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Short communication

Inhibition of cytochrome P450 2E1 by propofol in human and porcine liver microsomes

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Abstract

While almost anesthetics are metabolized by the cytochrome P450 (CYP) 3A4, some major volatile ones such as halothane and sevoflurane are metabolized by CYP2E1 in humans. To determine whether 2,6-diisopropylphenol (propofol), a widely used intravenous anesthetic agent, known to inhibit CYP3A4 and CYP1A2, also inhibits CYP2E1, 6-OH hydroxylation of chlorzoxazone, a prototypical CYP2E1 substrate, was estimated using two pools of human microsomes and one pool of porcine microsomes from seven livers. Basal human enzyme activities were characterized by a V_{max} of 1426 ± 230 and 288 ± 29 pmol min^{-1} mg^{-1} protein and a K_m of 122 ± 47 and 149 ± 42 μM, while the corresponding porcine activities were associated with a V_{max} of 352 ± 42 pmol min^{-1} mg^{-1} protein and a K_m of 167 ± 38 μM. A competitive inhibition of CYP2E1 by propofol was observed with low inhibition constants in the therapeutic range in both porcine (19 μM) and human (48 μM) liver microsomes. These *in vitro* results suggest that propofol could have a protective effect on toxic metabolite activation of compounds catalyzed by CYP2E1.

Keywords: Propofol; Cytochrome P450 2E1; Human; Pig; Liver microsomes; Chlorzoxazone

1. Introduction

Various CYPs have been reported to be involved in metabolism of anesthetics in humans [1]. CYP3A4 appears to be the most frequently implicated enzyme; however several volatile anesthetics such as halothane and sevoflurane are converted to oxidized metabolites by CYP2E1 [2]. Some anesthetics are also CYP inhibitors. Thus, propofol, a widely used intravenous anesthetic agent, has been shown to inhibit *in vitro* CYP3A4 [3,4] and CYP1A2 [3]. Moreover, two human studies have reported a possible influence of propofol on alfentanil clearance, that is predominantly metabolized by CYP3A4, with higher plasma alfentanil concentrations than those expected [5,6]. Indeed, it has been shown that continuous intravenous administration of propofol strongly decreased the clearance of midazolam, an other well-known substrate of CYP3A4 [7], and that acute and chronic administration of propofol lowered the metabolism of aminopyrine in rats [8].

Propofol was also found to inhibit CYP2E1-dependent activity in hamster and rat [9,10] and to decrease aniline oxidation, a CYP2E1-dependent reaction, in human liver microsomes but only with a high substrate concentration [11]. CYP2E1 accounts for 1–10% of total liver proteins with a wide interindividual variability; it is involved in metabolism of more than 100 chemicals, including carcinogens and a variety of endogenous compounds and is induced by alcohol, fasting, diabetes, and obesity [12]. Therefore, its inhibition could have important clinical implications.

The scarcity and unpredictable availability of fresh human liver samples limit their use in pharmacotoxicological research. Pig is often considered as an appropriate animal model [13] and is used for experimental [4] and clinical investigations on anesthetics [14]. Several studies have demonstrated that porcine hepatocytes express major phase 1 and 2 drug metabolizing enzymes [13,15,16].

This study was aimed to determine whether propofol is a potent CYP2E1 inhibitor at therapeutic concentrations. To

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Abbreviations: CYP, cytochrome P450; CLX, chlorzoxazone; 6-OH-CLX, 6-OH-chlorzoxazone.

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address this question, the effect of propofol on 6-OH hydroxylation of chlorzoxazone (CLX), a prototypical substrate of CYP2E1, was tested using human and porcine liver microsomes. Our results show that propofol inhibited CLX oxidation at therapeutic concentrations by a competitive mechanism.

2. Materials and methods

2.1. Chemicals

CLX and furafylline were products from Sigma Chemicals Co. NADPH and propofol were purchased from ICN Biomedicals. 6-OH-clorzoxazone (6-OH-CLX) was kindly provided by Biopredic. All other chemicals were of analytical grade and commercially obtained.

2.2. Materials

Human liver samples were obtained from patients undergoing liver resection for primary or secondary hepatomas. Access to this material was in agreement with French laws and fulfilled the requirements of our local Institutional Human Investigation Committee. Animal liver samples were obtained from large White/Pietrin female pigs, 2-month-old, weighing 20–25 kg (I.N.RA.) in compliance with French regulations for experimental animals and with the approval of our Institutional Animal Investigation Committee. Pig and human liver microsomal fractions were prepared according to a standard procedure [17]. Briefly, liver samples were homogenized in 50 mM Tris buffer (pH 7.4) containing 1 mM EDTA and 0.25 M sucrose and centrifuged (at 1800 *g*, 4°, 10 min then at 11,000 *g*, 20 min). After centrifugation of the supernatant (75,000 *g*, 4°, 1 hr), the resulting microsomal pellet was suspended in 0.1 M sodium chloride phosphate buffer (pH 7.4) containing 10% glycerol (v/v) for storage at −80° until use.

2.3. 6-OH-hydroxylation of CLX

The 6-OH-hydroxylation of CLX was measured as previously described [18] with modifications. Hepatic microsomes (80 μg of proteins) were incubated in glass tubes at 37° for 70 min with variable concentrations of CLX and selected concentrations of propofol in order to determine enzymatic parameters. All studied compounds were added in methanol at selected concentrations with corresponding controls. Propofol dilutions were prepared on ice and in glass tubes, immediately before use and vigorously shaken. The high lipophily of propofol is known to be responsible for its absorption on the wall of tubes. This effect is considerably decreased but not eliminated by the use of glass tubes [19]. Changes in propofol concentrations were analyzed as a function of time, in the absence of NADPH in the incubates, with an initial concentration of 100 μM. Propofol concentration decreased as an exponential function of incubation time (t) following the equation [propofol concentration] = [initial concentration]$e^{-0.0082t}$ ($r^2 = 0.99$). The half-life time was 68 min. With an initial concentration of 102 μM, the residual concentration was 57 μM after 70 min. Extrapolated propofol concentrations at the end of incubation for initial concentrations of 25, 50, 75, and 100 μM were respectively 14, 28, 41, and 55 μM. A possible metabolism of propofol has been previously investigated and was demonstrated that in these experimental conditions, it was quite low, if any (data not shown). The inhibitory effect of 50 μM propofol ($28 \pm 4\%$) on CLX (200 μM) 6-hydroxylation was not influenced by the incubation time between 20 and 70 min. The reaction was initiated with the addition of 5 mM NADPH and 0.1 M potassium phosphate buffer (pH 7.4) in a 150 μL incubation and terminated by adding 10 μL ice-cold citric acid. After 1 hr at −20° and centrifugation (15 min at 1800 *g*), supernatants were transferred in plastic HPLC vials and frozen at −20° until dosage. 6-OH-CLX, residual CLX, and propofol concentrations were quantified by HPLC (Hewlett Packard Series 1100 and Waters system). The inhibition of CLX hydroxylation was studied with both CLX and propofol dissolved in methanol; the final concentration of methanol in the assay not exceeding 0.5% (v/v). Because of the low water solubility of CLX, experiments were not conducted with CLX concentrations exceeding 600 μM.

2.4. HPLC analysis

Separation and quantification of 6-OH-CLX, CLX, and propofol were carried out on a 5 μM 120 A Nucleosil C18 (Spherisorb) column (4.6 mm × 250 mm) using a modification of HPLC techniques previously described [20–22]. The mobile phase (flow rate 1 mL/min) consisted of a gradient of acetonitrile/water with 1% acetic acid. Elution was monitored by UV detection for CLX and its hydroxylated metabolite at 287 nm. Detection of propofol was performed by fluorescence with excitation at 270 nm and emission at 310 nm. Retention times for 6-OH-CLX, CLX, and propofol were respectively 5.1, 16.4, and 20.2 min. Calibration curves were performed by injecting increasing known amounts of 6-OH-CLX, CLX or propofol. Measurements of CLX, 6-OH-CLX, and propofol were linear respectively for 30–700, 3–100, and 6.25–214 μM.

2.5. Data analysis

Enzymatic activities were expressed as pmol of metabolites formed per min and per mg of microsomal proteins or as percentage of control values. Initial concentrations of CLX were calculated by the sum of both measured residual CLX and 6-OH-CLX concentrations. Kinetic enzymatic parameters were estimated using a computer program

designed for nonlinear regression analysis (GraphPad Software, Prism 3.02), according to the Michaelis–Menten equation. The apparent Michaelis–Menten constant (K_m) and the maximal velocity (V_{max}) were obtained in presence of different propofol concentrations and corresponding controls by nonlinear regression analysis of enzymatic velocity (V) vs. different CLX concentrations. Inhibition constants were determined from secondary plot of K_m/V_{max} and $1/V_{max}$ vs. 1/[propofol]. The K_i was estimated by the negative value of X-axis intercept determined by linear regression where X was propofol concentrations and Y was K_m/V_{max}. The K_is were calculated in the same manner with Y equal to $1/V_{max}$. The ratio K_m/V_{max} corresponded to the slope of Lineweaver–Burk linear regression while $1/V_{max}$ was intercept with Y-axis. However, Lineweaver–Burk linear regression was only used for graphic plot of $1/V$ vs. 1/[CLX], while kinetic parameters were more accurately determined by nonlinear regression. Data were means and standard deviations from three different experiments except as otherwise specified. Statistical analysis was performed using the Student's t-test or two-way ANOVA followed by Bonferroni post-tests as appropriate. The value $P < 0.05$ was considered as significant.

The *in vivo* effect of propofol on the hepatic clearance of CLX was extrapolated from the *in vitro* decrement of reaction velocity of 6-OH-hydroxylation of CLX, using usual therapeutic substrate and inhibitor concentrations, inhibition constant, and equation depending on the type of inhibition [23]. The prediction was made with CLX concentration previously reported [24] after oral administration of a 500 mg caplet of CLX to healthy volunteers: the maximal plasma concentration and area under the plasma CLX concentrations vs. time were respectively 65 and 200 μM hr during the first 7.5 hr following CLX ingestion. We approximated the mean CLX plasma concentration during this period as being 27 μM, assuming that plasma concentrations of propofol and CLX reflected hepatocyte concentrations. The predicted CLX residual clearances in presence of propofol were expressed as percentage of basal values.

3. Results and discussion

3.1. Human microsomes

Preliminary experiments on human liver were performed with a microsomal pool (pool A) of six human liver samples. Formation of 6-OH-CLX was linear between 30 and 90 min. Incubation with 12 μM furafylline, an inhibitor of CYP1A2, had no effect on enzymatic activity: an apparent K_m of 156 ± 33 μM and a V_{max} of 341 ± 27 pmol min^{-1} mg^{-1} were determined vs. a K_m of 149 ± 42 μM and a V_{max} of 288 ± 29 pmol min^{-1} mg^{-1} (ns) in control samples. Although not strictly a specific substrate of CYP2E1, the centrally acting muscle relaxant CLX remains the only probe for estimating CYP2E1 activity *in vivo* [25]. Indeed, the formation of some 6-OH-CLX can also be catalyzed by CYP1A2 [26]. However, the absence of effect on 6-OH-CLX activity following addition of furafylline, a specific CYP1A2 inhibitor, indicated that oxidation of CLX by CYP1A2 was quite low if any.

Inhibition experiments were conducted with five CLX concentrations: 39 ± 5; 112 ± 7; 241 ± 25; 312 ± 37, and 442 ± 79 μM on a microsomal pool of seven different human liver samples (pool B). Basal activity was characterized by a V_{max} of 1426 ± 230 pmol min^{-1} mg^{-1} of proteins and a K_m of 122 ± 47 μM. The levels of CYP2E1 in the two pooled liver samples were consistent with the large range of 2333 ± 1690 pmol min^{-1} mg^{-1} protein (extremes: <500–9600) measured in 93 human liver samples with a concentration of 400 μM of CLX [22]. The marked interindividual variability of CYP2E1 activity in human liver samples is well recognized, due, at least, in part to different induction levels caused by environmental factors such as alcohol consumption and physiopathological conditions such as diabetes, fasting, and obesity [12].

Kinetic analysis showed that propofol was a potent competitive inhibitor with a K_i of 48 μM (Fig. 1) while K_is could not be determined: V_{max} was almost constant and not altered by propofol, while the observed K_m was increased, suggesting that propofol modified the affinity

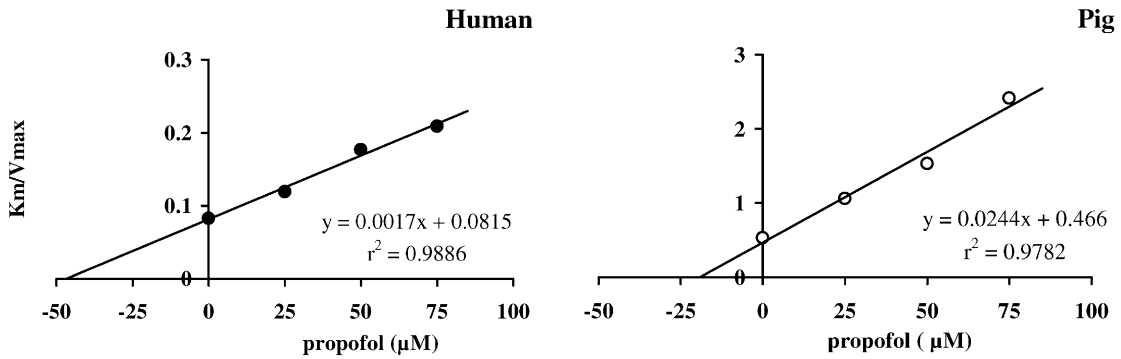

Fig. 1. Effect of propofol on 6-hydroxylation of CLX by pooled human (left graph) and porcine (right graph) hepatic pooled microsomes from seven livers. Plots of K_m/V_{max} were obtained from Michaelis–Menten nonlinear regression vs. propofol concentrations between 0 and 75 μM. Data were means from three different experiments. K_i, calculated as the negative value of X-axis intercept, was respectively 48 μM (human) and 19 μM (pig).

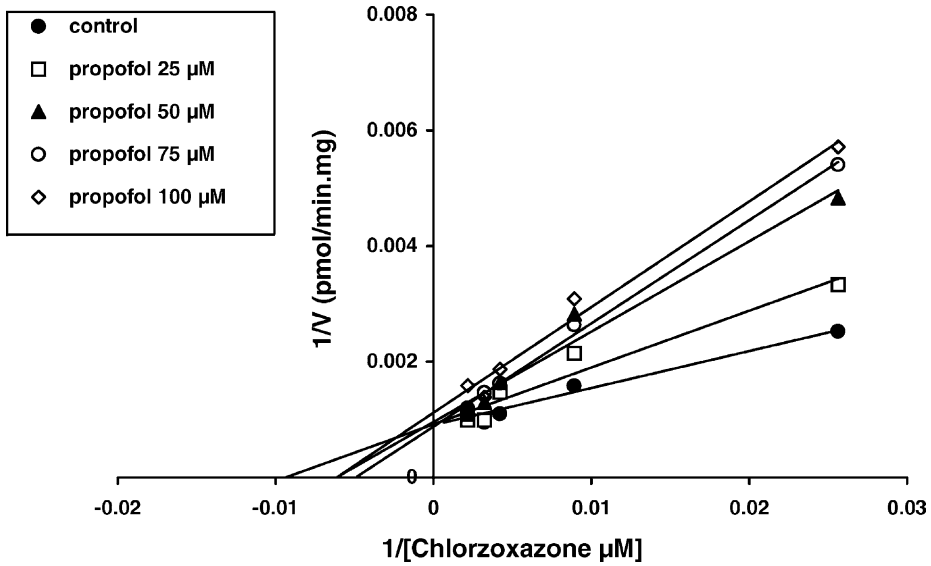

Fig. 2. Effect of propofol on 6-hydroxylation of CLX by human liver microsomes. Representation of Lineweaver–Burk linear regression for one of the three different experiments with pooled samples from seven livers. V = enzymatic activity (pmol min^{-1} mg^{-1} protein). Correlation coefficients were respectively 0.959 (control), 0.940 (25 µM), 0.967 (50 µM), and 0.996 (75 µM).

of CLX for CYP2E1 and bound to the CYP2E1 catalytic site. Lineweaver–Burk plot (Fig. 2) was consistent with a competitive inhibition. Therapeutic concentrations of propofol concentrations usually observed in adult patients range between 22 and 45 M for induction and between 17 and 34 M for maintenance of anesthesia [27].

The present study clearly demonstrates that in agreement with a previous report [11], propofol is also a CYP2E1 inhibitor and supports the view that it exerted its inhibitory effect at therapeutical concentrations by a competitive mechanism, that may result more likely from a binding to the catalytic site rather than from a competitive metabolism of two compounds by the enzyme since this compound is not known to be metabolized by CYP2E1. Propofol was recently demonstrated to be mainly oxidized by CYP2B6 [28,29].

As expected for this type of inhibition, the intensity of inhibition changed according to the substrate concentration. When CLX concentration (112 ± 7 µM) was in the range of the K_m, propofol exerted an inhibition of CLX 6-hydroxylation activity in a concentration-dependent manner (Fig. 3). For a higher CLX concentration (442 ± 79 µM), CLX 6-hydroxylation activity was only slightly inhibited. Chen *et al.* [11] found only a slight inhibition of aniline oxidation (17–21%) with 500 M of substrate. As shown with propofol, a competitive inhibitor was inactive at high substrate concentrations: it did not alter the maximal velocity and reduced the affinity of the enzyme for its substrate, as shown by an increase of the K_m.

3.2. Porcine microsomes

Inhibition experiments on pig microsomes were conducted on pooled samples from seven animals with five CLX concentrations: 81 ± 10, 162 ± 13, 345 ± 34, 443 ± 30, and 525±67 µM. Basal activity of this pooled porcine liver sample was characterized by a V_{max} of 352 ± 42 pmol min^{-1} mg^{-1} protein and a K_m of 167 ± 38 µM. Propofol also exerted a competitive inhibition in porcine microsomes. However, the inhibition constant (K_i = 19 µM) was lower than that determined in human microsomes (Fig. 1). As in human microsomes, the level of inhibition was influenced by the substrate concentration, suggesting a competitive inhibition (Fig. 3).

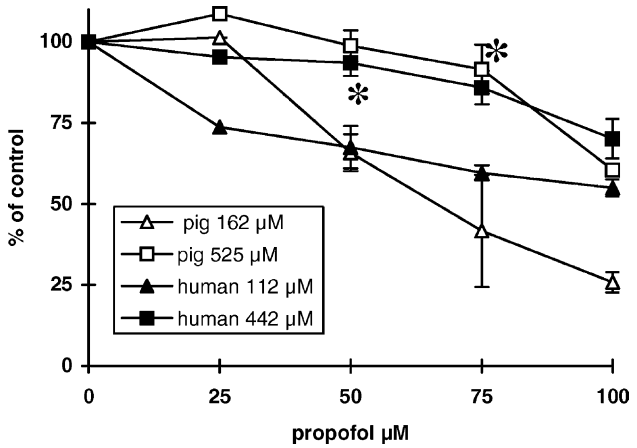

Fig. 3. Effect of propofol on 6-hydroxylation of CLX by human and porcine liver microsomes with high CLX concentrations (442 and 525 µM) or with substrate concentrations in the K_m range (112 and 162 µM). Data are expressed as the percentage of remaining activity (relative to control incubate) and are means and SEM of three different experiments with pooled samples from seven livers. Comparisons CLX 112 µM vs. 442 µM (human experiments) and CLX 162 µM vs. 525 µM (porcine experiments) by a two-way ANOVA analysis were significant. $^{*}P < 0.05$ for Bonferroni post-tests.

3.3. In vivo extrapolation from in vitro data

Prediction of a possible *in vivo* propofol–CLX interaction was performed under the assumption that the inhibition was competitive. The CLp was calculated as followed [23]: $CLp = 100(1 - [P]/([P] + K_i(1 + [CLX]/K_m))$ where [P], [CLX], and CLp were respectively propofol, CLX plasma concentrations, and predicted CLX residual clearance in presence of propofol. A significant decrease (23–43%) of the CLX hepatic clearance was predicted with propofol concentrations in the therapeutic range (17–45 M) for a 27 M CLX concentration.

CLX remains the only CYP2E1 probe that has received much clinical studies. In healthy subjects, a single oral dose of CLX followed 6 hr later by a plasma measurement of the 6-OH-CLX/CLX plasma ratio allows phenotyping CYP2E1 [25]. This ratio is increased by 150% in alcoholic patients compared with healthy subjects because of CYP2E1 induction [24]. The CLX test has been applied to detect patients with a high CYP2E1 activity justifying monitoring of the renal function when receiving sevoflurane [30].

This *in vivo* extrapolation from *in vitro* data favors the conclusion that propofol can interact with CLX at therapeutic dosages and consequently with other drugs metabolized by CYP2E1. However, such an extrapolation has some limitations since plasma concentrations of inhibitor do not always reflect hepatocyte ones, especially when as it is the case for propofol, the drug is extensively bound to proteins (96–99%) [31]. However, liver concentrations exceeding plasma ones have been reported [23] for highly lipophilic compounds exhibiting a high hepatic extraction ratio despite low unbound plasma concentrations [31].

In summary, our study demonstrated an inhibition of CYP2E1 activity in both human and pig liver, by propofol concentrations in the therapeutic range, suggesting a potential clinical interest of this anesthetic in preventing toxicity of pharmaceuticals undergoing hepatic activation through the metabolic pathway of CYP2E1. Although similar results are found in both species, additional data are needed to substitute porcine microsomes to human ones.

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