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Application of Deconvolution for Estimating Metoclopramide (Mcp) Presystemic Elimination Following Oral Administration to Healthy Volunteers

Research Article

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Introduction

Deconvolution is a model-independent method for evaluation of drug absorption kinetics, introduced in pharmacokinetic (PK) theory and practice by Rescigno and Segre in 1966 [1] but as pointed out by Levitt [2,3] this powerful tool for PK analysis is underutilized. Since deconvolution is a model-independent method it does not assume PK compartments and requires no assumptions about drug absorption kinetics. Linear drug disposition is presumed. Deconvolution requires data obtained after both oral (p.o.) and intravenous (i.v.) drug administration in the same subject and assumes no differences in the pharmacokinetics of drug distribution and elimination from one study to the other. Drug concentrations must be measured at the same times following both p.o. and i.v. administration during the time that drug is absorbed after p.o. intake.

The deconvolution method does not require the determination of drug concentrations in plasma at equally spaced intervals during or after the absorption phase [4]. The accuracy of the method depends on the size of the sampling interval [5].

When drug disposition after oral and intravenous administration is expressed in terms of drug concentrations in plasma the method is termed point-point. When drug disposition after i.v. input is given by the area under the drug concentration/time curve over the sampling interval the method is termed point-area [5]. The theoretical background of the method is well documented elsewhere [2,5,6].

We were interested in exploring the predictive ability of deconvolution point-point method in estimating metoclopramide (MCP) presystemic elimination and systemic availability following oral administration in comparison with the classical area method for assessment of drug systemic availability.

Subjects, Study Design and Methods

Subjects

Six healthy male Caucasians, aged between 18 and 55 years, BMI between 19 and 28.6 were included in the study. There were no drop-outs during the trial and accordingly, all 6 volunteers completed the trial successfully. In order to obtain greater homogeneity of the study sample, and for reasons of safety concerns the enrollment of each participant was according to well defined inclusion and exclusion criteria.

The study was performed in accordance with the relevant articles of the Declaration of Helsinki (1964) as revised in Tokyo (1975), Venice (1983), Hong Kong (1989), and Somerset West, RSA (1996) and Edinburgh (2000), Washington 2002 and Tokyo 2004 [7].

Written approvals of Study Protocol final version from Ethics Committee and Regulatory Authorities were obtained prior to study start. The investigator notified the Ethics Committee and Regulatory Authorities about the trial completion.

Before being admitted to the clinical study, each volunteer gave his informed consent to participate by signing the informed consent form, after reading the information for volunteers, and after the nature, scope and possible consequences of the clinical study were additionally explained orally by a physician in a form understandable to him.

The case report forms (CRFs) guaranteed that all the

data protection requirements of the individual volunteer were met. For each volunteer only the initials and the date of birth were recorded. Further information necessary for the identification of individual volunteers remained with the investigator. To serve in case of emergency at screening every volunteer was given a personal card stating the subject was enrolled into a clinical trial.

Study design

Single dose, monocentric, open, [8] treatments cross-over study in 6 healthy Caucasian volunteers under fasting conditions with at least 3 days wash-out period between treatments (pilot study). Each volunteer received, after overnight fasting a single dose of Reglan 10mg metoclopramide hydrochloride/2ml solution for intravenous injection and after completion of the wash-out period Reglan tab. 10mg metoclopramide hydrochloride for oral administration.

Blood sampling times: Pre-dose (0) and at 10 min, 20 min, 30min, 40 min, 50 min, 1h, 1.5h, 2h, 2.5h, 3h, 3.5h, 5h, 7h, 9h, 12h, and 24h post-dosing. Total blood loss was about 280 ml: 2x20 ml at Screening and Follow-up visits and 17x2x7 ml for the measurement of metoclopramide plasma concentrations. Blood samples (volume of 7 ml) were collected in test vacuum tubes with anticoagulant and immediately after centrifugation were frozen at – 20^0C.

Analytical method for determination of metoclopramide in plasma

High Performance Liquid Chromtography (HPLC) method for measurement of metoclopramide concentrations in plasma was validated in line with the FDA Guidance for Bioanalytical Method Validation and in accordance with GLP requirements. All plasma samples were kept at -20oC until analysis. The plasma samples were defrozen at room temperature immediately before the analysis. An appropriate aliquot of the sample undergoes liquid-liquid extraction procedure in organic solvent.

The HPLC-FLD system consists of a quaternery pump, model 1050 Hewlett–Packard; an autosampler, model 1100 Agilent Technologies; a degasser, model 1050 Hewlett–Packard; a programmable Fluorescence (FL) detector, model 1050 Hewlett – Packard and licensed software ChemStation, Agilent Technologies.

The chromatographic conditions include an analytical column Merck–CN (5μm) 250x4 and a guard column Merck–CN (5μm) 4x4. The mobile phase consists of buffer / Acetonitrile (70/30v/v); flow rate: 1.00 ml/min; FL Detection: λex=275nm, λem=350nm; injection volume 85 μl. Lower Limit of Quantification (LLOQ)=1 ng/ml with a precision of <20% and accuracy 80-120%. Limit of Detection (LOD)=0.3 ng/ml. Accuracy Acceptance Criteria: ±15% of the actual value for the calibration standards except at concentration level of LLOQ ±20%. Precision Acceptance Criteria: determined at each concentration level with coefficient of variation CV<15% except for the LLOQ CV<20%. Specificity: No interference with biological matrix was found.

Pharmacokinetic analysis and statistical evaluation

The absolute systemic availability, Fabs, is the fraction of the oral dose of unchanged MCP reaching the systemic circulation and was estimated according to [9] as:

$$\mathbf{Fabs = AUCinf\ (P.O.)\ /\ AUCinf\ (I.V.)} \qquad \mathbf{(1)}$$

where AUCinf (P.O.) / AUCinf(I.V.) are the areas under the MCP concentration/time curves from time zero to infinity after oral and venous drug administration and were calculated by the well-known equation:

$$\mathbf{AUCinf = AUC0\text{-}t + Ct\ /\ \lambda z} \qquad \mathbf{(2)}$$

where AUC0-t is the area under the concentration/time curve from time zero to time t (= 24h), Ct is the MCP level measured at time (t=24h) and λz is the first-order rate constant of the terminal postabsorption (in case of extravascular drug administration) and postdistribution phase.

AUC0-t were calculated by classical non-compartment pharmacokinetics as implemented in PKQuest PBPK software. Tmax values, as measure of drug absorption rate, were directly read from the concentration-time curves and fat fraction was calculated by PKQuest module based on subject's weight, height and age.

Deconvolution was run on the PKQuest PBPK software as implemented by Levitt (2003) [2,10] assuming drug transfer is blood flow-limited and clearance organs are well-stirred [11].

The module has [12] different deconvolution functions and the Hill function was selected for deconvolution as suggested by Levitt (2017) [3]. The Hill function fit to experimental data provides estimation of 'Amount of drug reaching systemic circulation, ARSC (mcg)',

'Estimated first-pass metabolism fraction (estimated presystemic elimination fraction)', 'Physiologically based pharmacokinetic modelling, PBPK total liver blood flow (L/min)', and 'Total amount of drug absorbed (mcg)'. PKQuest deconvolution Hill function calculates 'Estimated first-pass metabolism fraction (estimated presystemic elimination fraction)' as 'Clearance/PBPK liver blood flow'.

ARSC is a metric of systemic drug availability and the ratio ARSC/Oral Dose has the same pharmacokinetic and clinical interpretation as does the classical bioavailability parameter, Fabs. Thus, the deconvolution point-point method gives estimate of drug systemic availability after oral (extravascular) administration. Therefore, the conventional quantitative expression for presystemic drug elimination (first-pass metabolism) '1 - Fabs' [12] is identical to deconvolution estimated presystemic elimination fraction (estimated first-pass metabolism fraction).

Absorption half-life, t1/2a, of metoclopramide after oral intake was calculated by the method of inspection [13], as introduced in pharmacokinetic practice by Swintosky et al. (1969) [14]. The basic assumption done by the authors is that when drug blood level reaches its peak, absorption is 95-99 percent complete, i.e., Tmax is achieved after 5 absorption half-lives, t1/2a:

Tmax=5 x t1/2a and t1/2a=Tmax / 5 (3)

Statistical analysis was performed on Origin 9.0. MCP PK parameters were computed for each single subject and presented as mean +/- SD. The change in the values of variables were tested by paired sample Student's t-test. The null hypothesis of no differences between the means was rejected at $p<0.05$.

Results

(Table 1) summarizes deconvolution output parameters related to quantification of MCP systemic availability and presystemic elimination. Statistical analysis revealed no significant difference between the fraction of the oral dose MCP reaching systemic circulation, ARSC/DP.O., and absolute systemic availability, Fabs, of metoclopramide. Furthermore, the comparison between the presystemic elimination fraction of orally administered MCP, (1-Fabs), and the estimated presystemic elimination fraction by the deconvolution method did show statistically significant difference (Table 1).

Total amount absorbed drug is an estimator of how complete absorption is in gastrointestinal tract (GIT) and approximates the amount of absorbed drug entering the portal vein. As can be expected the total amount absorbed metoclopramide was significantly higher than the amount reaching systemic circulation (Table 1) due to MCP presystemic elimination.

Volunteers ID#	Amount Reaching Systemic Circulation (ARSC) (mcg)	ARSC/ DP.O.	Fabs	Estimated Presystemic Elimination Fraction	(1 - Fabs)	PBPK Total Liver Blood Flow (L/ min)	Total Amount Absorbed (mcg)
1.	7213	0.721	0.8099	0.176	0.1901	2.277	8756
2.	7137	0.714	0.8165	0.165	0.1835	1.983	8545
3.	6754	0.675	0.7994	0.261	0.2006	2.251	9138
4.	7095	0.710	0.7925	0.215	0.2075	1.721	9038
5.	8683	0.868	0.8048	0.290	0.1952	1.745	12240
6.	7479	0.748	0.7905	0.170	0.2095	1.863	9013
Mean	7394	0.739	0.8023	0.213	0.1977	1.973	9455
SD	673	0.067	0.0101	0.052	0.0101	0.244	1381

Table 1. Deconvolution estimates of presystemic elimination (first-pass metabolism) and absolute systemic availability of metoclopramide after 10mg oral dose in tablet

PKQuest uses the default PBPK hepatic flow of 1.575 L/min for the standard 70 kg, 21% fat subject (this is the sum of the PKQuest "portal" plus "hepatic" flow). However, this is just approximate and liver blood flow is variable, increasing after meals, and is decreased by

some drugs, such as β- blockers [3]. The PBPK total liver blood flow for volunteers ## 1 and 3 (=2.277 and 2.251 L/min, resp.) were somewhat higher as reported by the deconvolution output (Table 1). Highly significant positive correlation was observed between BMI values and calculated fat fractions (N=6, r=0.94, $p < 0.01$, Table 2). When plotting absorption half-lives on BMIs (Table 2) significant negative correlation was registered (N=6, r=- 0.93, $p < 0.01$) suggesting negative dependency of MCP absorption rate on obesity degree. This suggestion was further confirmed by the highly significant negative dependency between MCP absorption half-lives and the fat fraction estimates (N=6, r=- 0.99, $p < 0.001$).

Volunteers ID#	BMI (kg/m^2)	Fat Fraction (%)	Tmax (min)	t1/2a (min)
	26.3	18.8	60	12
	19.0	7.8	90	18
	26.9	18.8	60	12
	24.2	19.2	60	12
	28.0	25.4	40	8
	26.4	20.9	50	10
Mean	25.1	18.5	60	12
SD	3.2	5.8	17	3.4

Table 2. Bmi, fat fraction, tmax values and estimates of absorption half-life for mcp after oral administration

Volunteer #5 deserves special comments. The deconvolution estimates for the total amount MCP absorbed, correcting for presystemic elimination, was 12240 micrograms. This is somewhat greater than the actual dose administered which, of course, is impossible and indicates that PKQuest overestimated the first-pass metabolism (= 0.29) because it used 25% larger estimate for liver blood flow. Similar observation is reported by Levitt (2017) for nitrendipine [3]. On the other hand, a plausible explanation could be the large inter-individual variation in the degree of first-pass effect (0.47-1.14) observed by Ross-Lee et al. (1981) [15].

Furthermore, the shortest Tmax (=40 min), resp. t1/2a (=8 min) were registered for subject #5 suggesting the highest absorption rate of MCP in this volunteer (see Table 2). The same subject had the highest fat fraction (=25.4%), as calculated by PKQuest, and BMI=28 kg/m2 (Table 2). These results agree very well with the published data of Cho, SJ. et al (2013) and EMA Reflection Paper (2018) reporting accelerated gastric emptying and increased rate and extent of drug absorption in obese subjects. [16,17].

Taken together, these findings are a good assertion that the deconvolution point-point method, as implemented in PKQuest PBPK software, demonstrates good reliability in analyzing drug absorption features.

Discussion and Conclusion

The term first-pass effect coined by Harris and Riegelman [18] to designate reduction in plasma levels of a drug after oral intake compared to intravenous administration due to its elimination by both gut and liver [19,20], might be misleading when one recognizes that the liver eliminates the drug by hepatic metabolism and/or biliary excretion during each passage of the drug. In this context the term presystemic elimination [21, 22] is preferable in describing all events between absorption of a drug and its appearance in the systemic circulation [23]. Usually, presystemic elimination of a drug results in reduction of its pharmacological effectiveness.

Deconvolution was used to evaluate MCP presystemic elimination features. After MCP is absorbed into the blood and passes through the liver (first-pass effect, presystemic elimination), it has the same PK behaviour as if it has been injected intravenously. The mean value for deconvolution estimates of MCP total amount absorbed indicates that practically all of the dose administered orally is absorbed in GIT and one can assume complete MCP absorption which agrees with the good lipid-solubility and basic properties of metoclopramide (Log Po:w=2.62 and basic pKa=9.4, https://pubchem.ncbi.nlm.nih.gov/compound/metoclopramide).

The lack of significant differences between the deconvolution estimates of presystemic elimination fraction and (1- Fabs) values, as well as between ARSC/DP.O. and Fabs points out the opportunity these deconvolution metrics to be used instead of conventional comparison of AUCs ratios after oral and intravenous drug administration for calculating drug systemic availability.

Thus, the deconvolution method could be seen as a reliable estimator of MCP presystemic elimination after oral drug intake.

The mean value (=1.973 L/min) of deconvolution estimates for PBPK liver blood flow is somewhat higher than the PKQuest default PBPK value of 1.575 L/min and could be due to the prevalence of overweight individuals

in the group, 4/6, as assessed by their BMIs and fat fraction (Table 2). It is well documented that in obese subject's hepatic blood flow is increased. [8,17,24]. It is noteworthy to point out that volunteers #1 and #3 with the highest values for PBPK liver blood flow, 2.277 and 2.251 L/min, resp., had BMIs of 26.3 and 26.9 kg/m^2, resp.

Collectively taken, the results of the study demonstrate the reliability of the deconvolution method, as implemented in PKQuest PBPK software, to quantify presystemic elimination of MCP after oral administration and its absorption features.

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