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HPLC assay for bupropion and its major metabolites in human plasma

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Abstract

Bupropion is used clinically as an antidepressant and in smoking cessation. As it is metabolised to hydroxybupropion specifically by CYP2B6, bupropion has also been used as a probe to assess CYP2B6 activity. A specific and reproducible HPLC assay has been developed to simultaneously quantify bupropion and its major metabolites hydroxybupropion, threohydrobupropion and erythrohydrobupropion in human plasma. The analysis was performed on an Aqua C18 HPLC column, with a mobile phase consisting of 45:55 of methanol:0.05 M phosphate buffer (pH 5.5) and simultaneous UV detection at 214 nm (bupropion metabolites) and 254 nm (bupropion, internal standard timolol maleate). The assay showed a linear response for bupropion (2.5–250 ng/mL), threohydrobupropion (5–250 ng/mL), erythrohydrobupropion (10–250 ng/mL) and hydroxybupropion (10–1000 ng/mL). Extraction recovery was reproducible and greater than 55% for each analyte. The inter- and intra-day assay variability (measured as percent coefficient of variation; %CV) was less than 15% for all analytes. Limit of quantification was 2.5 ng/mL for bupropion, 5 ng/mL for threohydrobupropion and 10 ng/mL for hydroxybupropion and erythrohydrobupropion. This assay is more sensitive than currently published methods using HPLC with UV detection for the simultaneous quantitation of bupropion and metabolites and can be used for assessing CYP2B6 activity in vivo following a single dose of bupropion.

Keywords: HPLC; Bupropion; Hydroxybupropion; Threohydrobupropion; Erythrohydrobupropion; CYP2B6 phenotype

1. Introduction

Bupropion or amfebutamone ((±)-2-tert-butyl-amino)-3′-chloropriophenone hydrochloride) [1] is the water soluble hydrochloride salt of an aminoketone [2], with a pK_a of 7.9 [3]. Bupropion is structurally related to phenylethylamines, cathinone (a CNS stimulant from leaves of *Catha edulis)* and to the anorectic drug diethylpropion [4,5]. Bupropion is a second-generation antidepressant agent that is also used in the management of smoking cessation [6]. Bupropion is metabolised to a series of active metabolites, which are presented in Fig. 1.

Hydroxybupropion is the major active metabolite of bupropion found in human plasma [7], formed via hydroxylation of the tert-butyl group and the amino alcohol isomers [6] and subsequent formation of the morpholinol ring [8,9]. Threohydrobupropion and erythrohydrobupropion are also active metabolites of bupropion, formed by reduction of the carbonyl group [6,10], and are analogues of the sympathomimetic amines pseudoephedrine and ephedrine, respectively [4]. These compounds undergo further metabolism to meta-chlorohippuric acid, which is the major urinary metabolite of bupropion, and other free acids, bases and conjugated metabolites, not all of which have been characterised [6,8].

CYP2B6 is a polymorphic hepatic enzyme [11] of potential importance in the metabolism of drugs such as bupropion [12], efavirenz [13] and cyclophosphamide [14]. Wide interindividual variability in the hepatic expression of CYP2B6 has been reported [15,16], therefore a phenotypic marker can be useful to explore the association between CYP2B6 activity and drug metabolism. In vitro studies using human liver microsomes and recombinant cytochrome P450 isozymes have demonstrated that hydroxybupropion is generated from

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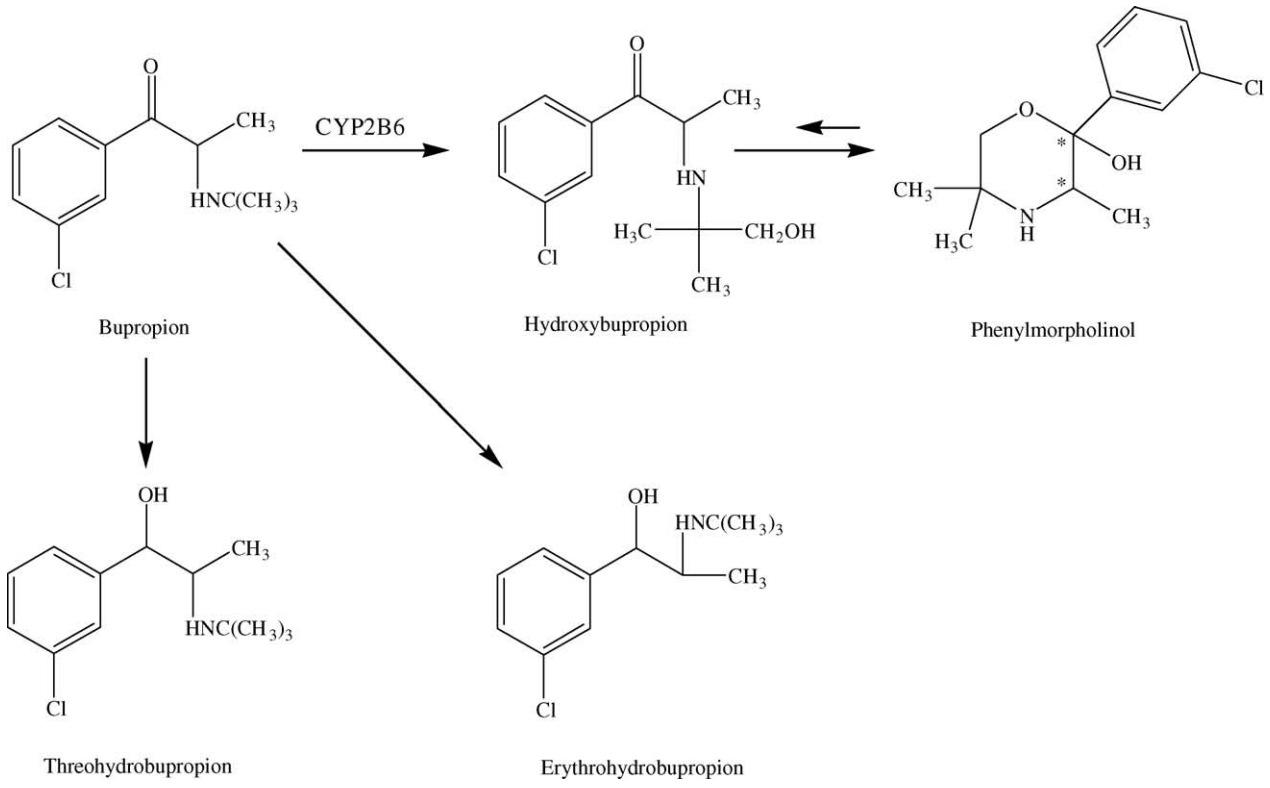

Fig. 1. Structure of bupropion and major active metabolites, figure adapted from [8].

bupropion almost exclusively by CYP2B6 [17]. Therefore, the formation of hydroxybupropion from bupropion has been used as a probe to assess CYP2B6 activity in vitro and in vivo [18,19]. In further studies the contribution of CYP3A4 to bupropion hydroxylation in human liver microsomes has been found to be insignificant [20].

To allow for the use of bupropion as a marker for CYP2B6 activity it is necessary to have a sensitive assay capable of simultaneous quantitation of bupropion and hydroxybupropion. Available HPLC assays using UV detection for simultaneous quantitation of bupropion and metabolites have poor sensitivity [21]. The most widely used HPLC method for simultaneous quantitation of bupropion and metabolites allows for quantitation of bupropion to concentrations of 10 ng/mL and all the metabolites to 100 ng/mL [21]. Newer HPLC methods for simultaneous quantitation allow for measurement of bupropion to concentrations of 5 ng/mL [22], and 10 ng/mL for both bupropion and hydroxybupropion [18]. The most sensitive published HPLC method for bupropion quantitation allows for quantitation of 1 ng/mL of bupropion, and unfortunately this method does not report the simultaneous quantitation of the metabolites [23]. The aim of this study was to develop and validate a sensitive HPLC assay using UV detection for bupropion and its major metabolites in human plasma, capable of quantifying bupropion in plasma for approximately 36 h after a single oral dose of sustained release bupropion HCl, in order to phenotype for CYP2B6.

2. Experimental

2.1. Chemicals

Bupropion hydrochloride (the molecular weight of bupropion hydrochloride is 276.2 and of the free base 239.7 Da [24]), hydroxybupropion, threohydrobupropion and erythrohydrobupropion standards were supplied by GlaxoSmithKline (Boronia, VIC, Australia). Timolol maleate (internal standard) was obtained from Sigma (Sydney, Australia). HPLC grade methanol and *n*-heptane were obtained from Lomb Scientific (Sydney, Australia), isoamyl alcohol, hydrochloric acid and phosphoric acid were all analytical grade and obtained from Sigma (Baulkham Hills, Australia). Human plasma used in this study was supplied by the Red-Cross Blood Bank (Sydney, Australia) and stored at −4 °C.

2.2. Apparatus

The HPLC system consisted of a Shimadzu Liquid Chromatography LC-10ADT pump, SIL-10AD Auto Injector, SPD-M10A Diode Array Detector and SCL-10A System Controller which were controlled by a Shimadzu Class-VP Chromatography Data System (Shimadzu, Rydalmere, Australia). Dual wavelength UV detection was used at 254 nm for bupropion and IS and at 214 nm for hydroxybupropion, threohydrobupropion and erythrohydrobupropion.

2.3. Chromatography

The analytical column was a Phenomenex Aqua C18 (4.6 mm × 250 mm, particle size 5 μm; Phenomenex, Sydney, Australia) with a column inlet filter (Model 7335, Alltech, Sydney, Australia). The mobile phase consisted of methanol and 0.05 M phosphate buffer adjusted to pH 5.5 with phosphoric acid (85%) before addition of methanol (45:55 v/v). The flow rate was maintained at 1.0 mL/min at ambient temperature.

2.4. Standard solutions

Stock solutions of bupropion, metabolites and internal standard (1 mg/mL) were prepared in distilled water. Working solutions were further diluted with water and stored at 4 °C. The standard curves for bupropion (2.5–250 ng/mL), hydroxybupropion (10–1000 ng/mL), threohydrobupropion (5–250 ng/mL) and erythrohydrobupropion (10–250 ng/mL) were freshly prepared on the day of analysis by spiking 10 μL of the appropriate working solutions to 1 mL of drug free plasma. Quality control (QC) samples were prepared in bulk at the concentration of 40 ng/mL bupropion, threohydrobupropion, erythrohydrobupropion and 120 ng/mL hydroxybupropion (QC A), as well as 220 ng/mL bupropion, threohydrobupropion, erythrohydrobupropion and 900 ng/mL hydroxybupropion (QC B) and stored at 4 °C.

2.5. Sample extraction

Internal standard (10 μL of 100 μg/mL solution for final concentration of 1 μg/mL) was added to 1.0 mL of standard, quality control and patient samples. The compounds were extracted from plasma using 0.5 M carbonate buffer pH 10.8 (0.5 mL) and 1.5% isoamyl alcohol in *n*-heptane (5 mL). The samples were vortexed for 20 s and then mixed on a roller mixer (Ratek Instruments, Boronia, Vic., Australia) for 20 min followed by centrifugation at 1500 × *g* for 15 min. The organic layer was transferred to a conical tube containing 0.1 M HCl (250 μL), vortexed and mixed as before. After centrifugation the organic layer was then discarded and the aqueous layer was dried under a stream of nitrogen at 37 °C as per Zhang et al. [23]. The residue was reconstituted with 80 μL mobile phase and 50 μL was injected onto the column.

2.6. Extraction efficiency

The recovery of each analyte was assessed over the concentration ranges for bupropion from 2.5 to 250 ng/mL for bupropion, for hydroxybupropion from 10 to 1000 ng/mL, for threohydrobupropion from 5 to 250 ng/mL and for erythrohydrobupropion from 10 to 250 ng/mL. The absolute recovery for each analyte was determined by comparing the peak height of extracted standards with the peak height of recovery standards injected directly onto the column to produce the identical 'on-column' concentrations.

2.7. Linearity and sensitivity

The calibration curves were constructed using seven analyte concentrations in human plasma. The concentrations of bupropion were 2.5, 5, 10, 25, 50, 100, and 250 ng/mL, hydroxybupropion were 10, 50, 100, 250, 500, 750, and 1000 ng/mL, threohydrobupropion were 5, 10, 25, 50, 100, and 250 ng/mL and for erythrohydrobupropion were 10, 25, 50, 100, and 250 ng/mL. The calibration curves were calculated as the peak height ratio of bupropion and metabolites to internal standard. Linearity of the least squares linear regression calibration curves was represented as the coefficient of determination (R^2) and the slope and y-intercept were also recorded. The limits of quantification (LOQ) was determined by measuring the lowest standard at least 6 times and accepted when %CV was less than 20% [25].

2.8. Precision and accuracy

Intra- and inter-day precision in assay performance were determined by assaying quality control samples of known concentrations of bupropion and metabolites. Intra-day precision was assessed by assaying 12 QC samples (6 QC A and 6 QC B) on the same day. Inter-day precision was evaluated by assaying QC samples on different days ($n = 12$). The precision was expressed as coefficient of variation (%CV) and the accuracy as percentage error.

$$\text{Error}(\%) = \frac{\text{Measured concentration} - \text{Nominal concentration}}{\text{Nominal concentration}} \times 100\%$$

2.9. Clinical application

This assay has been used to quantitate bupropion and metabolite plasma concentrations in a healthy male volunteer. After an overnight fast, 150 mg bupropion (Zyban SR, GlaxoSmithKline, Boronia, Australia) was administered orally with 200 mL of water. Blood samples were collected by indwelling cannula or by venepuncture over a 72 h period post dose and plasma concentrations were measured using the technique described. Ethics approval for the clinical study was obtained from St Vincent's Hospital Human Research Ethics Committee and from the University of Sydney Human Research Ethics Committee. Written informed consent was obtained from the subject before commencement of the clinical study.

3. Results

3.1. Chromatography

Fig. 2 shows the typical chromatograms at 214 and 254 nm for extracted drug free plasma and an extracted plasma sam-

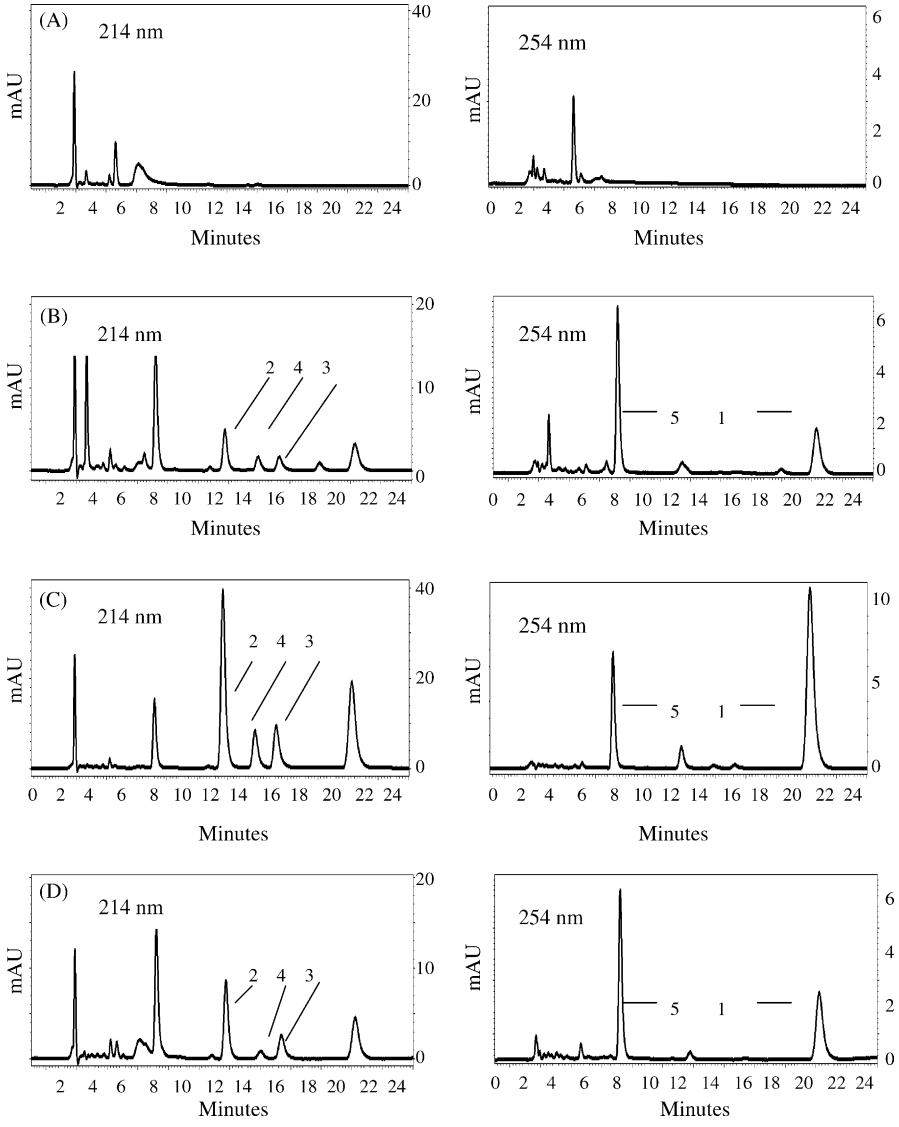

Fig. 2. Chromatograms of human plasma at 214 nm (hydroxybupropion (2), threohydrobupropion (3) and erythrohydrobupropion (4)) and 254 nm (bupropion (1), internal standard (5)). (A) Extracted drug free plasma, (B) QC A, (C) QC B, (D) Plasma sample in a healthy male volunteer 3 h after a 150 mg dose of bupropion (Zyban SR, GlaxoSmithKline).

ple following a single 150 mg bupropion dose. The internal standard eluted at 8.3 min, hydroxybupropion at 12.7 min, erythrohydrobupropion at 14.9 min, threohydrobupropion at 16.3 min and bupropion at 21.3 min, resulting in a total run time of 25 min. The assay at the wavelengths monitored was shown to be specific with no interfering peaks observed at retention times of interest in six different extracted drug free plasma samples.

3.2. Extraction efficiency

The recoveries of bupropion and metabolites were assessed over the concentration range of the calibration curve for each compound. The overall mean ± S.D. for the recovery of bupropion was 62.9 ± 12.5%, hydroxybupropion was 62.3 ± 11.7%, threohydrobupropion was 55.3 ± 7.0%, erythrohydrobupropion was 72.7 ± 11.4% (Table 1), and internal standard was 52.1 ± 9.1%. Extraction recovery was reproducible.

3.3. Linearity and sensitivity

Linearity was demonstrated over the concentration range from 2.5 to 250 ng/mL for bupropion, from 10 to 1000 ng/mL for hydroxybupropion, from 5 to 250 ng/mL for threohydrobupropion and from 10 to 250 ng/mL for erythrohydrobupropion. The parameters describing the linearities of the calibration curves are summarised in Table 2. The coefficients of determination of all standard curves for all analytes were greater than 0.998.

The limits of quantification for bupropion, hydroxybupropion, threohydrobupropion, and erythrohydrobupro-

Table 1
Extraction recovery (%) of bupropion, hydroxybupropion threohydrobupropion and erythrohydrobupropion from human plasma ($n = 3$)

Concentration (ng/mL)	Bupropion (%)	Hydroxybupropion (%)	Threohydrobupropion (%)	Erythrohydrobupropion (%)
2.5	69.9 ± 21.6	ND	ND	ND
5	65.9 ± 18.7	ND	48.4 ± 8.0	ND
10	57.7 ± 10.5	72.1 ± 25.3	44.3 ± 3.1	84.1 ± 21.0
25	50.5 ± 8.5	ND	47.0 ± 5.1	64.3 ± 8.1
50	67.8 ± 13.2	62.6 ± 12.9	63.4 ± 12.4	75.8 ± 14.8
100	64.1 ± 7.6	58.9 ± 11.4	62.1 ± 3.1	69.1 ± 2.7
250	64.3 ± 7.6	48.9 ± 8.7	66.7 ± 10.3	70.3 ± 10.2
500	ND	66.0 ± 11.4	ND	ND
750	ND	62.7 ± 3.4	ND	ND
1000	ND	65.2 ± 8.8	ND	ND
Overall	62.9 ± 12.5	62.3 ± 11.7	55.3 ± 7.0	72.7 ± 11.4

Data presented as mean ± S.D.. ND: not determined.

Table 2
Slope and *y*-intercept of least squares linear regression relationship between PHR and analyte concentration

	R^2	Slope	*y*-Intercept
Bupropion	0.9996 ± 0.0004	0.0061 ± 0.0005	−0.0114 ± 0.0070
Hydroxybupropion	0.9983 ± 0.0019	0.0058 ± 0.0002	−0.0969 ± 0.0518
Threohydrobupropion	0.9992 ± 0.0007	0.0052 ± 0.0004	−0.0012 ± 0.0099
Erythrohydrobupropion	0.9981 ± 0.0024	0.0045 ± 0.0004	0.0426 ± 0.0413

Coefficient of determination (R^2) is given. Data are presented as mean ± S.D., ($n = 30$).

pion were 2.5, 10, 5, and 10 ng/mL, respectively. The limits of detection (LOD; set as 3:1 signal to noise ratio) of bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion were 2.0, 7.5, 2.5, and 7.5 ng/mL, respectively.

3.4. Precision and accuracy

The intra-day and inter-day precision for each analyte and the accuracy, assessed by assaying QC A and QC B samples, are summarised in Tables 3 and 4. The intra-day precision for bupropion and hydroxybupropion expressed as the coefficient of variation was ≤4%. The inter-day precision was <7% for bupropion and for hydroxybupropion. The intra- and inter-day accuracy for both compounds was <9%.

3.5. Clinical application

This assay has been used in the clinical investigation of bupropion and metabolite plasma concentrations over a 72 h period in a healthy male volunteer after oral administration of 150 mg bupropion (Zyban SR, GlaxoSmithKline). The assay allowed for the quantitation of bupropion and erythrohydrobupropion in plasma for up to 36 h, whereas the metabolites threohydrobupropion and hydroxybupropion were quantitated for 72 h, (Fig. 3).

The C_{max}, t_{max}, $AUC_{0-\infty}$ and $t_{1/2}$ of bupropion observed in this subject were 59 ng/mL, 3 h, 556 ng/mL h and 13.5 h, respectively. The pharmacokinetic parameters observed in this subject were consistent with parameters reported in literature [19,26]. Using this study design more than 80% of the

Table 3
Intra-day precision and accuracy data for the measurement of bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion in plasma

Analyte	*n*	Nominal concentration (ng/mL)	Measured concentration (ng/mL) mean ± S.D.	Intra-day variability (%CV)	Accuracy (error%)
Bupropion					
QC A	6	40.0	39.1 ± 0.6	1.6	−2.4
QC B	6	220.0	209.8 ± 6.8	3.3	−4.6
Hydroxybupropion					
QC A	6	120.0	130.1 ± 3.1	2.3	8.4
QC B	6	900.0	866.2 ± 33.8	3.9	−3.8
Threohydrobupropion					
QC A	6	40.0	35.9 ± 1.8	5.1	−10.2
QC B	6	220.0	211.6 ± 5.7	2.7	−3.8
Erythrohydrobupropion					
QC A	6	40.0	43.7 ± 2.3	5.3	9.2
QC B	6	220.0	224.6 ± 5.7	2.5	2.1

Table 4
Inter-day precision and accuracy data for the measurement of bupropion, hydroxybupropion, threohydrobupropion and erythrohydrobupropion in plasma

	n	Nominal concentration (ng/mL)	Measured concentration (ng/mL) mean ± S.D.	Inter-day variability (%CV)	Accuracy (error%)
Bupropion					
QC A	12	40.0	39.4 ± 2.6	6.4	−1.4
QC B	12	220.0	220.2 ± 9.7	4.4	0.1
Hydroxybupropion					
QC A	12	120.0	127.9 ± 4.4	3.5	6.6
QC B	12	900.0	862.8 ± 48.8	5.7	−4.1
Threohydrobupropion					
QC A	12	40.0	39.2 ± 2.5	6.5	−2.0
QC B	12	220.0	221.4 ± 12.6	5.7	0.6
Erythrohydrobupropion					
QC A	12	40.0	37.9 ± 2.8	7.4	−5.2
QC B	12	220.0	223.2 ± 11.3	5.1	1.4

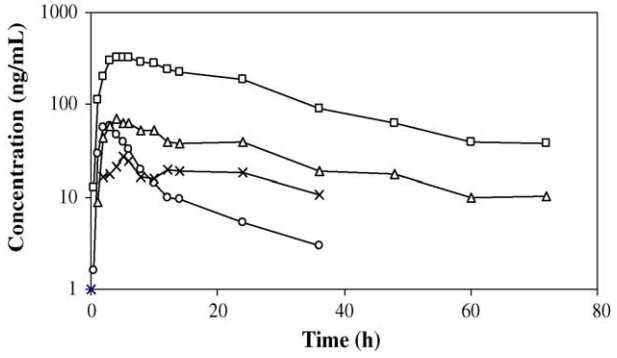

Fig. 3. Bupropion and metabolite plasma concentration-time profile in a healthy male subject following a single 150 mg dose of bupropion (Zyban SR, GlaxoSmithKline). Bupropion (◯), hydroxybupropion (□), threohydrobupropion (△), erythrohydrobupropion (×).

$AUC_{0-\infty}$ for bupropion and metabolites was characterised. This assay is reproducible and sensitive and can be used for pharmacokinetic studies of bupropion and metabolites after single oral dose administration. This will make it an appropriate tool for the determination of CYP2B6 activity in vivo.

4. Discussion and conclusion

The reverse phase isocratic HPLC assay described here allows for simultaneous quantitation of bupropion and its major active metabolites in human plasma. It provides increased sensitivity when compared to other published HPLC methods [18,21,22].

This novel assay uses a Phenomenex Aqua C18 HPLC analytical column, which allows for improved baseline separation of bupropion, active metabolites and the internal standard compared to other published methods [21,22]. The run time is longer compared to previous methods. The Aqua column, which has been specifically developed by the manufacturer to separate polar compounds, was chosen because of the strong retention of the compounds being analysed compared to other C18 columns, which were trialed in the development of this assay. Other columns used to separate bupropion and metabolites include silica based columns [21,22], or a CN column [18]. A similar octadecylsilane column was used by Zhang et al. to quantitate bupropion in plasma, however metabolite analysis was not reported [23].

Plasma concentrations of bupropion are low in comparison to its metabolites, therefore quantitation of all compounds at the same wavelength was not optimal. Bupropion and the internal standard were quantitated at 254 nm, as proposed by Cooper et al., hydroxybupropion, threohydrobupropion and erythrohydrobupropion were measured at 214 nm due to increased sensitivity relative to 254 nm [21]. Other methods have used wavelengths of 220 [18] or 248 nm [22] for bupropion and metabolite quantitation, however these methods have not achieved the same sensitivity as the assay reported here. Using two wavelengths selectively optimised detector response for all analytes and attained greater sensitivity than previously published HPLC methods.

The extraction method and mobile phase were based on previously published methods [21,23], however some modifications (increased plasma sample volume and decreased reconstitution volume compared to the method of Zhang et al.) have been made to achieve greater sensitivity [23]. For all analytes the precision of the assay is comparable with previously published methods.

The internal standard, timolol maleate, was chosen after extensive screening of compounds that were structurally related to bupropion. Many of the compounds, such as pseudoephedrine, were found to elute at a similar time to erythrohydrobupropion or threohydrobupropion and as baseline separation was not achieved they were considered unsuitable as internal standards. Timolol maleate was chosen due to its relatively early elution time with no interfering peaks from either the compounds analysed or endogenous substances in plasma.

Bupropion is a chiral compound administered as a racemate. The S-enantiomer of bupropion undergoes

rapid racemisation under physiological conditions [24]. Metabolism to hydroxybupropion introduces a second chiral centre, however, only (R,R) hydroxybupropion and (S,S) hydroxybupropion, two of the possible four diasteroisomers of hydroxybupropion, have been found human plasma. (R,R) hydroxybupropion represents approximately 96% of hydroxybupropion in plasma at steady state after bupropion administration [9]. The racemisation of bupropion in vivo and the predominance of only one hydroxybupropion diastereoisomer after bupropion administration mean that an achiral technique will still be a useful tool for characterising bupropion disposition and metabolism.

This assay has been tested in a clinical setting and allows for the accurate measurement of plasma bupropion and metabolite concentration time curves, (Fig. 3). The plasma concentrations observed in this study for bupropion and metabolites are consistent with the published literature [19,26].

LC–MS and LC–MS–MS methods for bupropion and metabolite quantitation have also been developed [19,26–28]. These methods allow for greater sensitivity than the published HPLC methods, with the reported LOQ down to 0.25 ng/mL for bupropion, 1 ng/mL for hydroxybupropion [19] and 1.25 ng/mL for threohydrobupropion [27]. These methods require LC–MS or LC–MS–MS equipment, which significantly increases the cost of the sample analysis, limiting the availability of these assays. HPLC is widely available at less cost. In addition some of these methods also require solid phase extraction, which can further increase the cost and time needed to perform the analysis.

In conclusion, a sensitive, robust, specific and reproducible method for the measurement of bupropion and metabolites concentrations in plasma after a single dose has been developed. It can be used to investigate CYP2B6 phenotype in healthy human subjects and patients, as well as studies investigating bupropion pharmacokinetics and potential drug interactions.

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