CORRECTION

Correction to: Pharmacokinetics of Fentanyl and Its Derivatives in Children: A Comprehensive Review

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Abstract Fentanyl and its derivatives sufentanil, alfentanil, and remifentanil are potent opioids. A comprehensive review of the use of fentanyl and its derivatives in the pediatric population was performed using the National Library of Medicine PubMed. Studies were included if they contained original pharmacokinetic parameters or models using established routes of administration in patients younger than 18 years of age. Of 372 retrieved articles, 44 eligible pharmacokinetic studies contained data of 821 patients younger than 18 years of age, including more than 46 preterm infants, 64 full-term neonates, 115

infants/toddlers, 188 children, and 28 adolescents. Underlying diagnoses included congenital heart and pulmonary disease and abdominal disorders. Routes of drug administration were intravenous, epidural, oral-transmucosal, intranasal, and transdermal. Despite extensive use in daily clinical practice, few studies have been performed. Preterm and term infants have lower clearance and protein binding. Pharmacokinetics was not altered by chronic renal or hepatic disease. Analyses of the pooled individual patients' data revealed that clearance maturation relating to body weight could be best described by the Hill function for sufentanil ($R^2 = 0.71$, $B_{\max}$ 876 mL/min, K_{50} 16.3 kg) and alfentanil ($R^2 = 0.70$, $B_{\max}$ (fixed) 420 mL/min, K_{50} 28 kg). The allometric exponent for estimation of clearance of sufentanil was 0.99 and 0.75 for alfentanil clearance. Maturation of remifentanil clearance was described by linear regression to bodyweight ($R^2 = 0.69$). The allometric exponent for estimation of remifentanil clearance was 0.76. For fentanyl, linear regression showed only a weak correlation between clearance and bodyweight in preterm and term neonates ($R^2 = 0.22$) owing to a lack of data in older age groups. A large heterogeneity regarding study design, clinical setting, drug administration, laboratory assays, and pharmacokinetic estimation was observed between studies introducing bias into the analyses performed in this review. A limitation of this review is that pharmacokinetic data, based on different modes of administration, dosing schemes, and parameter estimation methods, were combined.

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There are several errors in Tables 2, 3, 4, and 5 in the original published article. The full article with all tables corrected is republished here.

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Key Points

Fentanyl and its derivatives have been approved for some time, but there is still a lack of knowledge regarding pharmacokinetics in children.

In the future, opportunistic clinical trials should be performed on the pharmacokinetics and pharmacodynamics of fentanyl and its derivatives in much larger cohorts of pediatric patients, and in special subpopulations, such as preterm infants, obese children and children with liver or kidney impairment.

1 Introduction

Fentanyl is commonly used within the field of anesthesia owing to its high lipid solubility and potency. Based on the extensive use of fentanyl, its derivatives were developed and approved in the 1980–90s [1, 2].

Fentanyl and its derivatives exert their pharmacological action through interaction with the μ -opioid receptor, see Table 1 for the relative potencies, physicochemical properties, and pharmacokinetics of these substances in adults. Both fentanyl and sufentanil are drugs with a high extraction ratio while alfentanil has an intermediate extraction ratio [3, 4]. These compounds are metabolized by hepatic and intestinal cytochrome P450 (CYP) 3A to pharmacologically inactive metabolites and show dose-linear pharmacokinetics [5–13].

Remifentanil is mainly metabolized through hydrolysis by unspecific plasma and tissue esterases to a metabolite lacking pharmacodynamic activity. Remifentanil shows a dose-independent clearance (CL), and has a much smaller volume of distribution (V_d) than fentanyl, resulting in a much shorter half-life [14, 15].

There are also distinct differences in their context-sensitive half-time, which is defined as the time required for the plasma drug concentration in the central compartment to decrease by 50% as a function of the duration of a continuous infusion. However, this does not allow conclusions on the decrease in plasma concentration required for recovery from the drug's effect [16, 17]. While fentanyl has a markedly prolonged context-sensitive half-time with increased infusion durations compared with alfentanil and sufentanil, remifentanil has a context-sensitive half-time independent of the infusion duration.

Intravenous fentanyl is currently used intraoperatively during general anesthesia [18]. Rapid-onset fentanyl delivery systems such as buccal or sublingual tablets, nasal spray, and lollipop are mainly used off-label in children. Transdermal fentanyl matrix patches are approved for opioid-tolerant children over 2 years of age. Sufentanil is also mainly used during general anesthesia but alfentanil and remifentanil can be used for analgo-sedation. Remifentanil is well suited for short or outpatient surgical procedures [18].

Their adverse effects are related to dose and effect-site concentrations and are mainly mediated by their μ -opioid receptor agonism. Respiratory depression is the most relevant adverse effect. Other side effects include sedation, nausea, vomiting, constipation, pruritus, physical dependence, risk of addiction, bradycardia, and skeletal muscle rigidity, while hemodynamic responses rarely occur upon administration [18].

Despite the extensive use of fentanyl and its derivatives in children, only limited pharmacokinetic (PK) data in pediatric patients are available. This review considers the pharmacology of fentanyl and its derivatives sufentanil, alfentanil, and remifentanil in infants, children, adolescents, and special pediatric sub-populations.

2 Methods

2.1 Search Strategy and Selection Criteria

PubMed was searched systematically for articles published in English until 28 February, 2017, to identify PK studies of fentanyl, sufentanil, alfentanil, and remifentanil in pediatric patients (younger than 18 years of age). In the search string, each of the four compounds using Medical Subject Headings (MeSH), except remifentanil, was linked with AND to the following search terminologies: 'children', 'Pediatrics' [MeSH], 'infant, premature' [MeSH], 'infant, newborn' [MeSH], 'infant' [MeSH], 'child, preschool' [MeSH], 'child' [MeSH], 'adolescent' [MeSH]. To avoid missing data, an additional search was conducted: 'compound' AND pharmacokinetics AND (infant OR infants OR newborn OR newborns OR child OR children OR childhood OR pediatric OR pediatrics OR paediatric OR paediatrics).

2.2 Comprehensive Review

Abstracts of the selected articles were reviewed for eligibility. Studies were included if they contained relevant PK parameters or models, established routes of administration, and patients younger than 18 years of age. Identified studies and case reports were reviewed so that only those

Table 1 Overview of pharmacological properties of fentanyl and its derivatives [3, 4, 14, 15, 52, 112, 173–180]

	Fentanyl	Sufentanil	Alfentanil	Remifentanil
Potency compared with morphine	100–300	800–1000	40–50	100–200
IV induction dose ($\mu\text{g/kg}$)	2–6	0.25–2.0	25–100	1–2
IV maintenance dose ($\mu\text{g/kg}$)	0.5–2	2.5–10	5–10	0.1–1.0
IV infusion rate ($\mu\text{g/kg/h}$)	0.5–5	0.5–1.5	30–120	0.1–1.0
Other routes of administration than IV	Transdermal, transmucosal (buccal, nasal, sublingual), epidural	Epidural, sublingual		
Time to onset (min)	1.5	1	0.75	<1
Time to peak effect (min)	4.5–8	2.5–5	1.5	1.5
Duration of peak effect (min)	20–30	30	15	
Duration of analgesic effect (min)	60–120	100–150	30–60	5–10
Analgesic plasma concentration (ng/mL)	0.6–3.0	0.5–2.5	50–300	0.3–3
Plasma concentration associated with loss of consciousness (ng/mL)	>20.0	>2.5	>400	>4
$t_{1/2\alpha}$ (min)	1.7 $\pm$ 0.1	1.4 $\pm$ 0.3	1.31 $\pm$ 0.48	1
$t_{1/2\beta}$ (min)	13.4 $\pm$ 1.6	17.7 $\pm$ 2.6	9.4 $\pm$ 2.7	6
$t_{1/2\gamma}$ (min)	219 $\pm$ 10 (120–240)	164 $\pm$ 22 (120–180)	93.7 $\pm$ 8.3 (60–120)	10–20 (6–14)
V_d (L/kg)	0.36 $\pm$ 0.07	0.16 $\pm$ 0.02	0.12 $\pm$ 0.04	0.1
$V_{d\alpha}$ (L/kg)	4.0 $\pm$ 0.4 (3–5)	1.7 $\pm$ 0.2 (2.5–3.0)	1.0 $\pm$ 0.3 (0.4–1.0)	0.35 (0.2–0.4)
CL (mL/min/kg)	13 $\pm$ 2 (10–20)	12.7 $\pm$ 0.8 (10–15)	7.6 $\pm$ 2.4 (3–9)	40 (30–60)
Protein binding (%)	80–84	91–92.5	88.7–92.1	70
pKa	8.4	8.0	6.5	7.1
Non-ionized fraction at pH 7.40 (%)	8.5	20	89	67
Metabolism	CYP3A	CYP3A	CYP3A	Plasma and tissue esterases
Lipid solubility (octanol/water distribution coefficient)	813–816	1727–1778	128	18
References	[14, 52, 112, 173–179]	[3, 14, 112, 173–175, 177–179]	[4, 14, 112, 173–175, 177–180]	[14, 15, 112, 173–175, 177–179]

Italic numbers indicate information from the Summary of Product Characteristics

CL clearance, *CYP* cytochrome P450, *IV* intravenous, *pKa*, $t_{1/2\alpha}$ distribution half-life, $t_{1/2\beta}$ redistribution half-life, $t_{1/2\gamma}$ terminal elimination half-life, $V_{d\alpha}$ volume of distribution of the central compartment, $V_{d\alpha}$ volume of distribution at steady state

presenting original PK data were included. If individual children were considered in adult PK studies and individual pediatric data were given, these data were extracted and included. Studies reporting only drug concentrations in children were assessed in a descriptive manner.

In each publication, the following information was extracted and analyzed: type of study, the number of patients, the pediatric age group (according to the International Conference on Harmonization E11 guidelines [19]), the patient demographics, the used formulation, the route of administration, the number of PK samples taken from each patient, the sampling duration, the assay used for analysis, and relevant PK parameters (such as CL, half-life, and V_d). Special populations were defined as patients with chronic kidney or liver disease, obesity, or on cardiopulmonary bypass (CPB) or extracorporeal membrane oxygenation (ECMO).

2.3 Statistical Analysis

To assess the maturation of CL, published individual CL was related to bodyweight and, if relevant with respect to the literature, also to age by linear or non-linear regression models and allometric scaling. For non-linear regression, the Hill equation was applied [20, 21]. This equation describes CL saturation and allows sigmoidal behavior depending on the Hill coefficient h . Such a sigmoidal shape may be necessary for describing maturation processes of CL in infancy and early childhood. Parameter $B_{\max}$ stands for maximal CL at saturation, and K_{50} corresponds to bodyweight that produces half-maximal CL. Additionally, data were log-transformed to estimate the allometric exponent by the standard power law for CL [22].

Statistical analyses were performed using GraphPad Prism Version 7.00 (GraphPad Software, La Jolla, CA, USA). Pharmacokinetic data were converted into comparable units for presentation in Tables 2, 3, 4 and 5. Data are given as mean $\pm$ standard deviation, or range, if not indicated differently.

3 Results

3.1 Literature Search

The original search retrieved 8976 publications (fentanyl $n = 5900$, sufentanil $n = 590$, alfentanil $n = 776$, remifentanil $n = 1710$). After removal of duplicate entries and screening of the abstracts, 372 full text articles were downloaded. Five publications were found by scanning through the references of the articles.

Clinical studies were mostly prospective non-randomized open-label trials. Fentanyl and its derivatives were

mainly administered intravenously, but data on oral-transmucosal fentanyl citrate (OTFC), transdermal fentanyl, and epidural fentanyl and sufentanil were available. There were 44 publications focusing on pharmacokinetics [fentanyl $n = 19$ (1 including alfentanil), sufentanil $n = 8$, alfentanil $n = 13$ (1 including fentanyl), remifentanil $n = 5$], whereas drug concentrations were determined in another 30 studies (fentanyl $n = 18$, sufentanil $n = 8$, alfentanil $n = 3$, remifentanil $n = 1$).

The eligible PK studies presented data of 821 patients younger than 18 years of age, which included more than 46 preterm infants, 64 neonates, 115 infants/toddlers, 188 children, and 28 adolescents. In 380 patients, age was not specified. Congenital heart defects ($n = 312$), pulmonary/thoracic diseases ($n = 91$), neurological disorders ($n = 42$), and abdominal ($n = 38$) disorders were the most common underlying diagnoses. Nineteen patients with chronic kidney disease were included, nine with liver disease, six were obese, 282 were on CPB, and 25 were undergoing kidney or liver transplants. Studies were mainly conducted during anesthesia or analgo-sedation. Studies that measured plasma concentrations without PK assessments ($n = 27$) included data of 671 pediatric patients, including 130 preterm neonates, 134 neonates, 64 infants/toddlers, 80 children, and 9 adolescents.

3.2 Statistical Analysis

Maturation of fentanyl CL in preterm and term neonates showed a weak correlation to bodyweight ($R^2 = 0.22$; Fig. 1). Individual CL data were not available for older children and therefore these results cannot be extrapolated from children to adults in a linear manner for theoretical considerations. Maturation of sufentanil and alfentanil CL was assessed by fitting the Hill function ($R^2 = 0.71$ for sufentanil; Fig. 2, and $R^2 = 0.70$ for alfentanil; Fig. 3, both weighted by $1/y^2$) to the dataset of all available CL values including neonates for sufentanil and neonates and preterm infants for alfentanil.

For sufentanil, $B_{\max}$ as a parameter for maximum CL was estimated at 876 mL/min, which lies in the documented range of adults (10–15 mL/min/kg, 700–1050 mL/min for 70 kg). The bodyweight at which half-maximum CL is reached (K_{50}) was estimated at 16.3 kg, which corresponds to the 50th bodyweight percentile of a child aged ~ 4 to 4.3 years [23]. The allometric exponent for estimating sufentanil CL was determined at 0.99 for children aged older than 1 month (excluding neonates) weighing 3–70 kg (actual age 1 month to 18 years).

For alfentanil, $B_{\max}$ was fixed to 420 mL/min, which corresponds to average adult CL values (3–9 mL/min/kg, 210–630 mL/min for 70 kg) and K_{50} was estimated at 28.0 kg (corresponding to an age of ~ 8.8 years [23]). The

Table 2 Pharmacokinetic information on fentanyl in children [8, 24, 29, 32, 33, 37, 39–41, 43, 55, 56, 67, 75, 79, 88, 90, 92, 93, 103, 136, 181–187]

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
2	1 ± 0 days	3.2 ± 1.1	30.3 ± 16.0	IV, 2–10 min	16.2 ± 2.59*	294 ± 113	5.94 ± 1.47**	2	13/10 h	RIA	Age 0–1 month	[24]
2	7 ± 0.056 months	6.0 ± 1.2	19.1 ± 14.5	IV, 2–10 min	18.1 ± 1.41*	233 ± 137	4.45 ± 1.64**	2	13/10 h	RIA	Age 1 month–1 year	[24]
6	3.17 ± 0.68 years	17.3 ± 3.4	10.0 ± 3.1	IV, 2–10 min	11.5 ± 4.19*	244 ± 79	3.06 ± 1.02**	2	13/10 h	RIA	Age 1–5 years	[24]
3	12 ± 1.73 years	58.3 ± 13.3	4.3 ± 1.2	IV, 2–10 min	7.05 ± 1.24*	208 ± 71	1.92 ± 1.04**	2	13/10 h	RIA	Age 10–14 years	[24]
19	3.2 ± 4.2 years		Max 3.6 ± 3.1/h	IV, 5 min; cont. 70.5 (7–144) h	13.2 ± 9.6	1266	15.2	Non	> 11	RIA	All patients, cont. sedation	[33]
5	0.14 ± 0.08 years		Max 4.3 ± 3.7/h	IV, 5 min; cont. 72.6 (48–144) h	8.2 ± 4.6			Non	> 11	RIA	Age < 6 months ^a	[33]
9	1.4 ± 1.1 years		Max 3.9 ± 3.3/h	IV, 5 min; cont. 70.9 (19–136) h	18.9 ± 11.0			Non	> 11	RIA	Age 6 months–6 years	[33]
5	9.5 ± 2.8 years		Max 2.5 ± 2.3/h	IV, 5 min; cont. 68.2 (7–136) h	8.0 ± 3.9			Non	> 11	RIA	Age > 6 years ^a	[33]
15	1 day–10.9 years ^e		2/9 ± 7/h	IV, bolus, cont. 91 ^b (37–211) h	19.3 ± 12.4	954 ± 606	17.2 ± 14.7	Non	> 8/48 h	RIA	Comparison of fentanyl and alfentanil	[136]
14	3 ± 1 days ^d	2.9 ± 0.2 ^d	10–50	IV, 1–3 min	17.94 ± 4.38 ^d	317 ± 70 ^d	5.1 ± 1.0 ^d	2	> 8/18 h	RIA	All patients	[29]
4	0.6 ± 0.13 days ^d	3.5 ± 0.2 ^d	10–50	IV, 1–3 min	28.00 ± 11.00 ^d	188 ± 85 ^d	4.66 ± 1.74 ^d	2	> 8/18 h	RIA	Myelomeningocele repair	[29]
4	7.0 ± 2.48 days ^d	2.5 ± 0.5 ^d	50	IV, 1–3 min	21.43 ± 9.15 ^d	213 ± 37 ^d	5.87 ± 2.65 ^d	2	> 8/18 h	RIA	Thoracic surgery	[29]
6	1.8 ± 0.5 days ^d	2.7 ± 0.3 ^d	25–50	IV, 1–3 min	9.00 ± 1.00 ^d	473 ± 132 ^d	4.88 ± 1.42 ^d	2	> 8/18 h	RIA	Abdominal surgery	[29]
9		1.1 ± 0.3	30	IV, 1 min		1062 ± 558			3/6–9 h	GLC [181]	Preterm and term infants, GA 23–38 weeks	[41]
14	18.3 ± 23.6 days	2.7 ± 0.5	54.1 ± 2.3	IV, 2 min	22.4 ± 8.2	325.8 ± 181.8	8.3 ± 2.4	2/3	23/12 h	RIA [182, 183]	All patients	[32]
3	13.3 ± 20.3 days	2.9 ± 0.4		IV, 2 min	21.1 ± 8.5	336.3 ± 193.4	8.1 ± 2.5	2/3	23/12 h	RIA [182, 183]	Preterm infants, GA < 36 weeks	[32]
11	36.7 ± 30.4 days	2.0 ± 0.1		IV, 2 min	26.2 ± 7.1	294.3 ± 173.9	9.0 ± 2.7	2/3	23/12 h	RIA [182, 183]	Neonates	[32]

Table 2 continued

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	t _{1/2} (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
20		1.7 ± 0.8	5–12.5/0.68 ± 0.24/h	IV, 10 min, cont. 86 ± 47 h						RIA	All patients, GA 32.5 ± 3.6 weeks	[43]
12			5–12.5/0.64 ± 0.19/h	IV, 10 min, cont. 93 ± 55 h	12.1 ± 15.4					RIA	Preterm infants, GA < 34 weeks	[43]
8			5–12.5/0.75 ± 0.30/h	IV, 10 min, cont. 75 ± 24 h	13.0 ± 19.8					RIA	Preterm and term infants, GA ≥ 34 weeks	[43]
7	16 ± 9 days	1.9 ± 1.1	1.28 ± 0.58/h	IV, cont. 111 (48–206) h	19.2 ± 8.2	570 ± 156	17 ± 9	1	5	GC-MS [184]	Preterm and term infants GA 27–39 weeks; C _{max} 0.7–2 ng/mL	[39]
38	10 (5; 21) hours ^e	1.8 (1.2; 2.6) ^e	10.5/h/1.5/h	IV, cont. 58 (45; 78) h ^e	11.5 ± 4.0 (4.6–18.5)			Non	5/60h	RIA [185]	Preterm and term infants, GA 26–42 weeks	[40]
1	15 months	~ 8	50/18/h	IV, bolus, cont. 123 min	7.3	173	1.85		14/~ 5 h	GLC [56, 181]	Case report, renal failure, CPB	[55]
1	3 years	10.2	1.64/18/h	IV, bolus, cont. 136 min	0.41	4620	0.142		8 ~ 5 h	GLC [56, 181]	Case report, Wilm's tumor	[55]
10	18.9 ± 15.8 months	8.6	50/9–18/h	IV, 1 min; cont. 112 (81–141) min	12.8 ± 7.3	141 ± 98	1.385 ± 0.875	2		GLC [181]	CPB	[56]
19	3.54 years (5 months–16 years)	13.2 (3.5–50)	30–50/9–18/h	IV, bolus; cont.	13.3 ± 6.5	102 ± 85	1.203 ± 0.777	2	> 9/> 2 h	GLC [181]	CPB	[67]
12	5.5 ± 11.5 days	3.2 ± 0.6	5–10/3.3 ± 1.6/h	IV, bolus; cont.				Non	11	RIA	All patients, CPB, ECMO	[75]
9	6.7 ± 13.3 days	3.2 ± 0.6	5–10/3.2 ± 1.7/h	IV, bolus; cont.	25.3 ± 41.9			Non		RIA	Survivors, CPB, ECMO	[75]
3	2 ± 1.7 days	3.1 ± 0.8	5–10/3.6 ± 1.3/h	IV, bolus; cont.	8.1 ± 12.8**			Non		RIA	Non-survivors, CPB, ECMO	[75]
130	5.9 ^e months (1.2–28.4)	6.4 ^e (3.7–11.6)	2.67 ^e (1.46–4.08)/h	IV, bolus/cont.	14.8 ^e (5.7–24.0)			2	6 ^e (4–10)	MS	All patients, Pop-PK, covariate model	[37]
121	5.1 ^e months (1.0–21.8)	6.1 ^e (3.7–9.9)	2.79 ^e (1.67–4.17)/h	IV, bolus/cont.	5.9			2	6 ^e (4–11)	MS	< 40 kg, Pop-PK, allometric theory-based model	[37]

Table 2 continued

N	Age	Weight (kg)	Dose ($\mu\text{g/kg}$)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
93	8.1 ^e months (3.7–35.0)	7.6 ^e (5.1–12.8)	2.63 ^e (1.63–3.75)/h	IV, bolus	7.4			2	5 ^e (4–8)	MS	Bolus only, Pop-PK, allometric theory-based model	[37]
6	16.6 $\pm$ 1.5 years	137.4 $\pm$ 14.3	1.00 $\pm$ 0.36	IV, bolus	11.2 $\pm$ 2.6	290 $\pm$ 118	4.7 $\pm$ 2.1	Non	$\geq 10/24$ h	LC-MS/MS [8]	Obese adolescents	[79]
13	14 ^b (3–36) months	11 ^b (5–17)	2/1.12/h/ 0.375/h	EPI, cont. 38.0 ^b (37.3–38.8) h		334 ^b (137–1730)		Non	6	LC-MS/MS [186, 187]	$t_{1/2}$ calculated based on MRT: 954 ^b (215–1892) min	[88]
11	68 ^b (45–131) months	21 ^b (16–52)	2/1.12/h/ 0.375/h	EPI, cont. 38.0 ^b (35.5–39.0) h		358 ^b (206–563)		Non	6	LC-MS/MS [186, 187]	$t_{1/2}$ calculated based on MRT: 478 ^b (425–796) min	[88]
21	5.5 $\pm$ 1.3 years	20.9 $\pm$ 5.7	12.2 $\pm$ 1.09	OTFC	17.5		2.44	2	> 3 ≤ 4 h	RIA [182]	OTFC bioavailability 33%	[90]
21	5.5 $\pm$ 1.3 years	20.9 $\pm$ 5.7	12.2 $\pm$ 1.09	OTFC	46.0 $\pm$ 16.0 ^f	168 $\pm$ 90	9.8 $\pm$ 4.1 ^f	Non	> 3 ≤ 4 h	RIA [182]	C_{max} 1.60 $\pm$ 0.55 ng/mL, t_{max} 59 $\pm$ 32 min; AUC 5.03 $\pm$ 2.20 h·ng/mL	[90, 93]
17	6.7 $\pm$ 4.9 years	21.5 $\pm$ 4.9	12.7 $\pm$ 1.2	OTFC	15.2 $\pm$ 6.3	276	4.9 $\pm$ 2.8	2	12 $\pm$ 1/3.67 h	RIA [182]	OTFC bioavailability 36%, C_{max} 1.03 $\pm$ 0.31 ng/mL, t_{max} 53 $\pm$ 40 min; CL, $t_{1/2}$ and V_{dss} data combined with [90], $n = 38$	[90, 92]
17	6.7 $\pm$ 4.9 years	21.5 $\pm$ 4.9	12.7 $\pm$ 1.2	OTFC	68.5 $\pm$ 39.8 ^f	198 $\pm$ 222	11.6 $\pm$ 6.6 ^f	Non		RIA [182]	C_{max} 1.06 $\pm$ 0.31 ng/mL, t_{max} 56 $\pm$ 41 min, AUC 4.54 $\pm$ 3.60 h·ng/mL	[92, 93]
38	6.3 $\pm$ 1.6 years		12.4 $\pm$ 1.04	OTFC	57.7 $\pm$ 32.3 ^f	184 $\pm$ 168	10.7 $\pm$ 5.5 ^f	Non		RIA [182]	Combined data, C_{max} 1.32 $\pm$ 0.51 ng/mL, t_{max} 58 $\pm$ 36 min, AUC 4.78 $\pm$ 2.96 h·ng/mL	[90, 92, 93]
10	7.9 $\pm$ 1.94 years	28.2 $\pm$ 10.2	13.9 $\pm$ 1.41	PO	55.5 $\pm$ 37.5 ^f	282 $\pm$ 168	17.5 $\pm$ 7.20 ^f	Non	16 (8–16)/10 h	LC-MS/MS	C_{max} 1.83 $\pm$ 1.19 ng/mL, t_{max} 104 $\pm$ 98 min, AUC 6.46 $\pm$ 3.96 h·ng/mL	[93]

Table 2 continued

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
8	42.4 ± 16.4 months	14.6 ± 2.9	1.72/h (patch 25 µg/h)	TD		867 ± 373			18/144 h	RIA [182]	$C_{\max}$ 1.64 ng/mL, $t_{\max}$ 1080 min, AUC 91.75 h·ng/mL, C_{ss} 1.32 ng/mL	[103]

Reported statistical significance is indicated as follows: $p < 0.05^*$, $p < 0.005^{**}$, $p < 0.001^{***}$

AUC area under the plasma concentration–time curve, CPB cardiopulmonary bypass, CL clearance, CL/F apparent clearance after non-intravenous administration, $C_{\max}$ maximum plasma concentration, Comp compartmental analysis, cont continuous, C_{ss} concentration at steady-state, ECMO extracorporeal membrane oxygenation, EPI epidural, GA gestational age, GLC gas liquid chromatography, IV intravenous, Lab laboratory, LC–MS liquid chromatography–mass spectrometry, Max maximum, MRT mean residence time, OTFC oral transmucosal fentanyl citrate, PO per os, Pop-PK population pharmacokinetics, RIA radioimmunoassay, TD transdermal, $T_{\max}$ time to maximum plasma concentration, $t_{1/2}$ half-life, V volume of distribution, V/F apparent volume of distribution after non-intravenous administration

^aMean clearance values of the youngest and the oldest children were switched in the results section of the publication and recalculated for this review

^bMedian data (range)

^cDemographics also include alfentanil group

^dMean ± SEM

^eMedian data (interquartile range)

^fCL/V and V/F

allometric exponent for estimating alfentanil CL was determined to be 0.75 for children aged older than 1 month (excluding preterm and term neonates) weighing 4.3–51 kg (actual age 3 months to 14 years). Thus, the Hill function reasonably well described maturation of CL for both substances by a sigmoidal shape taking the maturation of CL in early childhood into account.

Maturation of remifentanil CL was described by linear regression ($R^2 = 0.69$; Fig. 4). The Hill function was fitted as well but $B_{\max}$ could not be determined probably owing to few data in the saturation phase. Moreover, linear maturation of remifentanil CL may be explained by the fact that remifentanil is metabolized by unspecific tissue and plasma esterases. Maturation of their metabolic capacity, however, has not yet been studied.

The allometric exponent for remifentanil CL was determined at 0.76 for children (including neonates) weighing 2.5–96.8 kg (actual age 5 days to 17 years). Results of linear or non-linear regression (solid line) together with allometric scaling (dotted line) are presented in the figures. Reported parameter values in the figure legends are from the linear analysis or the Hill equation fit.

4 Pharmacokinetics

4.1 Fentanyl

4.1.1 Intravenous Fentanyl

Few studies in neonates, infants, and children have reported age-dependent differences (see Table 2). Clearance and V_d in neonates and infants are higher than in adults and children, probably owing to an increased hepatic blood flow (normalized to weight) and/or altered protein binding [24]. In a single neonatal case report, protein binding was 63%, clearly lower than in adults [25].

Fentanyl plasma concentrations after an intravenous bolus (~ 30 µg/kg) were found to be lower in infants than in children, and in children lower than in adults [26]. These findings may result from a larger V_d or age-related differences in protein binding. An increase in CL probably reflects maturation of CYP enzymes suggesting that the Michaelis–Menten constant is age dependent [27, 28].

Neonates undergoing major surgery showed a highly variable disposition after a bolus of 25–50 µg/kg, which was hemodynamically well tolerated [29]. No difference was found between doses and postnatal age. A rebound phenomenon was described in half of the patients owing to tissue redistribution. Furthermore, half-life was prolonged in neonates with markedly increased intraabdominal pressure (1.5–3 times the population mean of 317 min), which may have compromised the blood flow in the splanchnic

Table 3 Pharmacokinetic information on sufentanil in children [108–110, 114–116, 119, 120, 188, 189]

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples/duration	Lab method	Remarks	References
9	11.0 ± 10.8 days	3.24 ± 0.36	10–15	IV, bolus	6.7 ± 6.1*	737 ± 346*	4.15 ± 1.01*	3	24/20 h	RIA [188]	Neonates 1–30 days	[108]
7	13.9 ± 9.1 months	8.7 ± 3.2	10–15	IV, bolus	18.1 ± 2.8*	214 ± 41	3.09 ± 0.95	3	24/20 h	RIA [188]	Infants 1 month–2 years	[108]
7	6.4 ± 3.2 years	21.0 ± 6.7	10–15	IV, bolus	16.9 ± 3.2*	140 ± 30	2.73 ± 0.50	3	24/20 h	RIA [188]	Children 2–11 years	[108]
5	15.4 ± 1.9 years	58.4 ± 9.4	10–15	IV, bolus	13.1 ± 3.6	209 ± 23	2.75 ± 0.53	3	24/20 h	RIA [188]	Adolescents 12–18 years	[108]
20	5.2 ± 1.7 years	19.1 ± 5.2	2.42 ± 0.67	IV, bolus	30.5 ± 8.8	97.0 ± 42.0	2.94 ± 0.63	2/non	17/8 h	RIA [188]	Surgical patients	[110]
1	7 days	3.0	10	IV, bolus	4.3	434	2.6	3	24/20 h	RIA [188]	Case report, congestive heart failure	[109]
1	28 days		10	IV, bolus	18.8	160	3.2	3	24/20 h	RIA [188]	Same patient	[109]
1	4 days	3.1	10	IV, bolus	6.7	332	2.9	3	24/20 h	RIA [188]	Case report, congestive heart failure	[109]
1	20 days		10	IV, bolus	19.3	242	3.3	3	24/20 h	RIA [188]	Same patient	[109]
1	2 days	3.3	10	IV, bolus	1.7	1140	2.7	3	24/20 h	RIA [188]	Case report, congestive heart failure	[109]
1	27 days		10	IV, bolus	12.9	248	3.6	3	24/20h	RIA [188]	Same patient	[109]
1	17 years	76	3	IV, bolus	28.3	39	1.137	2	13/8 h	RIA [188, 189]	Orthopedic surgery patient	[114]
1	10 years	45	2/4.44/h	IV, bolus, cont. (48 h)	15.8	2940	24.2	2	20 + 19/48 h + 24 h	RIA [188]	Head trauma patient	[115]
41	4.05 ^a (0.18–17.4) years	14 ^a (3.2–80)	1.42 ^a (0.47–4.39)/h Total dose: 2197 ^a (621–47,221) µg	IV, cont. 99 ^a (25–600) h	10.8	504 ^a (102–12,300)		2	> 3 + 10/24 h + 36 h	HPLC–MS		[116]
6	11.7 ± 3.8 years	44.7 ± 12.9	3–5	IV, 1 min	16.4 ± 6.1 ^b	89.7 ± 15.7 ^b	1.65 ± 0.6 ^b	2/non	11/3 h	RIA	Surgical patients	[119]
6	11.8 ± 1.7 years	28.7 ± 5.7*	3–5	IV, 1 min	12.8 ± 12.0 ^b	76.0 ± 32.8 ^b	1.28 ± 0.62 ^b	2/non	11/3 h	RIA	Chronic renal failure	[119]
7	5.2 ± 2.1 months	5.3 ± 1.1	15	IV, 1 min	27.5 ± 9.3	53 ± 15	1.6 ± 0.46*	2	10/2 h	RIA	Age < 10 months, not surface-cooled, pre-CPB	[120]
6	15.5 ± 5.2 months	8.9 ± 1.6	15	IV, 1 min	18.1 ± 10.7	55 ± 10	3.0 ± 1.35	2	10/2 h	RIA	Age > 10 months, not surface-cooled, pre-CPB	[120]
7	5.1 ± 3.4 months	5.3 ± 2.4	15	IV, 1 min	21.5 ± 5.0	120 ± 36*	3.7 ± 1.1	2	10/2 h	RIA	Age < 10 months, surface-cooled, pre-CPB	[120]

Reported statistical significance is indicated as follows: $p < 0.05^*$, $p < 0.005^{**}$, $p < 0.001^{***}$ CL clearance, C_{max} maximum plasma concentration, Comp compartmental analysis, cont continuous, CPB cardiopulmonary bypass, HPLC–MS high-performance liquid chromatography–mass spectrometry, IV intravenous, Lab laboratory, RIA radioimmunoassay, $t_{1/2}$ half-life, V volume of distribution^aMedian data (range)^bResults were switched by mistake in the publication

Table 4 Pharmacokinetic information on alfentanil in children [13, 131, 132, 134–137, 142–144, 148, 149, 188, 190, 191]

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
5	6.2 ± 4.2 months	7.4 ± 2.6	50	IV, 30 s	8.39 ± 0.80 ^a	76.2 ± 8.2 ^a	0.552 ± 0.105 ^a	2	14/6 h	RIA [188]	Age < 1 year; AUC 6.183 ± 0.602 ^a min-mg/L	[13]
8	5.4 ± 4.4 years	20.2 ± 11.3	50	IV, 30 s	7.73 ± 0.61 ^a	84.0 ± 12.8 ^a	0.416 ± 0.050 ^a	2	14/6 h	RIA [188]	Age > 1 year; AUC 6.784 ± 0.583 ^a min-mg/L	[13]
5	6.0 ± 6.4 years	23.9 ± 19.0	120	IV, 30 s	7.76 ± 0.89 ^a	64.0 ± 7.3 ^a	0.603 ± 0.138 ^a	2	14/6 h	RIA [188]	Age > 1 year; AUC 15.982 ± 1.760 ^a min-mg/L	[13]
20	2.8 ± 1.5 years (10 months–6.5 years)		23.0 ± 9.2	IV, bolus	11.1 ± 3.9	63 ± 24	1.07 ± 0.71	Non	12/5 h	RIA [188]	Orthopedic surgery patients; free fraction 11.5 ± 0.9%	[132]
18	2.8 ± 1.6 years		20	IV, bolus	10.9 ± 4.1	63 ± 25	1.07 ± 0.78	Non	12/5 h	RIA [188]	Low dose (20 µg/kg)	[132]
2	2.3 ± 0.6 years		50	IV, bolus	12.6 ± 1.1	60 ± 1	1.08 ± 0.08	Non	12/5 h	RIA [188]	High dose (50 µg/kg)	[132]
8	5.4 ± 1.1 years	21.0 ± 3.2	20	IV, bolus	4.7 ± 1.7	40 ± 9	0.164 ± 0.110	2	16/6 h	RIA [188]	Genitourinary surgery patients; plasma protein binding 94.4 ± 1.5% @ 50 ng/mL, 92.4 ± 2.4% @ 500 ng/mL	[131]
16	1 day–10.9 years ^c		20/100 ± 60/h	IV, cont. 109 ^b (29–304) h	2.3 ± 2.8	294 ± 222	1.3 ± 0.9	Non	> 8/> 48 h	RIA	Comparison of fentanyl and alfentanil, MRT 378 ± 294 min	[136]
9	5.0 ± 2.8 years (9 months–10 years)		25–100	IV, 30 s	5.6 ± 2.4	60 ± 11	0.48 ± 0.19	2	15/4 h	RIA [188]	Surgical patients	[135]
6	1–3 days	1.328 ± 0.546	25	IV, 30 s	2.2 ± 2.4 [*]	525 ± 305	1.0 ± 0.39	2	8/12 h	RIA [188]	Preterm infants, GA 29.5 ± 3.3 weeks	[135]
13	1.5 ± 1.4 days	3.34 ± 0.97	8/5.63 ± 1.88/h	IV, 10 min, cont. (27 h)	3.24 ± 2.23	248 ± 155	0.54 ± 0.21	Non	4 + 4/24 h + 12 h	RIA [188]	Neonates, GA 37.6 ± 2.4 weeks	[134]
5	1–3 days	2.97 ± 1.14	25	IV, 30 s	1.7 ± 0.47	328 ± 48	0.82 ± 0.30	Non	9/24 h	RIA [188]	GA 36.8 ± 0.98 weeks; MRT 473 ± 70 min	[143]
5	1–3 days	1.33 ± 0.59	25	IV, 30 s	1.35 ± 0.69	455 ± 111	0.84 ± 0.48	Non	9/24 h	RIA [188]	Preterm infants, GA 29.3 ± 2.1 weeks; MRT 657 ± 162 min	[143]
22	1–4 days	1.343 ^b (0.69–4.084)	19.8 ^b (17.8–22.1)	IV, 2 min	0.87 ^b (0.4–9.62)	321 ^b (64–1251)	0.50 ^b (0.13–1.04)	1/2	5–8/7 h	RIA [188]	Preterm infants, GA 30 ^b (25–36) weeks; C _{max} 66 ^b (20–606) ng/mL	[142]
7	19 ^b (7–51) h	2.3 ^b (1.46–3.32)	11 ^b (10–15)	IV, 1 min	2.1 ^b (1.7–7.2)	43 ^b (34–237)	0.27 ^b (0.08–0.62)	Non	5/6 h	CGC [191]	No muscle rigidity; mean GA 36 (30–40 weeks) of all patients	[144]

Table 4 continued

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
13	22 ^b (6–41) h	2.4 ^b (1.69–3.95)	11 ^b (9–15)	IV, 1 min	2.9 ^b (0.9–25.3)	153 ^b (31–650)	0.66 ^b (0.15–2.94)	Non	5/6 h	CGC [191]	Muscle rigidity; mean GA 36 (30–40 weeks) of all patients	[144]
10	5.0 ± 2.8 years (9 months–10 years)		25–100	IV, 30 s	7.25 ± 4.3	41.6 ± 16	0.40 ± 0.21	2	14/2 h	RIA [188]	Surgical patients; AUC ₁₂₀ /AUC _∞ ratio 0.90 ± 0.05	[137]
9	4.6 ± 4.5 years (9 months–15 years)		25–100	IV, 30 s	7.59 ± 3.6	45.8 ± 13.3	0.46 ± 0.16	2	14/2 h	RIA [188]	Cholestatic hepatic disease; AUC ₁₂₀ /AUC _∞ ratio 0.84 ± 0.08	[137]
3			25–100	IV, 30 s	11.2 ± 2.7	41 ± 19	0.47 ± 0.23	2	14/2 h	RIA [188]	Cholestatic hepatic disease, subgroup, before transplant	[137]
3			25–100	IV, 30 s	7.0 ± 3.8*	82 ± 38	0.83 ± 0.55	2	15/2 h	RIA [188]	Cholestatic hepatic disease, subgroup, same patients, 8–12 h post-transplant; AUC ₁₂₀ /AUC _∞ ratio 0.71 ± 0.17	[137]
10	12.6 ± 3.2 years		25–100	IV, 30 s	8.2 ± 4.4	41.5 ± 11	0.45 ± 0.10	2	14/2 h	RIA [188]	End-stage renal disease; AUC ₁₂₀ /AUC _∞ ratio 0.90 ± 0.07	[137]
6	6.7 ± 2.7 months	6.5 ± 1.7	20/60/h (total: 998 ± 257)	IV, bolus, cont. (130 ± 28 min)	8.2 ± 2.2	69 ± 25	0.48 ± 0.12	Non	> 4 + 14	CGC	Age < 1 year, CPB	[149]
5	5.1 ± 1.9 years	18.6 ± 7.6	20/60/h (total: 3396 ± 1144)	IV, bolus, cont. (147 ± 15 min)	6.3 ± 0.8	62 ± 9	0.31 ± 0.08	Non	> 4 + 14	CGC	Age > 1 year, CPB	[149]
5	0.8 ± 0.3 years (4–11 months)	6.5 ± 1.2	200	IV, 10 min				2	> 6/> 0.25 h	CGC	Same cohort, before CPB; V1 0.068 ± 0.037 L/kg, AUC 17.9 ± 2.9 min·mg/L	[148]
5	0.8 ± 0.3 years (4–11 months)	6.5 ± 1.2	80	IV, 10 min	11.5 ± 5.0	60 ± 18	0.63 ± 0.23	2	15/6 h	CGC	Same cohort, after CPB; V1 0.235 ± 0.058 L/kg, AUC 11.1 ± 2.9 min·mg/L	[148]
6	4.1 ± 2.9 years (1–9 years)	15.8 ± 6.9	200	IV, 10 min				2	> 6/> 0.25 h	CGC	Same cohort, before CPB; V1 0.080 ± 0.032 L/kg, AUC 18.3 ± 5.4 min·mg/L	[148]
6	4.1 ± 2.9 years (1–9 years)	15.8 ± 6.9	80	IV, 10 min	10.2 ± 4.6	48 ± 9	0.49 ± 0.10	2	15/6 h	CGC	Same cohort, after CPB; V1 0.179 ± 0.099 L/kg***, AUC 12.9 ± 3.4 min·mg/L*** compared to before CPB	[148]

Table 4 continued

N	Age	Weight (kg)	Dose (µg/kg)	Route	CL (mL/min/kg)	$t_{1/2}$ (min)	V (L/kg)	Comp	No of samples	Lab method	Remarks	References
14	1.5 ± 2.2 years	8.7 ± 5.6		IV, cont. (TCI)	2.5	799	2.462	3	20–40/24 h	RIA [188]	simple model; CL 2.4 mL/min/kg in CPB-adjusted model	[190]

Reported statistical significance is indicated as follows: $p < 0.05^*$, $p < 0.005^{**}$, $p < 0.001^{***}$

AUC area under the plasma concentration–time curve, CGC capillary gas chromatography, CL clearance, Comp compartmental analysis, cont continuous, CPB cardiopulmonary bypass, GA gestational age, IV intravenous, Lab laboratory, RIA radioimmunoassay, MRT mean residence time, $t_{1/2}$ half-life, TCI target-controlled infusion, V volume of distribution

^aMean ± SEM

^bMedian data (range)

^cDemographics also include fentanyl group

veins to the portal vein [30] impacting fentanyl metabolism [4, 31]. In neonates and infants during non-cardiac surgery, CL increased with age, with the most rapid increase at a postnatal age of 2 weeks, whereas V_d and half-life did not change after a bolus of 54.1 ± 2.3 µg/kg [32].

After a fentanyl continuous infusion, half-life was prolonged and V_d at steady state was increased owing to a slow redistribution from peripheral compartments [33]. Clearance was highest in children 6 months to 6 years of age compared with younger or older children (8.2 vs. 18.9 vs. 8.0 mL/min/kg), which was attributed to increased liver metabolism. There was considerable heterogeneity of patients regarding age and underlying disease.

The accuracy of a computerized-assisted continuous infusion using an adult PK dataset was evaluated in children between 2.7 and 11 years of age undergoing non-cardiac surgery [34]. The measured fentanyl concentrations mostly exceeded the predicted concentrations; thus, the finally derived pediatric two-compartment model included age and bodyweight as covariates. However, this model is only applicable to infusion durations of up to 4 h. This study also calculated a shorter context-sensitive half-time for children compared with adults after an infusion duration of up to 200 min, but the true effect-site concentrations in children vs. adults and whether there are any differences among them remain unknown.

An increase of plasma concentrations correlated with elevated CO_2 throughout all age groups. Therefore, infants were not more prone to ventilatory depression than children or adults [35, 36]. An opportunistic sampling strategy was applied in children after cardiac surgery, which proved that this technique is applicable to clinical routine because PK parameters were comparable to prior formal studies [37].

In summary, fentanyl was studied in children of all ages, but the majority of the data was generated in the newborn period. Age-related changes in pharmacokinetics were observed but data are scarce considering most studies were conducted when high doses of fentanyl were used.

4.1.1.1 Preterm Neonates Unfortunately, PK sampling in neonates is usually limited. Therefore, estimation of half-life may become inaccurate if extrapolation of data is not carefully performed [38]. Postnatal and postmenstrual age both affect pharmacokinetics because preterm infants showed slightly higher CL than neonates born at term (26.2 vs. 21.1 mL/kg/min), but the preterm infants were older regarding postnatal age (36.7 vs. 13.3 days) [29, 32]. Other studies reported a significant correlation between postnatal age ($R^2 = 0.64$) or gestational age (GA) ($r = 0.46$, $R^2 = 0.21$) and birth weight ($r = 0.48$, $R^2 = 0.23$) with CL [39, 40], but for the last two it was actually as weak as in the pooled analysis of this review (weight $R^2 = 0.22$; Fig. 1,

Table 5 Pharmacokinetic information on remifentanyl in children [150, 152, 153, 171, 172, 192, 193]

N	Age	Weight (kg)	Dose ($\mu\text{g/kg}$)	Route	C_{max} (ng/mL)	CL (mL/min/kg)	$t_{1/2}$ (min)	V (mL/kg)	Comp	No of samples	Lab method	Remarks	References
8	5.1 $\pm$ 2.9 weeks	3.7 $\pm$ 0.7	5	IV, 1 min	24.2 $\pm$ 10.2* 36.8* $\pm$ 1.8	90.5 $\pm$ 36.8* 36.8* $\pm$ 1.8	5.4 $\pm$ 1.8	452.7 $\pm$ 144.8*	Non	10/1 h	GC-MS [192]	Age < 2 months	[150]
6	7.6 $\pm$ 4.3 months	8.7 $\pm$ 2.6	5	IV, 1 min	25.4 $\pm$ 3.7* 25.8* $\pm$ 1.2	92.1 $\pm$ 25.8* 25.8* $\pm$ 1.2	3.4 $\pm$ 1.2	307.9 $\pm$ 89.2	Non	10/1 h	GC-MS [192]	Age 2 months–2 years	[150]
7	4.6 $\pm$ 1.8 years	16.5 $\pm$ 4.7	5	IV, 1 min	34.8 $\pm$ 8.2 76.1 $\pm$ 22.4	76.1 $\pm$ 22.4 22.4 $\pm$ 1.8	3.6 $\pm$ 1.8	240.1 $\pm$ 130.5	Non	13/4 h	GC-MS [192, 193]	Age 2–7 years; metabolite GR90291 ($n = 7$): C_{max} 5.8 $\pm$ 1.1 ng/mL, $t_{1/2}$ 81.0 $\pm$ 44.6 min	[150]
6	9.7 $\pm$ 2.3 years	36.3 $\pm$ 9.7	5	IV, 1 min	42.5 $\pm$ 13.7 59.7 $\pm$ 22.5	59.7 $\pm$ 22.5 22.5 $\pm$ 1.4	5.3 $\pm$ 1.4	248.9 $\pm$ 91.4	Non	13/4 h	GC-MS [192, 193]	Age 7–13 years; metabolite GR90291 ($n = 7$): C_{max} 6.9 $\pm$ 2.1 ng/mL, $t_{1/2}$ 64.2 $\pm$ 25.7 min	[150]
4	14.0 $\pm$ 1.2 years	58.6 $\pm$ 25.7	5	IV, 1 min	35.0 $\pm$ 10.2 57.2 $\pm$ 21.1	57.2 $\pm$ 21.1 21.1 $\pm$ 1.1	3.7 $\pm$ 1.1	223.2 $\pm$ 30.6	Non	13/4 h	GC-MS [192, 193]	Age 13–16 years; metabolite GR90291 ($n = 3$): C_{max} 6.5 $\pm$ 1.0 ng/mL, $t_{1/2}$ 55.5 $\pm$ 26.9 min	[150]
3	16.3 $\pm$ 0.6 years	60.6 $\pm$ 6.9	5	IV, 1 min	42.7 $\pm$ 12.9 46.5 $\pm$ 2.1	46.5 $\pm$ 2.1 2.1 $\pm$ 0.7	5.7 $\pm$ 0.7	242.5 $\pm$ 109.2	Non	13/4 h	GC-MS [192, 193]	Age 16–18 years; metabolite GR90291 ($n = 3$): C_{max} 10.7 $\pm$ 6.6 ng/mL, $t_{1/2}$ 103.2 $\pm$ 75.4 min	[150]
12	6.3 $\pm$ 4.6 years	27.0 $\pm$ 20	5	IV, 1 min	38.7 $\pm$ 9.6 9.6 $\pm$ 3	38.7 $\pm$ 9.6 9.6 $\pm$ 3	8.2 $\pm$ 3	234.5 $\pm$ 105.5	2	9/0.75 h	HPLC	Pre-CPB	[171]
12	6.3 $\pm$ 4.6 years	27.0 $\pm$ 20	5	IV, 1 min	46.8 $\pm$ 14* 14* $\pm$ 2.6	46.8 $\pm$ 14* 14* $\pm$ 2.6	6.9 $\pm$ 2.6	235.3 $\pm$ 110.2	2	9/0.75 h	HPLC	Post-CPB (same cohort)	[171]
26	1.77 ^a (0.08–9.25) years	10.5 ^a (3.1–39.8)	Max 48/h	IV, 194 ^a (19–1236) min	68.3	68.3			2	> 8	HPLC	Pop-PK (post-CPB $n = 21$)	[152]
9	2.19 (0.5–4.0) years	11.4 (6.4–14.7)	15.8 $\pm$ 12.3/h (entire study: 65.0 $\pm$ 32.6 $\mu\text{g/kg}$)	IV, cont. (entire study: 218 $\pm$ 77.9 min)	13.8 $\pm$ 7.80	21.4	4.02	124	1	3 ^a (1–9)	GC-MS [171]	Pop-PK, pre-CPB	[172]
9	2.19 (0.5–4.0) years	11.4 (6.4–14.7)	20.3 $\pm$ 7.2/h	IV, cont.	12.7 $\pm$ 6.39	21.4	9.65	298	1	3 ^a (1–5)	GC-MS [171]	Pop-PK, during CPB (same cohort)	[172]
9	2.19 (0.5–4.0) years	11.4 (6.4–14.7)	19.3 $\pm$ 10.5/h	IV, cont.	11.7 $\pm$ 7.03	21.4	9.65	298	1	7 ^a (3–8)	GC-MS [171]	Pop-PK, post-CPB (same cohort)	[172]

Table 5 continued

N	Age	Weight (kg)	Dose ($\mu\text{g/kg}$)	Route	C_{max} (ng/mL)	CL (mL/min/kg)	$t_{1/2}$ (min)	V (mL/kg)	Comp	No of samples	Lab method	Remarks	References
7	0.74 (0.3–1.0) years	7.59 (6.6–9.6)		IV, cont.		2.22 L/min/70 kg		168 L/70 kg	2	Total: 77	GC-MS [192]	Clearance 2.99 L/min/70 kg, volume of distribution 16.23 L/70 kg, remarks Pop-PK, final model parameter estimates	[153]

Reported statistical significance is indicated as follows: $p < 0.05^*$, $p < 0.005^{**}$, $p < 0.001^{***}$

C_{max} maximum concentration, V volume of distribution, Max. maximum, cont. continuous, $t_{1/2}$ elimination half-life, Pop-PK population pharmacokinetics, CPB cardiopulmonary bypass, IV intravenous, CL clearance, comp compartmental analysis, GC-MS gas chromatography–mass spectrometry, HPLC high-performance liquid chromatography

^aMedian data (range)

GA $R^2 = 0.23$), and for postnatal age was not even significant.

Difficulties in estimation of half-life were seen in preterm infants (GA 31.8 ± 4.7 weeks) in whom fentanyl plasma concentrations after a bolus ($30 \mu\text{g/kg}$) were almost stable from 0.5 to 2 h, resulting in an elimination half-life of 6–32 h [41]. There were no adverse hemodynamic changes towards fentanyl reported.

Although body fat mass is much lower and total body water is much higher in premature infants than in newborns or older infants [42], V_d was increased in comparison to newborns and older children and half-life was prolonged [29, 32, 33]. This may be attributed to lower plasma protein levels (albumin and α -1-acid-glycoprotein) in preterm infants and thus a higher free fraction of the drug [42].

Fentanyl showed dose-linear pharmacokinetics during continuous infusion in preterm neonates. Clearance was slightly lower in preterm infants <34 weeks GA than ≥ 34 weeks GA, but with high inter-individual and inter-day variability. Circulatory parameters were stable and fentanyl provided effective analgesia. Meconium excretion occurred later and plasma bilirubin was higher in the fentanyl group, most probably owing to a longer gastrointestinal transit time.

Premature neonates showed no signs of cardiorespiratory compromise during continuous infusions [39, 43] but baroreflex control of heart rate was depressed after fentanyl administration. Thus, the ability of neonates to adapt to a decrease in blood pressure by increasing heart rate and thus cardiac output is disturbed [44].

In preterm infants with a GA <33 weeks, a fentanyl bolus was more suitable for treating acute pain episodes in ventilated infants than a continuous infusion, which led to increased side effects such as longer ventilation duration and reduced gastrointestinal motility [45]. Chest wall rigidity and laryngospasm have been observed even after low bolus doses of 3–5 $\mu\text{g/kg}$ in preterm and term infants [46].

Plasma binding of fentanyl in vitro in umbilical cord blood was 77% in preterm infants compared with 70% in neonates [47], but fentanyl concentrations (125 ng/mL) considerably exceeding therapeutic ranges (1–20 ng/mL, factor 6.25–125) were used. Alpha-1-acid-glycoprotein levels were lower in preterm compared with term neonates, while albumin levels were similar. Fentanyl already caused an analgesic effect and respiratory depression at plasma concentrations of 1–3 ng/mL [48]. Samples from the umbilical cord in preterm and term infants undergoing ex utero intrapartum therapy owing to airway and lung pathologies [49] proved analgesic fentanyl concentrations in all patients.

In summary, fentanyl, which currently is the most frequently used opioid analgesic in the neonatal intensive care

Fig. 1 Linear regression of fentanyl clearance (CL) and bodyweight in preterm and term neonates ($R^2 = 0.22$, solid gray line)

Fig. 2 Nonlinear regression (Hill function) of sufentanil clearance (CL) and bodyweight in children including term neonates ($R^2 = 0.71$, solid gray line). Allometric function of sufentanil CL and bodyweight in children including term neonates ($R^2 = 0.67$, dotted black line). B_{max} maximum CL, h Hill coefficient, K_{50} bodyweight at which half-maximum CL is reached

unit, shows highly variable kinetics in preterm neonates after bolus dosing or continuous infusion (17-fold variation between individual patients with a range of 3.4–58.7 mL/min/kg; Fig. 1) [50]. Withdrawal symptoms may occur after several days of continuous infusion. Fentanyl may cause relevant side effects at low doses; therefore, studies are needed evaluating the PK-pharmacodynamic relationship of fentanyl in this vulnerable group of patients.

4.1.1.2 Kidney Disease Chronic kidney disease or end-stage renal failure not only impact renal elimination, but also non-renal CL of drugs [51]. Fentanyl does not undergo renal metabolism, but is excreted via the kidneys into the urine, predominantly as inactive metabolites [52–54]. Therefore, absent kidney function should not significantly alter pharmacokinetics.

Fig. 3 Nonlinear regression (Hill function) of alfentanil clearance (CL) and bodyweight in children including preterm and term neonates ($R^2 = 0.70$, solid gray line). Allometric function of alfentanil CL and bodyweight in children including preterm and term neonates ($R^2 = 0.65$, dotted black line). B_{max} maximum CL, h Hill coefficient, K_{50} bodyweight at which half-maximum CL is reached

Fig. 4 Linear regression of remifentanyl clearance (CL) and bodyweight in children including neonates ($R^2 = 0.69$, solid gray line). Allometric function of remifentanyl CL and bodyweight in children neonates ($R^2 = 0.72$, dotted black line)

Two children with renal disease receiving fentanyl for surgery are described in a case series [55]. While pharmacokinetics did not differ during corrective cardiac surgery from other studies in the first patient, the second patient showed an extreme prolongation of half-life [56]. A study described above included two children with renal failure, but their fentanyl CL was comparable to other patients [33].

4.1.2 Cardiopulmonary Bypass

Extracorporeal circulation (CPB or ECMO) leads to changes in pharmacokinetics, such as hemodilution owing to circuit priming, an increased V_d owing to the addition of a large exogenous volume, a prolonged half-life, changes

in plasma protein concentrations, and a reduction in renal or hepatic function [57]. Extracorporeal membrane oxygenation may have an even greater impact on pharmacokinetics than CPB owing to a longer treatment duration, such as days to weeks [57].

Hypothermia during CPB impacts drug metabolism, as hepatic CL decreases as a result of reduced liver blood flow and activity of drug-metabolizing enzymes [58]. Renal CL decreases during extracorporeal circulation owing to reduced glomerular filtration caused by impaired renal perfusion [59].

Drug sequestration and adhesion to the surface of circuit components cause alterations in drug disposition. Drug adsorption correlates with the lipophilicity of the drug, but adsorption also depends on the equipment used for ECMO [60]. In a series of studies, initiation of CPB leads to a 60–89% decrease of plasma concentrations, attributed to a rapid sequestration of fentanyl within the bypass circulation owing to binding of fentanyl to components of the CPB system [56, 61]. Therefore, fentanyl was not recommended as the primary analgesic agent in patients on ECMO because the lipophilic drug is highly adsorbed to ECMO circuit components and shows a decreased CL during hypothermia [62].

After the initial decrease, fentanyl plasma concentrations remained stable during the further course of CPB [55, 64], also during hypothermia [65]. Even priming of the pump with 20 ng/mL of fentanyl did not prevent this effect [66]. When more modern equipment was used, only minimal variability in plasma concentrations was observed before, during, and after hypothermic CPB using a low-volume circuit and constant fentanyl infusion [63]. A significant reduction in serum albumin levels was observed as a result of CPB, which was likely caused by hemodilution, probably not affecting the unbound fraction of fentanyl [66]. Additionally, the degree of hemodynamic impairment may be a major determinant of fentanyl distribution [67]. During modified ultrafiltration after CPB, at least stable [68] or increasing fentanyl plasma concentrations were reported [69].

In the studies conducted early after its introduction, higher doses of fentanyl per kilogram of bodyweight (>10 and up to 50 µg/kg) were used because there were only limited other anesthetic agents. Fentanyl suppressed the stress response to surgery and still provided hemodynamic stability as it lacks myocardial depressant effects [70, 71]. No correlation was found between fentanyl concentrations, bispectral index, and hemodynamic, metabolic, or hormonal markers of depth of anesthesia [72].

During ECMO, neonates rapidly developed tolerance towards the sedating effect of fentanyl, resulting in a progressive escalation of fentanyl infusion rates and rising steady-state plasma concentrations, increasing the risk of

neonatal abstinence syndrome [38, 73, 74]. Clearance may be impaired in seriously ill patients during ECMO, which may be owing to decreased liver blood flow during compromised circulatory function [75].

4.1.2.1 Obesity Obesity has become a challenge in pediatric anesthesia because the rates of pediatric overweight and obesity are rising [76, 77]. Pediatric obesity is defined by a body mass index >95th percentile [78].

A pilot study in morbidly obese adolescents (mean body mass index 49.6 kg/m²) showed enhanced CL while V_d was comparable to that in lean adults after dosing based on ideal body weight [79]. Although the results suggest that a loading dose of fentanyl may be based on total body weight followed by maintenance doses based on ideal body weight and/or lean body weight [80, 81], obese patients are more at risk for respiratory side effects of opioids [82–86].

4.1.3 Epidural Fentanyl

Epidural administration of fentanyl resulted in peak plasma concentrations 30 min after the loading dose, but a substantial variability during continuous epidural infusion supplemented by patient-controlled bolus doses in children aged 6–11 years was observed [87]. In children of comparable age, half-life was not only longer in infants than children (median 15.9 vs. 7.96 h) but longer than observed after intravenous administration [88]. In addition, an increase in plasma concentrations was noted after discontinuation of the infusion attributed to redistribution. Consequently, continued clinical monitoring is required during neuraxial analgesia.

4.1.4 Transmucosal Fentanyl

After comparable doses, maximal fentanyl concentrations were lower in children after administration of OTFC, whereas the time to achieve them was longer in adults [89]. Oral transmucosal fentanyl citrate given as a premedication to children aged 2–10 years resulted in a bioavailability of 33% compared with 50% in adults [90, 91]. The efficacy of 10–15 µg/kg of OTFC was comparable to 2 µg/kg of intravenous fentanyl. Bioavailability was also low (36%) in another study in patients of the same age, but pharmacokinetics was similar [92]. Time to maximum plasma concentration (C_{max}) was highly variable (14–121 min), most probably owing to variability in gastrointestinal absorption, resulting in difficulties in the timing of administration. When the intravenous solution was given orally (10–15 µg/kg, maximum 400 µg), pharmacokinetics was comparable to the previous two studies, but the apparent oral V_d was significantly larger and the time to C_{max} was much longer (the latter could be owing to

methodological difficulties) [93]. Side effects of OTFC for preoperative sedation were nausea and vomiting, pruritus, respiratory depression, and chest-wall rigidity. Oral transmucosal fentanyl citrate should be carefully used in children less than 6 years of age [94–97]. Intranasal fentanyl (dosed 1–2 µg/kg) has been effectively used in premedication, emergency analgesia, and palliative care [98–102].

4.1.5 Transdermal Fentanyl

Transdermal application is a convenient non-invasive route of administration. In children who were treated with transdermal fentanyl for postoperative pain control (dose 25 µg/h, 1.72 µg/h/kg), $C_{\max}$ was negatively correlated with the patients' age, but not with bodyweight [103]. Respiratory depression was not observed. In another study, time to reach $C_{\max}$ ranged from 18 to 66 h in children after patch application (25 µg/h) [104]. Transdermal pharmacokinetics is similar to those in adults [105–107].

4.2 Sufentanil

4.2.1 Intravenous Sufentanil

Sufentanil pharmacokinetics (Table 3) showed age-related differences in children undergoing cardiac surgery after a single dose (10–15 µg/kg) [108]. Clearance was lowest in neonates compared with infants, children, and adolescents. Half-life was longest and V_d at steady state was largest in newborns compared with the older age groups. Neonates needed additional anesthetic agents at significantly higher plasma concentrations compared with older children to suppress the hemodynamic response to painful stimuli, but younger infants did not receive premedication before surgery [38]. Clearance and V_d increased while the half-life decreased slightly in a case series of neonates who were studied twice during the first 4 weeks of life [109].

In children aged 2–8 years undergoing surgery, CL was twice as rapid as in adults after a bolus dose (1–3 µg/kg) [110]. Volume of distribution was larger than in adults when normalized to bodyweight, but similar to that in adults when normalized to body surface area. Sufentanil plasma binding was lowest in newborns (80.5%) compared with infants (88.5%), children (91.9%), and adults (92.2%), while sufentanil is usually highly protein bound (92.5%) in adults [111, 112]. Sufentanil was 79.3% plasma-protein bound in neonates compared with 90.7% in their mothers, while α 1-acid-glycoprotein levels in the neonates were 50% of the adult values [113].

Two studies investigating pharmacokinetics included one pediatric patient [114, 115]. Long half-lives were reported in patients receiving a continuous infusion [115, 116]. Allometric scaling for dose adaptation in

pediatric patients was suggested [116]. Dose linearity of 250–1500 µg of sufentanil was shown in adolescents and adults aged 14–68 years. Sufentanil metabolic CL was almost identical to hepatic blood flow [12].

In summary, sufentanil pharmacokinetics show weight-related increases in CL and V_d while most maturation processes occur around 4 years of age (Fig. 2) and during the first weeks of life [109]. Normalized to bodyweight, CL and V_d in infants and children older than 1 month of age reached twice the adult values [3, 12, 110]. The allometric exponent of 0.99 best describing the maturation of CL differs from previous practice, suggesting an allometric exponent of 0.75 in pediatric patients [117]. A linear model, however, would overestimate the CL of sufentanil in children exceeding 35–40 kg of bodyweight (Fig. 1).

4.2.1.1 Preterm neonates Sufentanil has been used in preterm neonates but no pharmacokinetics was assessed [118].

4.2.1.2 Kidney Disease Renal failure had no significant effect on the pharmacokinetics in children and adolescents undergoing general anesthesia before kidney transplantation [119]. Children with chronic renal failure, however, showed a higher individual variability in CL and half-life.

4.2.1.3 Cardiopulmonary Bypass Sufentanil V_d was significantly smaller in infants under 10 months of age, while half-life and CL were similar after a single intravenous dose (15 µg/kg) in infants and children undergoing CPB [120]. Surface cooling led to an increase in the V_d and almost twice the half-life value, while CL was similar to the uncooled groups. Hemodynamic responses could be observed upon sufentanil administration. Sufentanil plasma concentrations were clearly overestimated by a computerized-assisted continuous infusion, probably because of a rapid decline of plasma concentrations after initiation of CPB [121].

4.2.2 Epidural Sufentanil

Plasma concentrations after epidural administration reach a $C_{\max}$ 20 min after the loading dose [87]. Considerable redistribution was observed and a slow elimination after continuous infusion with a median half-life of 19.6 h in children aged 3–36 months comparable to an earlier study [122, 123].

4.2.3 Transmucosal Sufentanil

Intranasal application was described as a safe and effective method for premedication in children [124, 125]. Higher doses, however, led to a higher incidence of postoperative

nausea and vomiting. Compared with midazolam, the latter showed advantages regarding respiratory depression, postoperative nausea and vomiting, and time to discharge [126–128]. Plasma concentrations after intranasal application (single dose 2 µg/kg) showed a $C_{\max}$ 15–30 min after administration [129]. In another study, $C_{\max}$ occurred 13.8 min after application and bioavailability was 24.6% [130].

4.3 Alfentanil

4.3.1 Intravenous Alfentanil

Alfentanil (Table 4) CL in children aged 5.4 ± 1.1 years was similar to adults, but half-life was significantly less and V_d significantly smaller (0.16 ± 0.11 vs. 0.46 ± 0.16 L/kg) in children [131]. Protein binding was comparable (91.8–94.4%) in both groups. Similar protein binding (free fraction $11.5 \pm 0.9\%$) was reported in children aged 10 months to 6.5 years [132]. Half-life was shorter and CL was higher compared with adults (11.1 ± 3.9 vs. 5.9 ± 1.6 mL/min/kg). In contrast, plasma protein binding in neonates was clearly lower than in their mothers (67.2 vs. 88.2%) [113].

An increase in dose from 50 to 120 µg/kg resulted in a proportional increase in exposure in children between 3 months and 14 years of age undergoing surgery [13], suggesting dose-independent PK. Half-life, CL, and V_d were similar in infants compared with older children.

In contrast, a non-linear increase in plasma concentrations was observed when comparing different doses (85-µg/kg bolus with a 65-µg/kg/h infusion, and 65-µg/kg bolus with a 50-µg/kg/h infusion) in children aged 3–12 years [133]. Approximately doubled plasma concentrations were observed after the higher dose (279 ± 78 vs. 135 ± 30 ng/mL), suggesting dose-dependent pharmacokinetics [133]. Dose linearity was assessed in neonates but the results were inconclusive because a limited number of plasma samples was drawn [134].

Overall, pharmacokinetics seems to be dose independent because there was no evidence for saturation of metabolism and drug accumulation when PK parameters after dosing of 20–200 µg/kg were compared [13, 135]. Fentanyl (2 µg/kg/h) had a much longer half-life (15.9 vs. 4.9 h) and a much larger V_d at steady state (17.2 vs. 1.3 L/kg) given as continuous infusion when compared with alfentanil (20 µg/kg/h) [136]. Children who were controls in other studies had similar PK profiles than discussed above [135, 137].

Alfentanil pharmacokinetics was used to predict CYP3A-mediated drug CL by physiologically based PK modeling. Allometric scaling failed to predict alfentanil CL in neonates in one study [138], but another study reported no age-dependent bias in a model for term neonates up to the age of 18 years. However, in premature neonates, V_d

and half-life were underestimated [139]. A new physiologically based PK model [140] showed improved predictions regarding the ontogeny function for CYP3A when compared with previously reported models [141]. In the pooled analysis of this review, the allometric exponent describing maturation of CL was 0.75 for children between 3 months and 14 years of age.

In summary, alfentanil CL in infants and children normalized to bodyweight was comparable to adult values and occasionally exceeded them. Clearance in neonates and preterm neonates was significantly less, while half-life is prolonged. Most maturation processes of CL occur around the age of 8.8 years, but there were limited PK data in children with a bodyweight over 25 kg (Fig. 3).

4.3.1.1 Preterm Neonates Plasma protein binding in vitro in umbilical cord blood samples was 65% compared with 79% in term neonates, which correlated with gestational age (GA) and level of α -1-acid-glycoprotein, lower than in older children (92.4–94.4%) [47, 131]. In premature neonates with a GA of 29.5 ± 3.3 weeks, CL was lower (2.2 ± 2.4 vs. 5.6 ± 2.4 mL/kg/min), V_d was larger (1.0 ± 0.39 vs. 0.48 ± 0.19 L/kg), and half-life was much longer after a bolus (25 µg/kg) compared with older infants and children (age 5.0 ± 2.8 years) [135]. The differences in body composition in preterm infants, such as a higher body water content and less fat and muscle mass as well as reduced protein binding might explain these differences.

A high variability of pharmacokinetics was observed after a bolus dose (20 µg/kg) in another preterm cohort (GA 25–36 weeks), but CL was lower and half-life was longer, whereas the V_d was similar in older children [142]. No association was observed between weight, GA, age, or sex. Alfentanil did not seem to accumulate in preterm infants even if given as 5-µg/kg/h infusion. Although the total infusion duration was not reported, it seemed to be longer than 48 h.

Term and preterm neonates with a GA of 26–35 weeks who received a bolus dose (25 µg/kg) during their first 3 days of life showed no alterations in hemodynamics. Pharmacokinetics showed a considerable variability and did not differ between preterm and term neonates, but CL was lower and half-life was longer when compared with older children [143].

When low-dose alfentanil (mean 11.7 µg/kg) was administered to newborn and preterm infants during their first 3 days of life, 65% of patients showed symptoms of skeletal muscle rigidity which disappeared spontaneously after 10 min. Pharmacokinetics was not different between both groups [144].

In summary, half-life was longer and CL lower in newborns and preterm neonates compared with children,

while there were conflicting results for V_d [135, 143]. Reported chest wall rigidity remains a safety concern in this age group [144]. Therefore, more studies are needed to investigate the relationship of pharmacokinetics and pharmacodynamics [38].

4.3.1.2 Liver Disease Liver disease may have a variable effect on pharmacokinetics owing to altered intrinsic enzyme activity, hepatic blood flow, hepatocellular function, and protein binding. Existing data do not allow correlations between distinct hepatic diseases and specific PK alterations [145]. Hepatic diseases with preserved hepatic blood flow may not affect the pharmacokinetics of high-extraction ratio drugs. In contrast, the hepatic CL of low extraction-ratio drugs depends mainly on enzymatic activity [146].

Pharmacokinetics seemed to be unaffected by cholestatic liver disease in children aged 0.75–15 years [137]. Liver transplant patients were studied before the anhepatic phase and 8–12 h after reperfusion. A significant decrease in CL was found after liver transplant (7.0 ± 3.8 vs. 11.2 ± 2.7 mL/kg/min), while the increases in apparent V_d and half-life were not significant. Dose reduction of alfentanil is recommended during liver transplantation [147].

4.3.1.3 Kidney Disease No difference in pharmacokinetics compared with healthy children could be found in children with end-stage renal disease dependent undergoing peritoneal or hemodialysis who received alfentanil during anesthesia for kidney transplantation [11].

4.3.1.4 Cardiopulmonary Bypass The initial V_d was smaller and the dose-normalized area under the plasma concentration–time curve was significantly greater before (bolus 200 μ g/kg) than after (bolus 80 μ g/kg) CPB in infants and children [148]. Alfentanil administration led to a significant hemodynamic response in both patient and dose groups comparable to previous data [36, 149]. A higher recovery of alfentanil (80%) compared with fentanyl (29%) after 60 min circulation time through CPB was observed in vitro [61].

4.4 Remifentanyl

4.4.1 Intravenous Remifentanyl

The pharmacokinetics (Table 5) was studied in children of different age groups during surgery [150]. The half-life was similarly short across all age groups and comparable to adult values, while V_d was highest and CL was fastest in infants under 2 months of age compared with older infants, children, and adolescents, when normalized to bodyweight [150, 151]. About 17% of patients developed arterial

hypotension after a bolus dose of 5 μ g/kg. Another study described remifentanyl pharmacokinetics during postoperative sedation by a two-compartment allometric model [152]. Regarding the hypotensive effect in infants, it was estimated that a plasma concentration of 14 ng/mL would cause a 30% decrease in mean arterial blood pressure [153]. When compared with halothane, remifentanyl did not cause new-onset postoperative respiratory depression [154]. However, because of the short recovery time from anesthesia, supplemental analgesia has to be administered for postoperative pain management.

Although remifentanyl is not recommended during the first year of life, it was shown to have a favorable safety and efficacy profile in neonates [155, 156]. Remifentanyl is currently used for the sedation of neonates during mechanical ventilation [157, 158]. Despite higher dose requirements in newborns and young infants, they were more tolerant towards the respiratory depressant effect [159]. Recovery times were short even in neonates [160].

In summary, remifentanyl has predictable pharmacokinetics in children aged 5 days to 17 years and CL showed bodyweight-linear maturation. When assessed by an allometric function, however, the allometric exponent was 0.76 (Fig. 4), and both models described maturation of remifentanyl CL equally well ($R^2 = 0.69$ vs. $R^2 = 0.72$). However, in daily anesthetic practice, the linear regression might be a more practical approach. Neonates and infants younger than 2 months of age had an enhanced CL compared with older children normalized to bodyweight, thus they may require higher infusion rates.

Remifentanyl is well suited for analgo-sedation during short painful procedures, but a less favorable option for postoperative pain control in non-ventilated or sedated children owing to its short duration of action [161], and has gained wide acceptance [162–164]. Studies elucidating the PK-pharmacodynamic relationship are particularly needed in children of all age groups because of its popularity [165].

4.4.1.1 Preterm Neonates Remifentanyl degradation was assessed in the cord blood of preterm and term infants in vitro [166]. The in-vitro half-life and degradation rate did not differ between groups without any correlation to GA, indicating a high non-specific esterase activity already in very preterm infants. There are no PK data reported in preterm neonates, although remifentanyl is increasingly used in this age group [167, 168].

4.4.1.2 Liver Disease No reported dose adjustment is necessary owing to renal and hepatic impairment, but patients with severe hepatic disease may be more prone to respiratory depression [169, 170].

4.4.1.3 Kidney Disease A case report of a newborn with congenital malformations and impaired renal function who received remifentanyl for surgery proved a short duration of drug action [169].

4.4.1.4 Cardiopulmonary Bypass While there was no difference in V_d and half-life before/after CPB, CL increased 20% after CPB [171]. Because of low variability, plasma concentrations were well predicted even in the post-CPB phase. A study in patients who received remifentanyl by computer-controlled infusion pump during open heart surgery described changes in the V_d before, during, and after CPB [172].

5 Limitations of the Review

Between all studies was large heterogeneity regarding study design, setting, drug administration, and PK and pharmacodynamic parameters. Although most studies were prospective non-randomized clinical trials, a few randomized controlled and even double-blinded studies were included. Dosing schemes were variable in relation to bolus dose, short infusion, or continuous infusion, which may affect PK parameters, e.g. half-life.

Different laboratory methods for the quantification of the parent drug and its metabolites, for example radioimmunoassay or liquid chromatography–mass spectrometry, may account for the variability in pharmacokinetics. Reported results were calculated or estimated using compartmental and non-compartmental PK analysis. Effects of the previously described limitations are carried forward to linear and nonlinear regression analyses using individual patients' PK data because information on different doses, different dosing schemes, and data established by different PK parameter estimation methods were combined.

6 Conclusions

This review provides a comprehensive overview of the pharmacology of fentanyl and its derivatives sufentanil, alfentanil, and remifentanyl in the pediatric population. Despite the frequent use of these drugs in this population, there have been surprisingly few studies in children. There are some pediatric PK data available for all four drugs, but 800 patients are a relatively small number when compared with the extensive use of synthetic opioids in children. Most of the PK data pertains to fentanyl, which was the first synthetic opioid in its class.

Preterm and term infants showed lower CL and protein binding for fentanyl, sufentanil, and alfentanil with a large variation in drug disposition in these age groups for critical

illness and/or maturation processes. In contrast, remifentanyl CL was enhanced particularly in younger children.

Clearance of fentanyl, sufentanil, and alfentanil increases rapidly during the first years of life. Infants and young children even had higher CL normalized to bodyweight, which might be caused by a higher metabolic capacity in these age groups or, for high-extraction ratio drugs, by increased liver blood flow. The pharmacokinetics of fentanyl and its derivatives seemed not to be altered by chronic renal or hepatic disease, but sample sizes have been small and data need to be validated in larger cohorts of patients. To increase safety, studies in those age groups in which the drugs are used off-label are especially needed, such as remifentanyl in neonates and infants younger than 1 year of age.

Fentanyl and its derivatives have proven efficacy and hemodynamic safety in children with cardiac disease who were exposed to high drug doses during cardiac surgery. Nevertheless, chest wall rigidity may occur especially in preterm and term neonates. Respiratory depression may also occur after prolonged infusion of the synthetic opioids.

Routes of administration have shown to be safe and effective in children, such as transmucosal fentanyl or sufentanil delivery for premedication before surgery. Based on the widely established use of these drugs, opportunistic clinical trials should be conducted to elucidate the pharmacokinetics and pharmacodynamics of fentanyl and its derivatives in much larger cohorts of the pediatric population.

Compliance with Ethical Standards

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