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Bioavailability of moclobemide from two formulation tablets in healthy humans

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A „sine qua non" requirement for a generic formulation to be admitted for a medical use is to provide bioavailability studies in healthy subjects. Therefore, those studies were performed for 150 mg moclobemide tablets (Jelfa, Poland) versus 150 mg Aurorix (Hoffmann la Roche) reference tablets. An open-label, two-phase cross-over study was conducted with 10 healthy subjects. Pharmacokinetic parameters (AUC, ke, $t_{1/2}$, C_{max}, t_{max}, t_{lag}, V/f, Cl/f) obtained at the same time for moclobemide were supposed to be confronted with the literature data available for healthy volunteers. The plasma moclobemide levels as a function of time were calculated according to either an open one-compartment body model with lag time of absorption or non-compartmental method for calculation of bioavailability using Phoenix WinNonlin 8.0 software. For those reasons a suitable HPLC method was worked out. Carbamazepine was proposed as an internal standard and ammonia as well as Na_2HPO_4 as alkalizing agents for the mobile phase and the liquid-liquid extraction of moclobemide from human blood plasma, respectively. Basic pharmacokinetic parameters of moclobemide obtained in the paper are essentially equal to the literature data for the healthy subjects. However, bioavailability parameters ($AUC_{0\rightarrow t}$, $AUC_{0\rightarrow\infty}$, C_{max}, t_{max}) were greater for moclobemide tablets (Jelfa) if compared to Aurorix tablets (Roche) by more than 20 %. Furthermore, the extent of bioavailability (110.6 %) for the generic moclobemide tablets if compared to Aurorix tablets is not significantly different. It seems to us that the number of subjects should be increased from 10 to 24 to help to clarify that inconsequence.

1. Introduction

The benzamide moclobemide is a reversible inhibitor of monoamine-oxidase-A (RIMA). Unlike the first generation MAO inhibitors, the current drugs are readily reversible in their action, resulting in far less concerns about the former serious pressor effects. Since moclobemide launch in Sweden in December 1989, it has been marketed in over 50 countries, although not yet in the USA. Most comparative studies indicated that in the acute management of depression this drug is more efficacious than placebo and as efficacious as tricyclic (or some heterocyclic) antidepressants or selective serotonin reuptake inhibitors (SSRIs). Due to negligible anticholinergic and antihistaminic actions, moclobemide has been better tolerated than tri- or heterocyclic antidepressants. Gastrointestinal side effects and, especially, sexual dysfunction were much less frequent with moclobemide than with SSRIs (Bonnet 2003, 2002; Mayershon and Guenteri 1995). It was particularly effective in treating atypical depression and used also in the treatment of Parkinson's disease and several other disorders (Cristancho et al. 2011).

The elimination of moclobemide follows first-order pharmacokinetics, which is characterized by a short plasma terminal half-life (1.8±0.54 h), a relatively high systemic clearance (51 to 90 l), and a large steady-state volume of distribution (75 to 95 l) following oral administration suggesting extensive distribution. Clearance of moclobemide is almost exclusively due to hepatic metabolism, resulting in low and variable oral bioavailability (Mayershon and Guenteneri 1995; Gex-Fabry et al. 1995; Fitton et al. 1992; Caccia 1998). The marked time-dependent changes in the pharmacokinetics of moclobemide if comparing both single and chronic administration of relatively large doses is reflected in reduction of the oral clearance, an increase in the elimination half-life and an increase in the trough concentrations (Dingemanse et al. 1998). The primary routes of metabolism of moclobemide involve carbon and nitrogen oxidation of the morpholine moiety, deamination, and aromatic hydroxylation (Bonnet 2002; Mayershon and Guenteri 1995; Jauch et al. 1990). Four metabolites (homovanillic acid, 3,4-dihydoxyphenylacetic acid, 3-methoxy-4-hydroxy-phenylglycol and 5-hydroxyindoleacetic acid) were determined in the urine of healthy volunteers after oral administration of moclobemide tablets (Wiesel et al. 1985). The other assay permits separation and quantitation of moclobemide and 3 metabolites in plasma and urine by a sensitive HPLC technique (Mayershon and Guenteri 1995). For determination of moclobemide in human plasma HPLC with UV detection at approx. 240 nm, electrospray ionization–mass spectrometry and gas chromatography with nitrogen-sensitive detection is used among other techniques (Fitton et al. 1992; Wiesel et al. 1985; Cafer Saka 2017). The obtained LOQ values for moclobemide were in the range 10-500 ng/ml or 0.15-1 ng/ml for the methods with UV or UPLC-MS/MS detection, respectively (Cafer Saka 2017). The plasma sample for the extraction is alkalinized to pH approx. 11 and extracted with dichloromethane (Mayershon and Guenteri 1995) or n-butyl chloride (Jauch et al. 1990). Sample preparation (0.5 ml plasma) involved sometimes solid-phase extraction to replace a liquid extraction. As an internal standards are used in between: phenacetin, nadolol, metoclopramide (Hoskins et al. 2001; Rakic et al. 2007).

The aim of this work was to study the bioavailability of 150 mg moclobemide tablets (Jelfa, Poland) versus the reference 150 mg tablets (Aurorix, Hoffmann la Roche) in 10 healthy volunteers as well as calculation of other pharmacokinetic parameters by means of the WinNonlin program and to compare the parameters in healthy volunteers and provided for depressive patients in the literature.

2. Investigations and results

2.1. Study design

The study was conducted in compliance with the ethical principles of Good Clinical Practice and the latest version of the Declaration of Helsinki. The institutional review board of Human Investigations Ethical Committee at Poznan University of Medical Sciences approved the study protocol. The study had a non-blinded, open-label, single dose, double way crossover design. The subjects randomly swallowed either a 150 mg moclobemide generic tablet (Jelfa S.A. Poland, # 10196p) or a 150 mg Aurorix reference tablet (Hoffmann la Roche, # 17031) according to a drug assignment number from I to X. Dosing periods were separated by at least a 7 days washout period.

2.2. Subjects

Ten normal adults, non-smoking, male and female volunteers between 20 and 37 years (mean 25.0±5.7), weighing on average 66.5±9.2 kg of height 175.2±8.2 cm were selected for participation in the above examination. The volunteer subjects completed also their own thorough history and physical examination after normal laboratory examinations. The laboratory tests consisted of the following: hematology, serum chemistry, and urinalysis. All subjects were presented with full details of the investigations, both verbally and in written form, prior to providing written informed consent. Furthermore, the volunteers did not use any drugs and alcohol within 24 h before the experiments and during their course. The subjects were required to fast for at least 10 h prior to the timing of the next tablet administration.

2.3. Pharmacokinetic analysis

The plasma moclobemide levels as a function of time were simulated according to either an open one-compartment body model or non-compartmental method (calculation of bioavailability) using Phoenix WinNonlin 8.0 software (Certara L.P., Princeton N.Y.). That computer program let us to calculate following pharmacokinetic parameters: first-order overall elimination rate constant (ke, h^{-1}), biological half-life time ($t_{1/2}$, h), area under concentration-time curve (AUC_{tot}, $AUC_{0\rightarrow t,}$ *mg·h/l*), time to peak plasma concentration (t_{max}, h), peak plasma concentration (C_{max}), mean residence time (MRT, h), apparent volume of distribution (V/f, l), apparent clearance (Cl/f, l/h), where f – fraction absorbed, and lag time of absorption (t_{lag}). Calculated parameters were compared in a Statistica 13.1 software (Dell Inc., Tulsa, OK, USA). For normally distributed parameters the differences were analyzed by means of Student's paired t-test, while the parameters which lacked normal distribution (Cl/f, t_{max}. t_{lag}) were compared using a non-parametric Wilcoxon signed-rank test. Bioequivalence parameters of two formulation tablets were established on Food and Drug Administration Center for Drug Evaluation and Research Guidance (CDER) (2001) as well as a guideline of European Medicines Agency (2010). All calculations were performed in Phoenix Bioequivalence model. Average bioequivalence was estimated by total and peak exposures. As recommended by FDA, the values were ln-transformed before the analysis. Briefly, the results were analyzed by the two one–sided tests procedure. 90% confidence interval for the ratio of the geometric averages of the tested and reference formulations tablets was calculated. The confidence interval for the ratio should fall within 80-125% at the 5% significance level. The difference in $t_{1/2}$ was analyzed by means of Student's paired t-test, while the difference in t_{max} was calculated using a non-parametric Wilcoxon matched-pairs test.

2.4. Results

Calibration curves of peak area ratio *versus* authentic plasma moclobemide concentration were linear over the concentration range 0.02 to 2.00 mg/l and the intercept was essentially zero. The coefficient of variation (C.V.) of the individual data obtained for within- and between-run accuracy series, each of 7 concentration levels, fulfilled in triplicate, is not greater than 2.1 %. The correlation coefficient of that averaged calibration curve r is 0.999, its intercept b = 0.009±0.029 and slope a = 3.03±0.04. Therefore, the linear calibration curve equation is

$$\frac{A_{Mocl}}{A_{I.S.}} = (3.03 \pm 0.04) \cdot C$$

where A_{Mocl} and $A_{I.S.}$ are area under the peaks of moclobemide and I.S., respectively, and C is the concentration of the authentic moclobemide in plasma. The limit of detection (LOD = 0.005 mg/l) is the injected amounts of moclobemide that results in a peak with a height at least 3 times as high at the baseline noise level. The lower limit of quantification (LLOQ) is 0.02 mg/l (C.V. = 8.2%). The recovery of moclobemide and its I.S. is consistent and reproducible over the moclobemide concentrations range: 0.05 mg/l (99.7±1.3 %, n = 6), 0.5 mg/l (95.1±3.6 %, n = 6) and 1.5 mg/l (99.9±2.1, n = 6). The chemical stability of moclobemide and its I.S. was assessed in an autosampler, processed and extraction samples, during freeze-thaw cycle and in stock solutions over the concentrations of moclobemide: 0.05; 0.5; 1.5 and 2 mg/l I.S. They did not change significantly over 24 h (n = 6). The above three concentrations solutions of moclobemide were frozen at -20 °C and after 24 h they were thawed and determined again. The cycle was repeated three times and each time resulted in unchanged concentrations. The method worked out is also specific for the drug and its I.S. because it provides adequate separation from each other and endogenous plasma components (Fig. 1).

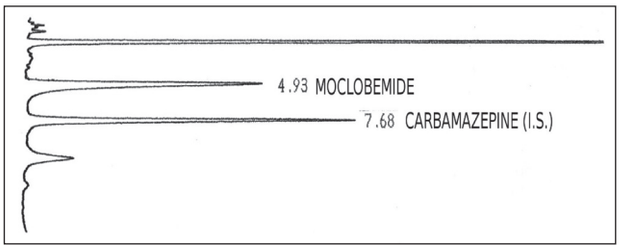

Fig. 1: HPLC chromatogram of a plasma subject sample collected after 3 h time elapsed from per oral administration of an Aurorix 150 mg tablet (Hoffmann la Roche) at moclobemide concentration 0.37 mg/l (retention time 4.93 min) separated from carbamazepine (internal standard) (retention time 7.68 min) and endogenous plasma components

Moclobemide plasma concentrations (C) as a function of time (t) after per oral administration of a single tablet (moclobemide, Jelfa or Aurorix), absorbed and eliminated according to the first-order processes with a lag time (t_{lag}) were well characterized by the difference in two exponentials (Fig. 2 and 3)

$$C = B \cdot e^{-k_e \cdot t \cdot} - A \cdot - e^{-k_a \cdot t \cdot} \qquad (1)$$

where A and B are the corresponding zero-time intercepts, k_e *and* k_a are the apparent first–order elimination and absorption rate constants, and t is the time of taking a subject plasma sample. Since a lag time of absorption is observed the correct calculation of AUC_{calc}^{true} should be (Hermann et al 1993):

$$AUC_{calc}^{true} = \int_0^{\infty} C \cdot dt - \int_0^{t_{lag}} C \cdot dt = AUC_{uncorr} - AUC_{t_{lag}} =$$
$$= B / \lambda_2 - A / \lambda_1 - [B \cdot (1 - e^{-\lambda_2 \cdot t_{lag}}) / \lambda_2 - A \cdot (1 - e^{-\lambda_2 \cdot t_{lag}}) / \lambda_1] =$$
$$= B \cdot e^{-\lambda_2 \cdot t_{lag}} / \lambda_2 - A \cdot e^{-\lambda_1 \cdot t_{lag}} / \lambda_1 \qquad (2)$$

The averaged moclobemide plasma data and their standard deviations as well the pharmacokinetic and suitable bioavailability parameters are given in Tables 1 and 2 for both tablet formulations.

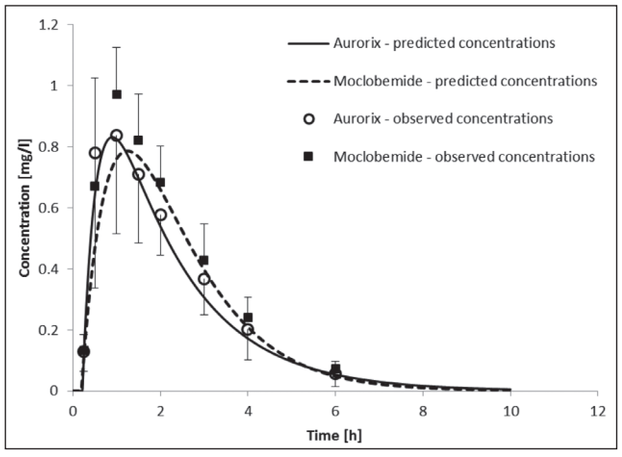

Fig. 2: Mean moclobemide plasma concentrations (mg/l) as a function of time [h] after a per oral crossover administration of a single 150 mg tablet either Moclobemide (Jelfa, Poland) or Aurorix (Hoffmann la Roche) to 10 volunteers simulated by Phoenix WinNonlin 8.0 software according to a one-compartment body model with a lag time of absorption

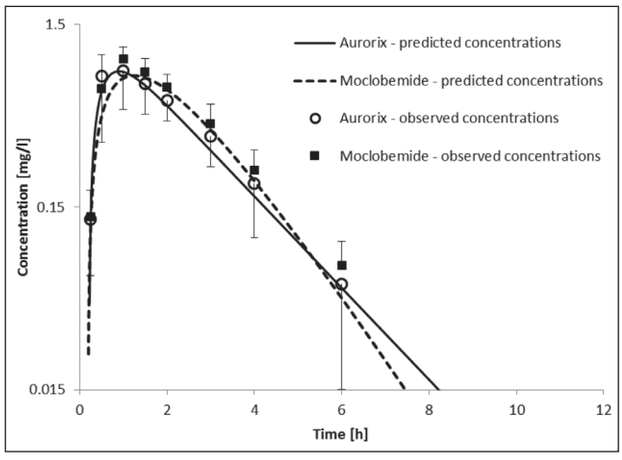

Fig. 3: Semi-logarithmic mean moclobemide plasma concentrations (mg/l) as a function of time [h] after a per oral crossover administration of a single 150 mg tablet either Moclobemide (Jelfa, Poland) or Aurorix (Hoffmann la Roche) to 10 volunteers simulated by Phoenix WinNonlin 8.0 software according to an open one compartment body model with a lag time of absorption

Table 1: Mean moclobemide plasma concentrations (± SD) as a function of time from 10 healthy subjects after a per oral crossover administration 150 mg dose tablet of Moclobemide (Jelfa) or Auroris (Hoffmann la Roche)

	Aurorix	Moclobemide		
Time [h]	Concentration [mg/l]		p	
0.5	0.78 ± 0.35	0.67 ± 0.44	0.546	NS
1	0.84 ± 0.15	0.97 ± 0.32	0.169	NS
1.5	0.71 ± 0.15	0.82 ± 0.22	0.086	NS
2	0.58 ± 0.12	0.68 ± 0.13	0.017	S
3	0.37 ± 0.12	0.43 ± 0.12	0.138	NS
4	0.20 ± 0.07	0.24 ± 0.10	0.243	NS
6	0.06 ± 0.03	0.07 ± 0.04	0.115	NS
Pharmacokinetic parameter				
AUC [(mg/ l) h]	2.36 ± 0.55	2.66 ± 0.64	0.092	NS
C_{max} [mg/l]	0.94 ± 0.27	1.05 ± 0.35	0.340	NS
t_{max} [h]	0.83 ± 0.30	1.01 ± 0.41	0.169	NS
t_{lag} [h]	0.202 ± 0.070	0.295 ± 0.111	0.114	NS
$t_{1/2}$ [h]	1.20 ± 0.28	1.16 ± 0.28	0.690	NS
k_e [1/h]	0.610 ± 0.148	0.633 ± 0.162	0.682	NS
V/f [l]	112.8 ± 25.0	96.1 ± 21.3	0.145	NS
CL/f [l/h]	67.8 ± 21.1	59.1 ± 13.4	0.139	NS

AUC – area under concentration-time curve, CL/f – apparent clearance, V/f – apparent volume of distribution, where f – fraction absorbed, C_{max} – peak plasma concentration, k_e – first-order elimination rate constant, t_{lag} – lag time of absorption, t_{max} – time to peak plasma concentration, $t_{1/2}$ – biological half-life time, S - significant, NS – not significant.

Table 2: Mean bioavailability parameters for Aurorix (Hoffmann la Roche) and Moclobemide (Jelfa) formulation tablets from 10 healthy subjects

Parameter	Aurorix	Moclobemide	Geometric mean ratio [%]	90% CI
$AUC_{0\to t}$ [(mg/l)·h]	2.24 ± 0.49	2.54 ± 0.58	113.1	95.2 – 134.6
$AUC_{0\to\infty}$ [(mg/l)·h]	2.32 ±0.53	2.66 ± 0.62	114.9	102.7 – 128.4
C_{max} [mg/l]	0.94 ± 0.25	1.08 ± 0.33	113.9	101.4 – 128.0
t_{max} [h]	0.85 ± 0.34	1.10 ± 0.39	131.9	101.2 – 172.0
MRT [h]	2.12 ± 0.22	2.19 ± 0.37	102.3	93.5 – 112.1

$AUC_{0\to t}$ – area under the concentration-time curve from zero time dosing to the last measurable concentration, $AUC_{0\to\infty}$ – area under the concentration-time curve from zero time dosing to infinity, C_{max} – peak plasma concentration, t_{max} – time to peak plasma concentration, MRT – mean residence time, CI – confidence interval. Pharmacokinetic parameters were calculated using a non-compartmental analysis (Phoenix WinNonlin 8.0 software).

3. Discussion

Our HPLC method is reliable, because the calibration curve is linear and the intercept is essentially zero. Its LLOQ (lower limit of quantification) is 0.02 mg/l, and is sufficiently suitable for bioavailability studies. The precision of the method is very satisfactory (2.1 %). The other validation parameters (LOD, recovery, accuracy, chemical stability) meet the requirements for a suitable HPLC assay in bioavailability studies. The method provides adequate separation of moclobemide from I.S. and endogenous plasma components and drug metabolites (Fig. 1). Therefore, the method is selective and specific. Carbamazepine was yet not used as an internal standard for moclobemide plasma level determination. For the first time, ammonia for the mobile phase and Na_2HPO_4 for the liquid- liquid extraction were used as alkalizing media for moclobemide.

Pharmacokinetic and bioavailability parameters of both formulation tablets (Moclobemide vs. Aurorix) were not significantly different (Table 1). However, those generic tablets (Moclobemide, Jelfa) are not bioequivalent to the reference tablets (Aurorix) if their AUC is concerned (Table 2) according to guidelines of FDA (2001) and EMA (2010), because their values for moclobemide tablets are greater than 20 %. Our experiments confirm characteristic pharmacokinetic parameters of moclobemide in healthy subjects (Table 1): short half-life (1.18 h), large apparent volume of distribution (104.5 l) and relatively high systemic clearance (63.5 l/h) if compared to the literature data: 1.8, 75-95, 51-90, respectively (Mayershon and Guenteri 1995; Gex-Fabry et al. 1995; Fitton et al. 1992; Caccia 1998). First-order rate constants of absorption (ka) were not included in the table (Table 1), because in the case of a short terminal plasma half-life times drug ($t_{1/2} \leq 2$h) are needed at least 4 plasma subject's samples within 1 h after p. o. administration, which were not available. However, they were calculated by WinNonlin software, but their standard deviation is quite large: 5.78 ± 6.29 *and* 10.74 ± 16.61 1/h for moclobemide (Jelfa) and Aurorix tablets, respectively. An open one-compartment body model with a lag time of absorption (0.25 h, Table 1) is suitable to simulate plasma concentration-time curve of moclobemide after per oral administration in healthy subjects (Figs. 2 and 3). A significant lag time (t_{lag}) (Figs.2 and 3) before the commencement of the first-order absorption leads to erroneous results of a calculated area by trapezoidal rule based on integration of Eq. 1, because the existence of the negative area from zero to time t_{lag} (Hermann et al. 1993). The correct calculation of the above area is explained in Eq. 2.

Bioavailability parameters of moclobemide 150 mg generic tablets and 150 mg Aurorix reference tablets ($AUC_{0\to t}$, $AUC_{0\to\infty}$, (mg/l) h; C_{max}, mg/l; t_{max} h) were not significantly different: 2.54,

2.66, 1.08, 1.10 and 2.24, 2.32, 0.94, 0.85, respectively (Tab. 2). However, the AUC data for moclobemide tablets are greater by 20 % if compared to suitable Aurorix data according to FDA (2001) and EMA guidelines (2010) (Table 2). Furthermore, in bioavailability studies a protocol provides quite often also the extent of bioavailability (EBA). It is calculated from the formula

$$EBA = \frac{AUC_{0\to\infty(gener)}}{AUC_{0\to\infty(refer)}} \cdot 100\%$$

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That parameter EBA = 2.66/2.32 x 100% = 114.7% (Table 2). The difference is lower than 20 % and indicates again that both tablet formulations are bioequivalent. Nevertheless, FDA (2001) and EMA (2010) guidelines do not consider that discrepancy. It seems to us that number of subjects should be increased from 10 to 24 to help to clarify that inconsequence.

In conclusion, the paper confirms that our HPLC method worked out with some innovative conditions (carbamazebine as an I.S., ammonia and Na_2HPO_4 as alkalizing agents for moclobemide mobile phase and its extraction from plasma, respectively) is suitable for pharmacokinetic and bioavailability studies in healthy humans. Basic pharmacokinetic parameters of moclobemide obtained in this paper are identical for both kinds of tablets and essentially equal to the literature data for the healthy volunteers. Bioavailability data for the generic formulation tablets (Jelfa, Poland) are significantly different if compared with the reference tablets (Aurorix) (Table 1). Precisely, bioavailability parameters (Table 2) are greater than 20 % for Moclobemide tablets according to FDA and EMA guidelines (2001; 2010). Therefore, Moclobemide 150 mg tablets (Jelfa, Poland) are not exactly equivalent to Aurorix tablets.

4. Experimental

4.1. Subjects, material, procedures

At zero hour the subjects were assigned to a phlebotomist to insert a heparin catheter for the purpose of collecting a 5 ml blood sample. The assigned tablet was swallowed with 200 ml water. All subjects abstained from food until 4 h blood specimen was obtained when a standardized low fat lunch was provided. Regular meals were resumed after 6 h blood samples were obtained. Following drug administration, venous blood samples were obtained (in Serum Gel tubes, S/4.7 mL, Sarstedt Monovette, Germany) from the subject's right or left antecubital fossa catheter at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, and 6.0 h after the administration. Within 30 min following blood withdrawal, the samples were centrifuged. The prepared plasma samples were frozen in plastic vials at -20 °C and labeled with the subjects I.D. number, the drug assignment numbers, treatment day and times of sampling. The red blood cells were discarded.

4.2. Drug assay

An authentic sample of moclobemide and carbamazepine (I.S.) were obtained from Pharmaceuticals S.A., Jelfa, Jelenia Góra, Poland and Sigma-Aldrich, Germany, respectively. Acetonitrile and methanol (Merck, Germany) and n-butyl chloride (Sigma-Aldrich, Germany) were of HPLC grade. Water was house distilled from a silica glass apparatus and other chemicals were of reagent grade (P.O.Ch. Gliwice, Poland).

An Isochrom Spectra Physics Chromatograph with a UV-VIS detector and an integrator (San Jose, CA, USA) was coupled to 5 µm RP-18 column (250 x 4.6 mm) protected by a guard RP-18 column (4 x 4 mm) (Merck, Darmstadt, Germany). Absorbances of eluent were monitored at 239 nm. The mixture 350:650:0.5 v/v acetonitryle – water - 25 % ammonia ratio was first filtered (Sartorius, Göttingen, Germany) and pumped at a rate 1 ml/min and the ambient temperature.

Stock solutions of moclobemide and I.S. containing 1 g/l each in methanol were prepared and were stable for at least two weeks when refrigerated. The above solutions were diluted in the 7:3 v/v mixture of water:methanol to yield 100 and 2 mg/l their concentrations, respectively. The 100 mg/l moclobemide solution was again diluted to result in its concentrations at the range 0.1 – 10.0 mg/l. Two hundred µl of each standard solution and 150 µl of I.S. were transferred to 16 mm culture tube containing 1 ml plasma, closed with PTTE lined screw cap and vortex-mixed for 1 min. The resulting plasma based standards containing 0.02, 0.04, 0.10, 0.20, 0.40, 1.00 and 2.00 mg/l moclobemide and 0.30 mg/l I.S. were processed according to the extraction procedure described below.

To each 1 ml plasma standard 1 ml of 0.5 M Na_2HPO_4 and 10 ml of n-butyl chloride were added. After shaking for 5 min and centrifuging at 2000 rev. per min. for 3 min, the organic layer was aspirated, and the aqueous layer was frozen at – 17 °C and the rest of the organic layer was aspirated again. The organic layer was evaporated to dryness under nitrogen flow. The residue was reconstituted in 400 µl of the mobile phase and 50 µl was injected onto the column.

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Conflicts of interest; None declared.

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