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Pharmacokinetic parameter sets of alfentanil revisited: optimal parameters for use in target controlled infusion and anaesthesia display systems

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Editor's key points

- This study investigated which published pharmacokinetic (PK) model best describes the time course of alfentanil plasma concentration after bolus administration and during continuous infusion.
- Out of the eight models tested, PK parameters by Scott and by Maitre were equally valid when alfentanil was given as repeated boluses.
- When given as infusion the Maitre parameters were less accurate and subject to a significant bias.
- Simultaneously administered hypnotics during alfentanil continuous infusion might affect the PK time course.

Background. In open TCI and anaesthesia display systems, the choice of pharmacokinetic (PK) parameter sets of opioids is clinically relevant. Accuracy and bias of the PK models may be affected by administration mode and the co-administered hypnotic drug. We retrospectively evaluated the performance of eight PK parameter sets for alfentanil in two data sets (infusion and bolus application).

Methods. With the dosing history from two studies in orthopaedic patients anaesthetized with propofol or inhalation anaesthetics the alfentanil plasma concentration over time was calculated with eight PK parameter sets. Median absolute performance error (MDAPE), log accuracy, median performance error (MDPE), log bias, Wobble, and Divergence were computed. Mann–Whitney rank test with Bonferroni correction was used for comparison between bolus and infusion data, repeated measures analysis of variance on ranks was used for comparison among parameter sets.

Results. The parameters by Scott (original and weight adjusted) and Fragen had a MDAPE ≤30% and a median log accuracy <0.15 independent of the administration mode, while MDPE was within ±20% and log bias nearly within ±0.1, respectively. The sets by Maitre and Lemmens were within these limits only in the bolus data. All other parameter sets were outside these limits.

Conclusions. In healthy orthopaedic patients, the PK parameters by Scott and by Maitre were equally valid when alfentanil was given as repeated boluses. When given as infusion, the Maitre parameters were less accurate and subject to a significant bias. We cannot exclude that the difference between bolus and infusion is partially because of the different hypnotics used.

Keywords: drug delivery, bolus, drug delivery, infusion; equipment, infusion systems; pharmacokinetics, alfentanil

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With the introduction of open target controlled infusion (TCI) systems, not only propofol but also opioids became available for application as TCI in clinical practice. Although remifentanil is most popular, also alfentanil and sufentanil parameters are offered by some manufacturers. The optimal PK parameters for propofol are still a matter of some debate,[1–3] whereas the parameter set for remifentanil reported by Minto and colleagues[4] is unchallenged except for a change of the lean body mass formula in the morbidly obese.[5]

Because of its PK profile with fast onset and acceptable offset characteristics, alfentanil might also be an interesting drug for TCI. The slower off-set compared with remifentanil

may offer some advantage in transition from intraoperative to postoperative analgesia.

Beside open TCI, also anaesthetic drug display systems recently became available.[6 7] They present predicted drug concentrations of i.v. anaesthetics and measured concentrations of inhalation anaesthetics and compute the combined anaesthetic potency of the applied drugs using interaction models.[8–10] The selection of appropriate models is essential for the performance of TCI and anaesthesia display systems. In anaesthesia display systems, also bolus application of i.v. drugs (especially opioids) is possible. An appropriate PK parameter set should therefore not be affected by the mode of

application. According to Schüttler and colleagues,[11] the PK parameters for propofol were significantly affected by the mode of administration.

The pharmacokinetics and -dynamics (PKPD) of alfentanil and its interaction with propofol has been thoroughly investigated in the 1980s and 1990s.[12–23]

An open TCI system to administer alfentanil is currently available only from one manufacturer using the PK parameter set by Maitre[18] which is based on data from bolus administration collected by several investigators.[12 14 24 19] The parameter set was later validated in 19 surgical patients anaesthetized with nitrous oxide and alfentanil (boluses and variable maintenance infusions).[25]

Raemer and colleagues[26] found a bias and an inaccuracy of >50% when using the Maitre[18] parameters to drive a TCI pump in healthy young women and elderly men, whereas bias and inaccuracy was only −1 and 17% with the Scott parameters.[20] They suspected different clearances and administration modes of alfentanil (bolus *vs* infusion) as possible explanation for this difference. Barvais and colleagues[27] administered alfentanil as infusion with different rates, took venous blood samples and developed a population and individual two-compartment models for alfentanil kinetics. Compared with infusion data, they found a higher elimination clearance and a higher performance error in data where a large bolus was rapidly applied. Mertens and colleagues[28] showed that propofol significantly reduces the clearance of alfentanil especially during induction.

Masui and colleagues[3] have compared different PKPD models for propofol using bolus, infusion and TCI data. A comparable study is not available for opioids.

We postulate that an optimal parameter set should not be affected by the mode of drug application (bolus or infusion) and should allow predictions of the plasma concentration with a performance error of ≤30%[29] and a bias within ±20%.[3] For safety reasons overprediction of the concentration rather than underprediction would be preferable for an opioid.[30]

The aim of this study was to compare the performance of previously published PK models for alfentanil and to determine which of the different models is most appropriate for use in TCI and anaesthesia drug display systems according to previously defined criteria. We used two data sets from the department of anaesthesia of the Bern University Hospital. Alfentanil was administered by TCI[31] and as repeated single bolus doses (unpublished data), respectively.

Methods

For this investigation, we retrospectively analysed the measured alfentanil plasma concentration and recorded dosing histories of two previously performed clinical studies.[31]

In the first study[31] (data set I, 'I' for infusion data), 30 patients undergoing orthopaedic surgery were randomly allocated to anaesthesia with 70 vol.% of xenon or 70 vol.% of nitrous oxide plus 2 vol.% of desflurane. Alfentanil was administered by TCI (Stanpump programme, S.L.

Shafer, MD., Palo Alto, CA, USA) using the parameter set by Shafer (as integrated in Stanpump) with target concentrations between 5 and 400 ng ml^{-1}. Arterial blood samples were obtained at baseline, before and after skin incision, before and after each change of the target concentration, after pump stop, and hourly in the recovery room for 3 h.

In the second study (unpublished, data set B, 'B' for bolus data), 40 patients undergoing orthopaedic surgery were anaesthetized with propofol TCI (plasma target mode) using the parameter set by Schnider and colleagues[32] and alfentanil administered as i.v. boli of 0.5–1.0 mg using an ASENA GH infusion pump (Carefusion Corporation, San Diego, CA, USA) which was connected to a laptop computer for recording of the dosing history. Arterial blood samples were obtained at baseline, before and after tracheal intubation, after skin incision, at the end of surgery, before pump stop, and after extubation.

For both studies approval from the ethics committee had been obtained and the patients gave their written informed consent (reference code: KEK Bern 156-97 and KEK Bern 82-06, respectively). In all patients, the arterial blood samples were centrifuged immediately after the end of the case and the supernatant was stored at −26°C. The plasma concentrations were measured by gas chromatography mass spectrometry with a lower detection limit of 2 ng ml^{-1}.[33]

The alfentanil dosing histories from the two studies (data set I and B) were used as input to calculate predicted plasma concentrations over time based on eight different PK parameter sets using the PKPD Tools for Excel by Minto and Schnider (PKPD Tools is freely available on the internet at www.pkpdtools. com). The following parameter sets were compared: Scott and Stanski,[20] Scott and Stanski weight adjusted (as integrated in Stanpump), Maitre,[18] Shafer (as integrated in Stanpump), Hudson,[16] Mertens,[28] Fragen,[15] and Lemmens[17] (Tables 1–3).

For every blood sample, the measured and the predicted alfentanil plasma concentrations were used to calculate the performance error of the different models according to Varvel and colleagues[30] (equation 1).

$$PE_{ij} = \frac{Cm_{ij} - Cp_{ij}}{Cp_{ij}}, \qquad (1)$$

where PE=performance error (%), Cm=measured concentration, Cp=predicted concentration, i=patient number and j=blood sample number in patient i.

The median absolute performance error (MDAPE$_i$) and the median performance error (MDPE$_i$) were determined for each patient according to the following equations 2 and 3:[30]

$$MDAPE_i(accuracy) = Median\{|PE_{ij}|, j = 1, ..., N_i\}, \qquad (2)$$

$$MDPE_i(bias) = Median\{PE_{ij}, j = 1, ..., N_i\}, \qquad (3)$$

where MDAPE$_i$ represents the accuracy and MDPE$_i$ the bias of patient i with j=1,…,N_i blood samples. Population estimates

Table 1 Characteristics of the study populations in the different PK studies on alfentanil. Data are total count of subjects, blood samples, males, and females. Weight and height are mean [standard deviation (SD)], age is mean (range). I, infusion; B, bolus; n.a., not available; NA, not applicable; (refers to single bolus application studies). The duration of the alfentanil infusion is presented as number, range or mean (SD). HALO, halothane; ENF, enflurane; SUF, sufentanil; Thio, thiopental; ETO, etomidate; Xe, xenon; DES, desflurane; ISO, isoflurane. From the parameters by Shafer (as implemented in the Stanpump software) no data on the study population are available

	Scott[20]	Fragen[15]	Maitre[18]	Lemmens[17]	Mertens[28]	Hudson[16]	Current study infusion	Current study bolus
Number of subjects	17	5	45	36	8	11	30	40
Number of blood samples	~680	~80	614	~1000	342	~253	649	201
Type of blood samples	Arterial	Venous	Arterial and venous	Arterial and venous	Venous	Arterial	Arterial	Arterial
Sex (M/F)	17/0	2/3	14/31	15/21	8/0	9/2	16/14	24/16
Age (yr)	52 (20–89)	39 (29–48)	47 (19–91)	53 (24–79)	24 (n.a.)	64 (51–76)	33 (18–54)	40 (18–81)
Weight (kg)	n.a.	72 (9)	65 (6)	74 (12)	74 (6)	75 (14)	71 (14)	74 (11)
Height (cm)	n.a.	n.a.	165 (7)	n.a.	182 (7)	n.a.	172 (9)	172 (9)
Application of drug	I	Single B and I	Single B	I	I	Single B	I	Repeated B
Max. plasma concentration (ng ml^{-1})	>1000	900	>1000	1000	<150	2000	500	1000
Duration of alfentanil administration (min)	3 (2)	60	NA	45–240	60	NA	195 (62)	264 (72)
Co-administered anaesthetics	Thio, ENF, N_2O	Thio, ENF, N_2O	Thio, N_2O ETO, N_2O, HALO Thio, N_2O, ENF or HALO	N_2O, SUF	Propofol	N_2O, ISO	Xe 70% or N_2O 70%/DES 2%	Propofol TCI
Type of surgery	Elective surgery with minimal blood loss	Elective surgery >1 h and blood loss <500 ml	Miscellaneous	Lower abdominal	Volunteers	Infrarenal aortic	Orthopaedic	Orthopaedic

were calculated according to equations 4 and 5 (two-stage approach).[30]

$$MDAPE \, (accuracy) = Median\{MDAPE_i, i = 1, ..., M\}, \quad (4)$$

$$MDPE \, (bias) = Median\{MDPE_i, i = 1, ..., M\}, \quad (5)$$

where MDAPE represents the population accuracy and MDPE represents the population bias of $i = 1, ..., M$ patients.

Wobble representing the variation of the performance error around MDPE and Divergence representing the expected time related changes in performance were calculated according to the following equations 6 and 7:

$$Wobble_i = Median(|PE_{ij} - MDPE_i|), \quad (6)$$

$$Divergence_i = 60 \times \frac{\sum |PE_{ij}| \times t_{ij} - (\sum |PE_{ij}|) \times (\sum t_{ij})/N_i}{\sum (t_{ij})^2 - (\sum t_{ij})^2/N_i}, \quad (7)$$

where $Wobble_i$ and $Divergence_i$ are the estimates for patient i with $j = 1, ..., N_i$ blood samples and t_{ij} is the time in min that the corresponding PE_{ij} was determined. Population estimates

were calculated similar to those of MDAPE and MDPE (equations 4 and 5).

For comparison, the recently proposed logarithmic indices for accuracy and bias described by Masui and colleagues[3] were calculated as well using the following equations 8 and 9:

$$Accuracy_i = Median\{|log(Cm_{ij}/Cp_{ij})|, j = 1, ..., N_i\}, \quad (8)$$

$$Bias_i = Median\{log(Cm_{ij}/Cp_{ij}), j = 1, ..., N_i\}, \quad (9)$$

where $Accuracy_i$ and $Bias_i$ are the estimates for patient i with $j = 1, ..., N_i$ blood samples. Population estimates were calculated by analogy with the population estimates of MDAPE and MDPE (equations 4 and 5).

We defined an optimal parameter set for use in TCI and display systems as follows: It should be unaffected by the mode of administration (bolus vs infusion), the MDAPE (accuracy) should be ≤30%[29] and the MDPE (bias) should be within ±20%.[3]

Acceptable ranges for the logarithmic accuracy and bias indices had been derived from MDAPE and MDPE with values of <0.1–0.15 for accuracy and of −0.1 to 0.1 for bias, respectively.[3]

Table 2 PK parameter sets. Parameters of the studies as published in the literature. The models are described either by their volumes and clearances or V1 and micro rate constants, which are convertible. Weight in kg, height in cm, body surface area (BSA) according to the Du Bois formula[38]: BSA=(weight 0.425 × height 0.725) × 0.007184. M, men; F, female

	Scott[20]	Fragen[15]	Shafer	Maitre[18]	Lemmens[17]	Mertens[28]	Hudson[16]
V1 (litre)	2.185 weight adjusted: 2.185/70 × weight	0.130 × weight	0.825× BSA	M: 0.111 × weight F: 0.128 × weight	M: 4.106 F: age≤50: 4.174 F: age>50: 3.566	0.115 × weight	0.044 × weight
V2 (litre)		0.220 × weight				0.208 × weight	0.189 × weight
V3 (litre)						0.136 × weight	0.399 × weight
Cl1 (litre min^{-1})	0.195			Age≤40: 0.356 Age>40 0.356−[0.00269 × (age−40)]		0.00564 × weight	0.0064 × weight
Cl2 (litre min^{-1})						0.0738 × weight	0.0138 × weight
Cl3 (litre min^{-1})						0.00248 × weight	0.0021 × weight
K10 (min^{-1})		0.02767	0.0748		M: 0.0679 F: age≤50: 0.1031 F: age>50: 0.0717		
K12 (min^{-1})	0.656	0.052167	0.515	0.104	M: 0.2818 F: age≤50: 0.3475 F: age>50: 0.1810		
K13 (min^{-1})	0.113		0.231	0.017	M: 0.0806 F: age≤50: 0.1298 F: age>50: 0.1352		
K21 (min^{-1})	0.214	0.03033	0.142	0.0673	M: 0.1219 F: 0.1580		
K31 (min^{-1})	0.017		0.0185	Age≤40 0.0126 Age>40 0.0126− [0.000113 × (age− 40)]	M: 0.0150 F: age≤50: 0.0170 F: age>50: 0.0143		

Table 3 PK parameters calculated for a standard patient. Volumes (litres) and clearances (litre min^{-1}) of the PK parameter sets calculated for a 70 kg, 170 cm and 30-year-old male

	Scott[20]	Fragen[15]	Shafer	Maitre[18]	Lemmens[17]	Mertens[28]	Hudson[16]
V1	2.19	9.1	1.5	7.77	4.11	8.05	3.08
V2	6.7	15.4	5.44	12.01	9.49	14.56	13.23
V3	14.52		18.73	10.48	22.06	9.52	27.93
Cl1	0.195	0.252	0.112	0.356	0.279	0.395	0.448
Cl2	1.433	0.467	0.772	0.808	1.157	5.166	0.966
Cl3	0.247		0.346	0.132	0.331	0.174	0.147

Statistics

MDAPE, MDPE, Wobble, and Divergence according to Varvel and colleagues[30] and logarithmic accuracy and bias according to Masui and colleagues[3] of the different parameter sets were compared. Mann–Whitney rank test with Bonferroni correction was used for comparison between the infusion and bolus application data. Repeated measures analysis of variance (ANOVA) on ranks with Tukey test was used for multiple pair-wise comparisons between the parameter sets for MDAPE, log accuracy and Wobble. For MDPE, log bias, and Divergence, the parameter set with an optimal bias nearest to zero was selected as control. Dunnett's test was used to compare the other sets with control (Sigmastat 3.5, Systat Software GmbH, Erkrath Germany). Using a statistical test with control for signed indices (MDPE, log bias and Divergence) allowed identifying sets differing significantly from the defined optimal range around zero instead of identifying significant differences between sets from low negative to high positive values. Significance was accepted at a P-value of <0.05 (with Bonferroni correction for eight comparisons yields a P-value of <0.006).

Results

The data from 30 patients (infusion) and 40 patients (bolus) were included. The characteristics of the study populations are presented in Table 1 (last 2 columns). The mean (range) age of the patients was 33 (18–54) in Group I and 40 (51–76) in Group B ($P=0.035$). The median (inter-quartile range) blood loss in Group I and B was 500 (400–760) and 400 (210–700) ml ($P=0.09$), the duration of the alfentanil administration was 264 (72) and 195 (62) min, respectively ($P<0.001$). The median (inter-quartile range) of the predicted plasma alfentanil concentration throughout the study was 72 (54–104) ng ml^{-1} in Group I and 143 (113–175) ng ml^{-1} in Group B ($P<0.001$). Twenty-six of 30 patients in Group I and 20 of 40 in Group B were ASA physical status I, the remainder was ASA II ($P=0.003$). The time course of the plasma concentrations in two typical patients of our study groups is presented in Figure 1.

A total of 850 blood samples were analysed, 649 in the infusion and 201 in the bolus study, respectively. All blood samples could be included in the analysis.

MDAPE and log accuracy

The median MDAPE and log accuracy in both populations was within the limits of acceptance with the parameter sets by Scott,[20] Fragen,[15] and Scott weight adjusted, whereas it was outside with the others (Fig. 2).

In the infusion data (green boxes in Fig. 2), the MDAPE with the Scott parameters was significantly lower than with the parameters by Hudson,[16] Mertens,[28] Lemmens,[17] and Shafer ($P<0.05$). MDAPE values were 22.3% (Scott),[20] 26.5% (Fragen),[15] 26.5% (Scott weight adjusted), and 41% (Maitre).[18] The log accuracy was significantly lower compared with Hudson,[16] Lemmens,[17] and Shafer ($P<0.05$).

In the bolus data (orange boxes in Fig. 2), the MDAPE and log accuracy of the parameter sets by Scott,[20] Fragen,[15] Scott weight adjusted, Maitre,[18] and Lemmens[17] were similar, whereas those of Shafer and Hudson[16] were significantly higher. MDAPE values were 30.2% (Scott),[20] 26% (Fragen),[15] 29.3 (Scott weight adjusted) and 24.1% (Maitre).[18]

In the parameter sets by Maitre[18] and Lemmens,[17] the MDAPE was higher when alfentanil was administered as infusion compared with bolus administration; whereas in the log accuracy this difference was significant with the parameters by Lemmens[17] ($P<0.003$). This was reflected by the multiple pairwise comparisons between the different parameter sets, which yielded different results when alfentanil was administered as multiple boluses or as infusion (as mentioned above).

None of the performance indices inside the Group I were affected by the different co-administered hypnotic drugs (desflurane plus nitrous oxide or xenon, $P \geq 0.361$).

The detailed results of the multiple pair-wise comparisons of all the parameter sets are presented in Figure 2.

MDPE and log bias

The parameter set by Fragen[15] was selected as control because MDPE and log bias were optimally within the acceptable range (Fig. 3). The median MDPE and log bias in the study populations were within or very close to the acceptable limits ($\pm20\%$ or ±0.1) with the parameters by Fragen,[15] Scott,[20] and Scott weight adjusted, whereas the others were all significantly different from control (Fig. 3).

In both data sets MDPE and log bias of the parameter sets of Scott,[20] Scott weight adjusted and Shafer showed tendency to overpredict whereas those of Maitre,[18] Hudson,[16] and Mertens[28] showed tendency to underpredict the measured concentration (Fig. 3). MDPE values were -18.4% (Scott),[20] -6% (Fragen),[15] -24% (Scott weight adjusted) and 39.4% (Maitre)[18] with the infusion data and -30% (Scott),[20] -18.3% (Fragen),[15] -24.6% (Scott weight adjusted) and 0.6% (Maitre)[18] with the bolus data. As MDAPE and log accuracy also MDPE and log bias were affected by the mode of administration (infusion or bolus) with the parameters by Maitre,[18] but not Lemmens ($P<0.001$).[17] None of the performance indices inside the Group I were affected by the different co-administered hypnotic drugs (desflurane plus nitrous oxide or xenon, $P \geq 0.263$). The detailed results of the multiple pair-wise comparisons of the different parameter sets are presented in Figure 3.

Wobble and divergence

In both populations, the variation of the PE around the MDPE (Wobble) in the Scott parameters (weight adjusted or not) was lower compared with those by Hudson,[16] Mertens,[28] Lemmens,[17] and Maitre.[18] The Wobble was also affected by the mode of administration with the parameters by Scott,[20] Fragen,[15] Maitre,[18] and Mertens.[28] Further details are reported in Figure 4.

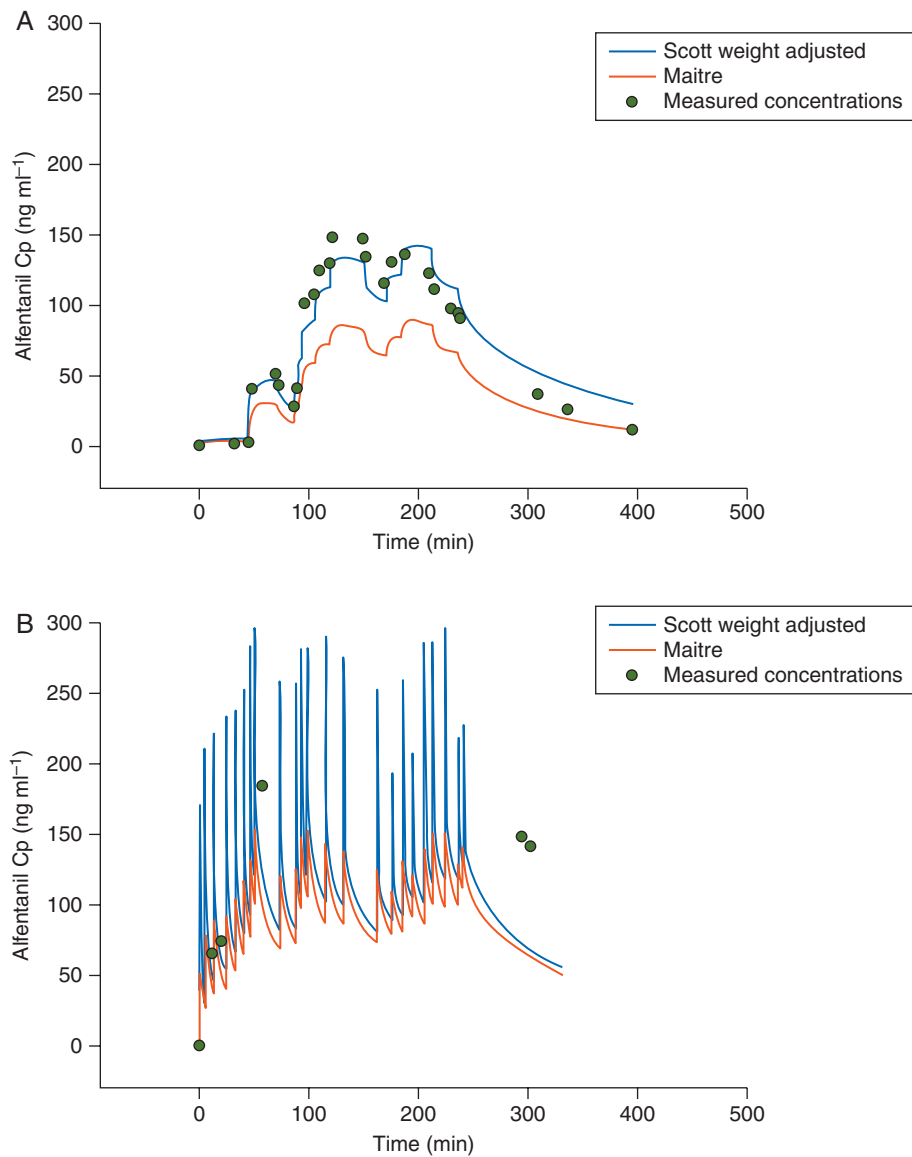In both populations, the Divergence was $\pm5\%$ or less in the parameters by Scott (weight adjusted or not), Fragen,[15]

Fig 1 Alfentanil plasma concentrations in the two study populations. Predicted and measured alfentanil plasma concentrations (Cp axis) against time of two typical patients of our study populations. A, infusion group; B, repeated bolus group. The predicted plasma concentrations according to Scott, weight adjusted (blue lines) and Maitre (red lines). Measured plasma concentrations are represented by green circles.

Maitre,[18] Lemmens,[17] and Mertens.[28] In the infusion group, the median (inter-quartile range) of the Divergence (% h^{-1}) for the Hudson[16] and Shafer parameters was 12 (0.8, 45) and 9 (7, 12), respectively. In bolus application, the Divergence values were 18 (2, 31) and 7 (5, 10), respectively (Fig. 4).

Discussion

The previously defined criteria for an optimal parameter set (being unaffected by mode of administration, MDAPE (accuracy) ≤30% and MDPE (bias) within ($\pm$ 20%) were met by the Scott[20] (original and weight adjusted version) and the

Fragen[15] parameters. The Scott[20] parameters overpredicted the measured concentration whereas those by Fragen[15] performed with almost no bias. Weight did not affect the PE of the Scott[20] parameters in our data set, which means that weight adjustment did not worsen the PE. Because all parameters used for TCI are at least weight adjusted we consider it reasonable to apply weight adjustment for alfentanil too. The Fragen parameters[15] represent a two-compartment model developed with data from five patients (venous blood samples) and belong to the earliest published parameters of alfentanil. Despite the limited database their performance was similar to the Scott parameters. Because the
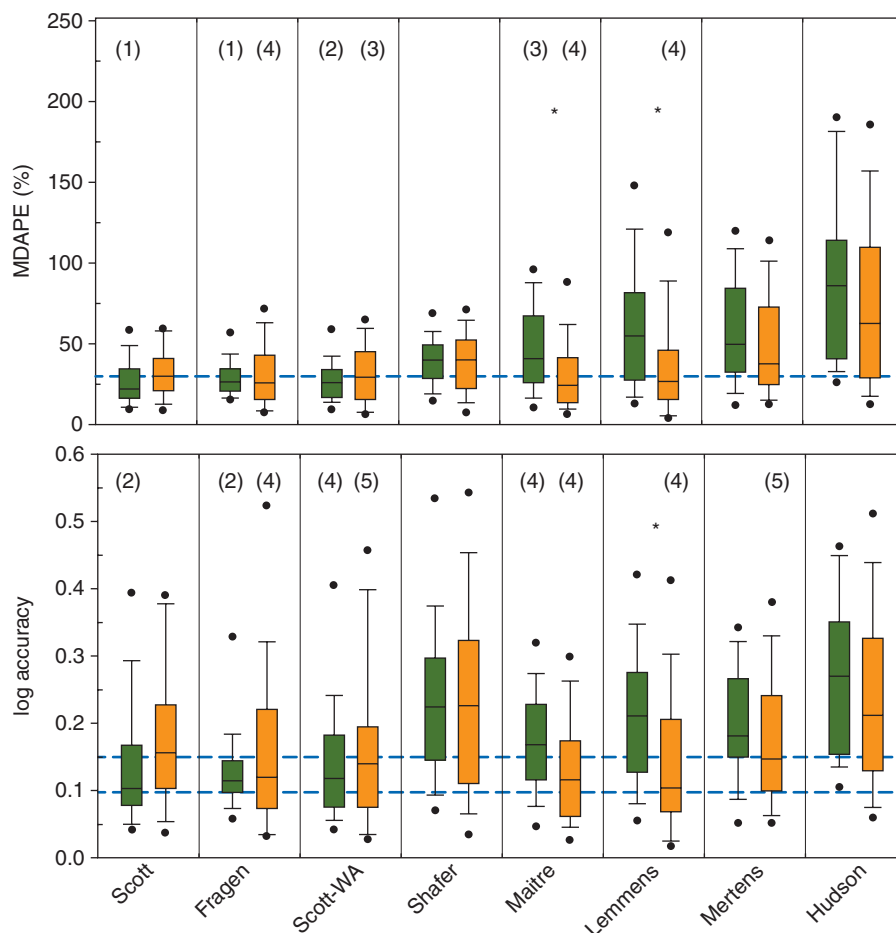
Fig 2 MDAPE and log accuracy of alfentanil concentrations: infusion and bolus data. MDAPE and log accuracy distribution as box-plot with median and percentiles. Green boxes, infusion data; orange boxes, bolus data. Error bars indicate the 10th/90th percentiles, black circles represent 5th/95th percentiles. Scott-WA, Scott weight adjusted version of the Scott parameters (as implemented in Stanpump). Dashed lines represent the borders of acceptable prediction errors ($\leq$30% and <0.1–0.15). *Significant differences between infusion and bolus administration (Mann–Whitney rank test and Bonferroni P<0.006). The numbers above the boxes refer to the repeated measures ANOVA on ranks with multiple pair-wise comparisons among the different parameter sets (Tukey test): (1) P<0.05 compared with Hudson, Lemmens, Shafer, and Mertens; (2) P<0.05 compared with Hudson, Lemmens, and Shafer; (3) P<0.05 compared with Hudson; (4) P<0.05 compared with Hudson and Shafer; (5) P<0.05 compared with Shafer. Where no reference is indicated the performance error is not significantly different from any other.

study population was very small the data did not allow estimating the parameters for the third compartment.

The Maitre parameter set[25] was developed from pooled bolus data from Bovill,[12] Camu,[14] Helmers,[24] and Schüttler[19] forming a representative study population with a large number of blood samples allowing to estimate the effect of age, sex and weight as covariates. With our data from repeated bolus application it performed as good as Scott[20] but was significantly inferior with the infusion data. The reason may be the higher elimination clearance of the Maitre parameters.[27] A comparable performance with similar differences regarding bolus and infusion application could be observed with the parameter set by Lemmens.[17] All other parameter sets did not meet our criteria and

cannot be recommended for use in TCI or anaesthesia display systems.

Contrary to Scott[20] and Fragen[15] the Maitre,[25] and Lemmens[17] parameters underpedicted the alfentanil concentration. From a safety point-of-view this might be a further disadvantage for clinical practice. If the concentration of a drug is underpredicted a TCI will administer more than if it is overpredicted. An inadequate analgesia is clinically detectable (e.g. by haemodynamic responses to surgical stimuli) and can be easily corrected.[30] Conversely, an overdose of analgesic drugs is more difficult to detect clinically. Underdosing is therefore preferable in order to avoid delayed recovery, opioid induced hyperalgesia, or postoperative respiratory depression.[30]
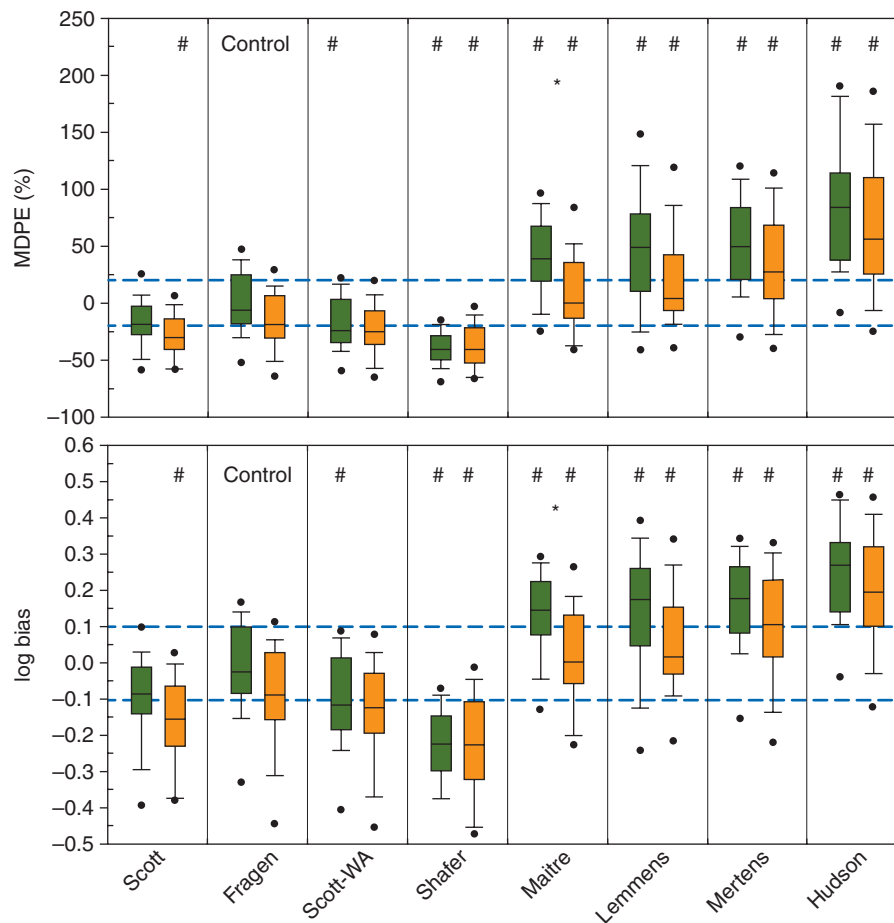
Fig 3 MDPE and log bias of alfentanil concentrations: infusion and bolus data. MDPE and log bias distribution as box-plot with median and percentiles. Green boxes, infusion data; orange boxes, bolus data. Error bars represent 10th/90th percentiles, black circles represent 5th/95th percentiles. Scott-WA, Scott weight adjusted version of the Scott parameters (as implemented in Stanpump). Dashed lines represent the range of acceptable prediction errors (between ± 20% and ± 0.1). *Significant differences between infusion and bolus administration (Mann–Whitney rank test and Bonferroni $P<0.006$). #Significant differences to control (repeated measures ANOVA on ranks with multiple pairwise comparisons of the different parameter sets *vs* Fragen as control, Dunnett's test).

Mertens and colleagues[28] described the PK interaction between alfentanil and propofol in healthy volunteers. A propofol Cp of 1.5 µg ml^{-1} reduced the Clearances 1, 2 and 3 by 15, 300 and 50%, respectively, which was attributed to a reduced hepatic blood flow because of the propofol induced vasodilatation. Because propofol and alfentanil both are bound to lung tissue (first pass effect) the alfentanil concentrations after the initial bolus of alfentanil were higher than expected in the presence of propofol. The population studied by Mertens and colleagues[28] is not representative for the patient population undergoing surgery. This may explain why the performance of the Mertens parameter set was inferior to others even in our data set where propofol was co-administered.

The intra-individual variation of the prediction error (Wobble) was higher when alfentanil was administered as boluses in most of the parameter sets. In the bolus data, it was lower in the Scott[20] than in the Maitre[25] parameters. The variation of the performance error over time (Divergence) was highest in the Hudson[16] parameters, probably because they were determined in cardiovascular high risk patients, which is a different population compared with our patients. The elimination clearance estimated by Hudson[16] is higher compared with parameter sets that were more stable over time. The lowest Divergence had the Scott[20] parameters, expressing the higher ability to produce stable plasma concentrations of this set compared with other sets, which can be seen as advantage for titration of analgesia in clinical use. Fragen's[15] negative Divergence values in both data sets mean that the performance error was higher at the beginning of the infusion.

Our results obtained in 70 patients with a total of 850 blood samples are consistent with those of Barvais and colleagues[27] obtained in eight volunteers and with those of
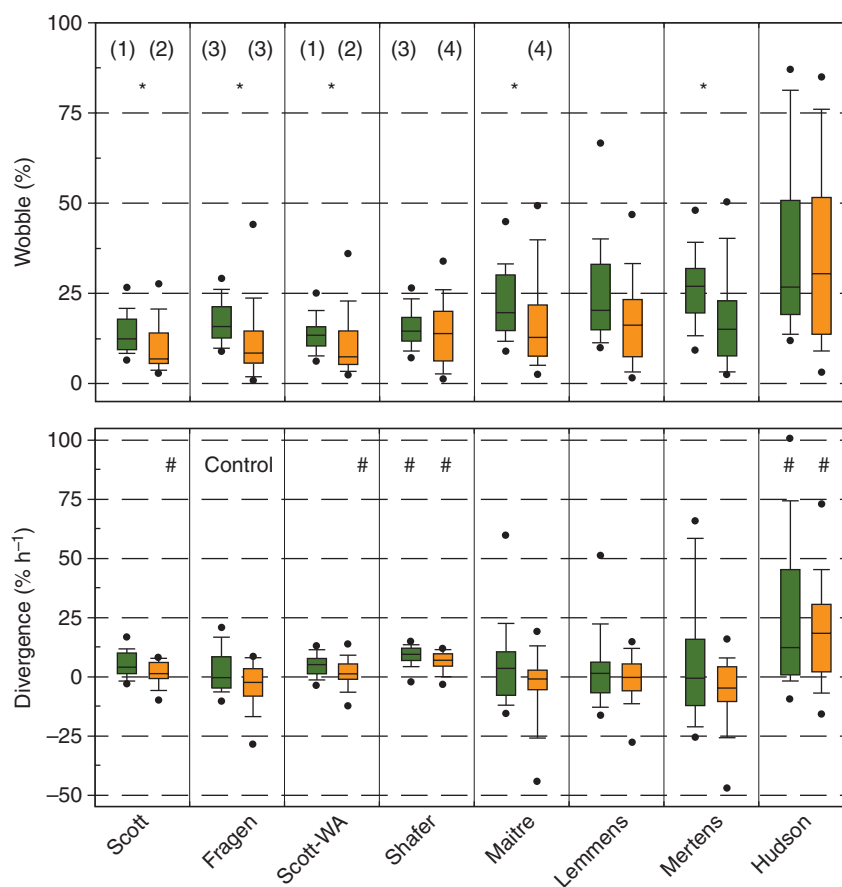
Fig 4 Variation of the performance error: Wobble and Divergence. Median intra-individual variation of the performance error around the MDPE (Wobble) and median intra-individual variation of the performance error over time (Divergence) as box-plots with median and percentiles. Green boxes, infusion data; orange boxes, bolus data. Error bars represent 10th/90th percentiles, black circles represent 5th/95th percentiles. Scott-WA, Scott weight adjusted version of the Scott parameters (as implemented in Stanpump). Wobble: repeated measures ANOVA on ranks with multiple pair-wise comparisons among the different parameter sets (Tukey test): (1) $P<0.05$ compared with Hudson, Mertens, Lemmens, and Maitre; (2) $P<0.05$ compared with Hudson, Mertens, Lemmens, Shafer, and Maitre; (3) $P<0.05$ compared with Hudson, Mertens, and Lemmens; (4) $P<0.05$ compared with Hudson. *Significant differences between infusion and bolus administration (Mann–Whitney rank test and Bonferroni correction, $P<0.006$). Where no reference is indicated the performance error is not significantly different from any other. Divergence: #significant differences to control (repeated measures ANOVA on ranks with multiple pair-wise comparisons of the different parameter sets vs Fragen as control, Dunnett's test).

Raemer and colleagues[26] obtained in 29 healthy women and 22 older men. They also confirm that the application mode may affect the prediction error of PK parameters.[26 27] In an earlier study on 25 patients where alfentanil was administered as TCI during surgery and for postoperative pain control[34] the MDAPE of the Scott parameters[20] was similar to the parameters by Lemmens[17] and Maitre.[18] The blood samples in that study[34] were obtained only in the postoperative study period where the subjects were closer to a PK pseudo-steady state. In the late phase of drug administration, the inaccuracy related to the volume of the central compartment (volume 1) which is 3-fold larger in the Maitre set, is less important than at the beginning. This may explain the different result compared with previous studies[26 27] and our data.

Perus and colleagues[35] recently evaluated the predictive performance of the Maitre[25] and the Scott[20] parameters in 10 obese and 6 non-obese women anaesthetized with desflurane after a propofol induction. During drug infusion, the Scott parameters were superior to the Maitre parameters in the non-obese controls, while they were similar in the obese. Conversely, the decay after infusion stop was better predicted by the Maitre parameters in both patient groups. As our study populations were non-obese, these results are consistent with ours.

None of the investigated parameter sets is perfect. Particularly, the initial phase of drug administration and the terminal phase of drug elimination are not well predicted. Most authors of the previous studies concluded that further studies are necessary. Because of the high costs and the

lack of clinical relevance in the absence of open TCI systems or anaesthesia display systems in the past, they have not been performed yet. It is even uncertain if larger studies would yield better parameter sets at all. Some arguments supporting this statement can be found in the paper by Schnider and colleagues[32] reporting the propofol PK parameter set. Beside developing a new PKPD parameter set the purpose of the study was to prove that adding ethylenediaminetetraacetate (EDTA) to the previous propofol formula does not change PKs. Therefore, each patient was examined twice, once with and once without EDTA admixture to propofol. As the PKPD parameters were identical between the two formulas the individual difference of the predicted plasma propofol concentrations in the two study sessions gives important information on the intra-individual prediction error. The ratio of the propofol concentrations with and without EDTA was between 0.96 and 1.15 with some individuals showing a negative, some a positive and others a fluctuating ratio, suggesting a substantial intra-individual variation of the PKs in the range of $\leq$30%.[32] This is supported by previous data by Hill and colleagues[36] who found a 15.9% performance error of alfentanil despite individual tailoring of PK parameters. This means that the individual PK parameter set may change from one study session to another, which would appear as random effect in the modelling process. The prediction error of a population is very unlikely better than the prediction error in an individual subject.

Volume 1 and clearance 1 are the most important parameters to define the initial bolus and maintenance infusion. By individual *post hoc* Bayesian corrections of these two parameters according to one measurement of the plasma alfentanil concentration, the prediction error of the individualized parameters was improved in some patients but

Fig 5 Comparison of the infusion rate in a TCI driven by the Scott and the Maitre parameters. A 120-min infusion of alfentanil at a target plasma concentration of 200 ng ml^{-1} was simulated for a 40-year-old person of 70 kg and 170 cm. The calculated infusion rates, when using the Scott (weight adjusted) and the Maitre parameters, are shown. The blue line represents the infusion rate according to Scott, the red solid and dashed lines the infusion rates according to Maitre (man and woman, respectively).

not in others.[37] The mean absolute performance error in the population did therefore not change but its standard deviation decreased. Interestingly, adding more than one measurement of the plasma concentration did not further improve the performance error.

In the Maitre[18] parameters compared with the Scott[20] parameters, the volume of the central compartment (V1) and the elimination clearance (Cl 1) are three times higher. A TCI pump driven with the Maitre[18] parameters will therefore infuse a higher amount of alfentanil in order to get a given target plasma concentration. The Maitre[25] parameters also predict a faster decay of the plasma concentration after the stop of infusion, which may be clinically irrelevant, however. The difference in the amount infused is lower with increasing age and higher in women compared with men attributable to the gender and age sensitivity of the Maitre parameters. A simulation of a TCI of 120 min with a target plasma concentration of 200 ng ml^{-1} in a 40-year-old man (70 kg, 170 cm) yielded a cumulative alfentanil dose of 9 mg with the Scott and 14 mg with the Maitre parameters. In a 40-year-old woman of the same height and weight, the amount infused would be 14.8 mg (Fig. 5). Reducing the target plasma concentration from 200 to 130 ng ml^{-1} in the Maitre driven pump would lower the cumulative dose to 9 mg. The 50% decrement time after a 2 h infusion would be 45 min according to Maitre and 47 min according to Scott. An anaesthesia display or TCI will predict lower plasma alfentanil concentrations with the Maitre parameters compared with the Scott parameters, as illustrated in Figure 1. By adjusting the target concentrations to clinical effect the clinician can successfully handle such differences between models.[29]

The prediction error as defined by Varvel[30] (equation 1) and used by many authors has been criticized[3] because parameter sets overpredicting the measured concentrations are favoured. With a given measured plasma alfentanil concentration of 100 ng ml^{-1} a predicted concentration of 80 ng ml^{-1} (Cm$-$Cp$=+20$ ng ml^{-1}=underprediction, see equation 1) yields an absolute PE of 25%. A predicted concentration of 120 ng ml^{-1} (Cm$-$Cp$=-20$ ng ml^{-1}=overprediction) yields an absolute PE of 16.7%. Masui,[3] therefore, proposed the logarithmic accuracy and bias, respectively (equations 8 and 9), which are not affected by the direction of the deviation (overprediction *vs* underprediction). Although there are some differences in the statistic pair-wise comparison between log accuracy and MDAPE and log bias and MDPE, respectively, the conclusions drawn from the different performance parameters are similar.

There are certainly some limitations in our study: the number and timing of blood samples are not balanced in the two data sets. It was not the intention of the two studies from where the data were used, to evaluate or even develop a new PK parameter set for alfentanil but only to control potential prediction errors of the used model. We cannot exclude that this may have affected the precision of MDAPE and MDPE in the bolus data set. Because the blood samples were obtained in the flat part
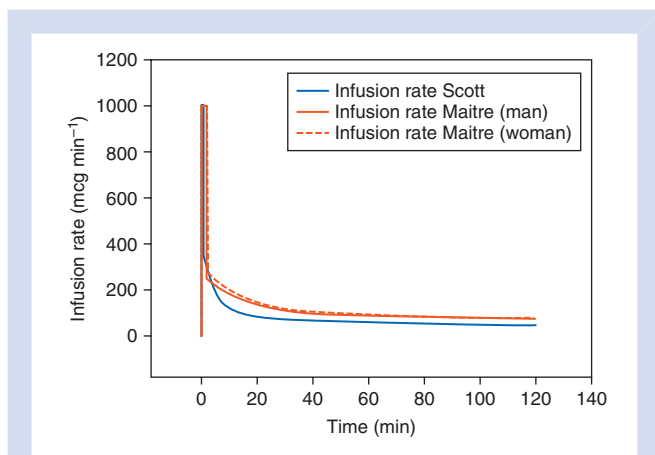
of the concentration-time curve and not during the peaks the performance error of the predicted plasma concentrations are unlikely to be biased.

The two study groups did not differ in gender distribution, but the patients of the bolus group were significantly older and 50% were ASA physical status II (compared with 13% in the infusion group). The reasons were obesity, hypertension, smoking of >20 pack years, diabetes, exercise asthma and clinically insignificant liver disease. It is very unlikely that these co-morbidities that were not associated with clinical symptoms in normal daily life would have substantially affected PKs of alfentanil.

The two groups also differed in the type of hypnotic drug (propofol in the bolus group *vs* xenon or nitrous oxide plus desflurane in the infusion group). It is not very likely however, that the propofol effect on alfentanil PKs as reported by Mertens[28] was the dominating reason for the difference seen in some parameter sets because the performance of the Mertens parameters was substantially inferior to the Scott parameters. Within Group I, there was no difference in the parameter sets' performance between patients receiving xenon and those receiving nitrous oxide plus desflurane.

Conclusion

In healthy orthopaedic patients, the PK parameters by Scott and Maitre were equally valid when alfentanil was given as repeated boluses. When given as infusion, the Maitre parameters were less accurate and subject to a significant bias. We cannot exclude that the difference between bolus and infusion is partially because of the different hypnotics used.

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Declaration of interest

N.S., M.B. and V.H., none declared; T.W.S. is involved in the joint development of a TCI system with CODAN Argus. M.L. and P.M.S. have been regular consultants of Dräger Medical GmbH in the development of Smart Pilot View System since 2004.

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