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Allometric scaling for predicting human clearance of bisphenol A

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ABSTRACT

The investigation of interspecies differences in bisphenol A (BPA) pharmacokinetics (PK) may be useful for translating findings from animal studies to humans, identifying major processes involved in BPA clearance mechanisms, and predicting BPA PK parameters in man. For the first time, a large range of species in terms of body weight, from 0.02 kg (mice) to 495 kg (horses) was used to predict BPA clearance in man by an allometric approach.

BPA PK was evaluated after intravenous administration of BPA in horses, sheep, pigs, dogs, rats and mice. A non-compartmental analysis was used to estimate plasma clearance and steady state volume of distribution and predict BPA PK parameters in humans from allometric scaling.

In all the species investigated, BPA plasma clearance was high and of the same order of magnitude as their respective hepatic blood flow. By an allometric scaling, the human clearance was estimated to be 1.79 L/min (equivalent to 25.6 mL/kg.min) with a 95% prediction interval of 0.36 to 8.83 L/min.

Our results support the hypothesis that there are highly efficient and hepatic mechanisms of BPA clearance in man.

Introduction

Bisphenol A (BPA) is widely used in its monomeric form in the manufacture of polycarbonate plastics and epoxy resins which in turn find applications in a wide variety of consumer products like plastic food and water containers and the lining on the inside of metal food and beverage containers (EFSA, 2006). The release of BPA monomers from consumer products leading to the contamination of drinking water, food, dust, and air is believed to contribute to the widespread human exposure to BPA. Indeed, Calafat et al. (2008) found measurable levels of BPA metabolites in more than 90% of urine samples from a representative cohort of the US population.

The urinary concentration of BPA metabolites is considered a relevant indicator of human BPA internal exposure since BPA is completely eliminated in the urine mainly as BPA glucuronide (BPAG, Völkel, 2002). Based on the measurement of urinary concentrations of BPA metabolites, mean and high BPA total intake values have been estimated at 39 and 184 ng/kg per day in adults from the geometric mean and the 95th percentile of BPA urinary concentrations reported by European studies (Lakind and Naiman, 2011). These exposure values remain well below the current tolerable daily intake (TDI) of 50 μg/kg BW per day (EFSA, 2006) and the newly proposed temporary TDI of 5 μg/kg BW per day (EFSA, 2014).

In fact the most relevant physiological variable for translating findings from animal studies to humans is the concentration level of BPA in the blood. Indeed any BPA systemic effects are related to the BPA blood (plasma) concentration that is the driving force controlling all other local tissue concentrations including the biophase concentrations, i.e. the concentration of BPA at the site of action. It should be recognized that any dosing rate (mass per unit of time) is related to a corresponding steady state plasma concentration (mass per unit of volume) by a key pharmacokinetic parameter, namely the blood (plasma) clearance (CL, volume per unit of time) and to a variable, namely the bioavailability (F, ranging from 0 to 1) according to the equation:

$$Dosing\ rate = CL \times C_{SS}/F \quad (1)$$

Abbreviations: AS, Allometric scaling; AUClast, Area under the plasma concentration–time curve from dosing time to the last sampling time; BPA, Bisphenol A; BPAG, Bisphenol A glucuronide; BW, Body weight; CL, Plasma clearance; IV, Intravenous; LOQ, Limit of quantification; MRT, Mean residence time; NOAEL, No-observed-adverse-effect-level; PK, Pharmacokinetics; PI, Prediction interval; TDI, Tolerable daily intake; V_{SS}, Steady state volume of distribution

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Inspection of Eq. (1) shows that the plasma clearance is the scaling factor linking any dose to its corresponding plasma concentration given a value of F. Currently, the plasma clearance of BPA has not been determined experimentally in man, most likely because it requires an IV BPA administration. In a toxicokinetic study of deuterated BPA (5 mg) orally administered to humans, only conjugated forms of BPA were detected in plasma, preventing the evaluation of even a BPA oral clearance (Völkel et al., 2002).

Given the inability to know experimentally the human BPA clearance, its prediction from animal data can be done using two approaches: allometric scaling and physiologically based pharmacokinetic (PBPK) modeling. PBPK is a mechanistic-based modeling involving mass-balance computation for organs and tissues; these models have the theoretical potential to predict the plasma BPA concentration–time curve in man but they are complex, labor-intensive to build and they require assumptions and/or experimental data that are not all well established for BPA, leading some scientists to challenge their predictions (Vom Saal et al., 2012). At the opposite end of the spectrum, the allometric scaling approach can be viewed as an easy empirical "black box approach" using a power function that has proved its usefulness for many substances to scale pharmacokinetic parameters obtained in different species such as clearance, volume of distribution and half-life (see Chappell and Mordenti, 1991 for review). Practically, the allometric scaling consists of establishing the quantitative relationship between the PK parameters and generally the Body Weight (BW) of the investigated species with a power equation.

Using this approach, BPA plasma clearance in humans has previously been estimated at about respectively 127 L/h and 100 L/h by extrapolating the allometric straight line fit to data from either rodents, rabbits and dogs (Cho et al., 2002) or rodents and monkeys (Doerge et al., 2012). However, high uncertainties remain for these estimates due to the low range of the BW of the animal species used (mouse, rat, dog and monkey) that did not encompass the human typical BW. Indeed, it has been shown that the accuracy of the predicted value of a human parameter increased with both the number and the BW range of animal species included in the regression (Tang and Mayerson, 2005) and it is a general property when using a regression model, that when larger animals than target species are employed, data (here the human PK parameter) are more confidently interpolated rather than extrapolated (Huang and Riviere, 2014).

This last condition is difficult to fulfill because routinely used laboratory species are lighter than man while in the present experiment, the use of the horse (495 kg BW) enabled us to estimate the human PK parameter by interpolation instead of extrapolation. Another issue that arises when using allometric scaling prospectively relates to the fact that a useful prediction interval (PI), i.e. the interval containing the prediction for a future observation with a certain probability (here 95%, Bonate and Howard, 2000) can only be computed when the human parameters are obtained by interpolation as in the present experiment. The log–log transformation that is routinely used to estimate the allometric parameters can lead to a different sort of bias especially when the allometric scaling encompasses a large range of BW as is the case for the present paper because the linear regression on logs places unduly heavy weight on values for small species and gives less importance to the value for the largest species (Packard and Boardman, 2008). This problem can be overcome through an alternative interspecies scaling technique, which uses the concept of '"species invariant time" proposed by Dedrick et al. (1970) and extended by Boxembaum and Ronfeld (1983) who introduced new units of pharmacokinetic space time, namely kallynochrons and apolysichrons. Using these species invariant times, each animal species potentially has the same impact on the prediction in man (Lave et al., 1995).

In the present study, human plasma BPA clearance and steady state volume of distribution (Vss) and their associated PI were estimated using classical allometric scaling from plasma BPA concentration–time curves obtained after BPA iv administration in a wide range of species (mice, rats, dogs, sheep, pigs and horses) whose BW encompass the point for humans enabling the interpolation of PK parameters in humans. PK parameters predicted using allometric scaling were compared to those obtained by computing the transformed concentration-time profiles using the species invariant time method.

Materials and methods

Animals. All experimental animal procedures were conducted in accordance with accepted standards of humane animal care under the agreement number 31-247 for animal experimentation from the French Ministry of Agriculture.

The study was conducted with 40 female CD-1 mice (Charles River Laboratories, L'arbresle, France) weighing 22.4 ± 0.9 g, 6 male Wistar rats (Harlan, Gannat, France) weighing 303 ± 11 g, 6 female Beagle dogs (Harlan, Gannat, France) aged from 4 to 6 years old and weighing 10.2 ± 0.6 kg, 8 male piglets weighing 22.4 ± 3.4 kg, 5 female Lacaune ewes weighing 61.7 ± 5.2 kg and 4 horses (2 geldings, 2 females, age 8–21 years) weighing 495 ± 64.5 kg.

All animals were acclimatized to standard housing and rooms for at least one week before the beginning of the experiment. Horses were housed in individual boxes and/or paddocks for the duration of the study. Sheep and pigs were housed indoors in collective pens.

Dogs were housed in pairs in 12-m^2 rooms, fed a standard diet, and had free access to drinking water. The animal rooms were illuminated by artificial light on a 12-h light/dark cycle, and the temperature was maintained at about 20 °C. The dogs had access to outdoor exercise areas for about 4 h/day. Prior to the study day, the animals were fasted overnight and had free access to drinking water. They were given a standard meal 4–5 h after dosing. During sampling periods, the dogs, rodents and pigs were housed individually in metabolism cages.

Experimental design. BPA PK were investigated after intravenous (IV) administration of BPA at a dose of 5 mg/kg BW in six mammalian species (mice, rats, dogs, pigs, sheep and horses) covering a large range of body weights. The time-course of plasma BPA concentrations was followed during the first 24–48 h following the BPA administration.

Test material and treatments. BPA (>99.9% purity) and all chemicals were purchased from Sigma Aldrich (N°CAS: 80-05-7, Saint-Quentin, Fallavier, France). All materials for the preparation of solutions, processing and analysis were in glass or in BPA-free plastic (polypropylene). The absence of BPA leaching from the administration and sampling materials was previously verified. BPA solutions were extemporaneously prepared by dissolving BPA at concentrations ranging from 1 to 50 mg/ml in 1% ethanol/49% propylene glycol (all species except mice) or 5% DMSO/95% physiological saline (mice). The volume administered to animals was adjusted to the individual BW recorded within the 2 days preceding BPA administration. The BPA concentrations of all the dosing solutions were verified by UPLC-MS/MS (*see BPA assay section*).

BPA was administered into the lateral tail vein of awake mice placed in a restraining tube for the duration of the administration (over 5 to 10 s) and of rats briefly anesthetized using volatile anesthesia (2% isoflurane, AErrane®, Baxter SA, Maurepas, France, in 0.7 L/min of O_2). The administrations were performed via an indwelling catheter (22 G) inserted into the right cephalic vein (dogs) or the auricular vein (pigs) or via an indwelling catheter (16 G) inserted into the left jugular vein (sheep, horses) just before administration.

Blood sampling. Blood samples were collected before and at 15, 30, 45 min and 1, 1.5, 2, 4, 8, 12, and 24 h after BPA administration from groups of three or four mice at each sampling time from individual rats the day before and each of the designed times at 10, 45 min and 1.5, 4, 12, 36 h ($n = 3$ rats) or at 30 min and 1, 2, 8, 24, 48 h ($n = 3$ rats) after BPA administration. Blood samples were obtained before