (32 ± 1 beats/min), cardiac output (38.2 ± 1.2 litres/min), mean pulmonary arterial pressure (32.3 ± 2.2 mm Hg), systolic arterial pressure (149 ± 4 mm Hg), diastolic arterial pressure (106 ± 4 mm Hg), mean arterial pressure (126 ± 3 mm Hg), respiratory rate (17 ± 3 breaths/min), arterial pH (7.41 ± 0.01), arterial PO_2 (97 ± 2 mm Hg) or arterial PCO_2 (45 ± 2 mm Hg) at any of the dosages studied.

Behavioural effects

The iv and oral administration of methocarbamol produced variable responses in all horses studied, although increased locomotor activity was never observed. Depression was observed in five of eight horses administered iv methocarbamol and in all horses administered oral methocarbamol. Depression was typified by loss of interest in surrounding activities, decreased locomotor activity, drooping of the head, neck and eyelids, a sawhorse stance in two horses (given 100 mg/kg bwt orally), and partial protrusion of the penis in the two geldings. The onset of central nervous system depression effects was most rapid following iv administration of methocarbamol, observed within 15 mins of administration and lasting up to 120 mins post drug administration. Central nervous system depression effects were observed within 60 mins of 50 mg/kg bwt or 30 mins of 100 mg/kg bwt oral methocarbamol, and lasted for 120 and 240 mins, respectively.

Pharmacokinetics and drug disposition

The disposition of methocarbamol after rapid administration of a

TABLE 1: Pharmacokinetic parameter estimates for methocarbamol after a single 30-mg/kg bwt intravenous dose to eight horses

Parameter	Range	Median
AUC, μg (min)/ml	2790 – 4258	3190
AUMC, μg $(min)^2$/ml	$1.84 – 4.26 \times 10^5$	2.89×10^5
CLp, ml/min/kg bwt	7.05 – 10.8	9.41
Vd_{ss}, ml/kg bwt	515 – 942	756
$V_{d(area)}$, ml/kg bwt	724 – 1130	953
$t_{1/2}$, mins	59.1 – 89.6	75.0

AUC: area under the plasma concentration-time curve; AUMC: first moment of concentration-time curve; CLp: total polasma clearance of methocarbamol; Vd_{SS}: volume of distribution at steady-state; Vd: volumes of distribution; $t_{1/2}$: half life of methocarbamol

single, large iv dose (30 mg/kg bwt) to each of eight healthy adult horses was investigated in this study. Plasma and urine methocarbamol concentrations were determined by a sensitive and specific high-performance liquid chromatographic procedure, which was used in an earlier investigation and verified for the present study (Muir *et al* 1984). The disappearance of methocarbamol from plasma after the iv dose was described adequately by a bi-exponential equation:

$$C_p = C_1e^{-\lambda 1t} + C_2e^{-\lambda 2t}$$

Where C_p is the plasma methocarbamol concentration at time t after injection of the drug, C_1 and C_2 are coefficients and λ_1 and λ_2 are exponential terms derived from the rapid and slow phases of the plasma methocarbamol concentration versus time curve, respectively.

Pharmacokinetic parameters describing the disposition of methocarbamol in the horses were calculated and are reported in Table 1. Plasma methocarbamol concentrations declined rapidly during the initial or rapid disposition phase with a half-life ranging from 4.58 to 18.3 mins. The terminal disposition phase was slower with a $t_{1/2}$ ranging from 59.1 to 89.6 mins (harmonic mean of 73.1 mins). The CLp ranged from 7.05 to 10.8 ml/min/kg bwt (median value of 9.41 ml/min/kg bwt). The $V_{d(ss)}$ ranged from 515 to 942 ml/kg (median value of 756 ml/kg).

The extent of bioavailability and the terminal half-life after single 50 and 100 mg/kg bwt oral doses of methocarbamol were determined and are reported in Table 2. Peak plasma methocarbamol concentrations occurred within 15 to 45 mins after oral administration, indicating rapid absorption of the drug.

Guaifenesin, a metabolite of methocarbamol, was detected in plasma samples. However, plasma guaifenesin was less than 0.5% of the corresponding plasma methocarbamol concentration.

TABLE 2: Pharmacokinetic parameter estimates for methocarbamol after a single 50- or 100- mg/kg bwt oral dose to eight horses

Parameter	Range	Median
AUC, ug (min)/ml (50 mg/kg bwt)	334 – 7196	4637
AUC, ug (min)/ml (100 mg/kg bwt)	4724 – 15886	11888
F, per cent (50 mg/kg bwt)	58.8 – 101	82.9
F, per cent (100 mg/kg bwt)	50.7 – 124	110
$t_{1/2}$, mins (50 mg/kg bwt)	66.9 – 119	95.4
$t_{1/2}$, mins (100 mg/kg bwt)	70.0 – 181	97.8

F: bioavailability of methocarbamol after oral administration. See Table 1 for other definitions

Discussion

This study determined the haemodynamic and behavioural effects of high iv and oral dosages of methocarbamol in adult horses. The doses tested were 1.5 to 3 time the iv and oral therapeutic recommendations of methocarbamol administered to horses for the relief of moderate muscular complications (Mayhew and MacKay 1982; Booth 1988). Similar to the findings of Muir *et al* (1984), haemodynamic and respiratory effects were not produced following either method of administration (Muir *et al* 1984). Mild sedation, decreased activity and disinterest in surrounding activity, all characteristics of mild sedation, were observed and were most prominant in horses receiving 100 mg/kg bwt of methocarbamol orally. This latter finding differs from previous studies investigating the cardiorespiratory and behavioural effects of methocarbamol in horses, but supports its classification as a skeletal muscle relaxant and mild sedative. This is the first report of mild sedative properties following the iv or oral administration of methocarbamol to horses and corroborates studies in rats and humans where methocarbamol has been demonstrated to increase suppressed responding in a conflict procedure, an effect generally associated with drugs with anti-anxiety and sedative properties (Preston, Guarino, Kirk and Griffiths 1988). Interestingly, studies performed in rats and man have demonstrated that dosages of up to three times the therapeutic recommendations have little or no effect on psychomotor performance (Esplin 1970; Preston *et al* 1988). These latter studies, if applicable to horses, likely explain why we did not observe changes in behaviour in our earlier study. Together, the current and previous studies emphasise the importance of investigating relatively large ranges of dose-response data prior to drawing conclusions relating to a drug's pharmacological activity.

Plasma methocarbamol concentrations after the iv dose averaged 38.5 μg/ml at 5 mins after dosing and declined rapidly to 7.69 μg/ml after 120 mins. Thus, the central nervous system depression that we observed was produced by plasma methocarbamol concentrations within this range. Plasma methocarbamol concentrations after the 50 mg/kg bwt oral dose averaged 29.2 μg/ml at 15 mins after dosing, reached a maximum concentration of 33.6 μg/ml after 30 mins, and decreased to only 13.8 μg/ml by 120 mins after drug administration. Thus, the central nervous system depression observed after the 50 mg/kg oral dose occurred at plasma methocarbamol concentrations equivalent to or greater than those producing the same effects after iv dosing. Plasma methocarbamol concentrations after the 100 mg/kg bwt oral dose averaged 64.3 g/ml at 15 mins after dosing, reached a maximum of 71.9 μg/ml at 30 mins, and decreased to 34.8 μg/ml and 15.1 μg/ml at 120 and 240 mins after dosing, respectively. Thus, the longer period of central nervous system depression after the 100 mg/kg bwt oral dose is consistent with the higher concentrations at 240 mins. Plasma methocarbamol concentrations producing central nervous system depression were greater than 7.69 to 15.1 μg/ml.

The total body clearance was 9.41 ml/min/kg bwt following 30 mg/kg bwt iv methocarbamol and reflected both metabolic and renal clearance because the metabolite guaifenesin was detected in plasma samples and methocarbamol was excreted in urine. The relative contributions of these two clearance processes to the total clearance, however, cannot be determined precisely from this study. The low concentrations of guaifenesin (less than 0.5 per cent) relative to methocarbamol in plasma suggest that metabolism of methocarbamol to guaifenesin is not a major contributor to the total clearance. Further, extensive metabolism of methocarbamol to guaifenesin or other metabolites by the liver would result in a high first-pass effect after oral administration. However, the extent of bioavailability after oral administration of methocarbamol was high (50.7 to 124 per cent), suggesting that

the extent of first-pass metabolism, and therefore hepatic clearance, must be low.

Estimates of the renal clearance of methocarbamol were obtained by assuming that renal elimination of methocarbamol was essentially complete in the 8 h urine collection period. The concentration of methocarbamol in each urine sample was then multiplied by estimates of the extremes of the normal rates of urine production in the horse (0.612 to 1.05 ml/h/kg bwt) (Kohn and Strasser 1986) to obtain the extent of urinary excretion of methocarbamol. These values were then divided by the dose to obtain the fraction of the dose eliminated in the urine. This figure was then multiplied by the total clearance to obtain an estimate of the renal clearance. The median values of renal clearance estimates were 0.44 ml/min/kg bwt (range, 0.14 to 1.55 ml/min/kg bwt) and 0.67 ml/min/kg bwt (range, 0.23 to 2.6 ml/min/kg bwt) for the two extremes of urine production rates. These estimates of renal clearance of methocarbamol were less than the normal creatinine clearance (1.92 ml/min/kg bwt) (Kohn and Strasser 1986), suggesting that tubular re-absorption of methocarbamol may occur. Our estimates of renal clearance could be low if large amounts of methocarbamol were excreted after the 8 h collection period, but this appears unlikely based on the low urinary methocarbamol concentrations in the last urine samples collected and the short half-life of methocarbamol. The renal clearance estimates also could be low if urine production was much greater than the upper estimates of 1.05 ml/h/kg bwt.

Our earlier study investigated the pharmacokinetics of methocarbamol after iv doses of 4.4, 8.8, and 17.6 mg/kg bwt in horses (Muir *et al* 1984). Clearance and volume of distribution were comparable at 8.8 and 17.6 mg/kg bwt and increased at 4.4 mg/kg bwt. Total body clearance and other pharmacokinetic values for methocarbamol in the present study were comparable to those reported earlier for 8.8 and 17.6 mg/kg bwt doses.

Methocarbamol, therefore, a centrally acting skeletal muscle relaxant, did not produce significant cardiovascular or respiratory behavioural changes when administered or orally at 1.5 to 3 times recommended dosages. Methocarbamol is metabolised by the liver after oral administration, although hepatic clearance is low, because bioavailability was high. Renal clearance data suggest tubular re-absorption of methocarbamol.

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References

Bennett, D. A. and Amrick, C. L. (1986) 2-Amino-7-phosphonoheptanoic acid (APT) produces discriminative stimuli and anticonflict effects similar to diazepam. *Life Sci.* **39**, 2455-2461.

Bianchine, J. R. (1980) Drugs for Parkinson's disease. Centrally acting muscle relaxants. In: *The Pharmacological Basis of Therapeutics*. 6th edn. Ed: A. G. Gilman, L. S. Goodman and A. Gilman. Macmillan Publishing Co., Inc., New York. pp 488-489.

Booth, N. H. (1988) Nonnarcotic analgesics. In: *Veterinary Pharmacology and Therapeutics*. Sixth edn. Ed: N. H. Booth and L. E. McDonald. Iowa State University Press, Ames, Iowa. pp 337-338.

Esplin, D. W. (1970) Centrally acting muscle relaxants; drugs for Parkinson's disease. In: *The Pharmacological Basis of Therapeutics*. Ed: L. S. Goodman and A. Gilman. The Macmillan Company, New York. pp 226-236.

Hubbell, J. A. E., Muir, W. W. and Sams, R. A. (1980) Guaifenesin: cardiopulmonary effects and plasma concentrations in horses. *Am. J. vet. Res.* **41**, 1751-1755.

Jusko, W. J. (1980) Guidelines for collection and pharmacokinetic analysis of drug disposition data. In: *Applied Pharmacokinetics: Principles of Therapeutic Drug Monitoring*. Ed: W. E. Evans, J. J. Schentag and W. J. Jusko. Applied Therapeutics Inc., San Francisco. pp 639-680.

Kohn, C. W. and Strasser, S. L. (1986) 24-Hour renal clearance and excretion of endogenous substances in the mare. *Am. J. vet. Res.* **47**, 1332-1337.

Mayhew, I. G. and MacKay, R. J. (1982) The nervous system. In: *Equine and Surgery*. Third edn. Ed: R. A. Mansman, E. S. McAllister and P. W. Pratt. American Veterinary Publications, Santa Barbara, California. pp 1209-1212.

Muir, W. W., Sams, R. A. and Ashcraft, S. (1984) Pharmacologic and pharmacokinetic properties of methocarbamol in the horse. *Am. J. vet. Res.* **45**, 2256-2260.

Preston, K. L., Guarino, J. J., Kirk, W. T. and Griffiths, R. R. (1988) Evaluation of the abuse potential of methocarbamol. *J. Pharmacol. exp. Therap.* **248**, 1146-1157.