Journal of Chromatography, 426 (1988) 283-294
Biomedical Applications
Elsevier Science Publishers B.V., Amsterdam — Printed in The Netherlands

CHROMBIO. 4084

HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC SEPARATION AND ELECTROCHEMICAL OR SPECTROPHOTOMETRIC DETERMINATION OF *R*(–)N-*n*-PROPYLNORAPOMORPHINE AND *R*(–)10,11-METHYLENEDIOXY-N-*n*-PROPYLNORAPORPHINE IN PRIMATE PLASMA

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(Received October 5th, 1987)

SUMMARY

The dopamine receptor agonist *R*(–)N-*n*-propylnorapomorphine (NPA) and its proposed prodrug *R*(–)10,11-methylenedioxy-N-*n*-propylnoraporphine (MDO-NPA) were isolated simultaneously from monkey plasma using a solid-phase extraction procedure. *R*(–)Apomorphine (APO) and *R*(–)10,11-methylenedioxyaporphine (MDO-APO) were added as internal standards, and separation and quantification were by high-performance liquid chromatography with electrochemical or ultraviolet detection of the free catechol and MDO compounds, respectively The detection limits for NPA and MDO-NPA in plasma were 0.5 and 10 ng/ml and the coefficient of variation (S.D./mean) within assays and between days of assays for both drugs was 5.6% or less. Quantification of plasma levels of NPA and MDO-NPA was possible at ranges of 2–1000 and 40–5000 ng/ml, respectively, including concentrations found after intravenous administration of these agents.

INTRODUCTION

The *R*(–)-isomers of apomorphine (APO) and its congener N-*n*-propylnorapomorphine (NPA) (Fig. 1) are potent dopamine (DA) receptor agonists [1] that have been proposed for use in the treatment of neurological and psychiatric disorders [2,3]. Their clinical application has been limited by their low oral bioavailability and short duration of action [1,4]. Efforts have been made to improve these pharmacological limitations by developing analogues in which

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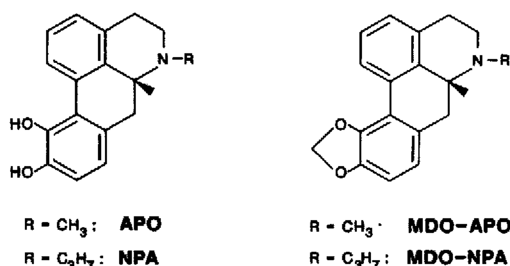

Fig. 1. Structures of *R*(−)N-*n*-propylnorapomorphine (NPA), *R*(−)apomorphine (APO); *R*(−)10,11-methylenedioxy-N-*n*-propylnoraporphine (MDO-NPA) and *R*(−)10,11-methylenedioxyaporphine (MDO-APO).

the catechol structure is derivatized to ester or ether functions to provide metabolically labile prodrugs [5–8]. One of these, the NPA analogue *R*(−)10,11-methylenedioxy-N-*n*-propylnoraporphine (MDO-NPA, Fig. 1), has proven to be an orally effective and relatively long-acting agent that appears to act as an agonist at cerebral DA receptors at least in part by liberating NPA [8–10].

While no method exists for the determination of MDO-NPA, several chromatographic assays have been described for the quantification of NPA in biological tissues. Gas chromatography has been used with electron-capture detection [11] or negative-ion chemical ionization mass spectrometry [12]; other analytical approaches employed high-performance liquid chromatography (HPLC) with ultraviolet (UV) [13,14], fluorescence [15], or electrochemical detection (ED) [10].

Some of these methods are limited in sensitivity (>100 ng/ml for NPA in plasma [11,13–15]) or simplicity [12], although an HPLC–ED assay previously reported from one of our laboratories [10] permits the detection of less than 1 ng/ml NPA by sensitive ED at separation times of ca. 5 min. Interfering substances that co-elute with the analyte of interest may limit detection in such assays [11]. Solid-phase extraction can be effective in isolating NPA and APO from biological tissues with high recoveries and good separation from co-extracted contaminants [16]. MDO-NPA gives no response with an electrochemical detector [10] due to its lack of a free catechol function but we find that it can be quantified at moderate sensitivity by use of UV absorbance by its aromatic aporphine structure.

We now report an improved, rapid and sensitive assay for the quantification of NPA as well as a method to determine its putative prodrug MDO-NPA, employing APO and MDO-APO as internal standards, and simultaneously extracting the analytes from plasma with the use of a solid-phase extraction procedure. HPLC analysis was performed with ED (NPA) or UV monitoring at 280 nm (MDO-NPA). The assays were applied in pharmacokinetic investigations of both agents in monkeys.

EXPERIMENTAL

Chemicals and reagents

NPA·HCl and APO·HCl used as standards and for the animal treatment were from Research Biochemicals (RBI) (Natick, MA, U.S.A.) and Merz

(Frankfurt/Main, F.R.G.). MDO-NPA·HCl and MDO-APO·HCl were synthesized and characterized in one of our laboratories using previously described methods [7,8]. The purity of all four aporphines was confirmed by reversed-phase HPLC to be $>99.5\%$.

Methanol and acetonitrile were HPLC grade (Baker, Phillipsburg, NJ, U.S.A.). Water was deionized and glass-distilled. All other chemicals and reagents were analytical or reagent grade and obtained from commercial sources. Pooled blank plasma (fortified with ascorbic acid, 1 mg/ml) from two untreated Cynomolgus monkeys was obtained from Inveresk Research International (Musselburgh, U.K.).

Glassware

Elution fractions from solid-phase cartridges were collected in 5-ml conical glass Reacti-vials (Pierce, Rockville, IL, U.S.A.) equipped with PTFE-lined screw caps. Prior to each experiment glassware was cleaned by soaking in RBS-35 detergent (Pierce) solution overnight, rinsing first with deionized water and then methanol, and drying at 110°C for 1 h. In order to avoid loss of analytes due to surface adsorption the cleaned glassware was also subjected to a vapor phase silanization with hexamethyldisilazane [17].

Solutions

Stock standard solutions of NPA, APO, MDO-NPA and MDO-APO were prepared at 0.1 mg/ml (calculated as free amines) in 0.01 *M* hydrochloric acid containing 0.1 m*M* Na_2EDTA and stored at 4°C in the dark for up to six weeks. Internal standard solutions of APO (200 ng/ml) and MDO-APO (10 μg/ml) were prepared in 0.01 *M* hydrochloric acid weekly from the stock solutions. Similarly, solutions of authentic NPA and MDO-NPA for standardizations were freshly prepared when used.

Phosphate buffer solutions for solid-phase extraction were prepared as follows: 6.80 g (50 mmol) potassium dihydrogenphosphate was dissolved in 1 l of 1 m*M* Na_2EDTA, with 10 *M* sodium hydroxide added to pH 7.4. For the acidic buffer, 4.08 g (30 mmol) potassium dihydrogenphosphate was dissolved in 1 l of 0.1 m*M* Na_2EDTA, with phosphoric acid added to pH 3.0. Buffers were stored at 4°C in the dark when not in use.

NPA solutions for intravenous (i.v.) administration were prepared fresh in 0.9% (w/v) sodium chloride containing 0.1 *M* citric acid. MDO-NPA solutions were in 0.1 *M* citric acid followed by neutralization to pH 7 with 10 and 1% (w/v) sodium hydroxide. All dosing solutions were diluted with 0.9% sodium chloride to a final volume of 2 ml.

Animal treatment

Animal studies were performed at Inveresk Research International under the direction of Merz; samples were shipped on dry ice to our laboratories for analyses. Four healthy Cynomolgus monkeys, each 3.0 to 6.1 kg, were used. Test agents were administered by a single bolus injection via the brachial saphenous vein. Food was withdrawn from the animals 2 h prior to dosing until 4 h after injection. NPA was given to two male monkeys at 1 and 5 mg/kg, separated by three days.

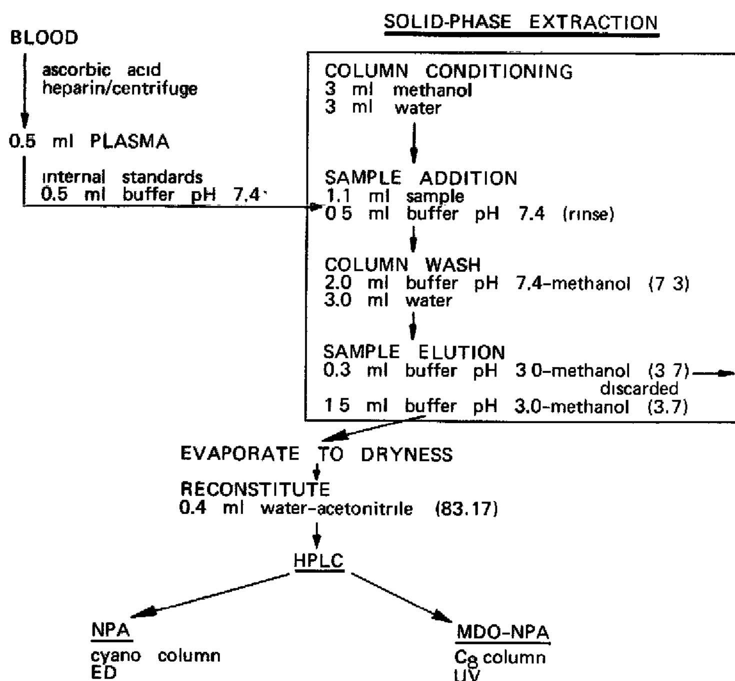

Fig. 2. Assay for the determination of NPA and MDO-NPA in the same sample using a single solid-phase extraction procedure (cartridges packed with 200 mg octadecyl silica, 40 μm particle size) followed by separate HPLC analyses for the two analytes.

MDO-NPA was injected to one female and one male monkey at 5 and 10 mg/kg, separated by eight days.

Blood samples (1 ml) were taken from the femoral vein (on the side contralateral to that of dose administration) into lithium-heparinized tubes at 5, 15, 30, 60, 120 and 240 min after injection of NPA or MDO-NPA and additionally at 6, 8, 24, 32 and 48 h after MDO-NPA. Immediately following blood sampling and centrifugation, plasma was aspirated and transferred to 2-ml stoppered polyethylene tubes containing ascorbic acid (1 mg/ml) and stored at -70°C until assayed, except during air shipment on dry ice.

Sample preparation

Plasma samples were subjected to solid-phase extraction with 3-ml disposable Bond-Elut C_{18} columns (200 mg octadecylsilica; Analytichem, Harbor City, CA, U.S.A.) as shown in Fig. 2. The solid-phase extraction cartridges were conditioned just before use by washing with 3 ml of methanol and 3 ml of water. Each thawed plasma sample (0.5 ml) was transferred to an ice-chilled glass culture tube containing 50 μl of the APO and MDO-APO internal standard solutions. After adding 0.5 ml of the pH 7.4 phosphate buffer and equilibration for 1 min the sample was applied to the column with an additional 0.5 ml of buffer used to rinse the tube. The column was washed with 2 ml of pH 7.4 buffer–methanol (7:3, v/v), followed by 3 ml water. All of these steps were performed at 3 ml/min by

applying compressed air. Elution was by gravity by adding pH 3.0 phosphate buffer–methanol (3:7, v/v) in two portions (0.3 and 1.5 ml). The first 0.3 ml was discarded and 1.5 ml of eluate was collected in a Reacti-vial. After evaporation to dryness in a vacuum centrifuge (Speed-Vac concentrator, Savant, Hicksville, NY, U.S.A.) sample extracts were redissolved in 0.38 ml of water–acetonitrile (83:17, v/v) by vortexing for about 5 min. Aliquots of approximately 60 μl were used for triplicate HPLC determinations of NPA and MDO-NPA.

Analysis of MDO-NPA usually was undertaken on the day following the determination of NPA in the same samples. When kept overnight, the Reacti-vials containing the redissolved sample extracts were stored at $-20°C$ in the dark and were vortexed (1 min) and centrifuged (500 *g*, 1 min) before use.

High-performance liquid chromatography

Analyses were carried out in an isocratic mode on a Rabbit HP solvent delivery system with pressure module (Rainin, Woburn, MA, U.S.A.) connected to a manual injection valve (No. 7125, Rheodyne, Cotati, CA, U.S.A.) with a 50-μl loop.

NPA was separated on a Supelcosil LC-CN column (7.5 cm $\times$ 4.6 mm I.D., 3 μm particle size, Supelco, Bellefonte, PA, U.S.A.) combined with a precolumn (Supelguard LC-CN, 2 cm $\times$ 4.6 mm I.D., , 5 μm particle size, Supelco). The mobile phase was prepared by dissolving 0.1 *M* potassium dihydrogenphosphate, 0.01 *M* trimethylamine, 0.1 m*M* Na_2EDTA and 0.5 m*M* sodium octyl sulphate in water, adjusting to pH 3.0 with phosphoric acid and adding acetonitrile to 17% (v/v). The electrochemical detector from Bioanalytical Systems (BAS) (West Lafayette, IN, U.S.A.) consisted of a TL-5 glassy carbon thin-layer transducer cell and an Ag/AgCl reference electrode with an LC-4B BAS amperometric controller. Detection was by oxidation at an applied potential of +0.7 V and a sensitivity at 1 nA f.s. or (if the NPA concentration in the sample exceeded 100 ng/ml) at 10 nA f.s.

MDO-NPA was separated on a Supelcosil LC-8-DB column (7.5 cm $\times$ 4.6 mm I.D., 3 μm particle size) with a Supelguard LC-8-DB precolumn (2 cm $\times$ 4.6 mm I.D., 5 μm particle size) and a UV III monitor (Milton Roy, Riviera Beach, FL, U.S.A.) with detection by monitoring absorbance at 280 nm (0.004 a.u.f.s.). The mobile phase consisted of 0.05 *M* potassium dihydrogenphosphate containing 0.01 m*M* Na_2EDTA with a pH adjusted to 3.0 and acetonitrile added to 35% (v/v).

All mobile phases were degassed with helium and filtered through a 0.2 μm Nylon-66 filter (Rainin). Flow-rates were 1.2 ml/min at ambient temperature. An on-line frit filter (Supelco) following the injection valve protected columns from particle contamination. Signals from electrochemical and UV detectors were integrated (System I computing integrator, Spectra Physics, Santa Clara, CA, U.S.A.) and recorded (Model 252A, Linear Instruments, Irvine, CA, U.S.A.).

Calibration, reproducibility and recovery

Calibration was effected by adding known amounts of NPA (0, 1, 2, 5, 10, 20, 50, 100, 200 and 500 ng) and MDO-NPA (0, 20, 50, 100, 200, 500, 1000 and 2500 ng) to blank plasma (0.5 ml) from drug-free monkeys and then treating these

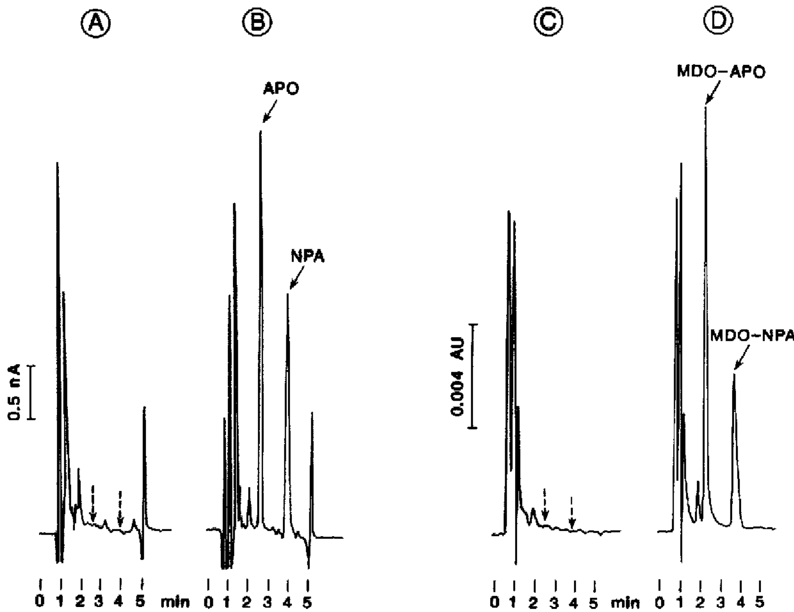

Fig. 3. Chromatograms of plasma extracts from a drug-free Cynomolgus monkey (A and C) and from a monkey treated with 10 mg/kg MDO-NPA i.v. 2 h previously (B and D). Samples B and D show the following drug concentrations: 10 ng/ml APO (internal standard), 10.5 ng/ml NPA (generated in vivo from MDO-NPA), 500 ng/ml MDO-APO (internal standard) and 236 ng/ml MDO-NPA at points free of signals (dotted arrows) in A and C. (A and B) Electrochemical detection; (C and D) UV detection.

samples as described above. Calibration curves were obtained by plotting the peak-area ratios (drug/internal standard) versus the corresponding concentration ratios, and linear regression analyses were performed.

To validate the assay, replicate analyses ($n=5$) of blank plasma spiked with NPA (20 ng/ml) and MDO-NPA (400 ng/ml) were made. The day-to-day reproducibility was checked by examining a plasma sample spiked with 100 ng/ml NPA and 200 ng/ml MDO-NPA on five different days. Blank samples were routinely processed alongside drug-containing samples. Recoveries were calculated by comparison of the peak areas of the extracted standards with peak areas that were obtained by injecting the standard dilutions directly into the HPLC apparatus.

TABLE I

LINEAR REGRESSION ANALYSIS OF NPA AND MDO-NPA CALIBRATION FUNCTIONS FOR PLASMA

$y = mx + b$; y = peak area analyte/peak area internal standard; x = concentration analyte/concentration internal standard; m = slope; b = y-intercept; r = Pearson correlation coefficient.

	m	b	r
NPA	0.8466	−0.0097	0.9991
MDO-NPA	0.8293	0.0087	0.9997

TABLE II

WITHIN-ASSAY AND DAY-TO-DAY REPRODUCIBILITY OF THE HPLC DETERMINATION OF NPA AND MDO-NPA IN PLASMA

In all cases $n = 5$.

Compound	Expected concentration (ng/ml)	Observed concentration* (ng/ml)	Precision (S.D./mean) (%)	Accuracy (observed/expected) (%)
Within assay				
NPA	20	20.6 ± 0.7	3.4	103.1
MDO-NPA	400	401.0 ± 9.2	2.3	100.3
Day-to-day				
NPA	100	96.8 ± 3.7	3.8	96.8
MDO-NPA	200	206.2 ± 11.5	5.6	103.1

*Individual concentrations were calculated as the mean of triplicate HPLC determinations ± S.D.

RESULTS

Chromatography

Chromatography of the extract of drug-free monkey plasma showed no significant matrix interference peaks at the retention times of NPA or the internal standard APO (ED) (see Fig. 3A) nor MDO-NPA or MDO-APO (UV monitoring) (see Fig. 3C).

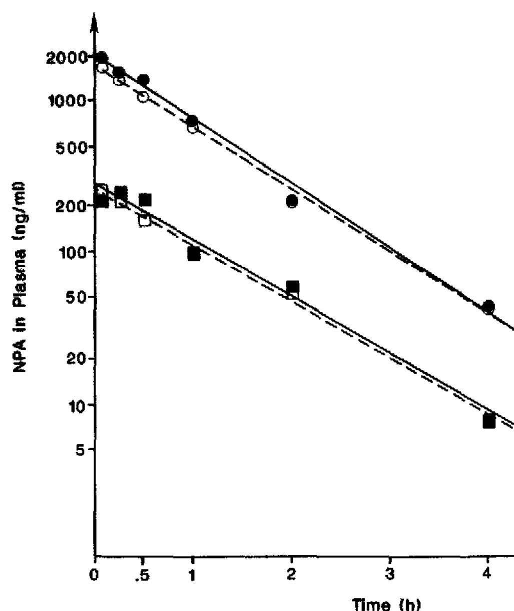

Fig. 4. Time course of NPA plasma concentration in two male Cynomolgus monkeys (subject 1: ●,■, —; subject 2: ○,□,---) after i.v. injection of NPA at doses of 1 (mg/kg) (■,□) or 5 mg/kg (●,○) with three days between doses. The lines were plotted by linear regression analyses: mean slope = −0.401 ($t_{1/2\beta}$ = 45 min) and mean $r = -0.996$, $n = 4$.

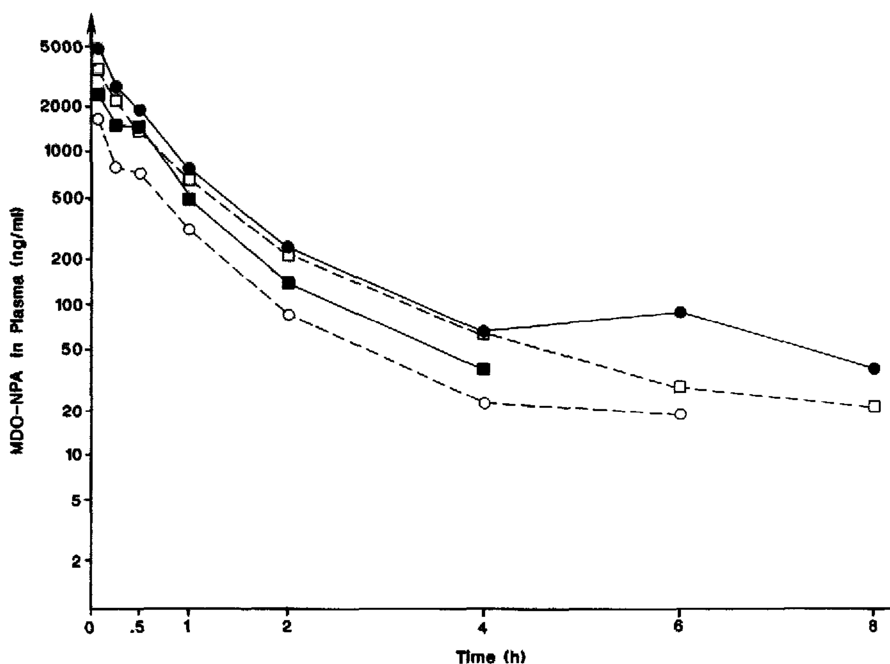

Fig. 5. Time course of MDO-NPA plasma concentration in one male (●,■) and one female (○,□) Cynomolgus monkey after i.v. administration of 5 mg/kg (■,□) or 10 mg/kg (●,○) doses of MDO-NPA with eight days between doses.

Aporphine compounds were eluted with capacity factors of $k'_{NPA} = 3.4$ and $k'_{APO} = 1.9$ or $k'_{MDO\text{-}NPA} = 3.2$ and $k'_{MDO\text{-}APO} = 1.8$, respectively, resulting in separation factors of $\alpha = 1.8$ for both chromatographic systems. NPA and MDO-NPA peaks in the chromatograms of plasma extracts from drug-treated monkeys were identified by performing superposition experiments with the pure standards under varying mobile phase conditions.

When HPLC was conducted for NPA determination, each sample injection generated a reproducible peak at $k' = 4.7$ that did not interfere with the analytes of interest (see Fig. 3A and B). MDO-NPA and MDO-APO give no measurable signal under similar conditions of ED [10] and so would not interfere.

Detection limits in plasma were ca. 0.5 ng/ml for NPA and 10 ng/ml for MDO-NPA at a signal-to-noise ratio of 5.

Recoveries

The absolute recoveries for NPA and APO from plasma were typically 80% and for MDO-NPA and MDO-APO 85%. The relative recovery (peak area analyte/peak area internal standard) of NPA from plasma over a concentration range of 2–1000 ng/ml ranged from 89.8% (at 2 ng/ml) to 104.4% (at 40 ng/ml), averaging ($\pm$S.D.) 98.3 $\pm$ 3.5% ($n=11$). The relative recovery of MDO-NPA from plasma (40–5000 ng/ml) was between 90.4% (at 40 ng/ml) and 108.2% (at 1000 ng/ml), averaging 97.6 $\pm$ 4.6% ($n=10$).

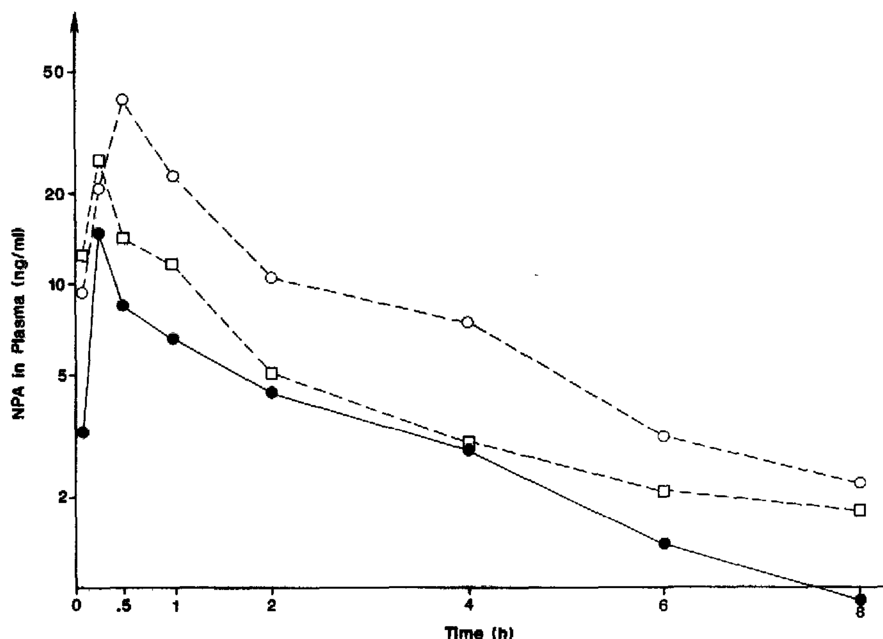

Fig. 6. Time course of plasma concentration of NPA in one male (●) and one female (○,□) Cynomolgus monkey after i.v. injection of 5 mg/kg (□) or 10 mg/kg (●,○) doses of MDO-NPA with eight days between doses.

Linearity, precision and accuracy

The calibration curves established for the quantification of NPA and MDO-NPA in plasma were linear at concentration ranges of 2–1000 and 40–5000 ng/ml, respectively (Table I).

The within-day and day-to-day coefficients of variation (S.D./mean) for the determination of NPA and MDO-NPA in plasma were consistently lower than 5.6%. Data concerning precision and accuracy are provided in Table II.

Pharmacokinetic studies in monkey

NPA concentrations in the plasma of two male Cynomolgus monkeys after i.v. injection of NPA (1 and 5 mg/kg) indicate an average half-life of elimination from plasma of approximately 45 min (Fig. 4).

MDO-NPA levels in plasma after doses of MDO-NPA of 5 and 10 mg/kg i.v. to one male and one female Cynomolgus monkey showed that this drug disappeared rapidly from plasma with an initial mean half-life of about 30 min (Fig. 5). NPA generated in vivo following i.v. MDO-NPA reached peak concentrations of 15–40 ng/ml in plasma at 15–30 min after dosing and was eliminated with a half-life of ca. 2 h (Fig. 6).

DISCUSSION

Methods for the HPLC separation of NPA in plasma have been described using mobile phases with high proportions (typically >40%) of organic solvents

[13,15]. Electrochemical detectors usually give higher responses with mobile phases containing smaller amounts of organic modifiers [18,19]. However, use of aqueous buffers with a relatively low concentration of methanol (20%) in combination with a non-polar C_{18} column resulted in HPLC run times of >10 min [10].

In order to shorten the elution time for NPA and the internal standard APO relatively polar Cyano columns were used and only 17% acetonitrile was necessary in the mobile phase to elute both analytes in less than 4 min, resulting in detection of about 500 pg/ml NPA, or less, in plasma. Since there were no significant interference peaks following elution of NPA (see Fig. 3A and B), the analysis time between injections was only about 5 min. This rapidity is important for practical applications, as in pharmacokinetic studies, with large numbers of samples. The excellent linearity of the detection of NPA levels between 2 and 1000 ng/ml and the precision and accuracy of this method permitted quantification of NPA in plasma in concentrations encountered in our preliminary pharmacokinetic studies, even at relatively late times (at least five half-lives, Fig. 4).

The HPLC separation of the relatively lipophilic aporphine derivatives MDO-NPA and MDO-APO was performed on an octylsilica column (Supelcosil LC-8-DB); addition of a competing base or an ion-pair reagent to the mobile phase was not necessary to obtain sharp and nearly symmetrical HPLC peaks (see Fig. 3). The selection of the organic modifier, however, was of great importance. Using methanol instead of acetonitrile for the mobile phase resulted in a significant loss of selectivity (separation factor $\alpha = 1.3$ and 1.8, respectively) and peak tailing occurred with methanol. As in the NPA assay, a lack of late-eluted interfering substances allowed analysis times of about 5 min between injections for the HPLC determination of MDO-NPA in plasma. Calibration and reproducibility studies (Tables I and II) demonstrated that quantification of MDO-NPA levels in monkey plasma is possible at a range of 40–5000 ng/ml, permitting the assay to be used in pharmacokinetic studies with this drug.

The solid-phase extraction procedure used proved to be superior to a liquid–liquid extraction method recently applied in a gas chromatographic–mass spectrometric assay for NPA in these laboratories [12]. Solid-phase extraction is more rapid, requires less material and generates less, potentially hazardous, organic waste.

A similar solid-phase extraction method has been used to extract APO from plasma (with NPA as internal standard) prior to HPLC analysis with ED [16]; however, the reported sensitivity for that assay with APO (40 ng/ml) was 80 times less than for NPA in plasma (0.5 ng/ml) in the present work. One reason for the lower sensitivity of the reported APO assay is that the solid-phase extraction method which we used to concentrate the analyte omitted an evaporation step (following the elution of the sample extract from the cartridge). We found that evaporating the eluate to dryness and reconstituting it in a small volume of salt-free mobile phase did not significantly degrade recovery of NPA and APO or MDO-NPA and MDO-APO (data not shown). Nevertheless, it is important to adjust the elution solvent to an acidic pH in order to protect the free catechol compounds NPA and APO from oxidation [20–22].

Slight losses of NPA through degradation during the sample preparation and washing steps involving neutral buffers did not affect the accuracy of the results because the internal standard APO is oxidized similarly to NPA (unpublished observation). Use of an internal standard also compensates for slight decreases (5–15%) in the sensitivity of the electrochemical detector found over a day of assays, probably due to build-up of oxidation products of the aporphines [23] or of co-extracted interfering substances at the working electrode.

An important feature of the present assays is the feasibility of determining NPA and its putative prodrug MDO-NPA in plasma after a single sample clean-up step that provides high absolute, and consistent relative recoveries for both analytes at concentration ranges encountered in our preliminary pharmacokinetic studies. Use of a constant-vacuum manifold for the solid-phase extraction procedure and the introduction of an automated sample injection unit and a computerized workstation to the HPLC system would provide even greater time efficiency when large numbers of samples are assayed. Furthermore, the NPA and MDO-NPA could be assayed simultaneously by use of two HPLC systems.

The i.v. administration of MDO-NPA to Cynomolgus monkeys confirmed previous reports that MDO-NPA was at least partially converted to NPA [9,10]. Nevertheless, the estimated area under the curve (AUC) for in vivo generated NPA after 5 mg/kg MDO-NPA i.v. differed by two orders of magnitude from the AUC for NPA after i.v. application of 5 mg/kg NPA itself (compare Figs. 4 and 5). This apparently limited bioavailability of NPA might be due to its rapid metabolism, for example, to O-glucuronide conjugates (not detectable with this assay) as has been reported for NPA [13] and APO [24] in mice.

CONCLUSIONS

Sensitive and selective HPLC separation methods following solid-phase extraction of plasma, coupled with ED and UV detection, were developed for determination of NPA and its proposed prodrug MDO-NPA. The use of a simultaneous solid-phase extraction procedure and the short chromatographic run times of about 5 min provide a time- and cost-effective assay for the quantification of NPA and MDO-NPA in large numbers of samples. Application of these methods in preliminary pharmacokinetic studies in monkeys confirmed that MDO-NPA is metabolized to free NPA in vivo and encourages further pharmacological investigations of $R(-)$MDO-NPA as well as its apparently limbic-selective dopamine antagonist isomer $S(+)$MDO-NPA [9,10,25].

ACKNOWLEDGEMENTS

This work was supported in part by grants and awards from the Deutsche Forschungsgemeinschaft, La 579/1-1 (P.L.), Merz (J.L.N.) and USPHS (NIMH) MH-47370, MH-34006, and the Bruce J. Anderson Foundation (R.J.B.). The authors thank Merz and Inveresk Research International (U.K.) for performing the animal studies, and Dr. R. Koch (Merz) for fruitful discussions.

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