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REVIEW

Pharmacokinetic variability of phenobarbital: a systematic review of population pharmacokinetic analysis

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Abstract

Aims and background Population pharmacokinetics with Bayesian forecasting provides for an effective approach when individualized drug dosing, while phenobarbital is a narrow therapeutic index drug that requires therapeutic drug monitoring. To date, several population pharmacokinetic models have been developed for phenobarbital, these showing a number of significant predictors of phenobarbital clearance and volume of distribution. We have therefore conducted a systematic review to summarize how these predictors affect phenobarbital pharmacokinetics as well as their relationships with pharmacokinetic parameters.

Method A systematic search for studies of phenobarbital population pharmacokinetics that were carried out in humans and that employed a nonlinear mixed-effect approaches was made using the PubMed, Scopus, CINAHL Complete, and ScienceDirect databases. The search covered the period from these databases' inception to March 2020.

Results Eighteen studies were included in this review, all of which used a one-compartment structure. The estimated phenobarbital clearance and volume of distribution ranged from 0.0034 to 0.0104 L/h/kg and 0.37 to 1.21 L/kg, respectively, with body weight, age, and concomitant antiepileptic drugs being the three most frequently identified predictors of clearance. Most models were validated through the use of an advanced internal approach.

Conclusion Phenobarbital clearance may be predicted from previously developed population pharmacokinetic models and their significant covariate-parameter relationships along with Bayesian forecasting. However, when applying these models in a target population, an external evaluation of these models using the target population is warranted, and it is recommended that future research be conducted to investigate the link between population pharmacokinetics and pharmacodynamics.

Keywords Phenobarbitone · Phenobarbital · Population pharmacokinetics · Systematic review · Nonlinear mixed-effect

Background

Phenobarbital, a conventional antiepileptic drug (AED), is commonly used for the treatment of generalized and partial seizures, and though its use has declined in favor of the new generation of AEDs, phenobarbital is still widely used for the treatment of neonatal seizures [1], as well as the prevention of neonatal hyperbilirubinemia [2]. In the past, it was also widely used for the prophylaxis of febrile convulsion [3].

Phenobarbital can be administered through a number of different routes including oral, intravenous, intramuscular, or rectal administration [3]. The rate of phenobarbital absorption may be influenced by drugs or diseases that affect gastrointestinal motility [4] but following oral or rectal dosing, approximately 90% of phenobarbital is bioavailable [4–6]. Phenobarbital distributes to all body tissues, and the volume of distribution (V_d) ranges from 0.5 to 1 L/kg [4]. Newborns have slightly higher V_d (0.9 L/kg) [3, 7] than children and adults (0.7 L/kg) [8]. Brain concentrations are well correlated with those of the plasma, and these have ratios ranging from 0.7 to 1 [9, 10]. Phenobarbital primarily binds to albumin, with a differential degree of binding depending on age [4],

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and the drug is then extensively metabolized by the liver utilizing cytochrome P450 (CYP) 2C9, CYP2C19, and CYP2E1, followed by conjugation or N-glucosidation [11, 12], with approximately 20–40% of the drug is eliminated by renal excretion [4, 5]. However, genetic polymorphisms of CYP2C9 and CYP2C19 may affect phenobarbital clearance (CL_{PB}) [13, 14], and the CL_{PB} varies across age groups, with the elderly having the lowest CL_{PB} (0.003 L/kg/h), followed by adults and neonates (0.004 L/kg/h), and children (0.008 L/kg/h). In addition to genetic polymorphisms and age, CL_{PB} can be affected by body size [13–27], and the presence of certain other drugs [14–18, 20, 28].

Phenobarbital has a narrow therapeutic index, with a suggested therapeutic range of 15–40 mg/L [5], although the optimal use of phenobarbital is complicated by its significant pharmacokinetic variation among subjects [4], and therefore, therapeutic drug monitoring (TDM) during phenobarbital therapy is warranted. The traditional approach used to determine phenobarbital dosage regimens is based on average pharmacokinetic parameters obtained from the traditional pharmacokinetic approach conducted in a selected population. However, such an approach might not be appropriate for some group, where significant intersubject variation exists and thus a population pharmacokinetic-based approach has been introduced to determine the population pharmacokinetic parameters and to identify any significant factors influencing drug pharmacokinetics. This approach, when combined with Bayesian forecasting, offers substantial benefits in optimizing drug therapy since it provides flexibility in clinical situations, e.g., non-steady-state concentrations or clinically unstable patients, while also allowing individual characteristics to be incorporated into the estimation of pharmacokinetic parameters [29, 30]. To date, a number of phenobarbital population pharmacokinetic models have been built and different predictors of CL_{PB} have been identified [13–28, 31, 32], and so we aim to summarize these and the significant covariates influencing phenobarbital pharmacokinetic parameters across different populations, as well as to identify any knowledge gaps that exist and that may necessitate further investigation.

Methods

Search strategy

A systematic search for phenobarbital population pharmacokinetic studies was performed using the PubMed, Scopus, ScienceDirect, and CINAHL Complete databases for the entire timespan from their inception to March 2020. The search terms employed are as follows: (phenobarbital OR phenobarbitone OR phenobarb*) AND ("population pharmacokinetics*" OR "nonlinear mixed effect" OR NONMEM)). To ensure a completeness of the search, references from identified articles were also reviewed.

Inclusion criteria and exclusion criteria

Studies were included in this systematic review if they were (1) conducted on humans, (2) based on the use of phenobarbital as a treatment, and (3) population pharmacokinetic studies employing a nonlinear mixed-effect approach. Reviews, methodology studies, expert opinions, or case reports, as well as studies that did not include model development process, were excluded. Non-English language articles were also excluded.

Data extraction

The following information was independently extracted by both reviewers: (1) study characteristics, e.g., study design, study site, sample size; (2) population characteristics, e.g., age, measurement of body size, gender, race, health conditions; (3) treatment regimens and pharmacokinetic data, e.g., phenobarbital daily dose, dosing interval, phenobarbital formulations, route of administration, sampling strategy, and phenobarbital concentration assay; and (4) population pharmacokinetic analyses, e.g., structural and statistical models, estimated parameters, significant predictors and their relationship with pharmacokinetic parameters, and model validation. In addition, the estimated population clearance values of the final population pharmacokinetic models were calculated using the mean weights of 3 kg, 20 kg, and 60 kg for neonates, children, and adults, respectively, with the exception of the study that fixed these values at those of the published literature. These values were graphically summarized for all studies.

For studies with the number of phenobarbital concentrations per patient of < 6, the sampling strategy was classified as a sparse approach, whereas for those with the number of phenobarbital levels of ≥ 6, the sampling strategy was defined as an extensive approach. The total number of samples divided by the number of subjects was used for the studies that did not report the number of samples per patient. As for model evaluation, three categories, namely, basic internal, advanced internal, and external evaluation, described by Brendel et al. [33], were used to summarize the data.

Quality assessment

Selected checklist items developed by Kanji et al. [34], Dartois et al. [35], and Abdel-Jalil et al. [36] were used to assess the quality of the published population pharmacokinetic models of phenobarbital.

Results

Study identification and characteristics

The systematic literature search identified 1710 non-redundant articles, and after filtering with the inclusion and exclusion criteria, 18 out of 62 articles were included in this review, all of which were published between 1985 and 2018. The reasons for excluding studies are presented in the PRISMA diagram (Fig. 1).

The overall aim of most population pharmacokinetic studies of phenobarbital has been to identify factors influencing phenobarbital pharmacokinetics and to provide population estimates of the pharmacokinetic parameters. Four studies specifically aimed to determine the effect of polymorphisms of CYP450 on CL_{PB} [13, 14, 20, 23], while two studies evaluated the effect of therapeutic hypothermia on phenobarbital pharmacokinetics [24, 25], with one of these [24] determined the influence of therapeutic hypothermia on phenobarbital pharmacodynamics. In addition, one study aimed to determine the absolute bioavailability of phenobarbital in neonates and infants [32], while another determined the effectiveness of enteral phenobarbital administered via a nasogastric tube in the treatment of childhood status epilepticus [21].

The number of studies conducted prospectively and retrospectively was approximately equal, and only two were multicenter studies [24, 25]. All studies were conducted either in Asia [13–15, 17–20, 22, 23] or in Europe [16, 21, 24–28, 31, 32], and overall, the studies had a median sample sizes of 62 (with a range of 16–539) and a median number of phenobarbital samples of 144 (with a range of 31–1002). Three studies were conducted solely on adults [13, 20, 28], three were carried out on both pediatrics and adults [14, 15, 18], and the remainder were performed on pediatrics. Table 1 summarizes the characteristics of the included studies.

Pharmacokinetic data

Though the majority of the studies developed their models using data drawn exclusively from oral administration

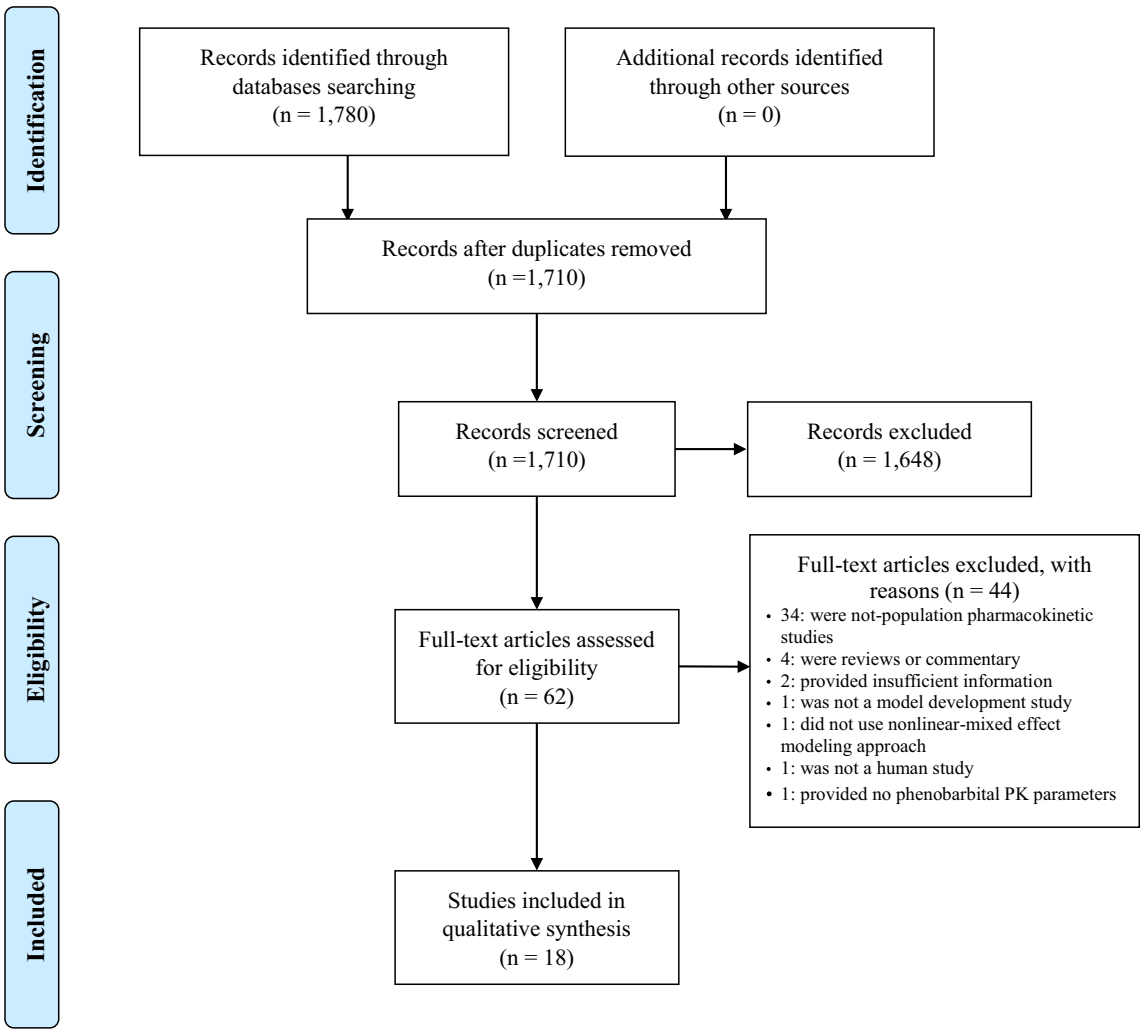

Fig. 1 A PRISMA diagram of the study identification

Table 1 Characteristics of the studied population

No	Study	Country	Center	N	Male (%)	Female (%)	Mean age (range)	Mean weight (range)	Patient characteristics	Co-medication causing drug nteraction	Genotypes
1	Grasela et al. 1985 [31]	USA	Single	59	35 (59.3)	24 (40.7)	GA: 31.0 ± 4.1 weeks (24–42 weeks)	1.52 ± 0.7 kg (0.6–3.62 kg)	Neonates in ICU receiving PB for prevention of intraventricular hemorrhage and treatment of seizure	NR (the majority received PB monotherapy)	No
2	Yukawa et al. 1992 [15]	Japan	Single	Total: 539 PB: 222 PB + AEDs (no VPA): 136 PB + AEDs (with VPA): 181	286 (53.1)	253 (47.0)	PB: 8.67 ± 5.6 years PB + AEDs (no VPA): 12.63 ± 6.65 y PB + AEDs (with VPA): 11.88 ± 5.78 years	PB: 27.98 ± 16.17 kg PB + AEDs (no VPA): 36.36 ± 16.55 kg PB + AEDs (with VPA): 34.33 ± 17.29 kg	Pediatrics and adults with epilepsy	VPA, other AEDs	No
3	Botha et al. 1995 [16]	South Africa	Single	32	24 (75)	8 (25)	5.5 ± 3.2 years	20.4 ± 9.6 kg	African and Indian children	VPA	No
4	Chan et al. 1997 [17]	Hong Kong	Single	65	24 (36.9)	41 (63.1)	8.84 ± 4.09 years (2.5–16 years)	15.44 ± 5.29 kg (7–30 kg)	Inpatients, severe psychomotor and growth retardation, unable to walk or feed themselves	CBZ, CBZ + PHT, PHT	No
5	Yukawa et al. 1998 [18]	Japan	NR	349 PB: 222 PB + CBZ: 63 PB + VPA: 64	[37]	[38]	10.4 ± 6.4 years (0.4–33.3 years	32.0 ± 17.7 kg (6.0–93.0 kg)	Pediatric and adult epileptic patients	CBZ, VPA	No
6	Mamiya et al. 2000 [13]	Japan	Single	74	42 (56.8)	32 (43.2)	50.5 ± 13.4 years (17–76 years)	59.0 ± 11.0 kg (35–85 kg)	Adult patients with epilepsy	CBZ, ZNS, DZP, CZP, NZP, acetazolamide, sulthiame, acetylpheneturide	No
7	Yukawa et al. 2005 [19]	Japan	Single	35	19 (54.3)	16 (45.7)	PNA: 20.8 ± 21.3 days (1–73) GA: 38.6 ± 2.5 weeks (30–42.1)	Current BW: 2888 ± 757.2 g (1312–5240 g) Born BW: 2812.1 ± 704.8 g (1290–4004 g)	Neonates and infants	NR	No
8	Yukawa et al. 2006 [20]	Japanese	NR	74	42 (556.8)	32 (43.2)	50.5 ± 13.4 years	59.0 ± 11.0 kg	Adult patients with epilepsy	PHT	Yes *1/*1: 53 *1/*2: 47 *1/*3: 17 *2/*2, *2/*3, *3/*3: 15
9	Goto et al. 2007 [14]	Japan	Single	79	47 (59.5)	32 (40.5)	CYP2C9*1/*1: 13.8 ± 8.9 years (0.8–43.8 years) CYP2C9*1/*3:	CYP2C9*1/*1: 35.4 ± 18.1 kg (8.5–80.2 kg) CYP2C9*1/*3:	Pediatric and adult epileptic patients	CBZ, VPA, PHT, ZNS, CZP, CLO	Yes CYP2C9 (*1/*1, *1/*3)

Table 1 (continued)

No	Study	Country	Center	N	Male (%)	Female (%)	Mean age (range)	Mean weight (range)	Patient characteristics	Co-medication causing drug nteraction	Genotypes
							12.6 ± 6.9 years (2.9–19.9 years)	31.0 ± 12.5 kg (12–42.6 kg)			CYP2C19 (*1/*1, *1/*2, *1/*3, *2/*2, *2/*3)
10	Wilmshurst et al. 2010 [21]	South Africa	Single	16	9 (56.3)	7 (43.7)	Median: 5 months (6 days-168 months)	Median: 5.8 kg (2.6–24 kg)	In patient with status epilepticus and nasogastric tube), septicemia ($n = 7$), meningitis ($n = 1$), gastroenteritis ($n = 2$), pneumonia ($n = 1$), otitis media ($n = 1$)	PHT	No
11	Yukawa et al. 2011 [22]	Japan	Single	70	39 (55.7)	31 (44.3)	PNA: 15.8 ± 18.5 days (1–73 days) GA: 38.2 ± 3.4 weeks (24.1–43 weeks)	Current BW: 2870 ± 779 g (670–5240 g) Birth BW: 2856 ± 735 g (670–4654 g)	Neonates and infants	No	No
12	Lee et al. 2012 [23]	Korea	Single	44 divided into 2 groups: gr 1 (8 days-3 months), gr 2 (4–6 months)	25 (56.8)	19 (43.2)	WT: 2.4 ± 1.9 months EM: 1.4 ± 1.6 months PM: 3.3 ± 2.5 months	WT: 5.0 ± 2.7 kg EM: 5.3 ± 4.3 kg PM: 6.4 ± 3.1 kg	Hospitalized neonates and infants	No	Yes WT (*1/*1), EM (*1/*2, *1/*3), PM (*2/*2, *2/*3):
13	Van den Broek et al. 2012 [24]	Netherlands	Multi	31	18 (58.1)	13 (41.9)	GA: 39.9 weeks (36.0–42.1 weeks)	3.62 kg (2.15–4.92 kg)	Newborns with gestational age of at least 36 weeks	No	No
14	Shellhaas et al. 2013 [25]	USA	Multi (reviewed from Vermont-Oxford Database)	39	24 (61.5)	15 (38.5)	GA: 39.5 ± 1.7 weeks	Birth WT: 3493 ± 578 g	Neonates with gestational age > 36 weeks treated for seizures with PB diagnosed with HIE	NR	No
15	Marsot et al. 2014 [32]	France	NR	48	29 (60.4)	19 (39.6)	GA:37.1 ± 3.3 week (27–42 weeks) PNA: 26.8 ± 64.0 days (0–206 days)	4.26 ± 3.19 kg (0.7–10 kg)	Neonates and young infants in ICU	No	No
16	Vucicevic et al.	Serbia	Single	136	69 (50.7)	67 (49.3)	42.4 ± 13.0 y	73.04 ± 14.20 kg	Adult outpatients diagnosed	VPA, CBZ, TPM, LTG	No

Table 1 (continued)

No	Study	Country	Center	N	Male (%)	Female (%)	Mean age (range)	Mean weight (range)	Patient characteristics	Co-medication causing drug nteraction	Genotypes
	2015 [28]								epilepsy on mono-, or co-therapy with PB		
17	Voller et al. 2017 [26]	Netherlands	Single	53	NR	NR	Retrospective: GA: 37 weeks (24–42 weeks) Retrospective: PNA: 4.5 days (0–22 days) Prospective: GA: 25 weeks (24–31 weeks) Prospective PNA: 15 days (1–76 days)	Retrospective: 2.7 kg (0.45–4.5 kg) Prospective: 1.07 kg (0.63–4.7 kg)	Neonates younger than 35 days	NR	No
18	Moffett et al. 2018 [27]	USA	Single	355	(50.3)	(49.7)	GA: median 39 week age: median 0.28 y PMA: median 50.6 years	Median: 4.9 kg	Children aged < 19 on IV or oral PB	F-PHT, OXC ZNS, TPM, MIDAZ PHT, LTG, VPA, RFP, FBM, VGB, LPZ, FCZ, PANTOP, MTZ	No

AEDs antiepileptic drugs, *CBZ* carbamazepine, *CLO* clobazam, *CZP* clonazepam, *DZP* diazepam, *EM* extensive metabolizer, *FBM* felbamate, *FCZ* fluconazole, *F-PHT* fosphenytoin, *GA* gestational age, *HIE* hypoxic-ischemic encephalopathy, *ICU* intensive care unit, *IV* intravenous, *LPZ* lansoprazole, *MIDAZ* midazolam, *MTZ* metronidazole, *N* sample size, *NR* not reported, *NZP* nitrazepam, *OXC* oxcabazepine, *PB* phenobarbital, *PHT* phenytoin, *PM* poor metabolizer, *PNA* postnatal age, *PMA* postmenstrual age, *PANTOP* pantoprazole, *RFP* rifampicin, *TPM* topiramate, *USA* the United States of America, *VGB* vigabatrin, *VPA* valproic acid, *WT* wild type, *ZNS* zonisamide

[14–18, 20, 21, 28], four studies were conducted using only intravenous data [23–25, 31], while the rest were performed using a combination of oral and intravenous data [26, 27, 32] or a combination of oral and suppository data [19, 22]. The phenobarbital doses for the adult population ranged from 1.07 to 1.78 mg/kg/day. All studies employed data collected using a sparse sampling strategy. For the assay method, most studies quantitated phenobarbital levels using immunoassay technique. The phenobarbital dosing regimens, sampling strategy, and assay method are summarized in Table 2.

Population pharmacokinetic analyses

NONMEM software was utilized in all but two studies, which used MULTI (ELS) program [17] or WinNonMix program [14]. All the studies developed the models by employing a one-compartment structure (Fig. 2), but six used a steady-state model [13, 15–18, 20] and therefore in these, the absorption rate constant (K_a) and V_d were not estimated. The first-order absorption process was employed for all studies that used oral administration [14, 19, 21, 22, 26–28, 32]; however, most studies fixed the K_a at the literature values ranging from 3 to 50 h^{-1}, except for one study which estimated K_a at a value of 0.8 h^{-1} for phenobarbital elixir [27]. Regarding the distribution process, the estimated V_d ranged from 0.37 to 1.21 L/kg [14, 19, 21–28, 31, 32], although one study fixed the V_d at 0.6 L/kg due to insufficient information during the distribution phase. Phenobarbital elimination was also modeled using a first-order process, with the estimated CL_{PB} ranging from 0.0034 to 0.0104 L/h/kg.

Stepwise forward addition and/or backward elimination were the most frequently used approach in covariate testing. The influence of body size (birth weight, current weight, fat-free mass (FFM)) was the most commonly screened covariate (16 studies), followed by age (15 studies), e.g., gestational age, postnatal age, postconceptional age, and postmenstrual age, gender (12 studies), concomitant medication (8 studies), e.g., phenytoin, carbamazepine, valproic acid, lamotrigine, and topiramate, and genotyping of CYP2C9 or CYP2C19 (4 studies). Other covariates that were tested included ethnicity [16, 27], phenobarbital daily dose [23], body temperature [24, 25], Apgar score [25, 26, 31], presence of therapeutic hypothermia [24, 25], laboratory values (e.g., amino alanine transferase (ALT), aspartate aminotransferase [10], serum creatinine (SCr), blood urea nitrogen (BUN)) [23, 25–28], and other conditions, i.e., severe mental retardation [14]. Of the tested covariates, body weight was the factor that most commonly affected CL_{PB} and/or V_d to a significant degree, followed by concomitant medication, age, and genotyping, respectively, but the effect of gender was not significant in any tested models. The screened and retained covariates are summarized in Table 3 and Fig. 3.

Proportional relationship was the most commonly used statistical model for both intersubject and residual variability (Fig. 2), and the magnitude of inter-subject variability of CL_{PB} and V_d ranged from 16.6 to 44.6% and from 8.4 to 61.2%, respectively. The covariate and statistical models, as well as phenobarbital population pharmacokinetic parameter estimates, are summarized in Table 4.

Only 12 studies performed a model evaluation and only one of them evaluated the model using all evaluation approaches including basic internal, advanced internal and external evaluation [26]. External model evaluation was performed in two additional studies [15, 31], with the sample size of the external datasets ranging from 15 to 82, accounting for 15 to 32% of the model building datasets. Seven studies performed an advanced internal model evaluation [19, 21, 24, 25, 27, 28, 32], while just a single study used only the basic internal approach [16]. A summary of the model evaluation is presented in Table 4 and Fig. 2.

Quality assessment

Overall, all studies made a sufficiently comprehensive report of the relevant information in their title/abstract and background section. The items most commonly not reported in the title/abstract and background section were "the route of administration" (72%) and "pharmacokinetic data relevant to the studied drug" (44%). In the methodology section, the three items most often not identified, these being absent from more than 50% of the studies, were sample storage (88.8%), estimation method (66.7%), and sampling time (55.6%). Additionally, approximately 40–60% of the studies did not report study limitations, funding, and potential conflicts of interest. The results of the quality assessment are summarized in supplementary data.

Discussion

Personalized phenobarbital dosing can be managed using population pharmacokinetics, but to our knowledge, this is the first systematic review of population pharmacokinetics of phenobarbital that summarizes the factors influencing phenobarbital pharmacokinetics and lays out the magnitude of its variability. Our review found that all the available phenobarbital population pharmacokinetic models were conducted using a one-compartment structure, which is expected given that all studies were based on samples collected using a sparse sampling approach, with most of them were obtained at trough concentrations, thus resulting in insufficient information during the distribution phase. One study reported a relatively lower V_d (0.37 L/kg) [14] than the others, nevertheless, a clear explanation for this could not be made. Although the most common significant covariate on V_d was body weight, one

Table 2 Dosing regimens, sampling strategy, and assay methods of the included population pharmacokinetic studies of phenobarbital

No	Study	Formulation	Route	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	PB Concentration (μg/mL) Mean [range]	PB dose/day (mg/kg/day) Mean [range]
1	Grasela et al. 1985 [31]	IV	IV (push)	Sparse	NR	2–3*	160	HPLC	NR	NR	NR
2	Yukawa et al. 1992 [15]	Powder	oral	Sparse	2–6 h after morning dose	1–2*	1002	FPIA	< 10%	PB monotherapy: 13.68 ± 5.75 PB + other AEDs: 17.62 ± 6.5 PB + other AEDs + VPA: 0.49 ± 8.23	PB monotherapy: 2.93 ± 1.01 PB + other AEDs: 2.59 ± 0.96 PB + other AEDs + VPA: 2.42 ± 1.03
3	Botha et al. 1995 [16]	NR	NR	Sparse	Long after the dose	1–2*	52	EMIT, FPIA	NR	NR	NR
4	Chan et al. 1997 [17]	Syrup	oral	Sparse	Before the next dose	1–2*	74	HPLC	NR	12.53 ± 5.56	3.02 ± 1.65 [15–120]
5	Yukawa et al. 1998 [18]	Powder	oral	Sparse	2–6 h after morning dose	1–2*	648	FPIA	< 10%	Total:15.2 ± 6.5 [3.1–50.4)] PB: 13.7 ± 5.8 [4.4–42.7] PB + CBZ:16.3 ± 6.5 [3.1–50.4] PB + VPA:18.2 ± 7.3 [3.2–40.5]	Total: 2.7 ± 1.1 [0.4–7.1] PB: 2.9 ± 1.0 [0.4–7.1] PB + CBZ: 2.4 ± 1.0 [0.5–5.0] PB + VPA: 2.3 ± 1.1 [0.6–6.8]
6	Mamiya et al. 2000 [13]	NR	NR	Sparse	NR	1–2*	144	FPIA	< 10%	Total: 10.0 ± 5.06 [1.3–23.7] WT: 9.90 ± 4.3 [2.3–19.6] EM: 10.1 ± 5.30 [1.3–21.3] PM: 6.93 [1.8–23.7]	Total: 1.07 ± 0.54 [0.12–2.56] WT: 1.15 ± 0.56 [0.25–2.56] EM: 1.03 ± 0.52 [0.12–2.50] PM: 0.97 ± 0.56 [0.14–2.00]
7	Yukawa et al. 2005 [19]	Suppository, powder	Suppository, oral	Sparse	NR (measured as part of routine patient care)	1–2*	69	EMIT	< 10%	29.1 ± 21.9 [5.1–88]	12.4 ± 10.7 [3–100] mg/d
8	Yukawa et al. 2006 [20]	Tablet or granule	oral	Sparse	NR (measured as part of routine patient care)	1–2*	144	FPIA	< 10%	Total: 10.1 ± 5.04 CYP2C19*1/*1: 9.87 ± 4.37 CYP2C19*1/*2: 9.73 ± 5.36 CYP2C19*1/*3: 12.2 ± 4.5 CYP2C19*2/*2: 11.3 ± 11.1 CYP2C19*2/*3: 10.1 ± 3.92	Total: 1.07 ± 0.54 CYP2C19*1/*1: 1.15 ± 0.56 CYP2C19*1/*2: 1.01 ± 0.54 CYP2C19*1/*3: 1.10 ± 0.54 CYP2C19*2/*2: 0.97 ± 0.87 CYP2C19*2/*3: 0.97 ± 0.37
9	Goto et al. 2007 [14]	NR	NR	Sparse	NR	3–4*	260	FPIA	NR	CYP2C9*1/*1: 18.8 ± 6.7 [3.6–36.7] CYP2C9*1/*3: 23.3 ± 12.2 [8.8–39.6]	CYP2C9*1/*1: 86.3 ± 29.8 [30–235] mg/d CYP2C9*1/*3: 74.7 ± 38.4 [20–120] mg/d

Table 2 (continued)

No	Study	Formulation	Route	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	PB Concentration (μg/mL) Mean [range]		PB dose/day (mg/kg/day) Mean [range]
10	Wilmshurst et al. 2010 [21]	NR	nasogastric tube	Sparse	1 h, 4 h, 12 h, and 24 h after the dose	4	31	FPIA	NR	[10.5–65.7]		Median LD: 20 [20–80]
11	Yukawa et al. 2011 [22]	Suppository, powder	Suppository, oral	Sparse	NR (routine data monitoring)	1–2*	109	EMIT	< 10%	25.6 ± 18.6 [5.4–88]		14.8 ± 13.5 [3–100] mg/d
12	Lee et al. 2012 [23]	IV	IV	Sparse	Before the next dose	1–4	115	FPIA	NR	8 d–3 mo CYP2C19*1/*1: 29.6 [17.0–38.2] CYP2C19*1/*2, *1/*3: 27.8 [19.9–61.8] CYP2C19*2/*2, *2/*3: 24.8 [20.3–33.7]	4–6 mo 22.3 [15.3–2-6.7] 16.4 [12.7–2-9.7] 14.0 [9.1–22-.2]	CYP2C19*1/*1: LD:25.6 ± 4.6, MD: 5.1 ± 0.5 CYP2C19*1/*2, *1/*3: LD: 23.1 ± 3.4, MD: 5.0 ± 0.3 CYP2C19*2/*2, *2/*3: LD: 26.7 ± 2.8, MD: 5.1 ± 0.4
13	Van den Broek et al. 2012 [24]	IV	IV	Sparse	Long after the dose	1–4	87	FPIA	< 10%	9.0–37.1		LD: 20 [5–40]
14	Shellhaas et al. 2013 [25]	IV	IV	Sparse	NR	4–5*	164	NR	NR	NR		NR
15	Marsot et al. 2014 [32]	IV, suspen-sion	IV, oral	Sparse	NR	1–2*	94	Immunoassay	NR	26 ± 9.8 [7.0–53.3]		4.6 ± 1.6 [3.1–10.6]
16	Vucicevic et al. 2015 [28]	Tablet	Oral	Sparse	NR	1–2*	205	EMIT	NR	19.26 ± 9.003		130.2 ± 58.37 mg/d
17	Voller et al. 2017 [26]	NR	IV, Oral	Sparse	NR	4–5*	229	FPIA	< 10%	[3.2-75.2]		LD: 20 [4–40.7], MD: 3.9 [1.3–20]
18	Moffett et al. 2018 [27]	IV, Elixir	IV, Oral	Sparse	Median 6.5 h after dose (IQR: 2.9–11.1)	NR	NR	CMIA	< 5%	41.1 ± 23.9		Oral: median 2.6 [IQR:1.9–3.9] mg/kg/dose IV: median 2.6 [IQR: 2.2–4.9] mg/kg/dose

*calculated using the number of total samples and sample size

CMIA chemiluminescent microparticle immunoassay, *d* day, *EM* extensive metabolizer, *EMIT* enzyme multiplied immunoassay technique, *FPIA* fluorescence polarization immunoassay, *IQR* inter-quartile range, *IV* intravenous, *LD* loading dose, *MD* maintenance dose, *mo* month, *NA* not applicable, *NR* not reported, *PM* poor metabolizer, *WT* wild type

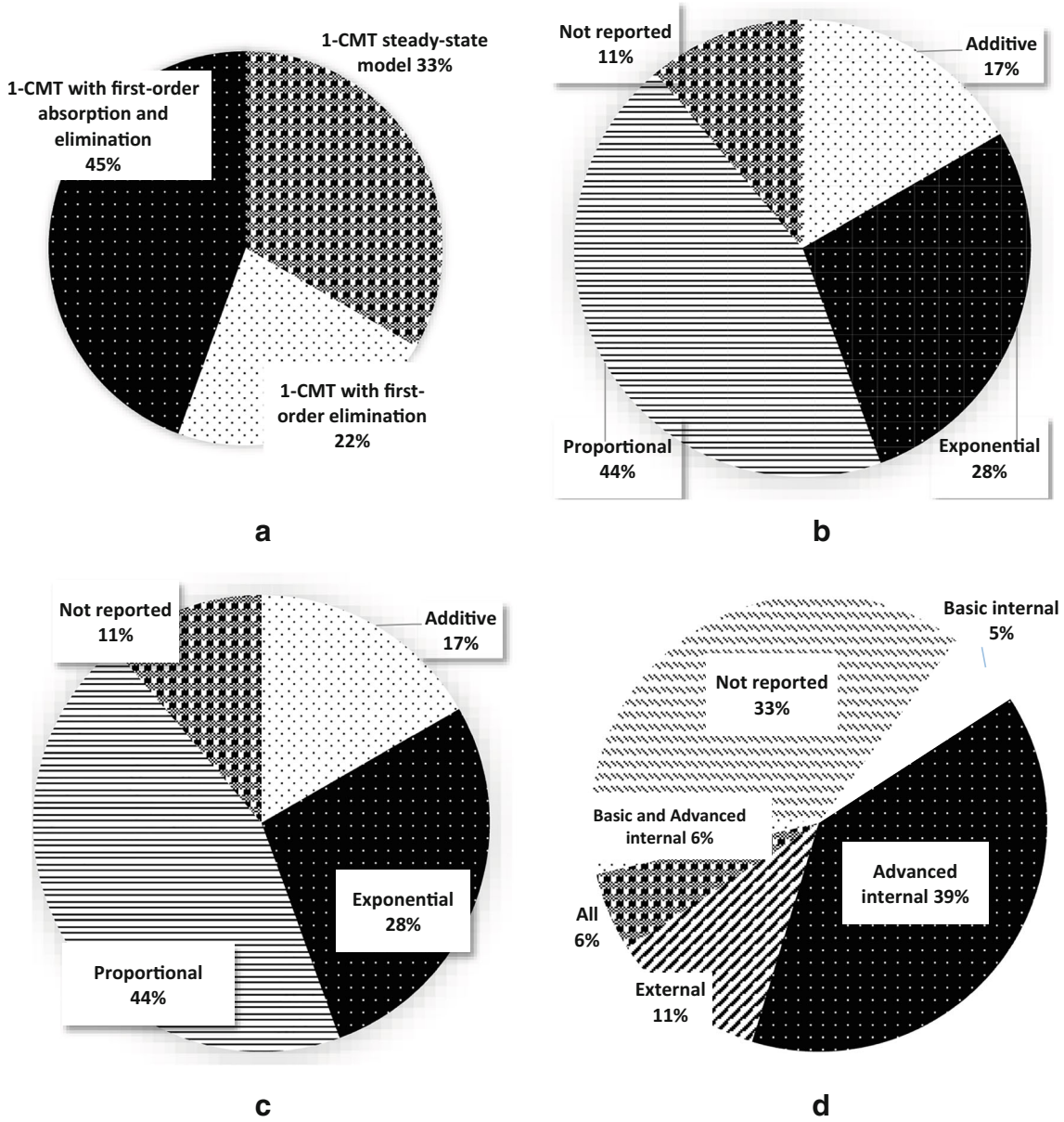

Fig. 2 The information on the structural models (**a**), statistical models (inter-individual (**b**), and residual (**c**) variability), and model evaluation (**d**) described in the included studies

study accounted for the effect of body size using FFM based on the greater reduction of the objective function value. However, such covariate might not be easily applied in clinical settings. Further, one study reported that a 5-min Apgar score of less than 5 resulted in an increase in V_d by 13% [31], which could be explained by the metabolic acidosis, resulted from asphyxia [39]. Phenobarbital is a weak acid with a pKa of 7.3, thus variations in blood pH can affect the V_d of phenobarbital, with the decrease in blood pH resulting in a significant increase in V_d of phenobarbital [40, 41]. However, other studies did not find such an effect on V_d [25, 26], and the Apgar score alone cannot be used as evidence for asphyxia [42], but despite this, a 5-min Apgar score of less than 5 had a high degree of concordance with metabolic acidemia [39] which could explain the 13% increase in V_d observed by Grasela et al. [31]. Waddell et al. also reported a significant increase in V_d of phenobarbital due to a decrease in blood pH [41], and further studies should be conducted to confirm this result. As for the effect of age on V_d, inconsistent results were reported, these showing either a decrease [27] or a less than proportional increase with increasing age [23]. In general, neonates and infants have a relatively large V_d compared to adults and elderly [4] which may be due to decreased binding to plasma proteins [43].

As regards CL_{PB}, body size was the most commonly identified significant covariate of this parameter, with one study

Table 3 Screened and significant covariates in the population pharmacokinetics of phenobarbital

No	Study	Screened covariates					
		Body size	Age	Gender	Race	Concomitant medication	Genotype
1	Grasela et al. 1985 [31]	√ (Birthweight)	√(GA)	√			
2	Yukawa et al. 1992 [15]	√ (TBW)	√			√ (AEDs)	
3	Botha et al. 1995 [16]	√ (TBW)	√	√	√	√ (PHT, CBZ)	
4	Chan et al. 1997 [17]	√ (TBW)	√	√		√ (PHT, CBZ)	
5	Yukawa et al. 1998 [18]	√ (TBW)	√	√		√ (VPA, CBZ)	
6	Mamiya et al. 2000 [13]	√ (TBW)					√
7	Yukawa et al. 2005 [19]	√ (TBW)	√ (GA, PNA, PCA)	√			
8	Yukawa et al. 2006 [20]	√ (TBW)				√ (PHT)	√
9	Goto et al. 2007 [14]	√ (TBW)	√	√		√ (PHT, VPA)	√
10	Wilmshurst et al. 2010 [21]						
11	Yukawa et al. 2011 [22]	√ (TBW)	√ (GA, PNA, PCA)	√			
12	Lee et al. 2012 [23]	√ (TBW)	√	√			√
13	Van den Broek et al. 2012 [24]	√ (TBW)					
14	Shellhaas et al. 2013 [25]	√ (TBW)*	√ (GA, PNA)				
15	Marsot et al. 2014 [32]		√ (GA, PNA)	√			
16	Vucicevic et al. 2015 [28]	√ (TBW)	√	√		√ LTG, TPM, CBZ, VPA	
17	Voller et al. 2017 [26]	√ (birthweight, TBW, height)	√ (GA, PNA)	√			
18	Moffett et al. 2018 [27]	√ (FFM)	√ (actual age, PMA)	√	√	√ (PHT, MDZ, PANTOP)	

No	Screened covariates	Significant covariates					
	Other	Body size	Age	Gender	Concomitant medication	Genotype	Other
1	Apgar score						Apgar score
2		√ (TBW)			√ (AEDs)		
3		√ (TBW)			√ (PHT, CBZ)		
4		√ (TBW)			√ (PHT, CBZ)		
5		√ (TBW)			√ (VPA, CBZ)		
6		√ (TBW)				√ (CYP2C19 PM)	
7		√ (TBW)	√ (PNA)				
8		√ (TBW)			√ (PHT)	√ (CYP2-C19*1/*3,*2/*2,*2/*3)	
9	√ (SMID)	√ (TBW)			√ (PHT, VPA)	√ (CYP2C9*1/*3)	√ (SMID)
10							
11	√ Neonates-infants clearance factor	√ (TBW)	√ (PNA)				

Table 3 (continued)

							√ (PB conc > 50 μg/mL)
12	PB dose, Lab (ALT, AST, TP, ALB, BUN, SCr)	√ (TBW on CL and V_d)	√ (on V_d)				
13	Body temperature						
14	LFT, Apgar scores, therapeutic hypothermia	√* (on CL and V_d)	√ (PNA on CL)				
15							
16	Lab (ALT, AST, SCr)				√ (VPA)		
17	LFT, RFT, APGAR score	√ (birthweight on CL, TBW on V_d)	√ (PNA on CL)				
18	SCr, Urine output, AST, ALT, body temp, ALB, BUN	√ (FFM on CL and V_d)	√ (PMA on CL, actual age on V_d)			√ (PHT, MIDAZ, PANTOP)	√ Scr

*allometric scaling

ALT alanine aminotransferase, *ALB* albumin, *AST* aspartate aminotransferase, *BUN* blood urea nitrogen, *CBZ* carbamazepine, *CL* clearance, *CYP2C19 PM* CYP2C19 poor metabolizers, *FFM* fat free mass, *GA* gestational age, *LFT* liver function test, *LTG* lamotrigine, *MIDAZ* midazolam, *PANTOP* pantoprazole, *PB* phenobarbital, *PCA* postconceptional age, *PHT* phenytoin, *PMA* postmenstrual age, *PNA* postnatal age, *RFT* renal function test, *SCr* serum creatinine, *SMID* severe mental retardation, *TBW* total body weight, *TP* total protein, *TPM* topiramate, V_d volume of distribution, *VPA* valproic acid

reporting on the significance of FFM for CL_{PB} and a further fourteen doing so for body weight. The influence of body size on CL_{PB} was mostly explained using a power relationship [13–15, 18, 20, 23–25, 27, 32], while two studies used an exponential [16, 17], and the other three utilized a linear relationship [26]. The effect of weight on CL_{PB} is variable, with some studies showing a decrease in CL_{PB} with an increase in body weight [13, 15–18, 20]. No definite explanation could be made on this finding, but it may be due to the decrease in liver volume per unit of body weight that occurs during childhood with increasing age [44] or it might be due to the decrease in the intrinsic activity of the liver with greater age [45]. In contrast, some studies found an increase in CL_{PB} with body weight [14, 19, 22] which could be explained by the maturation of liver enzymes with higher weight.

Age was a significant covariate of CL_{PB} in children, neonates, and infants [19, 22, 23, 25–27], with CL_{PB} shown to increase with age. This is unsurprising since a greater age is related to hepatic enzyme maturity in these populations, for example, with equal bodyweight, an older newborn should have a higher CL_{PB} than a younger newborn, and phenobarbital dose should be increased accordingly.

Co-administration of phenobarbital with phenytoin, carbamazepine, or valproic acid significantly decreased CL_{PB} [14–18, 20, 27, 28]; however, due to the difference of population characteristics among studies, a comparison of the magnitude of drug-drug interaction across studies was not performed. As expected, the concomitant administration of phenobarbital with valproic acid, a CYP450 inhibitor, reduced CL_{PB}. This effect is well described elsewhere [46–48], but the effects of phenytoin, a CYP450 inducer, on phenobarbital levels are controversial [49]. Some studies reported an increase in phenobarbital levels [38, 50], whereas another study failed to observe any significant elevation [51]. Nonetheless, results from population pharmacokinetic models confirm the former finding, and this may be rationalized by the competitive inhibition of phenobarbital hydroxylation by phenytoin [37, 52]. Similar to the effect of phenytoin, the influence of carbamazepine on phenobarbital pharmacokinetics is inconclusive. Some studies reported no effect of carbamazepine on phenobarbital levels in adults [53, 54], while the other reported a decrease in CL_{PB} when co-administered with carbamazepine in children [55], and results from population pharmacokinetic studies support the view that when carbamazepine is administered concurrently, this reduces phenobarbital clearance. Notably, Yukawa et al. proposed that the effects of carbamazepine on CL_{PB} are maximal in early childhood, and decline in a weight-based fashion in children, with only minimal changes found in adults [18]. Further, one study found a 24% decrease in CL_{PB} when co-administered with midazolam, and about 25% increase in CL_{PB} when co-

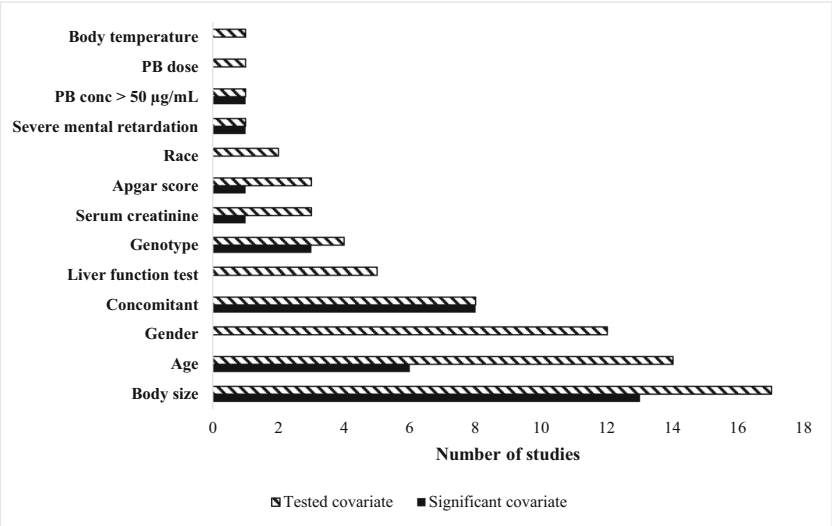

Fig. 3 Tested and significant covariates described in the included studies

administered with pantoprazole [27]. Midazolam is a substrate of CYP3A4 which is not associated with phenobarbital metabolism [56]; therefore, future studies should be conducted to confirm this finding. As for pantoprazole, it is known to induce CYP2C19 [57]; hence, an increase in CL_{PB} is expected when co-administered with this drug.

Two population pharmacokinetic studies [13, 20] showed a significant decrease in CL_{PB} in the poor metabolizers (*CYP2C19*2/*2*, *CYP2C19*2/*3*) compared to the homozygous (*CYP2C19*1/*1*) or heterozygous (*CYP2C19*1/*2*, *CYP2C19*1/*3*) extensive metabolizers. In addition, a lower CL_{PB} was observed in the heterozygous group, compared to that of the homozygous extensive metabolizers. However, it should be noted that these two studies excluded the effects of *CYP2C9* polymorphisms (*CYP2C9*1/*1* vs *CYP2C9*1/*3*) from the analysis. In contrast to these results, another study found no significant effect of *CYP2C19* polymorphisms on CL_{PB} after accounting for the effect of *CYP2C9* polymorphisms [14]; nonetheless, the number of subjects with *CYP2C9*1/*3* was relatively small and no model validation was performed. Given the limitations of the aforementioned studies, the influence of *CYP2C9* and *CYP2C19* polymorphisms should be confirmed simultaneously with larger sample size. Such findings will be of importance in individualized phenobarbital therapy, particularly when adjusting dosage regimes for patients from a diverse range of ethnic backgrounds.

Phenobarbital is eliminated by both hepatic metabolism and renal excretion, with the magnitude of the latter varying by approximately 20–40% in subjects with normal renal function [4]. Of all the published population pharmacokinetics of phenobarbital, only one found that renal function (represented as serum creatinine) had a significant effect on CL_{PB} [27], and as expected, this showed a linear decrease in CL_{PB} with an increase in serum creatinine.

Therapeutic hypothermia is a treatment commonly used for neonates with hypoxic-ischemic encephalopathy (HIE), and at times, phenobarbital is administered to a patient undergone therapeutic hypothermia experiencing seizures, but no significant effect of therapeutic hypothermia on phenobarbital pharmacokinetics could be identified [24, 25]. However, by employing a pharmacokinetic/pharmacodynamic model, van den Broek found that administration of phenobarbital to asphyxiated newborns under hypothermia resulted in the reduction of transition rate from a continuous normal voltage (CNV) to discontinuous normal voltage amplitude-integrated electroencephalography background level, providing evidence of neuroprotection of phenobarbital in infants with a CNV pattern [24].

The estimated population CL_{PB} values for phenobarbital monotherapy are graphically presented in Fig. 4. Though a direct comparison of CL_{PB} among studies could not be made given different patients' characteristics, there is a trend that CL_{PB} is higher in children than in adults or neonates, which could be due to the developmental changes in children's organs of elimination, although, as previously mentioned, the higher CL_{PB} in children than in adults could be explained by the decrease in liver volume per unit of body weight that occurs with increasing age [44].

With regard to the quality of the studies reviewed, two significant items relevant to population pharmacokinetic analysis were missing, these being sampling time and the estimation method, which have significant impacts on the repeatability and validity of the models. In terms of the model evaluation, most studies employed advanced internal evaluation; therefore, the generalizability of the developed models is not warranted. To apply such models in real clinical settings, an external evaluation using the target population is required.

Table 4 A summary of population pharmacokinetic models of phenobarbital

No	Author	Model	Software	Equation	IIV
1	Grasela et al. 1985 [31]	1 CMT with first-order elimination	NONMEM	CL (L/h/kg) = 0.0047 V (L/kg) = 0.96 + Apgar score*(13.5) Apgar score < 5 = 1, 0 otherwise	Additive of log transformed
2	Yukawa et al. 1992 [15]	1 CMT steady-state	NONMEM	PB monotherapy: CL/F (mL/kg/h) = 61*TBW$^{(-0.613)}$ PB + other AEDs: CL/F (mL/kg/h) = 19.4*TBW$^{(-0.345)}$ PB + other AEDs + VPA: CL/F (mL/kg/h) = 22.9*TBW$^{(-0.467)}$	Additive of log transformed
3	Botha et al. 1995* [16]	1 CMT steady-state	NONMEM (version 4)	CL (L/h) = [exp(0.029*WT-2.53)]*M M = 1 for monotherapy, 0.62 if VPA is present, 0.87 if CBZ or PHT are present	Additive
4	Chan et al. 1997 [17]	1 CMT steady-state	MULTI (ELS) program for microcomputer	CL/F (L/d/kg) = 0.830^{M}*exp(−0.479–0.057*WT) M = 1 for CBZ or PHT M = 0 for monotherapy	Exponential
5	Yukawa et al. 1998 [18]	1 CMT steady-state	NONMEM (version 4)	CL/F (mL/kg/h) = 52.3*TBW$^{(-0.567)}$*CO CO = 1 for PB monotherapy, 46.4$^{(-1/TBW)}$ for PB + CBZ, 0.642 for PB + VPA	Proportional
6	Mamiya et al. 2000 [13]	1 CMT steady-state	NONMEM (version 4)	CL/F (mL/kg/h) = 4.46*(TBW/60)$^{-0.633}$ * 0.812^{PM} PM = 1 for poor metabolizer of CYP2C19, 0 for extensive metabolizer of CYP2C19	Proportional
7	Yukawa et al. 2005 [19]	1 CMT with first-order absorption and elimination	NONMEM (version 5)	CL/F (mL/h) = 3.41*TBW + 1.64* (PNA) V/F (L) = 1.09*TBW K_a (h^{-1}) = 50 (fixed) *F* = 0.406 for oral, 1 for suppository	Proportional
8	Yukawa et al. 2006 [20]	1 CMT steady-state	NONMEM (version 5)	CL/F (mL/kg/h) = 5.29*(TBW/60)$^{-0.720}$*PHT conc$^{-0.0985}$*G1 G1 = 0.807 for *CYP2C19*1/*3, *2/*2, *2/*3*	Proportional
9	Goto et al. 2007 [14]	1 CMT first-order absorption and elimination	WinNonMix (version 2.0.1)	CL/F (mL/h) = 0.23*(TBW/40)$^{0.21}$ * 0.52$^{CYP2C9*1/*3}$ * 0.63^{VPA} * 0.85^{PHT} * 0.85 ^{SMID} *CYP2C9*1/*3* = 1, otherwise 0 VPA or PHT = 1 if it is co-administered, otherwise 0 SMID = severe mental retardation = 1, otherwise 0 V/F (L) = 14.78	Proportional
10	Wilmshurst et al. 2010 [21]	1 CMT with first-order absorption and elimination	NONMEM (version 6)	CL/F (mL/h/kg) = 7.6 (fixed) K_a (h^{-1}) = 5, 10, 25, 50 (fixed) V/F (L/kg) = 1.21	Proportional
11	Yukawa et al. 2011 [22]	1 CMT with first-order absorption and elimination	NONMEM (version 6)	CL/F (mL/h) = 5.95*TBW + 1.41* (PNA in weeks) * conc$^{-0.221}$ where conc = PB conc > 50 μg/L V/F (L) = 1.01*TBW K_a (h^{-1}) = 50 (fixed) F = 1 for suppository, = 0.483 for oral administration	Proportional
13	Lee et al. 2012 [23]	1 CMT with first-order elimination	NONMEM (version 6)	CL (mL/h) = 32.6*(TBW/4)$^{1.21}$ V (mL) = 3590*(TBW/4)$^{0.766}$*(AGE/2)$^{0.283}$	NR
12	Van den Broek et al. 2012 [24]	1 CMT with first-order elimination	NONMEM (version 6)	CL (mL/h) = 17.2*(TBW/3.5)$^{0.81}$ V (mL) = 3450*(TBW/3.5)$^{1.08}$	Exponential
15	Shellhaas et al. 2013 [25]	1 CMT with first-order elimination	NONMEM (version 7.2)	CL (L/h) = 0.672*(WT/70)$^{0.75}$*(PNAc/(PNA$_{c50}$ + PNAc)) PNAc50 = 22.1 V (L) = 64.9*(WT/70)	Exponential

Table 4 (continued)

14	Marsot et al. 2014 [32]	1 CMT with first-order absorption and elimination	NONMEM (version 7)	CL (L/h) = 0.191*(WT/70)$^{0.75}$ V (L) = 44.6*(WT/70) F = 0.489 K_a (h^{-1}) = 50 (fixed)	Exponential
16	Vucicevic et al. 2015 [28]	1 CMT with first-order absorption and elimination	NONMEM (version 7.2)	CL/F (L/h) = 0.314*(1–0.248*DVPA (mg/d)/100) DVPA = VPA daily dose (was centered at 1000 mg/d) V/F (L/kg) = 0.6 (fixed) K_a (h^{-1}) = 3 (fixed)	Exponential
17	Voller et al. 2017 [26]	1 CMT with first-order absorption and elimination	NONMEM (version 7.3)	CL (L/h) = 0.0091*(1 + 0.0533*(PNA-median))*(1 + 0.369*(bBW-median)) V (L) = 2.38*(1 + 0.309*(aBW-median)) K_a (h^{-1}) = 50 (fixed) F = 0.594	NR
18	Moffett et al. 2018 [27]	1 CMT with first-order absorption and elimination	NONMEM (version 7.3)	CL (L/h) $= 0.372*\left(\frac{FFM}{70}\right)^{0.75}*\left(\frac{0.3}{Scr}\right)^{0.265}*\left(\frac{1}{1+\left(\frac{PMA}{41}\right)^{-4.22}}\right)*0.596^{PHT}*0.761^{MIDAZ}*1.25^{PANTOP}$ $V = 62.5*\left(\frac{FFM}{70}\right)*0.981^{LN\left(\frac{AGE}{0.28}\right)}$ K_a (h^{-1}) = 0.8 F = 0.89	Proportional

No	IIV	RV		Evaluation
1	CL: %CV = 19 V: %CV = 16	Additive of log transformed	%CV = 10.7	External dataset (N = 15)
2	CL/F: %CV = 17.64 CL/F: %CV = 22.20 CL/F: %CV = 20.37	Additive of log transformed	%CV = 20.40 %CV = 18.65 %CV = 17.8	External dataset (N = 82)
3	CL: %CV = 18.1	Additive	%CV = 18.0	GOF plots
4	CL/F: %CV = 26.8	Additive	%CV = 14.8	No
5	CL/F: %CV = 21.2	Proportional	%CV = 19.7	No
6	CL/F: %CV = 22.9	Proportional	%CV = 14.7	No
7	CL/F: %CV = 31.9 V/F: %CV = 53.9 K_a: NA	Proportional	%CV = 25.2	ME, MAE
8	CL/F: %CV = 22.1	Proportional	%CV = 14.2	NR
9	CL/F: %CV = 17.3	Additive	SD = 3.49 μg/mL	No
10	CL/F: NA K_a: NA V/F: %CV = 52	Additive	SD = 36 μmol/L	Bootstrap, VPC
11	CL/F: %CV = 26.0 V/F: %CV = 61.2 K_a: NA	Proportional	%CV =22.5	GOF plots, ME, MAE

Table 4 (continued)

13	CL: %CV =27.0 V: %CV = 31.1	NR	NR	NR
12	CL: %CV =43.1 V: %CV = 8.4	Proportional	%CV =4.9	Bootstrap, NPDE for PK and VPC for PD model
15	CL: %CV =41.8	Combined	Proportional: %CV = 44.38 Additive: SD = 2.47 μg/mL	Bootstrap
14	CL: %CV =16.6 V: %CV = 49.5 F:%CV = 39.4	Additive	SD = 7.22 μg/mL	NPDE, bootstrap
16	CL/F: %CV =44.61 V/F: NA K_a: NA	Proportional	%CV = 38.34	Bootstrap, pcVPC
17	CL: %CV =29 V: %CV = 40 K_a: NA	Proportional	%CV = 22	GOF, NPDE, external validation (n = 17)
18	CL: %CV =42.5 V: %CV = 33.8	Proportional	%CV = 14.8	Bootstrap, pcVPC

AEDs antiepileptic drugs, *aBW* actual bodyweight, *bBW* birthweight, *CBZ* carbamazepine, *CL* clearance, *CMT* compartment, *CV* coefficient of variation, *F* bioavailability, *FFM* fat free mass, *GOF* goodness of fit, K_a absorption rate constant, *MAE* mean absolute error, *ME* mean error, *MIDAZ* midazolam, *NA* not applicable, *NPDE* normalized prediction distribution error, *PANTOP* pantoprazole, *PB* phenobarbital, *pcVPC* prediction-corrected visual predictive check, *PD* pharmacodynamics, *PHT* phenytoin, *PK* pharmacokinetics, *PMA* postmenstrual age, *PNA* postnatal age, PNA_c continuous postnatal age, PNA_{c50} postnatal age value at which clearance reaches half its maximal value, *SCr* serum creatinine, *SD* standard deviation, *TBW* total body weight, *V* volume of distribution, *VPA* valproic acid, *VPC* visual predictive, check, *WT* weight

*Note: bioavailability was considered complete

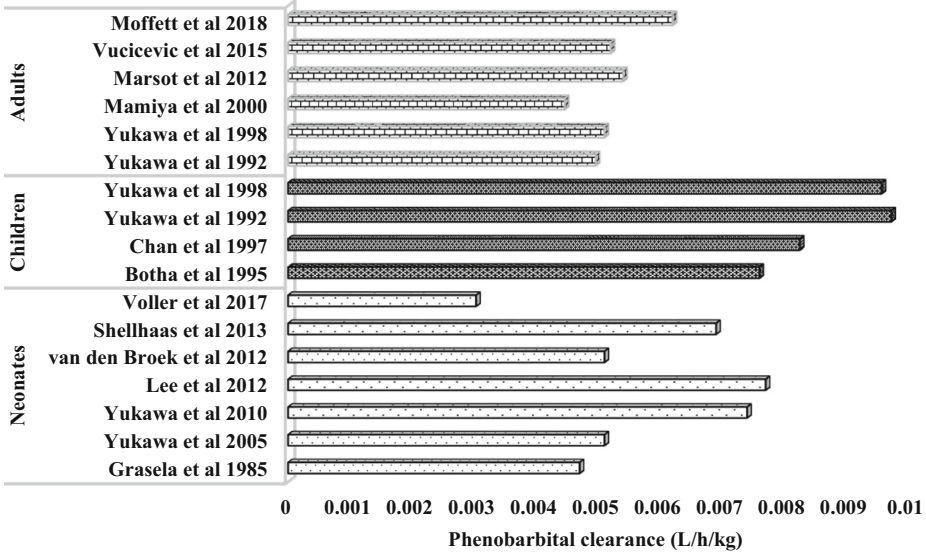

Fig. 4 The estimated population phenobarbital clearance from the included studies classified by the age group. The clearances were calculated assuming phenobarbital monotherapy and using the mean weights of 3 kg, 20 kg, and 60 kg for neonates, children, and adults, respectively

Conclusion

Based on our review, although extensive population pharmacokinetic studies of phenobarbital have been conducted, key information on model methodologies was missing in some studies which may hamper their reproducibility and their applicability in clinical settings. In addition, the research gap regarding the relationship between pharmacokinetic variability and pharmacodynamics of phenobarbital in populations other than neonate remains exist, thus predictions of phenobarbital treatment outcome using population pharmacokinetic/pharmacodynamic models are not well established. Further research focusing on a link between population pharmacokinetics/pharmacodynamics should be conducted to fill this knowledge gap.

Authors' contributions JM and NL planned and designed the systematic review. JM drafted the initial manuscript and revised the subsequent drafts. Both authors read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest that are relevant to the content of this article.

References

1. Boer HR, Gal P (1982) Neonatal seizures: a survey of current practice. Clin Pediatr 21(8):453–457
2. Wallin A, Jalling B, Boréus LO (1974) Plasma concentrations of phenobarbital in the neonate during prophylaxis for neonatal hyperbilirubinemia. J Pediatr 85(3):392–397
3. Battino D, Estienne M, Avanzini G (1995) Clinical pharmacokinetics of antiepileptic drugs in paediatric patients. Clin Pharmacokinet 29(4):257–286
4. Murphy JE. Clinical pharmacokinetics: ASHP; 2011
5. Winter ME. Basic clinical pharmacokinetics: Lippincott Williams & Wilkins; 2004
6. Graves NM, Holmes GB, Kriel RL, Jones-Saete C, Ong B, Ehresman DJ (1989) Relative bioavailability of rectally administered phenobarbital sodium parenteral solution. Dicp. 23(7–8):565–568
7. Touw D, Graafland O, Cranendonk A, Vermeulen R, Van Weissenbruch M (2000) Clinical pharmacokinetics of phenobarbital in neonates. Eur J Pharm Sci 12(2):111–116
8. Hvidberg EF, Dam M (1976) Clinical pharmacokinetics of anticonvulsants. Clin Pharmacokinet 1(3):161–188
9. Onishi S, Ohki Y, Nishimura Y, Itoh S, Isobe K, Hosoe A, Yamamoto T, Yamakawa T (1984) Distribution of phenobarbital in serum, brain and other organs from pediatric patients. Dev Pharmacol Ther 7:153–159
10. Painter M, Pippenger C, Wasterlain C, Barmada M, Pitlick W, Carter G et al (1981) Phenobarbital and phenytoin in neonatal seizures: metabolism and tissue distribution. Neurology 31(9):1107
11. Anderson GD (1998) A mechanistic approach to antiepileptic drug interactions. Ann Pharmacother 32(5):554–563
12. Riva R, Albani F, Contin M, Baruzzi A (1996) Pharmacokinetic interactions between antiepileptic drugs. Clin Pharmacokinet 31(6): 470–493
13. Mamiya K, Hadama A, Yukawa E, Ieiri I, Otsubo K, Ninomiya H, Tashiro N, Higuchi S (2000) CYP2C19 polymorphism effect on phenobarbitone. Pharmacokineties in Japanese patients with epilepsy: analysis by population pharmacokinetics. Eur J Clin Pharmacol 55(11–12):821–825
14. Goto S, Seo T, Murata T, Nakada N, Ueda N, Ishitsu T, Nakagawa K (2007) Population estimation of the effects of cytochrome P450 2C9 and 2C19 polymorphisms on phenobarbital clearance in Japanese. Ther Drug Monit 29(1):118–121
15. Yukawa E, Higuchi S, Aoyama T (1992) Phenobarbitone population pharmacokinetics from routine clinical data: role of patient characteristics for estimating dosing regimens. J Pharm Pharmacol 44(9):755–760

16. Botha JH, Gray AL, Miller R (1995) Determination of phenobarbitone population clearance values for South African children. Eur J Clin Pharmacol 48(5):381–383
17. Chan E, Chan K, Teoh R (1997) Determination of phenobarbitone population clearance values for physically and mentally handicapped Chinese children with epilepsy. J Clin Pharm Ther 22(5–6):399–403
18. Yukawa E, To H, Ohdo S, Higuchi S, Aoyama T (1998) Detection of a drug-drug interaction on population-based phenobarbitone clearance using nonlinear mixed-effects modeling. Eur J Clin Pharmacol 54(1):69–74
19. Yukawa E, Suematsu F, Yukawa M, Minemoto M (2005) Population pharmacokinetic investigation of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants. J Clin Pharm Ther 30(2):159–163
20. Yukawa E, Mamiya K (2006) Effect of CYP2C19 genetic polymorphism on pharmacokinetics of phenytoin and phenobarbital in Japanese epileptic patients using non-linear mixed effects model approach. J Clin Pharm Ther 31(3):275–282
21. Wilmshurst JM, Van Der Walt JS, Ackermann S, Karlsson MO, Blockman M (2010) Rescue therapy with high-dose oral phenobarbitone loading for refractory status epilepticus. J Paediatr Child Health 46(1–2):17–22
22. Yukawa M, Yukawa E, Suematsu F, Takiguchi T, Ikeda H, Aki H, Mimemoto M (2011) Population pharmacokinetics of phenobarbital by mixed effect modelling using routine clinical pharmacokinetic data in Japanese neonates and infants: an update. J Clin Pharm Ther 36(6):704–710
23. Lee SM, Chung JY, Lee YM, Park MS, Namgung R, Park KI, Lee C (2012) Effects of cytochrome P450 (CYP)2C19 polymorphisms on pharmacokinetics of phenobarbital in neonates and infants with seizures. Arch Dis Child 97(6):569–572
24. Van Den Broek MPH, Huitema ADR, Groenendaal F, Van Straaten HLM, Toet M, Egberts ACG et al (2012) Pharmacokinetics and pharmacodynamics of phenobarbital during therapeutic hypothermia in asphyxiated newborns. Pharmaceutisch Weekblad 147(24): 103–106
25. Shellhaas RA, Ng CM, Dillon CH, Barks JDE, Bhatt-Mehta V (2013) Population pharmacokinetics of phenobarbital in infants with neonatal encephalopathy treated with therapeutic hypothermia. Pediatr Crit Care Med 14(2):194–202
26. Völler S, Flint RB, Stolk LM, Degraeuwe PLJ, Simons SHP, Pokorna P, Burger DM, de Groot R, Tibboel D, Knibbe CAJ (2017) Model-based clinical dose optimization for phenobarbital in neonates: an illustration of the importance of data sharing and external validation. Eur J Pharm Sci 109:S90–SS7
27. Moffett BS, Weingarten MM, Galati M, Placencia JL, Rodman EA, Riviello JJ, Kayyal SY (2018) Phenobarbital population pharmacokinetics across the pediatric age spectrum. Epilepsia. 59(7):1327–1333
28. Vučićević K, Jovanović M, Golubović B, Kovačević SV, Miljković B, Martinović Ž, Prostran M (2015) Nonlinear mixed effects modelling approach in investigating phenobarbital pharmacokinetic interactions in epileptic patients. Eur J Clin Pharmacol 71(2):183–190
29. Methaneethorn J (2018) A systematic review of population pharmacokinetics of valproic acid. Br J Clin Pharmacol 84(5):816–834
30. Methaneethorn J (2018) Population pharmacokinetic analyses of lithium: a systematic review. Eur J Drug Metab Pharmacokinet 43(1):25–34
31. Grasela TH Jr, Donn SM (1985) Neonatal population pharmacokinetics of phenobarbital derived from routine clinical data. Dev Pharmacol Ther 8(6):374–383
32. Marsot A, Brevaut-Malaty V, Vialet R, Boulamery A, Bruguerolle B, Simon N (2014) Pharmacokinetics and absolute bioavailability of phenobarbital in neonates and young infants, a population pharmacokinetic modelling approach. Fundam Clin Pharmacol 28(4):465–471
33. Brendel K, Dartois C, Comets E, Lemenuel-Diot A, Laveille C, Tranchand B et al (2007) Are population pharmacokinetic and/or pharmacodynamic models adequately evaluated? Clin Pharmacokinet 46(3):221–234
34. Kanji S, Hayes M, Ling A, Shamseer L, Chant C, Edwards DJ, Edwards S, Ensom MHH, Foster DR, Hardy B, Kiser TH, la Porte C, Roberts JA, Shulman R, Walker S, Zelenitsky S, Moher D (2015) Reporting guidelines for clinical pharmacokinetic studies: the ClinPK statement. Clin Pharmacokinet 54(7):783–795
35. Dartois C, Brendel K, Comets E, Laffont C, Laveille C, Tranchand B et al (2007) Overview of model-building strategies in population PK/PD analyses: 2002–2004 literature survey. Br J Clin Pharmacol 64(5):603–612
36. Abdel-Jalil M, Abdullah N, Alsous M, Saleh M, Abu-Hammour K (2020) A systematic review of population pharmacokinetic analyses of digoxin in the pediatric population. Br J Clin Pharmacol
37. Patsalos PN, Lascelles PT (1981) Inhibition of in vitro diphenylhydantoin hydroxylation by different anticonvulsant drug combinations: a kinetic analysis. General Pharmacology: The Vascular System 12(1):51–55
38. Morselli P, Rizzo M, Garattini S (1971) Interaction between phenobarbital and diphenylhydantoin in animals and in epileptic patients. Ann N Y Acad Sci 179(1):88–107
39. Manganaro R, Mamì C, Gemelli M (1994) The validity of the Apgar scores in the assessment of asphyxia at birth. European Journal of Obstetrics & Gynecology and Reproductive Biology 54(2):99–102
40. Heimann G, Gladtke E (1977) Pharmacokinetics of phenobarbital in childhood. Eur J Clin Pharmacol 12(4):305–310
41. Waddell WJ, Butler TC (1957) The distribution and excretion of phenobarbital. J Clin Invest 36(8):1217–1226
42. (2015) The Apgar Score. Pediatrics 136(4):819–822
43. Morselli PL (1976) Clinical pharmacokinetics in neonates. Clin Pharmacokinet 1(2):81–98
44. Rylance GW, Moreland TA, Cowan MD, Clark DC (1982) Liver volume estimation using ultrasound scanning. Arch Dis Child 57(4):283–286
45. Chiba K, Suganuma T, Ishizaki T, Iriki T, Shirai Y, Naitoh H, Hori M (1985) Comparison of steady-state pharmacokinetics of valproic acid in children between monotherapy and multiple antiepileptic drug treatment. J Pediatr 106(4):653–658
46. Suganuma T, Ishizaki T, Chiba K, Hori M (1981) The effect of concurrent administration of valproate sodium on phenobarbital plasma concentration/dosage ratio in pediatric patients. J Pediatr 99(2):314–317
47. Kapetanovic IM, Kupferberg HJ, Porter RJ, Theodore W, Schulman E, Penry JK (1981) Mechanism of valproate-phenobarbital interaction in epileptic patients. Clin Pharmacol Ther 29(4):480–486
48. Pokrajac M, Miljković B, Varagić VM, Lević Z (1993) Pharmacokinetic interaction between valproic acid and phenobarbital. Biopharm Drug Dispos 14(1):81–86
49. Patsalos PN, Duncan JS (1993) Antiepileptic drugs. Drug Saf 9(3): 156–184
50. Lambie D, Johnson R, Nanda R, Shakir R (1976) Therapeutic and pharmacokinetic effects of increasing phenytoin in chronic epileptics on multiple drug therapy. Lancet 308(7982):386–389
51. Eadie M, Lander C, Hooper W, Tyrer J (1977) Factors influencing plasma phenobarbitone levels in epileptic patients. Br J Clin Pharmacol 4(5):541–547
52. Patsalos PN, Lascelles PT (1977) In vitro hydroxylation of diphenylhydantoin and its inhibition by other commonly used anticonvulsant drugs. Biochem Pharmacol 26(20):1929–1933

53. Cereghino JJ, Brock JT, Van Meter JC, Penry JK, Smith LD, White BG (1975) The efficacy of carbamazepine combinations in epilepsy. Clinical Pharmacology & Therapeutics 18(6):733–741
54. Sennoune S, Iliadis A, Bonneton J, Barra Y, Genton P, Mesdjian E (1996) Steady state pharmacokinetics of carbamazepine-phenobarbital interaction in patients with epilepsy. Biopharm Drug Dispos 17(2):155–164
55. Guelen PJM, van der Kleijn E (1978) Rational anti-epileptic drug therapy. Elsevier/North-Holland Biomedical Press
56. Wandel C, Bocker R, Bohrer H, Browne A, Rugheimer E, Martin E (1994) Midazolam is metabolized by at least three different cytochrome P450 enzymes. Br J Anaesth 73(5):658–661
57. Li X-Q, Andersson TB, Ahlström M, Weidolf L (2004) Comparison of inhibitory effects of the proton pump-inhibiting drugs omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole on human cytochrome P450 activities. Drug Metab Dispos 32(8):821–827