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CLINICAL PRACTICE

Effectiveness, safety, and pharmacokinetic and pharmacodynamic characteristics of microemulsion propofol in patients undergoing elective surgery under total intravenous anaesthesia[‡]

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Background. The aims of this study were to investigate the effectiveness, safety, pharmacokinetics, and pharmacodynamics of microemulsion propofol, Aquafol[TM] (Daewon Pharmaceutical Co., Ltd, Seoul, Republic of Korea).

Methods. In total, 288 patients were randomized to receive 1% Aquafol[TM] or 1% Diprivan[®] (AstraZeneca, London, UK) (*n*=144, respectively). A 30 mg test dose of propofol was administered i.v. over 2 s for assessing injection pain. Subsequently, a bolus of propofol 2 mg kg^{-1} (−30 mg) was administered. Anaesthesia was maintained with a variable rate infusion of propofol and a target-controlled infusion of remifentanil. Mean infusion rates of both formulations and times to loss of consciousness (LOC) and recovery of consciousness (ROC) were recorded. Adverse events and pharmacokinetic and pharmacodynamic characteristics were evaluated.

Results. Mean infusion rate of Aquafol[TM] was not statistically different from that of Diprivan[®] (median: 6.2 *vs* 6.3 mg kg^{-1} h^{-1}). Times to LOC and ROC were slightly prolonged in Aquafol[TM] (median: 21 *vs* 18 s, 12.3 *vs* 10.8 min). Aquafol[TM] showed similar incidence of adverse events to Diprivan[®]. Aquafol[TM] (*vs* Diprivan[®]) caused more severe (median VAS: 72.0 *vs* 11.5 mm) and frequent (81.9 *vs* 29.2%) injection pain. The dose-normalized AUC$_{last}$ of Aquafol[TM] and Diprivan[®] was 0.71 (0.19) and 0.74 (0.20) min litre^{-1}. The V_1 of both formulations were proportional to lean body mass. Sex was a significant covariate for k_{12} and Ce$_{50}$ of Aquafol[TM], and for k_{e0} of Diprivan[®].

Conclusions. Aquafol[TM] was as effective and safe as Diprivan[®], but caused more severe and frequent injection pain. Aquafol[TM] demonstrated similar pharmacokinetics to Diprivan[®].

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Aquafol[TM] (Daewon Pharmaceutical Co., Ltd, Seoul, Republic of Korea) is a microemulsion of propofol that has been developed for eliminating lipid solvent-related adverse events of long-chain triglyceride emulsion (LCT) propofol (Diprivan[®]; AstraZeneca, London, UK), such as

infection, fat embolism, hypertriglyceridaemia, and pancreatitis.[1] Originally, it was formulated with 8%

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polyethylene glycol 660 hydroxystearate and 5% tetrahydrofurfuryl alcohol polyethylene glycol ether.[2] A phase 1 study to assess the safety and tolerability of polymeric vehicles of this formulation in healthy volunteers showed dose-limiting toxicities,[3] such as skin rash [Common Terminology Criteria for Adverse Events (CTCAE) v3.0 grade 2],[4] pain, tenderness and redness at injection sites, urticaria, fever and dizziness, increases of total bilirubin and lactate dehydrogenase, vomiting, chest discomfort, or pain (CTCAE v3.0 grade 1 for all). Subsequently, Aquafol[TM] was reformulated with 10% purified poloxamer 188 (PP188) and 0.7% polyethylene glycol 660 hydroxystearate.

PP188 has been used to treat sickle-cell disease patients with acute chest syndrome because it improves microvascular blood flow by reducing blood viscosity and by reducing friction between red blood cells and vessel walls.[5] PP188 has been studied in more than 4000 patients, and its tolerability and safety have been described in normal subjects, acute myocardial infarction patients, and sickle cell patients.[6-8]

Alterations in propofol formulation may result in altered pharmacokinetic, pharmacodynamic, and safety characteristics,[9] although our previous microemulsion formulation and LCT propofol were similar in terms of these characteristics within the dose range in an earlier study.[2]

The aims of this study were to investigate the effectiveness (mean infusion rate of propofol during maintenance of anaesthesia), induction [time to LOC and bispectral index (BIS) value at LOC] and recovery characteristics [times to ROC and orientation, and BIS values at ROC and orientation], and safety (incidence and severity of adverse events) of microemulsion propofol in patients undergoing elective surgery under total i.v. anaesthesia. In addition, pharmacokinetic and pharmacodynamic characteristics were evaluated by population analysis using nonlinear mixed-effects modelling.

Methods

Study design

The study was designed as a single-centre, double-blind, randomized, active-controlled, parallel arm, phase 3 clinical trial. The sample size was calculated to detect the equivalence of mean infusion rate during maintenance of anaesthesia between the two propofol formulations.

Mean infusion rate was calculated as follows [equation (1)]:

$$\text{Mean infusion rate of propofol} \, (\text{mg kg}^{-1} \, \text{h}^{-1})$$
$$= \frac{\text{total dose of each propofol formulation}}{\text{body weight} \times \text{maintenance time}} \quad (1)$$

In an earlier study comparing the efficacy of generic propofol with Diprivan®, mean infusion rates of both formulations during induction and maintenance of anaesthesia were 5.4 (1.8) and 5.4 (1.2) mg kg^{-1} h^{-1}, respectively.[10] On the basis of this observation, a sample size of 138 patients per treatment arm was calculated to be sufficient to allow a detection of 15% difference in mean infusion rate with an 80% power at an α of 0.05.

Investigational drugs

The LCT propofol used was 1% Diprivan®; the microemulsion propofol formulation was Aquafol[TM], which was composed of 1% propofol, 10% PP188, and 0.7% polyethylene glycol 660 hydroxystearate.[3]

Patient population

The study was approved by the Institutional Review Board of the Asan Medical Centre (Seoul, Republic of Korea) and written informed consent was obtained from all patients. A total of 288 ASA PS I or II patients who were undergoing stomach, breast, or colorectal surgery were randomly allocated to receive microemulsion (n=144, microemulsion group) or LCT propofol (n=144, LCT group). Of these patients, those consented to arterial blood sampling for pharmacokinetic analysis were 88 (microemulsion group) and 84 (LCT group). The dropout rate was assumed to be 5%. Patients were excluded from the study if they had known allergy to LCT propofol, had abnormal laboratory findings with clinical significance, prior habitual use of psychoactive drugs, or evidence of pregnancy.

Study endpoints

The primary endpoint of this study was mean infusion rate (mg kg^{-1} h^{-1}) of each propofol formulation during maintenance of anaesthesia. The secondary endpoints were time to LOC, times to ROC and orientation, and BIS values at LOC, ROC, and recovery of orientation. Time to LOC was determined every 5 s after an i.v. bolus of propofol 2 mg kg^{-1} by the loss of response to verbal command (open your eyes). Time to ROC was assessed every 10 s after the administration of each propofol formulation was discontinued by eye opening to a verbal command. Time to recovery of orientation was assessed every 10 s by appropriate responses to time, place, and person after extubation. Finally, pain on injection, postoperative nausea and vomiting (PONV), postoperative pain, pharmacokinetic and pharmacodynamic characteristics, and safety profiles were evaluated for each formulation.

Study procedure

All patients fasted from midnight. Midazolam 7.5 mg was administered orally with sips of water 1 h before surgery. Once in the operating theatre, patients were monitored with electrocardiography, pulse oximetry, end-tidal carbon dioxide partial pressure, invasive arterial pressure (Datex-Ohmeda S/5, Planar Systems, Inc., Beaverton, OR, USA) and BIS (Aspect 2000, Aspect Medical Systems,

Inc., Newton, MA, USA). Using RS232C cables, these data were continuously downloaded to personal computers until recovery from anaesthesia. Each patient was preoxygenated with 100% oxygen via a facemask. To ensure that the trial was double-blind, an independent research nurse prepared the investigational drugs. Each formulation was loaded into 5 and 10 ml syringes for the assessment of pain on injection and induction, respectively, and into 50 ml syringes for the maintenance of anaesthesia. All syringes and tubings were wrapped in opaque and black vinyl. A 20 G catheter was placed into a large vein at the wrist and a second angiocatheter was placed in the contralateral radial artery for frequent blood sampling. A 30 mg test dose of propofol in a microemulsion or LCT formulation was administered i.v. over 2 s to assess pain on injection. Propofol-induced pain of moderate to severe intensity was assessed using a visual analogue scale (VAS $>$30 mm).[11] Subsequently, an i.v. bolus of propofol 2 mg kg^{-1} ($-$30 mg) was administered. If the patient did not lose consciousness within 1 min, 0.5 mg kg^{-1} of each propofol formulation was additionally administered i.v. When patients were unconscious, propofol was manually infused at variable rates, and remifentanil was administered by a target effect-site concentration-controlled infusion (Asan Pump, version 1.3, Bionet Co., Ltd, Seoul, Republic of Korea).[12] Tracheal intubation was facilitated by administering rocuronium 0.6 mg kg^{-1}. The lungs of the patients were then ventilated with oxygen in air (1:2), and the ventilation rate was adjusted to maintain the end-tidal carbon dioxide partial pressure between 35 and 45 mm Hg. The infusion rates of propofol were adjusted by an independent anaesthesiologist to maintain BIS values $<$60. Target effect-site concentrations of remifentanil were titrated to prevent signs of inadequate anaesthesia[13] (stepwise increase by 2 ng ml^{-1}) and to maintain stable haemodynamics [systolic arterial pressure (SAP) $>$80 mm Hg and heart rate (HR) $>$45 beats min^{-1}, stepwise decrease by 2 ng ml^{-1}]. If necessary, ephedrine or atropine was administered to maintain SAP above 80 mm Hg and HR above 45 beats min^{-1} during anaesthesia. Neuromuscular block was antagonized by the administration of pyridostigmine and glycopyrrolate at the end of surgery.

PONV and pain

Patients who had consented received i.v. patient-controlled analgesia (i.v. PCA). The i.v. PCA device (Accufuser plus®, Wooyoung Medical Co. Ltd, Seoul, Republic of Korea) contained fentanyl 10$-$15 µg ml^{-1}, ketorolac 1.2$-$1.8 mg ml^{-1}, and ondansetron 80 µg ml^{-1}. The analgesic maintenance dose was set at 10$-$15 µg fentanyl (i.e. 1 ml), with a lockout interval of 15 min. The maximum cumulative dose was set at 200$-$300 µg fentanyl every 4 h. To prevent PONV, ondansetron 4 mg was injected i.v. at the end of surgery.[14] PONV and pain were assessed by an independent research nurse at 6 and 24 h after discontinuation of each propofol formulation. An

investigator explained the VAS (0 mm, no pain or nausea; 100 mm, worst pain or nausea imaginable) for propofol-induced pain, postoperative pain, and nausea to patients on the first preoperative day. In this study, positive events of nausea, vomiting, or retching within 6 h and between 6 and 24 h after discontinuation of microemulsion or LCT propofol were designated as early and late PONV, respectively. Patients were instructed to record the frequency of vomiting and retching. An investigator recorded VAS scores for nausea and the frequency of emetic episodes (vomiting and retching). The incidence rates of PONV were assessed by VAS for nausea ($>$0) or incidence of emetic episodes ($>$0). Postoperative pain was assessed using a VAS. The need for rescue anti-emetic and analgesic agents was also recorded.

Safety

Safety profiles of microemulsion and LCT propofol were evaluated based on incidence rates of adverse events, vital signs, and clinical laboratory test results. Clinical laboratory tests were performed in the screening period, pre-induction period, during anaesthesia, and 24 h after discontinuation of investigational drugs. Hepatorenal function [urinalysis and alkaline phosphatase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), direct bilirubin, blood urea nitrogen, and creatinine levels], lipid parameters (triglyceride, cholesterol, high-density lipoprotein, and low-density lipoprotein levels), and coagulation parameters (prothrombin time, activated partial thromboplastin time, and platelet count) were assessed.

Blood sample acquisition and assay

Arterial blood samples (4 ml) were obtained at preset intervals: immediately before the administration of investigational drugs, at LOC, and 10, 30, and 60 min after the start of propofol formulation infusion. Samples were also obtained at 0, 1, 6, 12, and 24 h after each propofol formulation was discontinued. Samples were collected in ethylenediaminetetraacetic acid (EDTA) tubes, centrifuged for 10 min at 3500 rpm and then stored at $-$70°C until assay. Plasma concentrations of propofol were measured as described in our earlier study.[3] The lower limit of quantification of propofol was 10 ng ml^{-1}. The calibration curve was linear over the range of 10$-$10 000 ng ml^{-1} with the coefficients of determination (R^2) $>$0.999 for all cases. Intra-assay precision values were 0.2$-$11.0%. Inter-assay within-day and between-day precision values were $<$14.7% and 6.9%, respectively. Intra-assay accuracy values were 94.1$-$99.9% of the nominal value. Inter-assay accuracy values were 95.0$-$103.7% of the nominal value.

Selection of BIS

BIS data for pharmacodynamic modelling were selected based on the following criteria, which were similar to

the work of Minto and colleagues[12] and Kang and colleagues:[15] (i) a baseline BIS value; (ii) a BIS value between the administration of a 30 mg test dose and an i.v. bolus of propofol 2 mg kg^{-1} (-30 mg); (iii) every 10 s until LOC; (iv) every 30 s until the beginning of propofol infusion; (v) every 1 min during the first 5 min after dosing modulation, and every 5 min between dosing modulations; (vi) every 1 min after the termination of propofol infusion; (vii) at the time points of LOC, ROC, and recovery of orientation.

Pharmacokinetics and pharmacodynamics

The dose-normalized AUC$_{last}$ and AUC$_{inf}$ (area under the curve from administration to the last measured concentration and to infinity, respectively) were calculated using WinNonlin Professional 5.2 (Pharsight Corporation, Mountain View, CA, USA). The AUC$_{last}$ and AUC$_{inf}$ were calculated as described in our earlier study.[3]

One-, two-, and three-compartment models with linear pharmacokinetics were fitted using ADVAN 1, 3, and 11 subroutines and the first-order conditional estimation (FOCE) with interaction procedure of NONMEM® VI level 2 (ICON Development Solutions, Dublin, Ireland). Dissociation between the concentration of propofol and Effect (BIS) was linked with effect compartment.[2] The relationship between the effect-site concentration of propofol and BIS was analysed using a sigmoid E_{max} model:[2]

$$\text{Effect} = E_0 + (E_{max} - E_0)\frac{\text{Ce}^\gamma}{\text{Ce}_{50}^\gamma + \text{Ce}^\gamma}$$

where Effect is the BIS value, E_0 the baseline BIS when no drug is present, E_{max} the maximum possible drug effect, Ce the calculated effect-site concentration of propofol, Ce$_{50}$ the effect-site concentration associated with 50% maximal drug effect, and γ the steepness of the concentration *vs* response relation. A sigmoid E_{max} model was fitted using ADVAN 6 subroutine and the FOCE with interaction procedure of NONMEM® VI level 2.

Inter-individual random variability of pharmacokinetic and pharmacodynamic models was modelled using a log-normal or additive model as appropriate. A diagonal matrix was estimated for the different distributions of η, where η is inter-individual random variability with mean zero and variance ω^2. A proportional model was used for the residual random variability. The covariates analysed were age, sex, weight, height, body surface area,[16] lean body mass (LBM),[17] effect-site concentration of remifentanil, and SAP.

A 90% CI was calculated for the ratio of arithmetic mean of each individually predicted pharmacokinetic parameter (half-life, volume of distribution, clearance, volume of distribution at steady state) between microemulsion and LCT propofol, based on an analysis of variance with a linear mixed-effects model that contained an effect for formulation only.

Model diagnostics and validation

Pharmacokinetic and pharmacodynamic models were evaluated using statistical and graphical methods. The minimal value of the objective function (equal to minus twice the log-likelihood) calculated by NONMEM® was used as the goodness-of-fit characteristic to discriminate between hierarchical models using the log-likelihood ratio test.[18] A *P*-value of 0.05, representing a decrease in objective function value of 3.84 points, was considered statistically significant (χ^2 distribution, degrees of freedom=1). R (version 2.8.0; R Foundation for Statistical Computing, Vienna, Austria) was used for graphical model diagnostics.

The conditional weighted residuals (CWRES) of pharmacokinetic and pharmacodynamic models were calculated to reduce model misspecification that may result from utilizing weighted residuals with the FOCE method.[19] Predictive checks were performed by simulating 2000 iterations and comparing simulated prediction intervals with the original data.[20] A non-parametric bootstrap analysis was performed as an internal model validation (Wings for NONMEM, Nick Holford, Version 614, July 2007, Auckland, New Zealand).[21] Briefly, 2000 bootstrap replicates were generated by random sampling from the original data set with replacement. The final model parameter estimates were compared with the median parameter values and the 2.5–97.5 percentiles of the non-parametric bootstrap replicates of the final model.

Statistics

Statistical analysis was conducted using R (version 2.8.0, R Foundation for Statistical Computing, Vienna, Austria) or SigmaStat 3.5 for Windows (Systat Software, Inc., Chicago, IL, USA). Data are expressed as mean (SD) for normally distributed continuous variables, median (range) for non-normally distributed continuous variables, and counts and percentages for categorical variables. A *P*-value of <0.05 was considered statistically significant.

Results

Patient population

Enrolment, group assignment, and analysis are shown in Figure 1. Patient characteristics for the safety analysis are summarized in Table 1.

Effectiveness

A variety of variables to compare the effectiveness between the two formulations are shown in Table 2. An additional dose of propofol 0.5 mg kg^{-1} was required to induce LOC in two patients in the microemulsion group and one patient in the LCT group. Time to LOC was

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                        ┌─────────────────────────┐
                        │ 288 underwent randomization │
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| 144 were assigned to microemulsion propofol | 144 were assigned to LCT propofol |

| 143 were included in the ITT analysis | 141 were included in the ITT analysis |

| 88 were included in population pharmacokinetic analysis | 84 were included in non-compartmental and population pharmacokinetic analysis |

| 2 refused postoperative blood sampling | 1 was excluded for failure to obtain BIS data | 1 was excluded for failure to obtain BIS data |

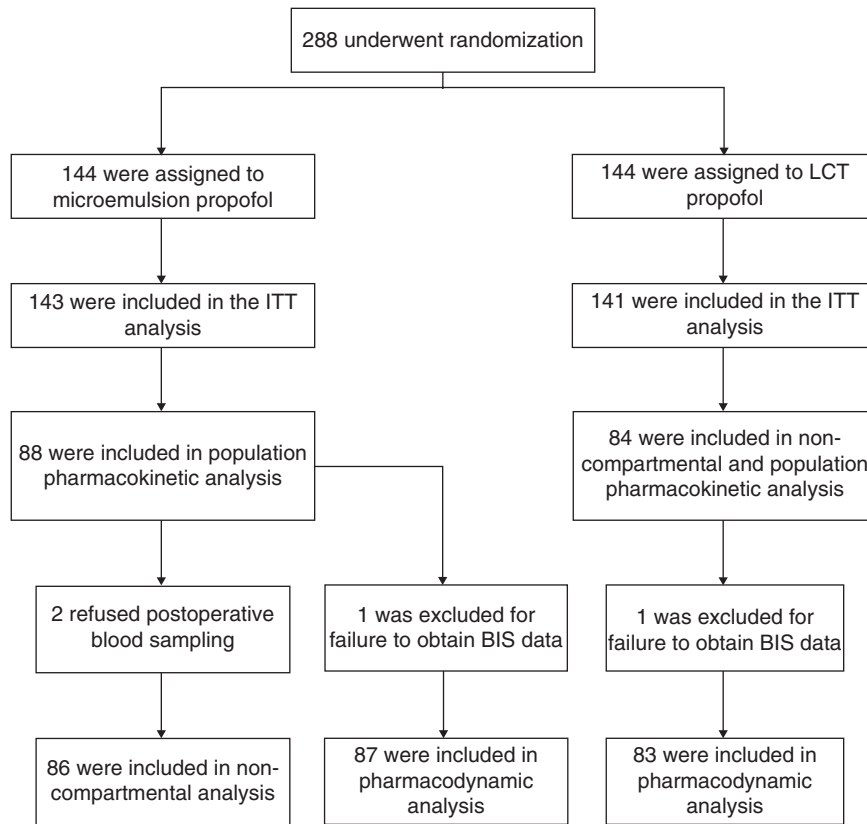| 86 were included in non-compartmental analysis | 87 were included in pharmacodynamic analysis | 83 were included in pharmacodynamic analysis |

Fig 1 Enrolment, group assignment, and analysis. In total, 288 patients were included in the safety and intention-to-treat analyses (n=144 in the microemulsion group, 144 in the LCT group). Of these patients, four were excluded from $Time_{LOC}$ and BIS_{LOC} analyses because they were too deeply sedated before the administration of investigational drugs, owing to premedication with midazolam. Therefore, 284 patients were included in $Time_{LOC}$, $Time_{ROC}$, $Time_{ROO}$, BIS_{LOC}, BIS_{ROC}, and BIS_{ROO} analyses (n=143 in the microemulsion group, 141 in the LCT group). $Time_{LOC}$, time to loss of consciousness after an i.v. bolus of propofol 2 mg kg^{-1}; $Time_{ROC}$, time to recovery of consciousness after infusion of each propofol formulation was terminated; $Time_{ROO}$, time to recovery of orientation after extubation; $BIS_{LOC, ROC, ROO}$, bispectral index values at LOC, ROC, and ROO.

Table 1 Patient characteristics for safety analysis. Data are expressed as mean (SD), median (25%, 75%), or count as appropriate. Patient characteristics were compared using the two-sample t-test, Mann–Whitney rank-sum test, or χ^2 test as appropriate. LCT propofol, long-chain triglyceride emulsion propofol; ASA PS, American Society of Anesthesiologists Physical Status. No significant differences between microemulsion and LCT propofol were found between any of the observations. *Inguinal hernia, cholelithiasis, neoplasm of the liver and intrahepatic bile ducts, and malignant neoplasm of the uterus

	Microemulsion propofol (n=144)	LCT propofol (n=144)
ASA PS I/II	35/109	32/112
Age (yr)	55 (48, 61)	53 (44, 61)
Weight (kg)	63.1 (9.6)	62.3 (9.4)
Height (cm)	163 (158, 169)	163 (158, 169)
Sex (M/F)	91/53	84/60
Type of surgery		
Colorectal	75	90
Stomach	48	32
Breast	15	16
Other*	6	6

longer than 100 s in these patients. The remainder of the participants lost consciousness after the administration of an i.v. bolus of propofol 2 mg kg^{-1} (−30 mg). The bolus dose of propofol did not show significant difference between the two formulations: 122.4 (22.4) mg for microemulsion propofol vs 119.7 (21.9) mg for LCT propofol (P=0.297). Times to LOC and ROC of microemulsion propofol were significantly prolonged, but within clinically acceptable ranges. In particular, there were statistically significant differences between sexes in times to LOC, ROC, and time to recovery of orientation (Fig. 2).

Propofol-induced pain

The incidence rates of pain on injection were 81.9% and 29.2% with microemulsion and LCT propofol, respectively (P<0.001). These values were estimated from the percentage of all patients in each group who experienced pain on injection (VAS >30 mm).[11] The distribution of VAS scores for propofol-induced pain is shown in Figure 3.

PONV and pain

A total of 122 patients in each group received i.v. postoperative patient-controlled analgesia. The doses of fentanyl, ondansetron, and ketorolac did not show significant differences between the two formulations (P>0.05 for all, Mann–Whitney rank-sum test). The incidence rates of

Table 2 The comparison of effectiveness between microemulsion and LCT propofol. Data are expressed as mean (SD) or median (range) as appropriate. Of these patients, four were excluded from $Time_{LOC}$ and BIS_{LOC} analyses because they were too deeply sedated before the administration of investigational drugs, owing to premedication with midazolam. Therefore, 284 patients were included in $Time_{LOC}$, $Time_{ROC}$, $Time_{ROO}$, BIS_{LOC}, BIS_{ROC}, and BIS_{ROO} analyses ($n=143$ in the microemulsion group, 141 in the LCT group). *Total dose of each propofol formulation/body weight×maintenance time; [†]median of all infusion rates of propofol or all target effect-site concentrations of remifentanil used during maintenance of anaesthesia; [‡]$P<0.05$ *vs* LCT propofol, otherwise unremarkable (Mann–Whitney rank-sum test). $Time_{LOC}$, time to loss of consciousness after an i.v. bolus of propofol 2 mg kg^{-1} (-30 mg); $Time_{ROC}$, time to recovery of consciousness after infusion of each propofol formulation was terminated; $Time_{ROO}$, time to recovery of orientation after extubation; $BIS_{LOC,ROC,ROO}$, bispectral index values at LOC, ROC, and ROO

	Microemulsion propofol ($n=144$)	LCT propofol ($n=144$)
Propofol		
Mean infusion rate (mg kg^{-1} h^{-1})*	6.2 (3.8, 8.9)	6.3 (3.2, 10.9)
Total dose (mg)	979.0 (177.3, 4742.5)	899.7 (287.3, 2521.3)
Frequency of infusion rate adjustment	8 (3, 26)	8 (2, 19)
Median infusion rate during maintenance of anaesthesia (mg kg^{-1} h^{-1})[†]	6 (1, 15)	6 (1, 14)
Remifentanil		
Mean infusion rate (µg kg^{-1} min^{-1})	0.4 (0.1)	0.5 (0.1)
Total dose (µg)	4044.5 (190.0, 19 388.4)	4049.0 (639.3, 11 915.4)
Frequency of target effect-site concentration adjustment	17 (6, 50)	16 (7, 40)
Median target effect-site concentration during maintenance of anaesthesia (ng ml^{-1})[†]	9 (1, 30)	9 (1, 28)
Duration of anaesthesia (h)	2.0 (0.4, 9.0)	2.1 (0.5, 5.8)
$Time_{LOC}$ (s)	21.0[‡] (0.0, 134.0)	18.0 (1.0, 109.0)
$Time_{ROC}$ (min)	12.3[‡] (0.3, 54.4)	10.6 (1.9, 26.8)
$Time_{ROO}$ (min)	1.7 (0.4, 32.4)	1.7 (0.2, 23.1)
BIS_{LOC}	82 (37, 98)	82 (44, 97)
BIS_{ROC}	76 (47, 92)	76 (46, 94)
BIS_{ROO}	81 (67, 95)	79 (66, 95)

early and late PONV were 9.7% and 8.4% for the microemulsion group and 14.7% and 16.2% for the LCT group, respectively. There were no significant differences in the severity of PONV and postoperative pain between the two formulations (Table 3).

Safety

Overall, a total of 840 adverse events were reported in 288 patients during the study period. A total of 116 patients (80.6%) in the microemulsion group experienced 383 adverse events, and 132 patients (91.7%) in the LCT group experienced 457 adverse events ($P<0.05$, χ^2 test). The numbers of mild, moderate, and severe adverse events were 177, 155, and 51, respectively, in the microemulsion group, and 214, 150, and 93, respectively, in the LCT group ($P<0.05$, χ^2 test). There were no significant differences in measured levels of cholesterol, high-density lipoprotein, and low-density lipoprotein between the two formulations, but serum triglyceride levels in the LCT group were significantly increased during anaesthesia [163 (47, 991) *vs* 82 (30, 189) mg dl^{-1}, respectively, $P<0.05$, Mann–Whitney rank-sum test]. No patient with increased triglyceride levels in the LCT group showed clinical symptoms or signs of pancreatitis.

In nine patients, increased AST and ALT levels spontaneously returned to normal levels within 10 days. Seven patients underwent total gastrectomy (one in each group), distal gastrectomy with gastroduodenostomy (two in the microemulsion group and one in the LCT group), and low anterior resection and abdominoperitoneal resection of the rectum (two in the microemulsion group). Two patients in the LCT group underwent partial hepatectomy and lateral segmentectomy of the liver.

Adverse events of the cardiovascular and hepatorenal systems and lipid and coagulation parameters with causal relation to microemulsion or LCT propofol are shown in Table 4. Ephedrine was administered 39 times in 22 patients of the microemulsion group and 50 times in 27 patients of the LCT group. One patient of the LCT group received one dose of phenylephrine. Atropine was administered 14 times in 10 patients of the microemulsion group and 29 times in 21 patients of the LCT group. Antihypertensive agents (labetalol or nicardipine) were administered 102 times in 56 patients of the microemulsion group and 62 times in 36 patients of the LCT group. Esmolol was administered 14 times to five patients of the microemulsion group and five times to five patients of the LCT group. There were no significant differences in the number of patients who received these drugs between the two groups (χ^2 test).

Other adverse events that were less common ($<1\%$), or considered unrelated to investigational drugs included hypomagnesaemia, hypoproteinaemia, haemorrhagic shock, postoperative bleeding, abdominal distension, haematochezia, thrombocytopenia, headache, myodesopsia, delirium, dyspnoea, s.c. emphysema, hyperglycaemia, fever, and low back pain.

One serious adverse event occurred in each of the two groups: postoperative bleeding due to failure of mesenteric artery ligation in the microemulsion group and massive intraoperative bleeding due to rupture of the superior mesenteric vein in the LCT group.

Pharmacokinetics and pharmacodynamics

A total of 863 plasma concentration measurements from 88 patients (71 males and 17 females) receiving
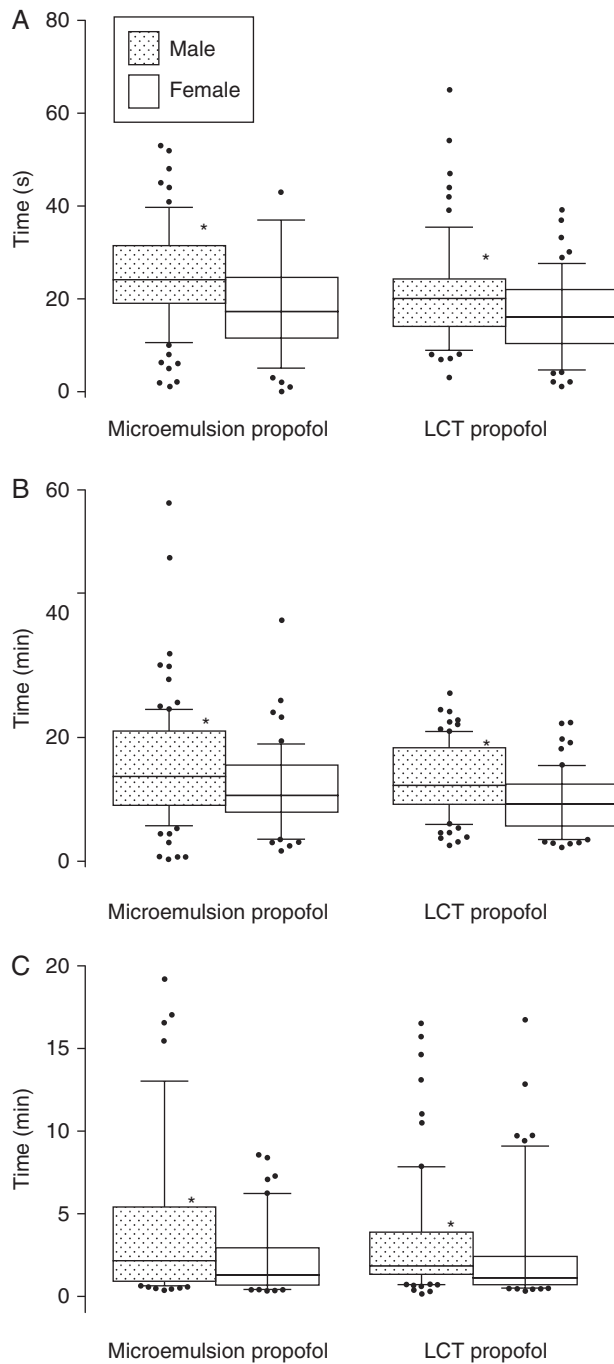
Fig 2 Differences in times to (A) LOC, (B) ROC, and (C) recovery of orientation between male and female patients in the microemulsion and LCT groups. The central box covers the inter-quartile range with the median indicated by the line within the box. The whiskers extend to the 10th percentile and 90th percentile values. More extreme values (filled circle) are plotted individually. Data are expressed as median (25–75%). $Time_{LOC}$ between male and female in microemulsion were 23.0 (16.0–31.0) and 18.0 (12.0–26.0) s, respectively. $Time_{ROC}$ and $Time_{ROO}$ between male and female in microemulsion were 13.9 (9.1–20.6), 10.8 (7.7–15.2), 2.2 (1.0–5.3), 1.3 (0.7–2.9) min, respectively. $Time_{LOC}$, $Time_{ROC}$, and $Time_{ROO}$ between male and female in LCT were 20.0 (14.0–24.3), 16.0 (10.3–22.0) s, 11.7 (8.8–17.9), 9.0 (5.4–12.0), 1.9 (1.4–3.6), 1.2 (0.7–2.5) min, respectively. *$P<0.05$ vs female (Mann–Whitney rank-sum test).
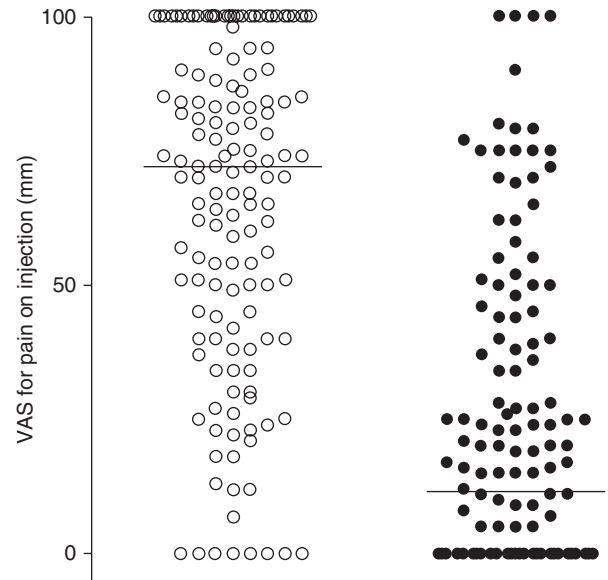

Fig 3 The distribution of VAS scores for pain on injection with microemulsion and LCT propofol after a 30 mg test dose of propofol. The median VAS scores (25–75%) for pain on injection of microemulsion and LCT propofol were 72.0 (40.0–92.0) and 11.5 (0.0–39.8) mm, respectively ($P<0.001$, Mann–Whitney rank-sum test). The solid horizontal lines represent median VAS scores.

microemulsion propofol and 834 measurements from 84 patients (67 males and 17 females) receiving LCT propofol were used to determine the pharmacokinetics. Plasma propofol concentration at LOC for one patient receiving microemulsion propofol was 0.02 μg ml^{-1}; this was considered a measurement error and excluded from the non-compartmental and population pharmacokinetic analyses. Body weight, height, and age were 64.8 (9.9) kg, 166.5 (148.0–182.0) cm, and 57.5 (28.0–71.0) yr, respectively, for patients receiving microemulsion formulation, and 64.3 (8.6) kg, 167.0 (150.0–182.0) cm, and 54 (25.0–72.0) yr, respectively, for patients receiving LCT formulation. There were no significant differences in any of these characteristics, including sex, between the two formulations (two sample t-test, Mann–Whitney rank-sum test or χ^2 test as appropriate). A total of 7448 BIS values from 87 patients receiving microemulsion propofol and 6777 BIS values from 83 patients receiving LCT propofol were used to determine the pharmacodynamics.

The cumulative propofol dose of microemulsion propofol at each sampling point was not significantly different from that of LCT propofol (Fig. 4A). At LOC, there were no significant differences in the plasma concentrations of microemulsion (13.3, 0.02–32.0 μg ml^{-1}) and LCT propofol (11.9, 2.3–38.0 μg ml^{-1}) (Mann–Whitney rank-sum test) (Fig. 4B). Plasma propofol concentrations during infusion (except at LOC) and up to 1 h after discontinuation of propofol infusion were consistently lower in patients receiving microemulsion propofol (Fig. 4C). The dose-normalized AUC_{last} and AUC_{inf} were 0.71 (0.19)

Table 3 Postoperative nausea, vomiting, and pain. Data are expressed as median (25%, 75%) or count with percentage as appropriate. Positive events of nausea, vomiting, or retching within 6 h and between 6 and 24 h after discontinuation of microemulsion or LCT propofol were designated as early and late PONV, respectively. $P>0.05$ for all (χ^2 test or Mann–Whitney rank-sum test as appropriate). *VAS scores for nausea in patients who complained of nausea. [†]Dolasetron, ondansetron, or metoclopramide were administered as rescue anti-emetics. [‡]Aspirin, piroxicam, propacetamol, ketoprofen, ketorolac, nimesulide, meperidine, tramadol, or fentanyl were administered as rescue analgesics

| | Microemulsion propofol | | LCT propofol | |
	Within 6 h ($n=144$)	Between 6 and 24 h ($n=143$)	Within 6 h ($n=143$)	Between 6 and 24 h ($n=142$)
Number (%) of patients with VAS for nausea >0	13 (9.0)	11 (7.7)	18 (12.6)	21 (14.8)
VAS for nausea (mm)*	26 (3, 53)	25 (4, 34)	28 (4, 43)	9 (4, 33)
Number of patients (%) with frequency of emetic episodes >0	2 (1.4)	3 (2.1)	5 (3.5)	10 (7.1)
Number of patients who needed rescue anti-emetics (dosing frequency)[†]	3 (8)		2 (2)	
VAS for postoperative pain (mm)	45 (27, 59)	30 (19, 50)	43 (26, 58)	30 (20, 41)
Number of patients who needed rescue analgesics (dosing frequency)[‡]	123 (197)		118 (202)	

Table 4 Adverse events of the cardiovascular system, hepatorenal system, lipid parameters, and coagulation parameters with causal relation to microemulsion or LCT propofol. Data are expressed as number of adverse events. *$P<0.05$ *vs* microemulsion propofol, otherwise unremarkable (χ^2 test). [†]Platelet count=73 000 mm^{-3}. [‡]Total adverse events occurred during the study period. HDL, high-density lipoprotein; LDL, low-density lipoprotein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; PT (INR), prothrombin time (international normalized ratio); aPTT, activated partial thromboplastin time; BUN, blood urea nitrogen. Abnormal laboratory tests were defined as follows; triglyceride, LDL cholesterol and cholesterol ≥120% of the screening value, HDL cholesterol ≤90% of screening value, AST and ALT >80 IU litre^{-1}, ALP >240 IU litre^{-1}, total bilirubin >2.4 mg dl^{-1}, direct bilirubin>1 mg dl^{-1}, PT (INR) and aPTT ≥2 times the screening value, BUN >40 mg dl^{-1}, serum creatinine ≥1.8 mg dl^{-1}, albuminuria and glycosuria ≥2+ on the spot test, otherwise determined clinically

| | Microemulsion propofol ($n=144$)/LCT propofol ($n=144$) | | | | |
	Definitely related	Possibly related	Probably not related	Definitely not related	Unknown
Cardiovascular					
Hypotension	0/0	30/36	3/0	0/3	0/0
Bradycardia	0/1	13/36	2/5	2/0	0/0
Hypertension	0/0	0/0	98/64	12/10	0/1
Tachycardia	0/0	1/0	22/10	1/6	1/1
Hepatic					
Elevated AST	0/0	0/0	2/2	2/2	0/0
Elevated ALT	0/0	0/0	3/1	2/2	0/0
Elevated ALP	0/0	0/0	0/0	0/0	0/0
Elevated total bilirubin	0/0	0/0	0/0	0/0	0/0
Elevated direct bilirubin	0/0	0/0	0/0	0/0	0/0
Renal					
Elevated BUN	0/0	0/0	0/0	0/0	0/0
Elevated serum creatinine	0/0	0/0	1/0	0/0	1/1
Proteinuria	0/0	0/1	0/0	1/0	5/4
Glycosuria	0/0	0/1	0/2	2/0	3/2
Lipids					
Elevated triglyceride	0/43*	0/0	0/1	0/0	0/0
Elevated cholesterol	0/0	0/0	0/0	0/0	1/0
Lowered HDL cholesterol	0/0	0/0	0/1	0/1	66/103
Elevated LDL cholesterol	0/0	0/0	0/0	0/0	2/0
Coagulation					
Prolongation of PT (INR)	0/0	0/0	0/0	0/0	0/0
Prolongation of aPTT	0/0	0/0	0/0	0/0	0/0
Thrombocytopenia	0/0	0/0	0/1[†]	0/0	0/0
Total[‡]	0/44	53/77	192/167	53/54	85/115

and 0.74 (0.20) min litre^{-1} for microemulsion propofol and 0.74 (0.20) and 0.77 (0.20) min litre^{-1} for LCT propofol, respectively. Ninety per cent confidence intervals calculated for the ratio of geometric means of dose-normalized AUC$_{last}$ and AUC$_{inf}$ were 89.3−108.4 and 89.6−108.9, respectively.

The final pharmacokinetic model of microemulsion propofol included LBM and sex as a significant covariate for V_1 and k_{12}, respectively, whereas that of LCT propofol, LBM for V_1. The final pharmacokinetic models resulted in an improvement in the objective function values (31.58, $P<0.0001$ for microemulsion propofol; 18.24, $P<0.01$ for LCT propofol) compared with the basic models. Sex was a significant covariate for Ce$_{50}$ and k_{e0} in the final model of microemulsion propofol and LCT propofol, respectively. The final pharmacodynamic models resulted in an improvement in the objective function values (15.297, $P<0.001$ for microemulsion propofol; 13.206, $P<0.001$ for LCT
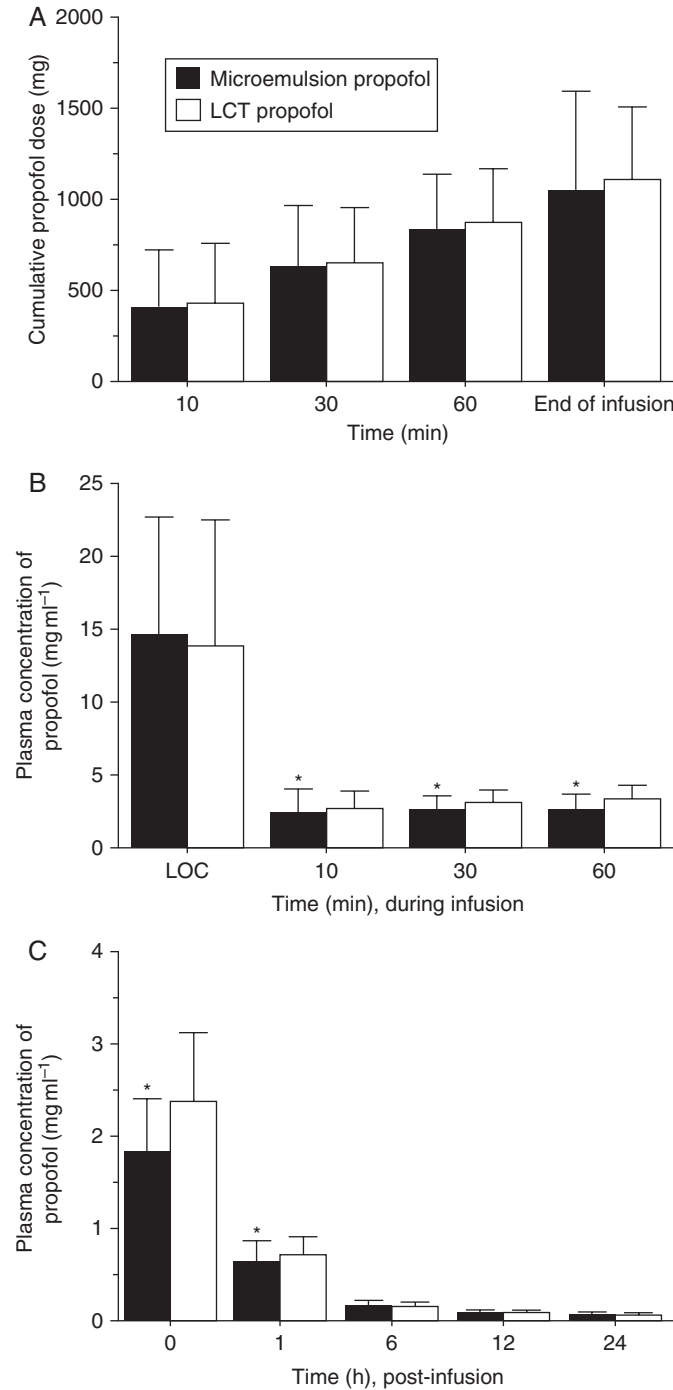
Fig 4 Cumulative propofol dose at each sampling point during infusion of microemulsion and LCT and the plasma concentrations of propofol over time. *$P<0.05$ vs long LCT propofol. (A) Cumulative propofol dose at 10, 30, and 60 min after the start of propofol formulation infusion and at the end of infusion. (B) Plasma propofol concentrations at LOC, 10, 30, and 60 min after the start of propofol formulation infusion. (C) Plasma propofol concentrations at 0, 1, 6, 12, and 24 h after each propofol formulation was discontinued.

propofol) compared with the basic models. The CWRES vs predicted propofol concentrations or BIS values, and predictive checks of the final models are shown in Figure 5 (pharmacokinetics) and Figure 6 (pharmacodynamics), respectively. Population parameter estimates and median parameter values (2.5−97.5%) of the non-parametric

bootstrap replicates of the final pharmacokinetic and pharmacodynamic models for microemulsion and LCT propofol are summarized in Tables 5 and 6, respectively. Table 7 shows the 90% CI of the ratio of arithmetic mean of each individually predicted pharmacokinetic parameters between microemulsion and LCT propofol.
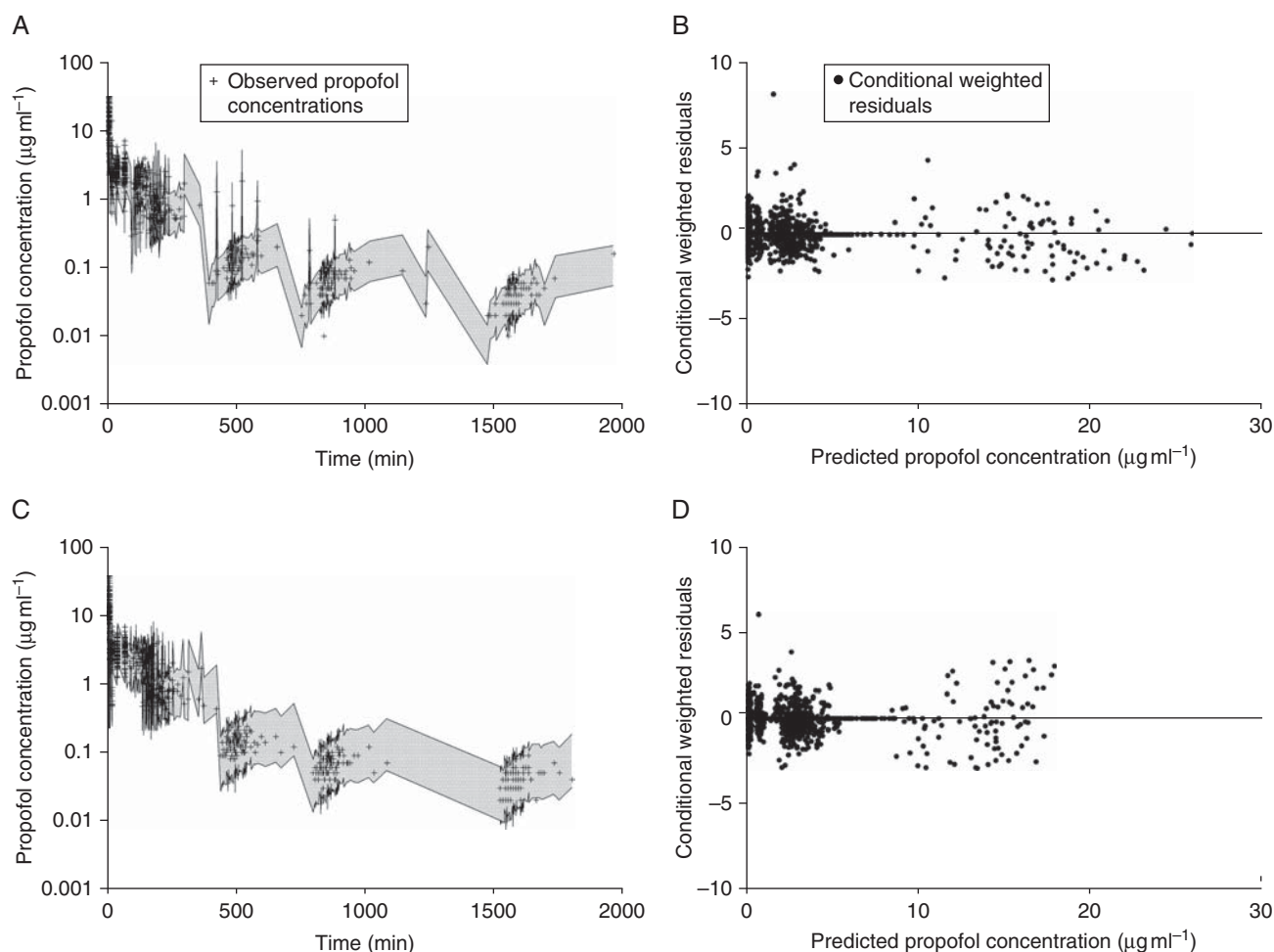
Fig 5 Predictive checks of the final pharmacokinetic models and the CWRES *vs* predicted propofol concentrations. (A) Predictive check for microemulsion propofol. (B) CWRES *vs* predicted propofol concentration for microemulsion propofol. (C) Predictive check for LCT propofol. (D) CWRES *vs* predicted LCT propofol concentration. Less than 10% of the data distributed outside the 90% prediction intervals (5.94% for microemulsion propofol and 5.47% for LCT propofol), indicating that the final pharmacokinetic models for both formulations adequately describe the time-courses of propofol plasma concentrations. Grey area between solid lines: 90% prediction intervals.

Discussion

Microemulsion propofol was as effective and safe as LCT propofol, and demonstrated similar pharmacokinetic characteristics to LCT propofol in terms of dose-normalized AUCs. As expected, microemulsion propofol did not increase serum triglyceride levels during administration, but caused more severe and more frequent pain on injection.

The increased frequency and severity of pain on injection seen with current microemulsion formulation may be associated with a high aqueous-free propofol concentration: 63.3 (1.2) *vs* 12.4 (0.7) μg ml^{-1} in LCT propofol.[3] However, lipid solvent-induced hypertriglyceridaemia and pancreatitis can be avoided with microemulsion propofol. Moreover, we observed good stability at stress condition [temperature=60 (sd 2)°C] for 4 weeks and good compatibility with various drugs and fluids used during anaesthesia (data not shown, July 28, 2008, Tae-Won Song, MS, Central Research Laboratories, Daewon Pharmaceutical Co.). As a result, microemulsion propofol may reduce the

occurrence of fat embolism caused by phase separation of LCT formulation.[22]

The safety evaluation of PP188 has focused on its effects on the kidney, liver, and platelets. Renal function was not influenced by PP188.[5] Hepatic function tests showed modestly but transiently increased levels of markers, particularly direct bilirubin and ALT levels.[5 8] Transient and mild thrombocytopenia was also observed, but there were no dose- or time-related significant decreases in platelet count.[8] In this study, we did not observe any abnormal laboratory test results of the liver, kidney, and platelet with causal relation to microemulsion propofol. In three patients receiving microemulsion propofol who underwent gastrectomy, the potential causes of increased AST and ALT levels are unknown. An aberrant left hepatic artery, arising from the left gastric artery either as an accessory or replacing the left hepatic artery, is seen in 44% of patients with gastric cancer.[23] Like PP188,[5 8] resection of this artery as part of the gastrectomy
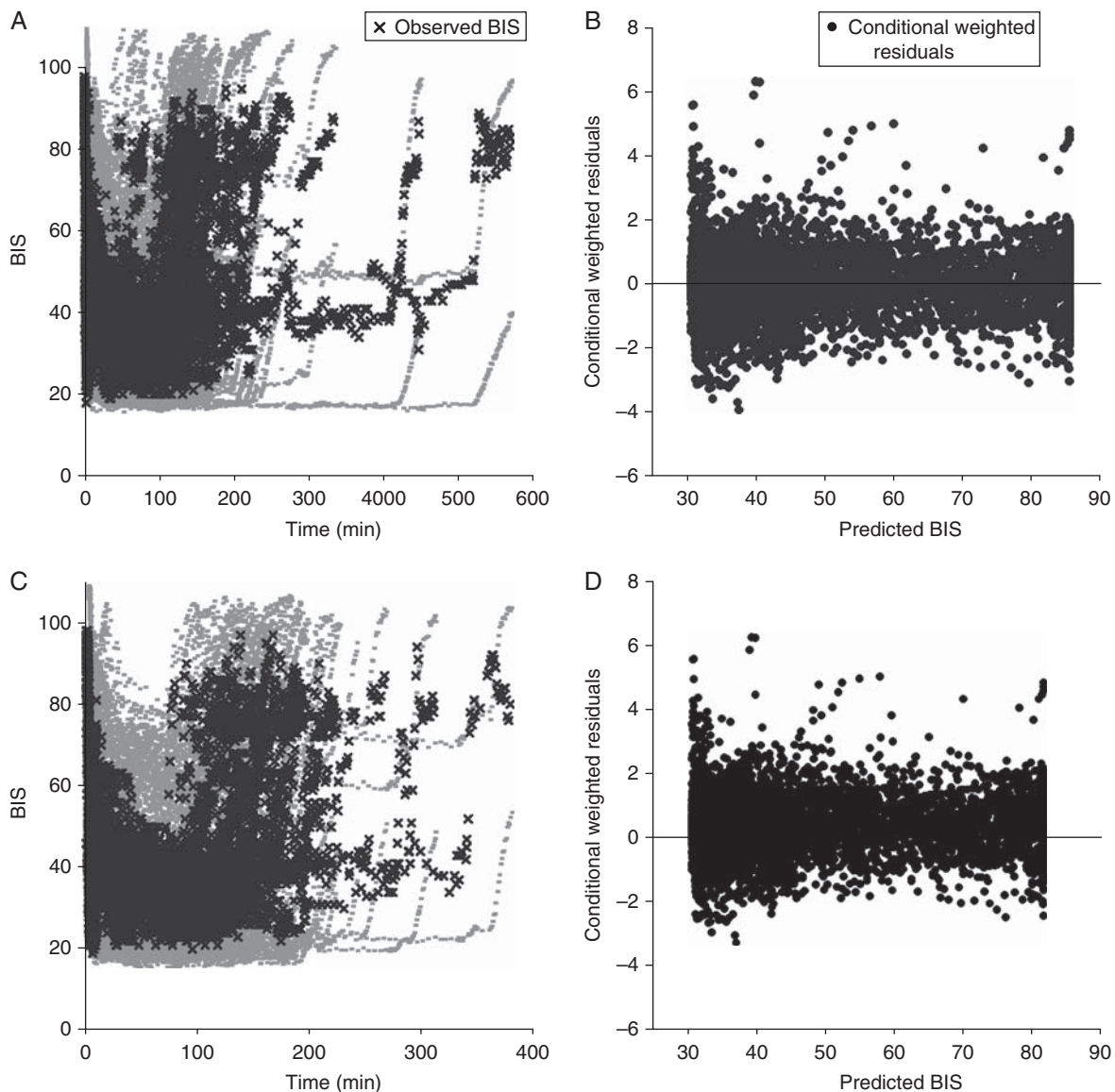
Fig 6 Predictive checks of the final pharmacodynamic models and CWRES *vs* predicted BIS. (A) Predictive check for microemulsion propofol. (B) CWRES *vs* predicted BIS for microemulsion propofol. (C) Predictive check for LCT propofol. (D) CWRES *vs* predicted BIS for LCT propofol. Less than 10% of the data distributed outside the 90% prediction intervals, indicating that the final pharmacodynamic models (3.0% for microemulsion propofol and 2.4% for LCT propofol) for both formulations adequately describe the time-courses of BIS. Empty area between grey horizontal marks (−): 90% prediction intervals.

procedure may cause transient and reversible liver dysfunction.[24] Unfortunately, we did not identify aberrant left hepatic arteries in these patients.

PP188 has been reported to cause three cases of non-immunoglobulin E-mediated hypersensitivity reaction, known as C-activation-related pseudoallergy (CARPA),[25] although perioperative anaphylaxis to LCT propofol has also been reported.[26] Less than 5% of PP188 is metabolized and renal excretion accounts for more than 90% of its clearance from the human body.[27] Clinical investigations for CARPA and in patients with renal insufficiency are required to further demonstrate the safety of microemulsion propofol.

Our previous microemulsion formulation showed smaller V_1 and less extensive peripheral distribution (smaller V_3 and V_{dss}) than those of LCT propofol.[2] However, current microemulsion propofol showed smaller V_1 and more extensive peripheral distribution (larger V_2, V_3, and V_{dss}) than those of LCT propofol. The opposite findings in peripheral distribution between previous and current microemulsion propofol may be attributed to different polymeric vehicles of propofol. Although pharmacokinetic studies of polyethylene glycol 660 hydroxystearate and tetrahydrofurfuryl alcohol polyethylene glycol ether were not found in the literatures, we thought that previous microemulsion formulation was less extensively distributed to peripheral

Table 5 Population pharmacokinetic parameter estimates, inter-individual variability, and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of the final pharmacokinetic model of microemulsion and LCT propofol. Inter-individual and residual random variabilities for both formulations were modelled using log-normal and proportional models, respectively. Non-parametric bootstrap analysis was repeated 2000 times. CV, coefficient of variation; σ^2, variance of residual random variability; RSE, relative standard error=SE estimate$^{-1}\times100$ (%). *Lean body mass (kg)

Model	Parameter	Microemulsion propofol ($n=88$)			LCT propofol ($n=84$)		
		Estimate (RSE, %CV)	Median	2.5–97.5%	Estimate (RSE, %CV)	Median	2.5–97.5%
Basic	V_1 (litre)	4.49 (12.9, 25.2)	—	—	6.76 (6.67, 17.7)	—	—
	k_{10} (min^{-1})	0.347 (12.9, 9.68)	—	—	0.212 (6.89, 14.5)	—	—
	k_{12} (min^{-1})	0.286 (17.8, 28.1)	—	—	0.150 (9.60, 21.4)	—	—
	k_{21} (min^{-1})	0.0131 (5.32, —)	—	—	0.0134 (4.31, —)	—	—
	k_{13} (min^{-1})	0.105 (13.7, —)	—	—	0.0539 (7.50, —)	—	—
	k_{31} (min^{-1})	0.000909 (6.27, —)	—	—	0.000925 (4.94, —)	—	—
	σ^2	0.0871 (12.06, —)	—	—	0.0731 (7.65, —)	—	—
Final	V_1 (litre)	0.088 (12.1)×LBM* (21.2)	0.088	0.063–0.113	0.134 (6.48)×LBM* (14.5)	0.134	0.104–0.152
	k_{10} (min^{-1})	0.355 (13.1, 6.36)	0.352	0.272–0.501	0.213 (6.76, 13.5)	0.214	0.186–0.292
	k_{12} (min^{-1})	0.312 (17.0, 27.9) for male	0.309	0.217–0.477	0.150 (9.53, 21.2)	0.151	0.125–0.253
		0.222 (18.6, 27.9) for female	0.221	0.149–0.351			
	k_{21} (min^{-1})	0.0131 (7.38, —)	0.0131	0.0114–0.0151	0.0134 (4.68, —)	0.0135	0.0124–0.0169
	k_{13} (min^{-1})	0.108 (12.7, —)	0.107	0.082–0.152	0.0542 (7.34, —)	0.0541	0.0468–0.0821
	k_{31} (min^{-1})	0.000 896 (9.83, —)	0.000893	0.000739–0.001050	0.000 923 (6.28, —)	0.000927	0.000831–0.001090
	σ^2	0.0881 (12.03, —)	0.0870	0.0708–0.1089	0.0740 (7.88, —)	0.0731	0.0625–0.0845

Table 6 Population pharmacodynamic parameter estimates, inter-individual variability, and median parameter values (2.5–97.5%) of the non-parametric bootstrap replicates of the final pharmacodynamic model of microemulsion and LCT propofol for the electroencephalographic BIS. *Inter-individual random variability was modelled using additive model. †No inter-individual random variability was assumed; inter-individual random variability of other structural model parameters including E_{max} of LCT propofol was modelled using a log-normal model. ‡Residual random variability was modelled using a proportional model. Non-parametric bootstrap analysis was repeated 2000 times. CV, coefficient of variation; σ^2, variance of residual random variability; RSE, relative standard error=SE estimate$^{-1}\times100$ (%)

Model	Parameter	Microemulsion propofol ($n=87$)			LCT propofol ($n=83$)		
		Estimate (RSE, %CV)	Median	2.5–97.5%	Estimate (RSE, %CV)	Median	2.5–97.5%
Basic	E_0*	85.4 (1.02, —)	—	—	83.0 (1.19, —)	—	—
	E_{max}*	30.2 (4.80, —)	—	—	27.2 (5.77, 29.7)	—	—
	Ce_{50} (µg ml^{-1})	1.72 (3.05, 26.7)	—	—	1.96 (3.68, 29.8)	—	—
	γ†	5.56 (8.29, —)	—	—	4.35 (8.09, —)	—	—
	k_{e0} (min^{-1})	0.0802 (3.70, 33.8)	—	—	0.140 (5.58, 48.1)	—	—
	$\sigma^{2\ddagger}$	0.0246 (8.98, 15.7)	—	—	0.0226 (0.33, —)	—	—
Final	E_0*	85.4 (1.02, —)	85.4	83.6–87.0	83.0 (1.25, —)	83.0	80.9–85.0
	E_{max}*	30.2 (4.77, —)	30.2	26.9–32.7	27.5 (5.78, 29.6)	27.5	23.9–30.5
	Ce_{50} (µg ml^{-1})	1.63 (2.97, 24.3) for male	1.63	1.54–1.73	1.95 (3.61, 29.8)	1.95	1.81–2.10
		2.15 (7.07, 24.3) for female	2.15	1.86–2.47			
	γ†	5.57 (8.19, —)	5.59	4.78–6.62	4.39 (8.27, —)	4.36	3.74–5.23
	k_{e0} (min^{-1})	0.0803 (3.67, 33.6)	0.0804	0.0750–0.0862	0.135 (6.10, 51.8) for male	0.134	0.119–0.152
					0.189 (17.4, 51.8) for female	0.185	0.133–0.324
	$\sigma^{2\ddagger}$	0.0246 (8.98, 15.7)	0.0244	0.0206–0.0293	0.0239 (11.5, 15.5)	0.0237	0.0189–0.0296

Table 7 Comparison of population pharmacokinetic parameters between microemulsion and LCT propofol. *On the basis of an analysis of variance with a linear mixed effects model that contained an effect for formulation only

Parameter (unit)	Microemulsion propofol ($n=88$)		LCT propofol ($n=84$)		Ratio*	90% confidence interval*
	Mean	SD	Mean	SD		
V_1 (litre)	4.50	0.99	6.78	1.01	66.32	62.62–70.03
V_2 (litre)	105.00	33.29	77.25	15.52	135.93	127.38–144.47
V_3 (litre)	542.83	118.91	398.11	59.15	136.35	130.36–142.35
V_{dss} (litre)	652.39	148.007	482.14	74.10	135.31	129.14–141.48
CL_1 (litre min^{-1})	1.60	0.37	1.46	0.28	109.63	103.94–115.32
CL_2 (litre min^{-1})	1.38	0.44	1.04	0.21	132.78	124.38–141.17
CL_3 (litre min^{-1})	0.49	0.11	0.37	0.05	132.37	126.52–138.23
$t_{1/2\alpha}$ (min)	0.91	0.08	1.63	0.12	55.39	53.85–56.93
$t_{1/2\beta}$ (min)	86.99	7.55	81.32	4.09	106.98	105.08–108.87
$t_{1/2\gamma}$ (min)	1021.14	8.63	951.79	21.69	107.29	106.85–107.72

tissues, compared with LCT propofol.[2] On the other hand, PP188 is a highly water-soluble non-ionic polymer with preferential distribution to the extracellular fluid and widely distributed throughout the well-perfused organs and tissues in rats.[27] In this study, the number of the first post-dose blood samples was 87 for microemulsion propofol and 84 for LCT propofol. Of these, plasma propofol concentrations (median, 25–75%) of the samples obtained before 1 min after an i.v. bolus of propofol 2 mg kg^{-1} were (13.8, 9.2–21.0) μg ml^{-1} for microemulsion propofol ($n=62$) and (12.4, 8.5–19.2) μg ml^{-1} for LCT propofol ($n=68$). These higher propofol concentrations before 1 min after an i.v. bolus may account for smaller V_1 of microemulsion formulation. After 1 min after an i.v. bolus, the difference of plasma propofol concentrations of the first post-dose samples between the two formulations was decreased, that is, 11.1, 8.9–19.6 μg ml^{-1} for microemulsion propofol ($n=25$), 10.9, 5.1–15.8 μg ml^{-1} for LCT propofol ($n=16$). On the basis of these findings, we speculated that during the initial period ($<$1 min after an i.v. bolus), LCT propofol may distribute more extensively in blood due to lipid solvent, compared with previous and current microemulsion formulations, and current microemulsion nanodroplets may begin to extensively distribute to well-perfused peripheral organs and tissues after the initial period, owing to the property of PP188.

Slightly slower onset of sleep in patients receiving microemulsion propofol can be explained by the smaller k_{e0} value of microemulsion propofol. More prolonged recovery of microemulsion propofol can be explained pharmacokinetically in the whole population (higher V_{dss}) and pharmacodynamically in male patients receiving microemulsion propofol (lower Ce_{50} than that of patients receiving LCT propofol).

In agreement with results of our previous study,[2] there were differences in clinical endpoints such as times to LOC, ROC, and recovery of orientation between male and female patients. We observed that all of the individually predicted clearances and volumes, including V_{dss}, were significantly greater in males than in females, irrespective of formulations (data not shown). For microemulsion propofol, larger V_2 [114.4 (28.8) vs 65.9 (19.3) litres for female], with possibly lower rate of increasing of effect-site concentrations of propofol may partly account for the slightly delayed onset of sleep in males.[2] For LCT propofol, larger V_2 [80.9 (14.5) vs 62.7 (10.2) litres for female] as well as lower k_{e0} may account for the slightly delayed onset of sleep in males. Prolonged recovery in male patients receiving microemulsion propofol may be attributed to V_{dss} [683.3 (139.7) vs 523.2 (108.7) litres for female] as well as smaller Ce_{50} in male patients. For LCT propofol, larger V_{dss} [502.2 (64.0) vs 403.2 (57.4) litres for female] may account for prolonged recovery in male patients.

There were several issues to be considered as limitations of this study. First, the initial plasma propofol concentrations after a bolus dose were not measured extensively.

This sparse sampling may not be sufficient for describing pharmacokinetics of rapidly acting propofol formulations. However, we believe that population analysis in a relatively large patient population and a relatively wide range of the time points for the first post-dose samples (0.9–3.5 min and 0.9–3.1 min after a bolus of propofol, for microemulsion and LCT propofol, respectively) may, at least in part, counterbalance this issue. Secondly, most pharmacokinetic models used for target-controlled infusion of propofol were derived from infusion data and the initial plasma propofol concentrations after a bolus are significantly underpredicted by the parameters obtained from the infusion data.[28] Therefore, pharmacokinetic and pharmacodynamic study using zero-order infusion of microemulsion propofol should be performed. Thirdly, pharmacodynamic characteristics of both formulations were described without considering the effects of remifentanil on the BIS. However, this might be a minor issue, because the relationship between the effect-site concentration of propofol and BIS was preserved with or without opioids.[29]

In conclusion, Aquafol^{TM} is an effective and safe microemulsion formulation of propofol. However, current microemulsion propofol caused more severe and frequent pain on injection compared with LCT propofol, for which aggressive prevention is essential. Population pharmacokinetic and pharmacodynamic modelling well described the differences of effectiveness between the two formulations. Microemulsion propofol should be further evaluated in patients with renal insufficiency and for any increased incidence of CARPA.

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