PHARMACOKINETICS OF GLYCOPYRRONIUM IN URAEMIC PATIENTS

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SUMMARY
We studied the pharmacokinetics of glycopyrronium in 11 uraemic patients undergoing cadaveric renal transplantation and in seven ASA I control patients undergoing general surgery. Glycopyrronium 4 μg kg⁻¹ was given i.v. before induction of anaesthesia. Blood and urine samples were collected for up to 24 h for measurement of glycopyrronium concentrations using a radioreceptor assay. Volume of distribution in the elimination phase (V₁) was similar in both groups, the elimination half-life (T₁/₂) was longer (P < 0.05), area under the plasma concentration-time curve (AUC) larger (P < 0.01) and plasma clearance (CL) smaller (P < 0.01) in the uraemic patients. In 3 h, mean 0.7 (range 0–3)% and 50 (21–82)% of glycopyrronium was excreted in the urine in the uraemic and healthy patients, respectively (P < 0.001). The 24-h renal excretion was 7 (0–25)% in uraemic and 65 (30–99)% in control patients (P < 0.001). We conclude that the elimination of glycopyrronium is severely impaired in uraemic patients. (Br. J. Anaesth. 1993; 71: 437–439)

KEY WORDS

Eighty per cent of glycopyrronium is excreted unchanged in the urine [1]. The metabolic pathways of the remaining 20% are unknown, and little is known about the pharmacokinetics of glycopyrronium in patients with renal failure.

The development of a sensitive radioreceptor assay (RRA) has enabled us to measure concentrations as small as 60 ng litre⁻¹ and thus to determine the plasma and urinary concentrations of the drug [2]. We have studied the pharmacokinetics of glycopyrronium in uraemic patients undergoing renal transplantation.

METHODS AND RESULTS
We studied 11 uraemic patients undergoing renal transplantation and seven ASA I control patients undergoing general surgery. Patients receiving medications which could interfere with the RRA were excluded. The study was approved by the Hospital Ethics Committee and all patients gave informed consent.

Mean serum creatinine concentration was 731 (SD 267) μmol litre⁻¹ and 75 (17) μmol litre⁻¹ in the uraemic and control patients, respectively. The serum albumin concentrations in the uraemic patients were normal. The patients had no known liver dysfunction, and in the uraemic patients serum concentrations of transaminases and prothrombin time were within normal limits. The uraemic and control patients were comparable in age and weight.

All the uraemic patients had undergone renal dialysis within the previous 24 h. Patients were premedicated with oral diazepam 0.2 mg kg⁻¹. In the operating theatre, a forearm vein was cannulated and in the uraemic patients a central venous catheter was inserted. Thereafter, potassium-free Ringer’s acetate (Na⁺ 140, Ca²⁺ 2, Cl⁻ 90, CH₃COO⁻ 54 mmol litre⁻¹) and 4% human albumin solution were administered until central venous pressure was at least 4 mm Hg.

Control patients received an infusion of Ringer’s acetate solution (approximately 500 ml) as volume loading. Glycopyrronium 4 μg kg⁻¹ was given i.v. via the peripheral cannula. Approximately 15 min after injection of glycopyrronium, patients were anaesthetized with thiopentone 3–5 mg kg⁻¹ and fentanyl 0.15–0.25 mg i.v. Vecuronium 1 mg + 0.1 mg kg⁻¹ was used to produce neuromuscular block. Anaesthesia was maintained with fentanyl and isoflurane with 70% nitrous oxide in oxygen. Blood samples (10 ml) were taken into EDTA tubes before and 2, 4, 6, 10, 15 and 30 min and 1, 2, 3, 6, 12 and 24 h after injection of glycopyrronium. Samples were obtained from the central venous catheter in the uraemic patients and from a peripheral cannula inserted into the contralateral cubital vein in control patients. Plasma was separated and stored at −70 °C. Urine samples were collected 0–3, 3–6, 6–8, 8–12 and 12–24 h after the injection of glycopyrronium. Urine volumes were measured and samples taken from each fraction for measurement of glycopyrronium.

The concentrations of glycopyrronium in plasma and urine were measured using the radioreceptor assay (RRA) described by Kaila and colleagues [2].

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The sensitivity of the assay for glycopyrronium was 60 pg ml\(^{-1}\) and the coefficients of intra-assay and interassay variation were less than 10\%. The pharmacokinetic parameters were calculated by fitting the concentration–time data to a bi-exponential model:

\[ C(t) = Ae^{-\alpha t} + Be^{-\beta t}, \]

where \( C \) = plasma concentration of glycopyrronium at time \( t \); \( A, B = \) zero-time intercepts; \( \alpha, \beta = \) rate constants for disposition and elimination.

For computations, a commercial software package was used (PCNonlin 3.0 SCI Software, Lexington, KY, U.S.A.). AUC values were calculated using the trapezoidal rule.

If serum creatinine decreased significantly within the first day after operation, this was considered as immediate kidney function.

Pharmacokinetic data were analysed with the Mann–Whitney \( U \) test, using Stat View 512+ software (Brain Power Inc., Calabasas, CA, U.S.A.).

Figure 1 shows the mean plasma concentrations of glycopyrronium in both groups. Volume of distribution in the elimination phase (\( V^p \)) was 0.41 (0.16) litre kg\(^{-1}\) and 0.44 (0.33) litre kg\(^{-1}\), elimination half-life (\( T^p \)) was 0.78 (0.45) h and 0.31 (0.29) h (\( P < 0.05 \)), the area under the concentration–time curve (AUC) 10.62 (3.29) h µg litre\(^{-1}\) and 3.73 (1.03) h µg litre\(^{-1}\) (\( P < 0.01 \)), and the plasma clearance (\( Cl \)) 0.43 (0.22) litre h\(^{-1}\) kg\(^{-1}\) and 1.14 (0.31) litre h\(^{-1}\) kg\(^{-1}\) (\( P < 0.01 \)) in the uraemic and healthy patients, respectively. In 3 h, a mean 0.7 (range 0–3)\% and 50 (21–82)\% of glycopyrronium was excreted in the urine in the uraemic and healthy patients, respectively (\( P < 0.001 \)). The 24-h renal excretion was 7 (0–25)\% in uraemic and 65 (30–99)\% in control patients (\( P < 0.001 \)). In the patient with immediate postoperative kidney function, 25\% of glycopyrronium was excreted in the urine in 24 h, but the plasma concentrations of glycopyrronium in this patient did not differ from those in the other uraemic patients. Probably, the plasma concentrations of glycopyrronium in this patient would have been even greater without this increased excretion rate. The interindividual variation of plasma glycopyrronium concentrations was large; therefore no conclusions can be drawn from this one subject.

**COMMENT**

These data indicate that the elimination of glycopyrronium in plasma was significantly prolonged in uraemic patients compared with non-uraemic control patients. Theoretically, using the central venous catheter in the uraemic patients and a peripheral venous cathula in the control patients for sampling might have affected the results. However, because venous blood was sampled in both groups and a large cubital vein with good flow was used in the control patients, it is very unlikely that this would have changed our conclusions. The effects of anaesthetics, other medication or protein binding on the pharmacokinetics of glycopyrronium are unknown; our opinion is that they did not influence our results.

The \( T^p \) of glycopyrronium (0.78 h) in the uraemic patients was similar to that (0.83 h) in elderly patients (mean age 66 yr) with no renal disease reported in a previous study by Ali-Melkkilä, Kaila and Kanto [3]. This might be attributable in part to an approximately 50\% greater \( V^p \) in elderly patients (0.64 litre kg\(^{-1}\)) compared with our uraemic group.

In uraemic patients, the average 24-h renal excretion of glycopyrronium was only 7\%, whereas the control patients excreted 65\% of the dose within
24 h. It has been shown previously that the 8-h excretion of glycopyrronium is approximately 60% after i.m. administration [4]. It should be noted that, 6 h after drug administration, plasma concentrations of glycopyrronium were nearly 10 times greater in our uraemic patients compared with the control patients, and that in the uraemic patients the concentration was 200–300 pg ml⁻¹ 24 h after i.v. administration. These small concentrations have little effect on heart rate, but may produce prolonged antisecretory effects [3]. Anticholinergic drugs also disrupt peristaltic bowel activity [5], and glycopyrronium decreases gastric emptying by 40–50%, when used in doses similar to those in our study [6]. Thus, in uraemic patients, delayed bowel function after surgery caused by opioids and other medication may be aggravated by the use of glycopyrronium.

We conclude that the elimination of glycopyrronium is severely impaired in uraemic patients. Therefore we feel that, in these patients, repeated or large doses of glycopyrronium should be avoided or, perhaps, the drug should not be used.

REFERENCES