Recovery and long-term renal excretion of propofol, its glucuronide, and two di-isopropylquinol glucuronides after propofol infusion during surgery

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Background. The metabolism of the short-acting anaesthetic agent propofol has been described over the first 24 h. However, the long-term disposition of propofol and its metabolites is unclear. We describe the pharmacokinetics (renal excretion rates and renal clearance) of propofol and its metabolites over 60 h.

Methods. Ten patients undergoing lung surgery were included in the study. They received anaesthesia with continuous i.v. propofol at an average rate of 10 mg min−1. During surgery and 60 h thereafter, we sampled blood and urine. Propofol and its metabolites were measured using gradient high performance liquid chromatography (HPLC).

Results. In nine patients, propofol and its glucuronides were found in the plasma over the first 15 h. In the urine, however, even after 60 h, propofol and its quinol glucuronides were still detectable. One patient had a markedly different pharmacokinetic profile, showing a limited renal excretion or absorption of 12% of the dose.

Conclusions. After an infusion of propofol, patients excrete propofol and its metabolites in the urine over a period in excess of 60 h. We hypothesize that (re)absorption of propofol and its metabolites by the kidney is a major process in elimination and that the reabsorbed compounds are gradually conjugated in the kidney and excreted in the urine. One patient showed a different pharmacokinetic profile for which we currently have no explanation.

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Propofol, 2,6-di-isopropyl phenol (P), is an i.v. anaesthetic agent used for induction and maintenance of anaesthesia and sedation in intensive care and during regional anaesthesia. It is rapidly redistributed and is present in tissue and blood for a few hours after a single injection. It is metabolized in the liver and kidneys and possibly in other tissues. Propofol is oxidized to 1,4-di-isopropyl quinol (Q). Both P and Q are conjugated with glucuronic acid to propofol-1-glucuronide (Pgluc) and quinol-1-glucuronide (Q1G) and quinol-4-glucuronide (Q4G).1 Another metabolite is the 4-sulphate conjugate of Q. Recently, additional minor P metabolites have been identified in the urine.2 From an infused dose of propofol, 0.3% is recovered from urine unchanged, 53% is retrieved as water-soluble conjugates, and 38% as hydroxylated metabolites.3

Owing to the short half-life of propofol in plasma (t1/2=1 h), relatively little research has focused on the long-term disposition of propofol and its metabolites. We decided to investigate and describe the longer-term pharmacokinetics (renal excretion rates and renal clearance) of propofol and its metabolites after an infusion during surgery.

Methods

Ten male patients [age, 44.5 yr (18–69); ASA I–III; and weight 72 kg (56–86 kg)] were selected for this pharmacokinetic investigation in the long-term renal excretion of propofol and its metabolites during and after surgery.
All gave written informed consent to participate in the research, which was conducted with the approval of the ethical committee of the University Lung Clinic Dekkerswald. The patients were all undergoing a thoracotomy for lung surgery. Patients below 18 yr of age or with hepatic or renal disease were not included. Patient characteristics are noted in Table 1.

Anaesthesia

All patients received standardized anaesthesia. Premedication consisted of midazolam 7.5 mg and acetaminophen 1000 mg orally, 1 h before surgery. Before the surgical procedure, prophylactic antibiotic therapy was given (cefazolin 1000 mg). Analgesia was achieved with a thoracic epidural catheter inserted at the level Th 3–4 intervertebral space using a paravertebral approach with a hanging drop technique. Bupivacaine 0.5%, with adrenaline 1:200 000, was titrated to achieve an adequate sensory block and niconorphine (5 mg in 5 ml NaCl 0.9%) was added. Anaesthesia was induced with a continuous i.v. infusion of propofol (average 33 mg kg$^{-1}$ h$^{-1}$ and a bolus injection of rocuronium (0.6 mg kg$^{-1}$) and fentanyl (0.1 mg) for tracheal intubation. After intubation, the propofol infusion was reduced and titrated to maintain anaesthesia (6–12 mg kg$^{-1}$ h$^{-1}$).

Propofol was infused at an average rate of 10 mg min$^{-1}$ as summarized in Table 2.

All patients received an arterial line before and a central venous line and urine catheter directly after induction of anaesthesia.

After operation, the patients were extubated and analgesia was maintained with acetaminophen and a continuous epidural infusion with a 2 ml h$^{-1}$ mixture of bupivacaine 0.75% and morphine 0.2 mg ml$^{-1}$.

Sampling

Arterial blood (3 ml) and urine samples were collected over a period of 60 h according to a predetermined schedule. Blood sampling schedule: 0, 0.1, 0.4, 0.7, 1, 1.2, 1.5, 1.7, 2, 2.2, 2.4, 2.6, 3, 4, 5, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, and 41 h. Arterial samples were centrifuged and the serum was removed and stored at $-20^\circ$C until analysis. After the start of propofol administration during surgery, all urine from each patient was collected every 30 min and after surgery every 3 h. Urine sampling schedule: 0, 30, 60, 90, 120, 150, 180, 210, and 240 min (4 h) during surgery. Thereafter in the recovery room and ward, at 1, 2, 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54, 60 h. The volume of urine for each time period was measured and after thorough mixing, a 40 ml aliquot was stored at $-20^\circ$C until analysis.

Sample analysis

Analysis of the urine and the serum samples has been described previously$^4$ and is briefly summarized here.

Chemicals

Propofol (Diprivan®) was obtained from AstraZeneca (Zoetermeer, The Netherlands).

Propofol (2,6-di-isopropylphenol, $C_{12}H_{16}O$, MW 178.27; CAS number 2078-54-8), 1,4-quinone (2,6-di-

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<th>Infusion (min)</th>
<th>Rate (mg min$^{-1}$)</th>
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<th>Total time (h)</th>
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Table 1: Patient characteristic data. All subjects are male. BSA, body surface area

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<th>Age (yr)</th>
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<th>BMI (kg m$^{-2}$)</th>
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isopropyl-1,4-quinone C\textsubscript{12}H\textsubscript{16}O\textsubscript{2}, MW 192.27), and 1,4-quinol (2,6-di-isopropyl-1,4-quinol, C\textsubscript{12}H\textsubscript{18}O\textsubscript{2}, MW 194.27) were obtained from AstraZeneca (Zoetermeer, The Netherlands).

**HPLC analysis**

The HPLC system consisted of a Marathon autosampler (Separations, H.I. Ambacht, The Netherlands), a Spectra Physics quaternary P4000 HPLC pump, a Spectra Physics UV 1000 UV detector, a Spectra Physics Fluorimeter FL 2000 (Spectra Physics, Thermo Separations, Breda, The Netherlands), and a Hitachi D 2500 integrator.

We used a C\textsubscript{18} Spherisorb ODS 5 \textmu m, 250 x 4.6 mm ID column (Chrompack, Cat. No. 28812, Bergen op Zoom, The Netherlands) with a guard column 75 x 2.1 mm, packed with pellicular reversed-phase Spherisorb (Chrompack Cat. No. 28603).

**Glucuronides in serum and urine**

The *gradient* eluent was a mixture of 6 g litre\textsuperscript{-1} orthophosphoric acid in water–acetonitrile with a solvent flow of 1 ml min\textsuperscript{-1}, at a pressure of 23.30 MPa. The gradient was 80/20 (v/v) water–acetonitrile at the start and changed over 25 min to 40/60 (v/v) where it remained constant for 20 min.

The injection volume was 50 \mu l. The chromatographic analysis was carried out at room temperature. UV detection was achieved fluorimetrically at 270 nm excitation and 310 nm emission.

The intraday and interday coefficient of variation for the glucuronides of propofol and quinol in plasma and urine was \( \leq 5\% \)\textsuperscript{4}.

**Propofol and quinone in serum and urine**

The *isocratic* eluent was a mixture of 6 g litre\textsuperscript{-1} orthophosphoric acid in water–acetonitrile–methanol (40/50/10, v/v/v) with a solvent flow of 1 ml min\textsuperscript{-1}. All other details were as for glucuronides above.

The intraday and interday coefficient of variation for propofol in plasma and urine was \( \leq 3\% \)\textsuperscript{4}.

**Sample treatment**

**Glucuronides**

Serum samples (0.3 ml) were deproteinized with 0.3 ml 2 M trichloroacetic acid, centrifuged at 3000g, and 50 \mu l of the supernatant was injected onto the column.

Urine samples were centrifuged at 3000g, the supernatant was diluted 1:9 with 0.02 M KH\textsubscript{2}PO\textsubscript{4} buffer pH 6.8, and 50 \mu l was injected onto the column.

**Propofol and quinone**

To 0.3 ml of serum, 0.1 ml ammonium sulphate (saturated) and 0.3 ml acetonitrile were added. The mixture was vortexed for 30 s and centrifuged at 3000g for 5 min. The organic layer was injected onto the column (50 \mu l).

Urine was centrifuged at 3000g, the supernatant was diluted 1:9 with 0.02 M KH\textsubscript{2}PO\textsubscript{4} buffer pH 6.8, and 50 \mu l was injected onto the column.

**Results**

Propofol parent drug is present in plasma, together with its glucuronide metabolites. The plasma concentrations can be measured for 15 h, whereas the renal excretion rates (urine concentration, \( \mu \text{g} \text{ml}^{-1} \times \text{urine flow, ml min}^{-1} \)) can be measured for 60 h after an average infusion time of 2.5 h.

Figure 1 shows the time profiles of plasma concentration and renal excretion rate of propofol and its glucuronide metabolites. In the urine, only the glucuronides of propofol (P\textsubscript{gluc}) and of its metabolite 1,4-di-isopropylquinol (Q\textsubscript{1gluc} and Q\textsubscript{4gluc}) could be detected and measured in large quantities.

Nine out of 10 patients showed this pharmacokinetic profile of propofol.

The mean renal excretion rate–time profiles of the nine patients are shown in Figures 2 and 3. Figure 2 shows the mean (sd) renal excretion profile of propofol glucuronide in order to show the relatively large variation in excretion rates between the patients. Figure 3 shows the time profile of mean renal excretion rate of propofol glucuronide and the glucuronides of the metabolite quinol (quinol-1-glucuronide and quinol-4-glucuronide). The individual and mean renal excretion rates of the glucuronides run parallel in 20–60 h post-recovery room period.

Table 2 presents the cumulative renal excretion (% dose) of propofol and its quinol metabolites in these nine patients.

**Fig 1** Time profiles of plasma concentration and renal excretion rate of propofol (solid dots) and its glucuronide metabolites after a dose of propofol (P) (1800 mg 150 min\textsuperscript{-1} infusion) in an example surgical subject.
One patient (#10) showed a pharmacokinetic profile different from that of the other patients (Fig. 4). This patient showed a mono-exponential decline in propofol and its metabolites in plasma and urine. The total time over which the compounds could be measured was 25 h. Note that there is no second phase in the renal excretion, or it is so low that it is below the level of detection. Despite the high dose of propofol (solid dots), the plasma concentration during surgery is irregular.

### Discussion

This study in nine (of 10) patients shows that propofol metabolites are excreted in the urine over a period of at least 60 h and that the renal excretion rate is variable.

The excretion rates of propofol glucuronide and of both glucuronide conjugates of the metabolite 1,4-di-isopropylquinol paralleled the corresponding plasma concentrations, but only for the first 15 h after induction of anaesthesia. This pharmacokinetic behaviour of parent drug and metabolites was expected. Infused propofol enters the liver, becomes oxidized by CYP2B6, and subsequently conjugates with glucuronic acid. Thereafter, the water-soluble glucuronides are excreted via the kidney by the process of glomerular filtration [renal clearance (120 ml min⁻¹); 700 ml min⁻¹ is the highest achievable renal clearance for a drug (para-aminohippuric acid)]. Thus, it is incorrect to calculate renal clearance as a ratio of milligrams excreted divided by AUC, because other processes must take place, presumably renal absorption followed by renal glucuronidation, and then excretion. During this process, the plasma concentrations of the metabolites are well below the limit of quantification, making the calculated renal clearances unphysiological and thus meaningless.
elimination. Propofol glucuronides will again display first-order kinetics, renal glucuronidation capacity, renal excretion conjugated and excreted in the urine. We did not observe elimination and that the resulting compounds are gradually metabolites by the kidney is a major process in the overall disposition period of the drug. This enables the calculation of the renal clearance (milligrams excreted divided by AUC, ng h ml\(^{-1}\) = ml min\(^{-1}\)). Here, it seems that propofol and its quinol metabolites enter the kidney, are stored, and slowly released in the glucuronidated form. The kidney is able to glucuronidate drugs, as we have shown for sulphadimethoxine and probenecid.

The lower limit of detection in urine of the glucuronides is 0.3 µg ml\(^{-1}\), with a mean urine flow of 1 ml min\(^{-1}\) and a renal excretion rate of 0.3 µg min\(^{-1}\). At 60 h post-infusion, the renal excretion rate is still 50–100 times higher than the minimal excretion rate. It will take several further hours or days before propofol and its glucuronide metabolites will be totally eliminated from the body.

We hypothesize that (re)absorption of propofol and its metabolites by the kidney is a major process in the overall elimination and that the resulting compounds are gradually conjugated and excreted in the urine. We did not observe the end of the glucuronidation process in the 60 h sampling period; presumably, a further 2–3 days are required. The plateau-like renal excretion rate (20–60 h) may indicate that renal glucuronidation is capacity-limited (compared with probenecid). At the end of the maximum renal glucuronidation capacity, renal excretion of propofol glucuronides will again display first-order elimination.

One patient showed markedly different pharmacokinetics. Plasma concentration–time curves and renal excretion rate–time curves did run parallel, enabling the calculation of renal clearance values for each of the components. Despite the intentionally high infusion dose, the elimination kinetics were first-order and the overall renal elimination was 12% of the dose. This behaviour could be explained by assuming that only a small part of the infusion reached the general circulation, the liver oxidized and conjugated the propofol, and the conjugates were excreted renally. However, this patient had no recollection of surgery, thus had had ‘sufficient’ anaesthesia. The reabsorption of propofol and metabolites by the kidney is likely to be a minor process. Propofol sulphation was not measured in our analysis and this may underlie the difference in kinetics.

A smaller total dose of propofol was administered to 18 female and 17 male patients by Favetta and colleagues. In their measurements, the renal excretion was also highly variable but was measured for 24 h. The cumulative renal excretion showed that the renal excretion process was almost complete in 24 h.

Clinical implication for long-term treatment in the ICU

In prolonged sedation (low dose) such as in the ICU, we expect the mechanism to be the same as in the short high-dose infusions. There was no accumulation of propofol in ICU patients. During the infusion period, a proportion of propofol metabolites will be absorbed by the kidney and subsequently glucuronidated and excreted. As long as the absorption and glucuronidation are in equilibrium, the kinetics will be first order. Only when maximum glucuronidation is reached will the excretion of the glucuronides be prolonged after stopping the infusion and sedation. The sampling time should therefore have been longer than 60 h in this study. The plateau in the metabolite excretion rate will be present in ICU patients also. However, these data are not yet available.

In conclusion, we have shown that after an infusion of propofol, patients excrete propofol metabolites in the urine over a period in excess of 60 h. We hypothesize that (re)absorption of propofol and its metabolites by the kidney is the main process in overall elimination and that the compounds are gradually conjugated and excreted in the urine. One patient showed a different pharmacokinetic profile for which we currently have no explanation.

Acknowledgement

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Funding

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