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REVIEW ARTICLE

Predictive Value of Microdose Pharmacokinetics

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Abstract
Phase 0 microdose trials are exploratory studies to early assess human pharmacokinetics of new chemical entities, while limiting drug exposure and risks for participants. The microdose concept is based on the assumption that microdose pharmacokinetics can be extrapolated to pharmacokinetics of a therapeutic dose. However, it is unknown whether microdose pharmacokinetics are actually indicative of the pharmacokinetics at therapeutic dose. The aim of this review is to investigate the predictive value of microdose pharmacokinetics and to identify drug characteristics that may influence the scalability of these parameters. The predictive value of microdose pharmacokinetics was determined for 46 compounds and showed adequate predictability for 28 of 41 orally administered drugs (68%) and 15 of 16 intravenously administered drugs (94%). Microdose pharmacokinetics were considered predictive if the mean observed values of the microdose and the therapeutic dose were within twofold. Nonlinearity may be caused by saturation of enzyme and transporter systems, such as intestinal and hepatic efflux and uptake transporters. The high degree of success regarding linear pharmacokinetics shows that phase 0 microdose trials can be used as an early human model for determination of drug pharmacokinetics.

Key Points

The predictive value of microdose pharmacokinetics could be determined for 46 compounds and showed adequate predictability for 28 of 41 orally administered drugs (68%) and 15 of 16 intravenously administered drugs.

Nonlinearity was caused by saturation of the enzyme and transporter systems, especially intestinal and hepatic efflux and uptake transporters such as organic anion transporting polypeptides (OATPs).

The high degree of success regarding linear pharmacokinetics confirms the strength of phase 0 microdose trials in gaining early pharmacokinetic data, thereby providing safety and reducing developmental costs.

1 Introduction

Drug development is an extensive endeavor in which only 10% of newly developed compounds eventually gain market authorization [1–3]. Although clinical failure is mainly attributed to lack of efficacy or poor drug tolerability, 10% of failure is caused by undesirable pharmacokinetics such as poor absorption or a short half-life ($t_{½}$) [4]. Early determination of drug pharmacokinetics could increase success rates in further development and thereby reduce costs. In recent times, drug pharmacokinetics in human are estimated by extrapolation of pharmacokinetics from in vitro and preclinical studies to a clinical setting. The predictability of human pharmacokinetics from preclinical data is based on assumptions about the behavior of the drug across species [5–7]. Although interspecies scaling may be used to predict

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pharmacokinetic parameters, extrapolation from animals to humans is complex. Therefore, a more accurate predictive model of pharmacokinetic parameters could improve selection of drugs and increase clinical approval.

The European Medicines Agency (EMA) introduced the concept of microdose studies as a human model, in which a small portion of a drug is administered to participants with the aim of investigating pharmacokinetics. Currently, the EMA M3 (R2) guideline is widely accepted as guidance for microdose studies. A microdose is defined as 1% of the anticipated therapeutic dose, with a maximum of 100 µg for chemical entities and 30 nmol for protein drugs [8]. Because these trials are conducted prior to traditional phase I trials, they are denoted phase 0 microdose trials.

The main feature of phase 0 microdose trials is early assessment of human pharmacokinetics of new chemical entities, with limited drug exposure, including mass balance and metabolite profiling. Hereby, phase 0 microdose trials have the potential to make drug development more efficient by earlier selection of promising candidates. Microdoses are considered harmless because of the limited drug exposure, therefore less extensive preclinical toxicology studies are required. Due to this nontoxic nature of a microdose, neither a therapeutic effect nor adverse events are to be expected [8].

The microdose concept is based on the assumption that microdose pharmacokinetics can be extrapolated to pharmacokinetics of a therapeutic dose. However, it is unknown whether microdose pharmacokinetics are really indicative of the pharmacokinetics at therapeutic dose. A previous review assessed microdose predictability in human for 25 orally administered drugs and 12 intravenously administered drugs. It was shown that 62% of orally administered drugs and 100% of intravenously administered drugs tested between microdose and therapeutic dose demonstrated scalable pharmacokinetics within twofold [9]. Many new microdose trials have been published since. Furthermore, the last review did not discuss the influence of enzymes or transporter systems on the linearity of microdose pharmacokinetics. In this review, we collect drug characteristics, including relevant metabolizing enzymes and transporters, to identify similarities between drugs with nonlinear pharmacokinetics in terms of saturation mechanisms. The aim of this review is to update previous data by investigating whether the pharmacokinetics in a clinically relevant therapeutic dose can be predicted from the pharmacokinetics of a microdose, and to identify drug characteristics that may influence the scalability of these parameters.

2 Methods

2.1 Literature Search

The Pubmed and EMBASE databases were searched to identify pharmacokinetic microdose trials, using the following terms: microdose OR microdosing OR 'phase 0'. The search was performed on 19 November 2018 and results were restricted to the English language and to studies in humans. Additional papers were selected from review articles. Initial screening was based on title and abstract, while inclusion was performed manually by full-text assessment of eligibility. Furthermore, publications were only included if pharmacokinetic outcome measures were available for both the microdose and a clinically relevant therapeutic dose. Microtracer studies, in which a radio-labeled microdose is coadministered with a nonradiolabeled therapeutic dose, were excluded as the total administered dose exceeds the criteria to be regarded a microdose (> 1/100th of the therapeutic dose, with a maximum of 100 µg) [9].

For each oral drug investigated in the included microdose trials, the following drug characteristics were gathered: solubility, lipophilicity (log *P*) and Biopharmaceutical Drug Disposition and Classification System (BDDCS) class (Fig. 1). Furthermore, metabolizing enzymes and relevant drug transporters were collected. Information on registered drugs were obtained from a review article on BDDCS class [10] and FDA documents (prescribing data, clinical pharmacology and biopharmaceutics review, label text). Drug characteristics of nonregistered drugs were collected from the literature, and the BDDCS classification was based on solubility and permeability: good solubility was defined as being soluble in 250 mL water or less at the highest marketed dose strength, and good permeability was defined as the log *P* being greater than the log *P* of metoprolol (1.88), as proposed by Benet et al. [10].

2.2 Pharmacokinetic Scalability

The predictive value of microdose pharmacokinetics was determined by comparing pharmacokinetic parameters of the microdose with those of the therapeutic dose. For the area under the curve (AUC), the value to infinity in ng h/mL was used, unless otherwise denoted, and was presented

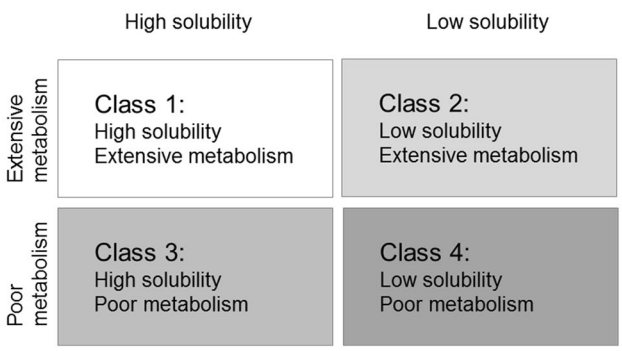

Fig. 1 Biopharmaceutics Drug Disposition Classification System (BDDCS) as described by Benet et al. [10]

dose-adjusted to 100 µg. Furthermore, $t_{½}$ was reported in hours, clearance (CL) was reported in liters/hour, and volume of distribution (V_d) was reported in liters. Pharmacokinetic data from trials in which only microdose pharmacokinetics were determined were complemented with literature data on therapeutic pharmacokinetics. Microdose pharmacokinetics were considered predictive if the mean observed values of the microdose and the therapeutic dose were within twofold, as described previously [11, 12]. The predictive value was determined for all pharmacokinetic parameters that were available for both the microdose and therapeutic dose. Drugs with at least one poorly scalable parameter (i.e. outside the twofold threshold) were denoted as having nonlinear pharmacokinetics

3 Results

3.1 Studies

The literature search identified 2107 publications, of which 35 articles were found eligible for inclusion. Four more papers were selected from the references cited in other review articles. Microdose pharmacokinetics were available for 46 different drugs; eight drugs were investigated in more than one trial. Table 1 shows the characteristics of drugs investigated in crossover trials (n = 25) in which a microdose and a therapeutic dose were administered, thereby facilitating a direct comparison of pharmacokinetic parameters. Furthermore, Table 2 contains pharmacokinetic parameters of drugs from trials in which only a microdose was administered. Results from these studies were compared with pharmacokinetics of the therapeutic dose as described in literature. In general, three types of study designs could be distinguished; single-drug microdose trials (n = 24), multiple-drug microdose trials (n = 9), and cassette microdose trials (n = 6). In multiple-drug microdose trials, more than one drug was administered separately to participants, while a combination of drugs was administered simultaneously in cassette microdose trials.

3.2 Pharmacokinetics

Microdose pharmacokinetics were reported for 30 drugs investigated in crossover trials and for 20 drugs studied in single microdose trials. In total, the predictive value could be determined for 45 drugs, of which 41 were administered orally and 16 were administered intravenously. Twelve drugs were administered both orally and intravenously. Microdose pharmacokinetics were predictive within the twofold criteria for 28 of 41 (68%) oral formulations and 15 of 16 (94%) intravenous formulations. Conflicting data were found for atorvastatin, verapamil, and fexofenadine [13–17]. Pharmacokinetic linearity was determined in crossover trials, in which both a microdose and therapeutic dose were administered (Table 1), or comparing microdose data with the literature (Table 2). As a crossover design reduces interindividual variability, the results of the crossover trials were regarded to be more accurate. Therefore, verapamil and fexofenadine were considered as having predictive microdose pharmacokinetics, while atorvastatin was regarded as having poor predictability.

Pharmacokinetic nonlinearity of oral drugs was predominantly reflected in the exposure (AUC), with 11 of 13 (85%) drugs showing poorly scalable AUC. A nonlinear increase in AUC after dose escalation was seen for atorvastatin (2.3-fold), celiprolol (2.2-fold), mirodenafil (3.3-fold), nicardipine (2.2-fold), omeprazole (3.2-fold), propafenone (2.3-fold), quinidine (2.6-fold), telmisartan (5.6-fold), and verapamil (2.3-fold), while a decrease in AUC was shown for sumatriptan (2.9-fold) and rosuvastatin (2.2-fold) [13–15, 17–23]. Bioavailability (F) was determined for two of these drugs, with a nonlinear increase at therapeutic dose for propafenone (2.3-fold) and a decrease for sumatriptan (2.6-fold) [17].

Nonlinearity in V_d was described for intravenous administration of docetaxel and oral administration of warfarin [24, 25]. V_d decreased 3.5-fold for docetaxel and 3.8-fold for warfarin following dose escalation.

Five microdose trials specifically focused on the metabolism of a drug and metabolite pharmacokinetics. Linear metabolite pharmacokinetics were described for nicardipine and verapamil (1.0-fold) [13, 23], while quinidine exhibited nonlinear pharmacokinetics for both the parent compound and three major metabolites (2.6-fold) [13]. The pharmacokinetics of celiprolol, telmisartan and tolbutamide were assessed for various cytochrome P450 (CYP) enzyme genotypes, responsible for metabolic conversion [14, 19, 26]. The predictive value was similar for poor, extensive, and ultra-rapid metabolizers. Moreover, the pharmacokinetics of intracellular metabolites were described for zidovudine and tenofovir. These antiretroviral drugs are phosphorylated intracellularly to pharmacologically active triphosphate metabolites. The pharmacokinetics of the intracellular metabolites of tenofovir (measured in peripheral blood mononuclear cells and CD4+ cells) and of the parent compound in plasma were found to be linear (1.3- to 1.5-fold) [27], while the pharmacokinetics of zidovudine triphosphates were nonlinear, with a 3.9-fold higher dose-adjusted AUC at therapeutic dose compared with microdose [27].

Kusuhara et al. specifically focused on the pharmacokinetics of metformin after inhibition of the multidrug and toxin extrusion (MATE) protein that is responsible for renal elimination of this drug, and reported linear pharmacokinetics [28]. Celiprolol, warfarin and pitavastatin showed a nonlinear decrease in $t_{½}$ at therapeutic dose compared with microdose, of 2.2-fold, 5.8-fold, and 3.1-fold, respectively [14, 21, 24].

Table 1 Pharmacokinetic parameters of drugs from crossover trials in which a microdose and a therapeutic dose were administered

Drug	Microdose (μg)	Therapeutic dose (mg)	Route of administration	Pharmacokinetic microdose[a]	Pharmacokinetic therapeutic dose[a]	Linear pharmacokinetics (NR)	References
Atenolol	100	50	PO	$t_{½}$ = 7.11 AUC = 8.88	$t_{½}$ = 7.23 AUC = 7.27	Yes	[43]
Atorvastatin	100	10	PO	AUC = 0.20	AUC = 0.45	No	[15]
Celiprolol	37.5	100	PO	$t_{½}$ = 13.35 AUC_{24} = 0.232 CL/*F* = 488	$t_{½}$ = 6.14 AUC_{24} = 1.29 CL/*F* = 109	No	[14]
Clarithromycin	100	250	IV	$t_{½}$ = 4.10 AUC = 4.78	$t_{½}$ = 4.50 AUC = 5.44	Yes	[17]
	100	250	PO	$t_{½}$ = 4.00 AUC = 0.99 *F* = 22%	$t_{½}$ = 3.40 AUC = 1.96 *F* = 39%	Yes	[17]
Diltiazem	30	30	PO	AUC = 0.138	AUC = 0.264	Yes	[20]
Docetaxel	100	100	IV	$t_{½}$ = 5.10 AUC = 3.64 V_d = 3.91	$t_{½}$ = 3.41 AUC = 2.23 V_d = 13.7	No	[44]
Enalapril	100	10	PO	$t_{½}$ = 12.1 AUC = 13.0	$t_{½}$ = 11.8 AUC = 12.0	Yes	[43]
Fexofenadine	100	120	IV	$t_{½}$ = 8.10 AUC = 8.06 CL = 13	$t_{½}$ = 10 AUC = 7.47 CL = 16	Yes	[45]
	100	120	PO	$t_{½}$ = 16 AUC = 2.77	$t_{½}$ = 12 AUC = 1.84	Yes	[45]
	100	60	PO	$t_{½}$ = 3.2 AUC = 3.19	$t_{½}$ = 2.90 AUC = 2.39	Yes	[46]
hRESCAP	53	5.3	IV	$t_{½}$ = 108 AUC = 531	$t_{½}$ = 104 AUC = 716	Yes	[37]
Losartan	100	50	PO	$t_{½}$ = 3.31 AUC = 3.62	$t_{½}$ = 3.41 AUC = 3.41	Yes	[43]
Metformin	100	250	PO	AUC_{12} = 2.13 CL_R = 623	AUC_{12} = 2.24 CL_R = 395	Yes	[28]
Midazolam	100	7.5	IV	$t_{½}$ = 4.87 AUC = 4.53 CL = 21.2	$t_{½}$ = 2.55 AUC = 4.68 CL = 20.4	Yes	[24]
	1	1	IV	$t_{½}$ = 3.55 AUC = 3.79	$t_{½}$ = 4.02 AUC = 3.90	Yes	[47, 48]
	100	7.5	PO	$t_{½}$ = 3.95 *F* = 22.8%	$t_{½}$ = 3.31 *F* = 22.1%	Yes	[24]
	3	3	PO	$t_{½}$ = 3.26 AUC = 0.89 *F* = 23.4%	$t_{½}$ = 3.96 AUC = 0.81 *F* = 20.9%	Yes	[47, 48]
	0.3	3	PO	$t_{½}$ = 3.54 AUC = 3.67 *V*/*F* = 376	$t_{½}$ = 4.11 AUC = 3.53 *V*/*F* = 353	Yes	[49]
Mirodenafil	100	100	PO	$t_{½}$ = 1.80 AUC = 0.27 CL/*F* = 538	$t_{½}$ = 1.32 AUC = 0.89 CL/*F* = 131	No	[18]
NBI-1	100	10	PO	$t_{½}$ = 6.70 AUC = 2.86	$t_{½}$ = 8.40 AUC = 3.28	Yes	[50]
Nicardipine	100	20	PO	Comparable concentration-time curves for the metabolites		Yes	[23]
	30	30	PO	AUC = 0.098	AUC = 0.22	No	[20]
Nifedipine	40	20	PO	AUC = 2.13	AUC = 2.76	Yes	[20]
Omeprazole	100	20	PO	$t_{½}$ = 1.21 AUC = 2.59	$t_{½}$ = 2.40 AUC = 8.24	No	[22]

Table 1 (continued)

Drug	Microdose (μg)	Therapeutic dose (mg)	Route of administration	Pharmacokinetic microdose[a]	Pharmacokinetic therapeutic dose[a]	Linear pharmacokinetics (NR)	References
Paracetamol	0.024[b] 0.024[b]	15 15	IV PO	$t_{½}$ = 3.78 AUC_6 = 8.4 CL = 2.72 $t_{½}$ = 1.6 AUC_8 = 9.0 CL = 1.5	$t_{½}$ = 2.62 AUC_6 = 5.4 CL = 2.93 $t_{½}$ = 2.6 AUC_8 = 7.0 CL = 2.9	Yes Yes	[51]
PF-05089771	100	2400	IV	$t_{½}$ = 6.50 AUC = 33	$t_{½}$ = 8.20–11.4 AUC= 33	Yes	[52]
Propafenone	100 100	150 150	IV PO	$t_{½}$ = 5.40 AUC = 1.90 V_d = 273 $t_{½}$ = 3.80 AUC = 0.12 *F* = 5.8%	$t_{½}$ = 4.70 AUC =2.20 V_d = 214 $t_{½}$ = 2.60 AUC = 0.27 *F* = 13.0%	Yes No	[17]
Quinidine	100	100	PO	$t_{½}$ = 5.07 AUC = 0.813	$t_{½}$ = 5.59 AUC = 2.08	No	[13]
RDEA806	80	200	IV	NR	NR	Yes	[53]
Sumatriptan	100 100	50 50	IV PO	$t_{½}$ = 6.50 AUC = 2.20 V_d = 426 $t_{½}$ = 1.90 AUC = 0.44 *F* = 20%	$t_{½}$ = 5.60 AUC = 2.10 V_d = 397 $t_{½}$ = 1.40 AUC = 0.15 *F* = 7.6%	Yes No	[17]
Telmisartan	100	80	PO	*UGT1A1*1/*1*: AUC_{24} = 1.76 CL/*F* = 64.0 *UGT1A1*1/*28*: AUC_{24} = 0.771 CL/*F* = 126	*UGT1A1*1/*1*: AUC_{24} = 3.97 CL/*F* = 23.6 *UGT1A1*1/*28*: AUC_{24} = 1.57 CL/*F* = 50.8	No	[19]
Tenofovir[c]	100	300	PO	$t_{½}$ = 14.1 AUC = 9658 CL/*F* = 31.3 Intracellular metabolites: C_{max} = 13.1 AUC = 2334 Intracellular metabolites CD4+: C_{max} = 13.2 AUC = 1925	$t_{½}$ = 21.4 AUC = 6653 CL/*F* = 45.6 Intracellular metabolites: C_{max} = 10.4 AUC = 1526 Intracellular metabolites CD4+: C_{max} = 5.1 AUC = 1500	Yes Yes	[27]
Unknown integrase inhibitors A	50	NR	IV PO	$t_{½}$ = 3.30 AUC = 4.37 $t_{½}$ = 3.02 AUC = 2.69 *F* = 57%	NR[d]	Yes[c]	[54]
Unknown integrase inhibitors B	50	NR	IV PO	$t_{½}$ = 2.75 AUC = 5.20 $t_{½}$ = 2.28 AUC = 2.62 *F* = 54%	NR[d]	Yes[c]	[54]
Unknown integrase inhibitors C	50	NR	IV PO	$t_{½}$ = 4.08 AUC = 4.12 $t_{½}$ = 3.31 AUC = 1.60 *F* = 43%	NR[d]	Yes[c]	[54]

Table 1 (continued)

Drug	Microdose (µg)	Therapeutic dose (mg)	Route of administration	Pharmacokinetic microdose[a]	Pharmacokinetic therapeutic dose[a]	Linear pharmacokinetics (NR)	References
Unknown integrase inhibitors D	50	NR	IV PO	$t_{½}$ = 2.22 AUC = 3.96 $t_{½}$ = 1.69 AUC = 1.75 *F* = 53%	NR[d]	Yes[c]	[54]
Verapamil	50	80	IV	K_1 = 0.030 V_d = 0.66	K_1 = 0.031 V_d = 0.56	Yes	[55]
	100	80	PO	$t_{½}$ = 2.48 AUC = 0.139	$t_{½}$ = 3.21 AUC = 0.320	No	[13]
Zidovudine[c]	100	300	PO	Intracellular metabolites in PBMCs: AUC = 1837 Intracellular metabolites CD4+: AUC = 1266	Intracellular metabolites in PBMCs: AUC = 578 Intracellular metabolites CD4+: AUC = 151	No	[27]
ZK253	100 100	50 50	IV PO	$t_{½}$ = 61.4 AUC = 7.42 CL = 9.29 *F* = 0.16%	$t_{½}$ = 56.2 AUC = 7.15 CL = 14.8 *F* < 1%	Yes Yes	[24]

IV intravenously, *PO* orally, *PBMCs* peripheral blood mononuclear cells, $t_{½}$ half-life, *AUC* area under the curve, AUC_x area under the curve from time zero to *x* hours, *CL/F* apparent clearance, *F* biological availability, V_d volume of distribution, *CL* clearance, CL_R renal clearance, *V/F* apparent volume of distribution, AUC_∞ AUC from time zero to infinity, C_{max} maximum concentration, *NR* not reported

[a]Pharmacokinetic parameters: AUC = AUC_∞ in ng·h/mL unless otherwise denoted, and is shown dose-normalized to 100 µg; $t_{½}$ is reported in hours, CL is reported in liters/hour, and V_d is reported in liters

[b]Study in children with a dose of 6 ng/kg and a mean weight of 4 kg

[c]Intracellular pharmacokinetics in PBMCs and CD4+ cells. C_{max} of intracellular metabolites in fmol/10^6 cells, and AUC of intracellular metabolites in fmol*h/10^6 cells

[d]Therapeutic dose pharmacokinetics were not given in the literature, however linearity was determined based on unpublished data

3.3 Drug Characteristics

Drug characteristics were collected for orally administered drugs of the included microdose trials (*n* = 41). Table 3 shows the solubility, lipophilicity (log *P*), BDDCS class, metabolizing enzymes, and relevant drug transporters of these compounds. The majority of drugs with linear pharmacokinetics are BDDCS classes 1 and 3, while the majority of drugs with nonlinear pharmacokinetics are classes 1 and 2. Drugs were metabolized or transported by a great variety of proteins, such as organic anion transporting polypeptides (OATP), P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), breast cancer resistance protein (BCRP), and organic cation transporting proteins (OCT), with the majority of BDDCS class 2 drugs being transported by OATPs.

4 Discussion

The predictive value of microdose pharmacokinetics was determined for 46 compounds and showed adequate predictability for 68% of orally administered drugs (*n* = 41) and 94% of intravenously administered drugs (*n* = 16). These results are in line with previously reported data [9]. Importantly, these numbers may underestimate the predictive value as included studies examined compounds known or suspected to have nonlinearity issues. This overview is different to the last literature survey because more drugs are included and drug characteristics are identified that may influence the pharmacokinetic scalability. Furthermore, the relevance of metabolizing enzymes and transporters was discussed with regard to saturation mechanisms. With this increased number of microdose data, our review provides new information on microdose predictability, while confirming findings from previous literature.

Microdose pharmacokinetics were considered predictive if all given pharmacokinetic parameters of the microdose and the therapeutic dose were within twofold [11, 12]. This twofold criterion is commonly used in allometry, however limitations should be acknowledged. For example, the AUC increased nonlinear, with an average of 2.4-fold for 12 drugs, being just outside the twofold threshold. Although these drugs are denoted as having nonlinear pharmacokinetics, the question arises whether the predictive value would be

Table 2 Pharmacokinetic parameters of drugs from trials in which only a microdose was administered; microdose pharmacokinetics were compared with pharmacokinetics of the therapeutic dose as described in literature

Drug	Microdose (µg)	Therapeutic dose (mg)	Route of administration	Pharmacokinetic microdose[a]	Pharmacokinetic therapeutic dose[a]	Linear pharmacokinetics (NR)	References
AFN-1252	100	400	PO	$t_{½}$ = 7.40 AUC = 16.8	$t_{½}$ = 7.74 AUC = 13.5	Yes	[56, 57]
Anastrozole	1.98	1	PO	$t_{½}$ = 37.2 AUC = 65.2	$t_{½}$ = 56.3 AUC = 104	Yes	[58, 59]
Atenolol	30	50	PO	$t_{½}$ = 6.47 AUC_{24} = 10.2 T_{max} = 3.13	$t_{½}$ = 7.23 AUC[b] = 7.27 T_{max} = 4.14	Yes	[14, 43]
Atorvastatin	33	40	PO	AUC_{10} = 0.19	AUC_{24}[b] = 0.22	Yes	[16, 60]
	50	40	PO	$t_{½}$ = 9.00 AUC = 0.24	$t_{½}$ = 8.05 AUC = 0.25	Yes	[21, 60]
Caffeine	25	250	PO	$t_{½}$ = 4.13 AUC = 10.8	$t_{½}$ = 5.20 AUC = 13.0	Yes	[61–64]
Diazepam	100	10	IV	$t_{½}$ = 45.1 AUC = 65.5 CL = 1.38	$t_{½}$ = 35.7 AUC = 55.8 CL = 1.30	Yes	[24, 65]
Diphenhydramine	100 100	50 50	PO IV	$t_{½}$ = 12.0 F = 34.0% AUC = 1.35 $T_{½}$ = 9.30	$t_{½}$ = 6.32 F = 66.3% AUC = 1.01 $T_{½}$ = 7.30	Yes Yes	[50, 66–70]
Fexofenadine	25 30	120 120	PO PO	$t_{½}$ = 5.75 AUC = 2.00 $T_{½}$ = 7.05	$t_{½}$ = 2.90 AUC = 2.12	Yes No	[14, 45, 46, 61]
IDX899 (Fosdevirine)	100	800	PO	$t_{½}$ = 4.40 AUC = 7.60	$t_{½}$ = 8.30 AUC = 8.90	Yes	[71, 72]
Midazolam	25	7.5	PO	$t_{½}$ = 4.01 AUC = 1.76	$t_{½}$ = 3.31 AUC = 1.16	Yes	[24, 61]
	10	7.5	PO	$t_{½}$ = 5.80 AUC = 1.97	$t_{½}$ = 3.31 AUC = 1.16	Yes	[21, 24, 61]
	33	7.5	PO	AUC_{10} = 1.41	AUC_{12}[b] = 2.14	Yes	[16, 73]
NS-304 (Selexipag)	100	0.8	PO	$t_{½}$ = 1.7 AUC = 5.8	$t_{½}$ = 2.3 AUC = 3.12	Yes	[74, 75]
Paracetamol	100 100	1000 1000	PO PO	$t_{½}$ = 2.41 AUC = 4.11 $t_{½}$ = 5.80 AUC = 4.80 F = 88%	$t_{½}$ = 3.61 AUC = 5.46 F = 89%	Yes Yes	[17, 76–80]
	100	1000–1500	IV	$t_{½}$ = 4.60 CL = 19.0 V_d = 123	$t_{½}$ = 2.50 CL = 19.7 V_d = 66.5	Yes	[17, 80, 81]
Phenobarbital	100	240	PO	$T_{½}$ = 180	$T_{½}$ = 98.0	Yes	[17, 82]
Pitavastatin	10	1	PO	$t_{½}$ = 12.3 AUC = 4.61	$t_{½}$ = 4.0 AUC = 2.90	No	[21, 83]
Pravastatin	33	600	PO	AUC_8 = 0.60	AUC_8 = 0.36	Yes	[16, 84–87]
Raltegravir	50	400	PO	AUC = 3.86 T_{max} = 0.50	AUC = 2.64 T_{max} = 1.00	Yes	[54, 88]
Rosuvastatin	25	5	PO	$t_{½}$ = 7.70 AUC = 1.03	$t_{½}$ = 12.8 AUC = 0.47	No	[21, 83]

Table 2 (continued)

Drug	Microdose (µg)	Therapeutic dose (mg)	Route of administration	Pharmacokinetic microdose[a]	Pharmacokinetic therapeutic dose[a]	Linear pharmacokinetics (NR)	References
Tolbutamide	100	125	PO	*CYP2C9*1/*1*: $t_{½}$ = 7.90 CL = 0.82 AUC = 123 *CYP2C9*1/*3*: $t_{½}$ = 13.9 CL = 0.50 AUC = 206	*CYP2C9*1/*1*: $t_{½}$ = 7.30 (7.10–7.50) CL = 0.91 (0.85–0.97) AUC = 119 *CYP2C9*1/*3*: $t_{½}$ = 13.1 (12.2–13.9) CL = 0.91 (0.56–0.60) AUC = 166	Yes	[26, 89–91]
	25	125	PO	$t_{½}$ = 8.13 AUC = 167	$t_{½}$ = 7.70 AUC = 143	Yes	[61, 92]
Warfarin	100	5	PO	$t_{½}$ = 274 AUC = 571 V_d = 67.3	$t_{½}$ = 48.6 AUC = 416 V_d = 17.9	No	[24, 93]
Zidovudine	100	300	PO	$t_{½}$ = 4.5 AUC = 4269 CL/*F* = 70.5	$t_{½}$ = 6.6 AUC = 4458 CL/*F* = 68.2	Yes	[27, 94, 95]

AUC area under the curve, AUC_t AUC from time zero to time *t*, AUC_x area under the curve from time zero to *x* hours, *CL* clearance, *CL/F* apparent clearance, *F* biological availability, *IV* intravenously, *NR* not reported, *PO* orally, $t_{½}$ half-life, t_{max} time to reach maximum concentration, V_d volume of distribution

[a]Pharmacokinetic parameters: AUC = AUC_∞ in ng·h/mL unless otherwise denoted, and is shown dose-normalized to 100 µg; $t_{½}$ is reported in hours, CL is reported in liters/hour, and V_d is reported in liters

[b]The AUC_t calculated for microdose exposure was not found in the literature for therapeutic dose exposure, therefore the closest AUC_t time point was chosen

significantly different with an AUC increase of 1.9-fold, indicating linear pharmacokinetics within twofold. With this in mind, microdose data should be regarded as exploratory, providing early pharmacokinetic information for newly developed compounds.

Data gathered in this review clearly show that the absorption phase is pivotal for predictability of microdose pharmacokinetics. Nonlinearity may arise in the gastrointestinal dissolution process, or when enzymes or transporter systems saturate at therapeutic doses [9, 29, 30]. Dissolution, solubility, and intestinal uptake are reflected in the BDDCS class. Saturation of enzyme and transporter systems may occur at different sites: intestinal and hepatic efflux transporters, uptake transporters, and metabolizing enzymes. The most important intestinal and hepatic efflux transporters in drug pharmacokinetics are P-gp, MRP2, and BCRP, and the most relevant uptake transporters are OATP 1B1/3 and 2B1 [31]. In an attempt to identify drug characteristics responsible for nonlinearity, scalability was examined in relation to BDDCS class, metabolizing enzymes, and drug transporters. Drugs in BDDCS classes 2 and 4 might be prone to nonlinearity regarding low solubility, where class 2 will be even more challenging due to potential extensive metabolism. The majority of drugs with linear pharmacokinetics are classes 1 and 3, while the majority of drugs with nonlinear pharmacokinetics are classes 1 and 2. Extensive metabolism seems to complicate the scalability of pharmacokinetics, while solubility is less of a problem.

When further zooming into specific metabolizing enzymes and transporters, great variety is shown among linear and nonlinear compounds. Although nonlinearity could be caused by saturated metabolism [13, 18, 22], in most cases it may be attributed to saturation of transporters in the gut wall [13–15, 17, 21]. Among these transporters are OATP, P-gp, MRP2, BCRP, and OCTs, with the majority of BDDCS class 2 drugs being transported by OATPs. OATPs mostly transport large, hydrophobic organic anions from the portal blood into hepatocytes and may therefore influence the rate of elimination [32]. Although saturation of OATPs may be a cause of nonlinearity, due to great interpatient variability in transporter abundance and difference in transporter affinity for each drug, it is difficult to predict nonlinearity beforehand. This is reflected in the group of seven drugs with linear pharmacokinetics that are also transported by OATPs. Based on current data it is hard to draw conclusions, however drugs in BDDCS class 2

Table 3 Drug characteristics of orally administered drugs (n = 41), with linear pharmacokinetics (n = 28) and nonlinear pharmacokinetics (n = 13)

Linear PK drugs (n = 28)	Solubility[a] (mg/mL)	Lipophilicity (log P)	BDDCS class	Metabolizing enzymes	Transporter proteins	References
AFN-1252[b]	0.003–0.01	3.21	3	NR	Passive transport	[56, 96]
Anastrozole	0.5	1.29	1	CYP3A4/5 CYP2C8 UGT1A4	P-gp	[10, 97–99]
Atenolol	24.8	0.16	3	Minimal metabolism	OATP2B1 OATP1A2	[10, 100, 101]
Caffeine	21.5	−0.07	1	CYP1A2	Passive transport	[10, 102, 103]
Clarithromycin	2	3.16	3	CYP3A4	P-gp	[10, 104–106]
Diltiazem (hydrochloride)	30–100	2.70	1	CYP3A4/5	P-gp	[10, 107, 108]
Diphenhydramine	1000	3.27	1	CYP2D6 CYP1A2 CYP2C9 CYP2C19	NR	[10, 109]
Enalapril	25	0.67	1	Carboxylesterase	OATP1B1 MRP2	[10, 110, 111]
Fexofenadine	1–10	1.96	3	Minimal metabolism	P-gp OATP2B1/3 OATP1A2	[10, 101, 112, 113]
Fosdevirine[b]	0.0094	3.50	3	NR	NR	[114]
Losartan (potassium)	0.048	4.10	2	CYP3A4 CYP2C9	P-gp	[10, 115–117]
Metformin	30–100	−1.63	3	Minimal metabolism	OCT1/2	[10, 118–122]
Midazolam (hydrochloride)	30–100	3.27	1	CYP3A4/5/7	P-gp	[10, 123, 124]
NBI-1[b]	Highly soluble	Highly permeable	1	NR	NR	[50]
Nifedipine	0.006	2.20	2	CYP3A4	P-gp	[10, 125]
Selexipag	<0.1	4.40	3	CYP2C8	P-gp OATP1B1 OATP1B3 BCRP	[126]
Paracetamol	23.7	0.20	1	UGT1A1/6/9 SULT1A1/3/4 CYP1A2 CYP2E1	P-gp MRP1/5	[10, 127]
Phenobarbital	1	1.47	1	NR	P-gp	[10, 128]
Pravastatin	300	2.18	3	CYP3A4	P-gp OATP2	[10, 129, 130]
Raltegravir (potassium)	71	1.16	2	UGT1A1	P-gp BCRP	[10, 131, 132]
Tenofovir (disoproxil)	13.4	0.80	3	Carboxylesterase	OATP1/3 MRP4	[10, 133]
Tolbutamide	0.109	2.34	2	CYP2C9	OATP2	[10, 134, 135]
Unknown integrase inhibitors A[b]	NR	NR	NR	NR	NR	[54]
Unknown integrase inhibitors B[b]	NR	NR	NR	NR	NR	[54]
Unknown integrase inhibitors C[b]	NR	NR	NR	NR	NR	[54]
Unknown integrase inhibitors D[b]	NR	NR	NR	NR	NR	[54]

Table 3 (continued)

Linear PK drugs (n = 28)	Solubility[a] (mg/mL)	Lipophilicity (log P)	BDDCS class	Metabolizing enzymes	Transporter proteins	References
Zidovudine	25	0.08	1	UGT2B7	SLC28A1/3 SLC 22A6/7/8/11	[10, 136–138]
ZK253[b]	NR	Poor permeability	NR	NR	NR	[24]

Nonlinear PK drugs (n = 13)	Nonlinear PK parameters	Solubility[a] (mg/mL)	Lipophilicity (log P)	BDDCS class	Metabolizing enzymes	Transporter proteins	References
Atorvastatin (calcium)	AUC	0.0000204	4.46	2	CYP3A4	OATP1B1 P-gP	[10, 139]
Celiprolol	AUC, $t_{½}$	151	1.92	3	Minimal metabolism	OATP2B1 OATP1A2	[10, 101, 140]
Mirodenafil[b]	AUC, CL/F	0.181	2.85	3	CYP3A4 CYP2C19 CYP2D6	NR	[141–143]
Nicardipine	AUC	7.9	3.82	1	CYP3A4	NR	[10, 144]
Omeprazole	AUC	0.5	2.23	1	CYP2C19 CYP3A4	NR	[10, 145]
Pitavastatin	$t_{½}$	0.1–1	3.59	2	UGT1A3 UGT2B7 CYP2C9	OATP1B1/3 BCRP	[10, 146, 147]
Propafenone (hydrochloride)	AUC, F	0.093	3.64	2	CYP2D6 CYP1A2 CYP3A4	NR	[10, 148, 149]
Quinidine (sulfate)	AUC	11.1	3.77	1	CYP3A4	P-gp	[10, 150]
Rosuvastatin (calcium)	AUC	10–33	1.90	3	CYP2C9 CYP2C19 CYP3A4 CYP2D6	OATP1B1/3 BCRP P-gp	[10, 151–153]
Sumatriptan (succinate)	AUC, F	21.4	0.93	1	Monoamine oxidase-A	OCT1	[10, 154]
Telmisartan	AUC, CL/F	<0.1	7.54	2	UGT	OATP1B3 P-gp MRP2 BCRP	[10, 155–157]
Verapamil (hydrochloride)	AUC	0.75	4.47	1	CYP3A4 CYP1A2	P-gp OCT	[10, 106, 158]
Warfarin	V_d, $t_{½}$	0.018	2.60	2	CYP2C9	BCRP	[10, 134, 159]

AUC area under the curve, *BDDCS* Biopharmaceutical Drug Disposition Classification System, *BCRP* breast cancer resistance protein, *CL/F* apparent clearance, *CYP* cytochrome p450, *F* biological availability, *MRP* multidrug resistance-associated protein, *NR* not reported, *OATP* organic anion transporting polypeptide, *OCT* organic cation transporting proteins, *P-gP* p-glycoprotein, *PK* pharmacokinetics, $t_{½}$ half-life, *SLC* solute carrier family, *SULT* sulfotransferase *UGT* uridine diphosphate (UDP)-glucuronosyltransferase, V_d volume of distribution

[a]Experimental solubility in 250 mL or less of aqueous media over a pH range of 1–7.5 at 37 °C. When experimental solubility was not reported, qualitative evaluation such as 'highly soluble in water' was used and a range is given in the table

[b]Drug characteristics of nonregistered drugs were collected from the literature, other than FDA documents or the article by Benet et al. [10], and the BDDCS class was based on these literature values

and drugs with affinity for drug transporters may be prone to having nonlinear pharmacokinetics.

The percentage of predictable pharmacokinetics, especially for intravenous administration, is much higher in microdose studies than for extrapolation from preclinical models. When predicting human pharmacokinetics with physiologically based pharmacokinetic modeling (PB-PK) or in vitro to in vivo extrapolation (IVIVE), the degree of success for predicting V_d, CL, and oral AUC is only 78% (n = 18), 78% (n = 19), and 51% (n = 108) of cases, respectively [6, 33–36]. This may be not only due to physiological differences between animal and human but also due to poor animal models of human illness and conflicting data from in vivo and/or in vitro experiments. Results from this review clearly show an added value of microdose data to predict pharmacokinetics at a therapeutic dose.

Microdose trials have been performed for small molecule drugs, but there is only one trial in which a protein drug, human recombinant alkaline phosphatase (hRESCAP), has been administered to healthy volunteers [37]. A major concern regarding microdosing with targeted therapies is the expectation of nonlinear pharmacokinetics as is seen for monoclonal antibodies [38, 39]. Target-mediated drug disposition (TMDD) of these drugs causes poor linearity in the low dose range by saturated target binding and CL pathways [40]. However, TMDD could also occur for small molecules when the target is expressed at relatively high concentrations and the compound has a high affinity for this target [41]. An example of such a drug is warfarin, a small molecule with high affinity to vitamin-K epoxide reductase. Nonlinearity due to TMDD is reflected in nonlinear V_d and $t_{½}$, while the exposure is well-predicted from the microdose [24]. Although very few small molecules show this type of nonlinearity, one should be aware of the possible implications of TMDD for microdose trials.

Based on all data available, it is difficult to describe specific drug characteristics that influence the predictability of microdose pharmacokinetics. When performing a microdose study, guidance on the predictive value may be derived from preclinical data. In their decision tree model, Bosgra et al. [42] showed how to integrate available preclinical data by combining information on dissolution, active transport or metabolism, and protein binding. Of 10 previously published cases, this decision tree was able to identify drugs with nonlinear pharmacokinetics. Combining microdose trials with preclinical data, as well as modeling and simulation methods, may improve the reliability of decision making in the future.

5 Conclusion

In this review, we questioned whether the pharmacokinetics in a clinically relevant therapeutic dose could be predicted from a microdose. Additionally, we incorporated drug characteristics in order to explain causes of nonlinearity. Overall, 94% of intravenously administered drugs and 68% of orally administered drugs displayed linear pharmacokinetics within the twofold criterion. Nonlinearity was caused by saturation of the enzyme and transporter systems, especially intestinal and hepatic efflux and uptake transporters. The high degree of success regarding linear pharmacokinetics confirms the strength of phase 0 microdose trials in gaining early pharmacokinetic data, thereby providing safety and reducing developmental costs.

Compliance with Ethical Standards

Conflict of interest Jos H. Beijnen is a part-time employee, stock holder, and patent holder for Modra Pharmaceuticals B.V. (a spin-out company developing oral taxane formulations). However, this activity is not related to the content of the current manuscript. Merel van Nuland, H. Rosing, and A. D. R. Huitema have no conflicts of interest to declare.

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