SIMPLE PHYSICOCHEMICAL PROPERTIES AS EFFECTIVE FILTERS FOR RISK ESTIMATION OF DRUGS AND ENVIRONMENTAL POLLUTANTS TRANSPORT INTO HUMAN BREAST MILK

KOSMIDI A.[1], VASIOS G.K.[1,2] and GIAGINIS C.[1]

[1] Department of Food Science and Nutrition, School of Environment, University of the Aegean, Myrina, Lemnos, 81400, Greece; [2] Department of Geography, School of Social Sciences, University of the Aegean, University Hill, Mytilene, Lesvos, 81100, Greece
E-mail: vasios@aegean.gr

ABSTRACT

For many decades serious concerns have been raised by the international scientific committee regarding the presence of drugs and environmental pollutant contaminants in human breast milk. In this aspect, milk/plasma concentration (M/P) ratio is considered as a crucial parameter for neonatal exposure, determining the extent of transport of drugs and environmental pollutants into human breast milk. In this aspect, the present study is aimed to assess whether simple physicochemical properties could be used as effective filters for risk estimation of drugs and environmental pollutants transport into human breast milk. In view of the above, a large data set of 350 structurally diverse drugs, bioactive food ingredients and environmental pollutants with literature available experimental M/P data was compiled and explored with respect to well recognized physicochemical properties. Compounds with M/P value ≥1 are considered to be present in human breast milk at higher levels than in maternal plasma, being classified as high risk compounds, while those with M/P <1 were classified as low risk compounds. By the use of the above cut-off point, 67% of the compounds were classified as low and the remaining 33% as high risk compounds among the whole data set as far as concern their extent to be transferred into human breast milk. High risk compounds were significantly characterized by increased lipophilicity compare to low risk ones ($p<0.05$). Enhanced polarity was significantly more frequently observed in low risk compared to high risk compounds ($p<0.001$). A significantly increased incidence of high risk compounds presented positive charge at pH 7.4 due to their basic properties ($p<0.001$). In contrast, negative charge at pH 7.4 related to acidic properties was significantly more frequently observed in the subgroup of low risk compounds ($p<0.001$). Enhanced flexibility and molecular size, expressed by the number of rotatable bonds included in the chemical structure and molecular weight, respectively, were significantly more frequently observed in low compared to high risk compounds ($p<0.05$). In conclusion, the present study supported substantial evidence by the use of a large data set of structurally diverse xenobiotic compounds that simple physicochemical properties related with lipophilicity, polarity and ionization could be used as adequate effective filters for risk estimation of drugs and environmental pollutants transport into human breast milk for which non experimental M/P data are currently available.

Keywords: Breast milk transfer; physicochemical properties; drugs; environmental pollutants; xenobiotic compounds; lipophilicity; polarity; ionization; molecular weight

1. Introduction

For many decades serious concerns have been raised by the international scientific committee regarding the presence of drugs contaminants in human breast milk. Alarming enough most of the drugs consumed by breastfeeding women during medication can pass, at a low, intermediate or even at a high extent, into maternal breast milk, which may exert short- and/or long-term harmful effects on their infant (Ito and Lee, 2003; Fleishaker 2003). In the last few years, there has been also additional serious concern with respect to the presence of

environmental pollutants in human breast milk, since breastfeeding women are systematically exposed to toxic chemicals through contaminated air and food, contact with contaminated soil, as well as by the use of commercial products, which may contain toxicants (e.g. pesticides, food additives, cosmetics and medications). In this aspect, milk/plasma concentration (M/P) ratio is considered as a crucial parameter, which has been proposed and used to determine the extent of transport of drugs and environmental pollutants into human breast milk (Ito and Lee, 2003; Fleishaker 2003). M/P ratio is considered to identify the equilibrium concentration between human breast milk and blood, being equivalent to the xenobiotic compounds concentration in the breast milk divided by the maternal plasma concentration. Notably, the vast majority of the xenobiotic compounds transer from maternal plasma into breast milk by passive diffusion. Substantial evidence has suggested that passive diffusion of drugs and chemicals through cellular membranes is mainly affected by well-recognized physicochemical properties, such as lipophilicity, polarity and molecular size (Giaginis and Tsantili-Kakoulidou, 2008; 2012). Thus, the M/P ratio is mainly affected by milk composition (lipid, protein), as well as by the physicochemical properties of the xenobiotic compounds (lipophilicity, polarity, ionization, molecular size) (Ito and Lee, 2003; Fleishaker 2003). In view of the above, the present study is aimed to assess whether simple physicochemical properties could be used as effective filters for risk estimation of drugs and environmental pollutants transport into human breast milk.

2. Material and Methods

2.1. Data set

Breast milk transfer data expressed as milk/plasma xenobiotic compound concentration (M/P ratio) values were systematically compiled from English international literature sources published in Medline over the past six decades. In total 350 xenobiotic compounds, including 317 drugs, 8 nutrients, 17 environmental pollutants and 8 insecticides were included in the present study.

2.2. Descriptors

The chemical structure of compounds was designed by the software ChemDrawn Ultra 7.0 (CambridgeSoft Corp., Cambridge, USA). The software ADME Boxes 3.0 (Pharma-Algorithms, Toronto, Canada) was used to calculate lipophilicity expressed by the logarithm of octanol-water partition coefficient (logP) and the logarithm of octanol-water distribution coefficient at pH 7.4 ($logD_{7.4}$), hydrogen bond acceptor (HBA) and donor (HBD) sites, total polar surface area (TPSA), number of rotatable bonds (RB), positive (F^+) and negative (F^-) fraction at pH 7.4, number of ionizable group (Ion.Gr) and molecular weight (MW).

2.3. Statistical analysis

Graphics and descriptive statistics (maximum, minimum and mean values) were initially performed. Kolmogorov-Smirnov test was used to assess the normality of property-distribution. T-test and Mann-Witney test were applied to assess the influence of physicochemical properties on M/P ratio. Statistical analysis was performed by Statistica – Axa 7.0 software package (StatSoft, Tulsa, Oklahoma, USA).

3. Results

3.1. Descriptive statistics of the data set

Among the whole data set, 67% of the compounds were classified as low risk and the remaining 33% as high risk with respect to their transport into human breast milk (Figure 1). The mean value (±S.D) of the M/P ratio was 1.35±2.63, with a minimum (min) and maximum (max) values of 0 and 23.5, respectively. The vast majority of compounds (81%) presented M/P values between 0 and 2.

At a next step, physicochemical properties-distribution analysis was performed in order to assess the descriptive statistics of the data set. More to the point, the mean logP value of the data set was 2.57±3.11 (min: -13.12 and max: 15.07) with the vast majority (55%) of the compounds to present logP values between 0 and 4. The mean $logD_{7.4}$ value of the data set was 1.41±1.97 (min: -13.12 and max: 15.07) with the vast majority (55%) of the compounds to present $logD_{7.4}$ values between -1 and 0. Most of the compounds possessed ≤2 sites, exerting

hydrogen bonding capability as donors (HBD), and ≥5 sites, exerting hydrogen bonding capability as acceptors (HBA) (53% and 58%, respectively). As far as concern HBD and HBA properties, mean values were 2.04±2.81 (min 0 and max 25) and 5.11±4.78 (min 0 and max 44), respectively. The mean TPSA value was 79.67±80.80 A^2 (min 0 A^2 and max 734.46 A^2). A significant number of compounds (35%) presented TPSA values between 0A^2 and 50A^2 and another significant number of compounds (33%) between 50A^2 and 100A^2. The mean RB value was 4.63±4.37 (min 0 and max 44). In fact, the vast majority (63%) of compounds included in their structure ≤5 rotatable bonds. The mean MW value was 348.36±175.19 (min 46.07 and max 1639.91) with a significant number of compounds (44%) to present MW values between 250 and 350. The mean Ion.Gr value was 1.29±1.16 (min 0 and max 10). In fact, a significant number of compounds (45%) included 1 ionizable group in their chemical structure.

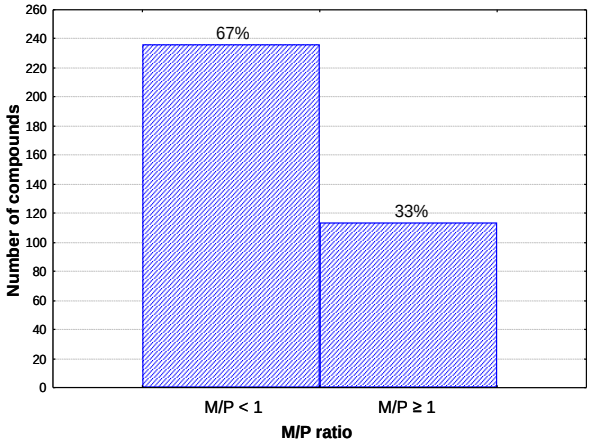

Figure 1: Classification of the compounds of the data set according to the extent of their transport into human breast milk

3.2. Influence of physicochemical properties on the xenobiotic compounds transport into human breast milk

High risk compounds that can pass into breast milk at a high extent (M/P≥1) were significantly characterized by increased lipophilicity compare to low risk ones ($p<0.05$). In fact, high risk compounds were significantly characterized by enhanced lipophilicity of the neutral species expressed by logP (mean logP value: 3.06±2.83) compared to low risk (mean logP value: 2.32±3.21) ones (Figure 2A, p=0.0371). Accordingly, high risk compounds were significantly characterized by enhanced lipophilicity of the ionized species at pH 7.4 expressed by $logD_{7.4}$ (mean $logD_{7.4}$ value: 2.10±3.18) compared to low risk (mean $logD_{7.4}$ value: 1.07±3.75) ones (Figure 2B, p=0.0116).

Enhanced polarity was significantly more frequently observed in low compared to high risk compounds ($p<0.001$). More to the point, low risk compounds presented significantly elevated TPSA values (mean TPSA: 92.40±85.06 A^2) compared to high risk (mean TPSA: 53.67±64.20A^2) ones (Figure 3A, p=0.00002). Moreover, low risk compounds included in their structure a significant increased number of HBD sites (mean HBD value: 2.29±2.97) compared to high risk (mean HBD value: 1.53±2.39) ones (Figure 3B, p=0.0168). Accordingly, low risk compounds included at their structure a significant increased number of HBA sites (mean HBA value: 5.81±4.99) compared to high risk (mean HBA value: 3.67±3.98) ones (Figure 3C, p=0.0001). The sum of HBD and HBA sites were also significantly elevated in low compared to high risk compounds (Figure 3D, mean HBDA value: 8.12±7.61 *vs* 5.20±6.15, p=0.0004). Low risk compounds also presented a significantly increased number of ionizable groups (mean Ion.Gr value: 1.40±1.22) compared to high risk (mean Ion.Gr value: 1.09±1.01) ones (p=0.0195).

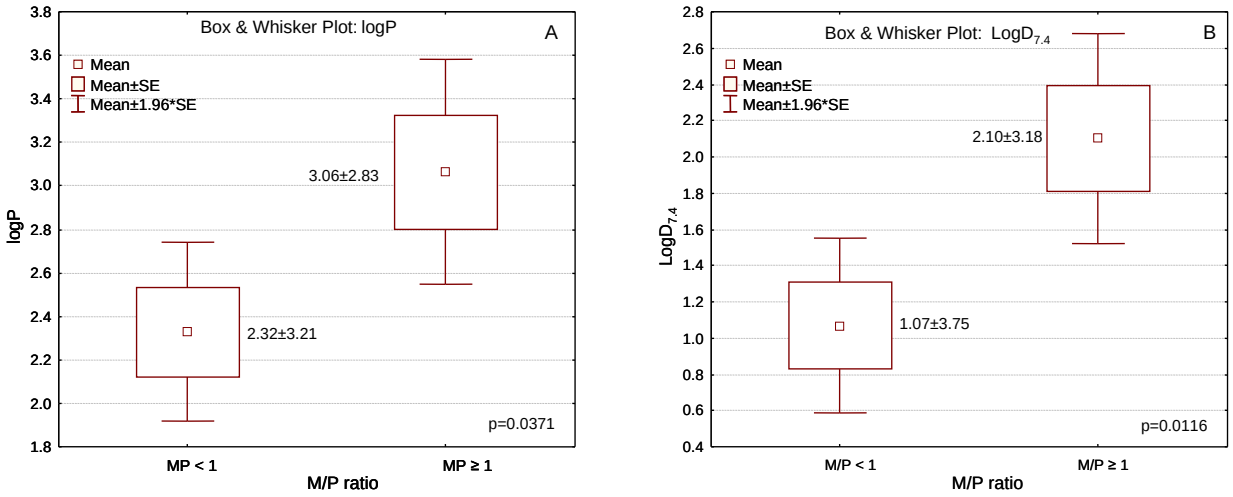

Figure 2: Association of the lipophilicity expressed by logP **(A)** and $logD_{7.4}$ **(B)** with the extent of the xenobiotic compounds transport into human breast milk

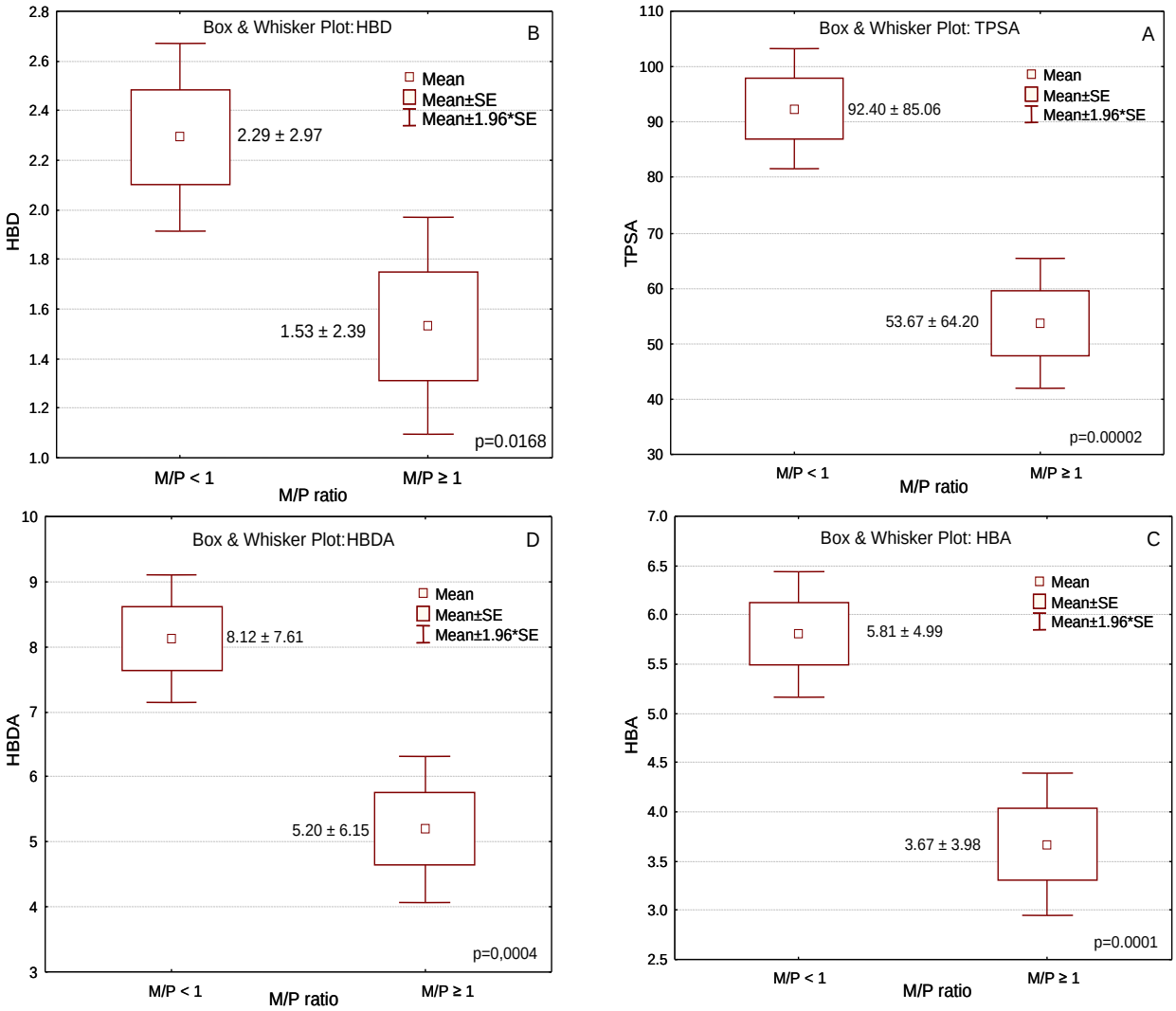

Figure 3: Association of the polarity expressed by TPSA **(A)**, HBD **(B),** HBA **(C),** HBDA **(D)** with the extent of the xenobiotic compounds transport into human breast milk

Enhanced flexibility and molecular size, expressed by RB and MW, respectively, were significantly negatively associated with the extent of xenobiotic compounds to transport into human breast milk ($p<0.05$). In fact, low risk compounds presented a significantly increased number of flexible rotatable bonds (mean RB value: 4.97±4.82) compared to high risk (mean RB value: 3.94±3.16) ones (Figure 4A, $p=0.0385$). Moreover, low risk compounds were characterized by increased MW (mean MW value: 361.21±183.90) compared to high risk (mean MW value: 322.10±153.94) ones (Figure 4B, $p=0.0497$).

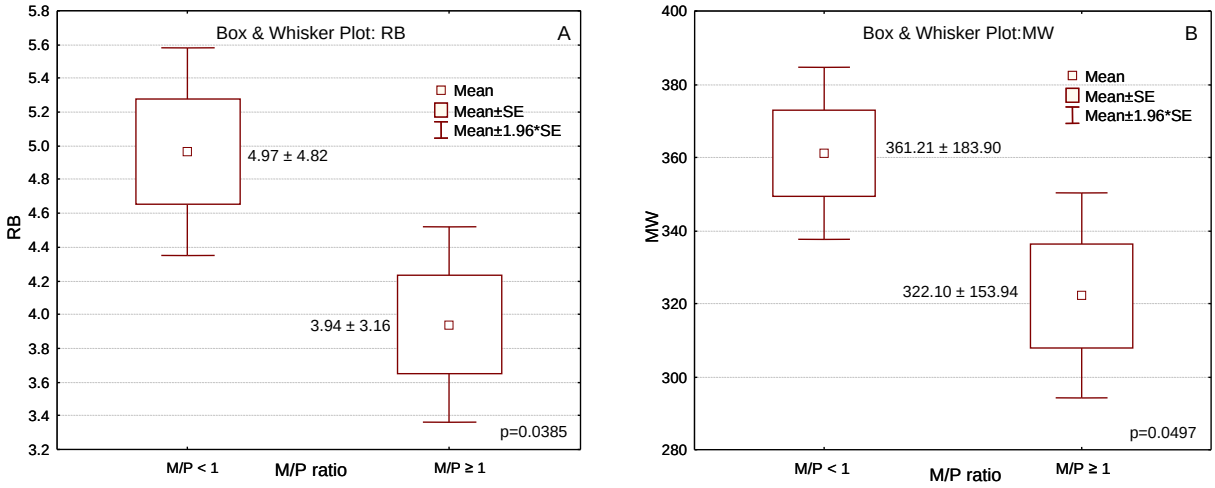

Figure 4. Association of the flexibility and molecular size expressed by RB **(A)** and MW **(B)** with the extent of the xenobiotic compounds transport into human breast milk

As far as concern the impact of ionization status at pH 7.4 on the extent of the xenobiotic compounds transport into human breast milk, high risk compounds were significantly more frequently characterized by basic properties expressed by F^+ compared to low risk ones ($p<0.0001$). In contrast, low risk compounds were significantly more frequently characterized by acidic properties expressed by expressed by F^- compared to high risk ($p<0.0001$). The above may mainly be ascribed to the fact that basic compounds were trapped into human breast milk due to its lower pH 7.08 compared to plasma pH 7.42.

4. Conclusions

The present study analyzed a large data set of 350 drugs and environmental pollutants, supporting substantial evidence that simple physicochemical properties related with lipophilicity, polarity and ionization status may be used as effective filters for their risk estimation to transport into human breast milk. High lipophilicity and low polarity were found to be associated with increased risk for drugs and environmental pollutants transport into human breast milk. Acidic and basic properties of xenobiotic compounds also exerted a significant impact on their extent to transport into human breast milk. Such a methodology used in the present study could effectively be applied to estimate the risk of xenobiotic compounds with unknown experimental data concerning their transport into human breast milk.

REFERENCES

1. Ito S. and Lee A. (2003), Drug excretion into breast milk-Overview, Adv. Drug Deliver. Rev., **55**, 617-627.
2. Fleishaker J.C. (2003), Models and methods for predicting drug transfer into human milk, Adv. Drug Deliver. Rev., **55**, 643-652.
3. Giaginis C. and Tsantili-Kakoulidou A. (2008), Alternative measures of lipophilicity: from octanol-water partitioning to IAM retention, J. Pharm. Sci. **97**, 2984-3004.
4. Giaginis C., Theocharis S. and Tsantili-Kakoulidou A. (2012), Current toxicological aspects on drug and chemical transport and metabolism across the human placental barrier, Expert Opin. Drug Metab. Toxicol., **8**, 1263-75.