Population Pharmacokinetic and Pharmacodynamic Modeling of Acetazolamide in Peritoneal Dialysis Patients and Healthy Volunteers

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ABSTRACT - Purpose. To characterize the pharmacokinetics (PK) and pharmacodynamics (PD) of acetazolamide (ACTZ) in peritoneal dialysis patients, ACTZ 500 mg was administered intravenously to 7 healthy subjects (HV) and 8 peritoneal dialysis patients (CAPD). **Methods**. Population PK/PD modeling was performed with ACTZ serum (total and unbound), urine and dialysate concentrations, intra-ocular pressure (IOP) and covariates. A multi-compartment PK model (accounting for non-linear protein binding) and an inhibitory Emax (maximal change in IOP) PD model were selected. **Results.** As expected, renal clearance (which almost equals total body clearance) was severely decreased in CAPD (1.2 vs 80.3 L/h) and the elimination half-life of total ACTZ was prolonged (20.6 vs 3.4 hours). The protein binding was significantly altered with a mean free fraction 4.2% in HV and 8.6% in CAPD. Moreover protein binding of ACTZ was concentration dependent in both HV and CAPD. Despite a higher free fraction of ACTZ, the Emax was lower in CAPD: 4.4±1.4 vs 7.4±2.8 mmHg. **Conclusion**. Both PK and PD are significantly altered in dialysis patients.

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INTRODUCTION

Acetazolamide (ACTZ) is a carbonic anhydrase (CA) inhibitor that is used as an adjunctive treatment for open-angle glaucoma or secondary glaucoma and post vitrectomy, but that is also indicated for short-term preoperative therapy in angle-closure glaucoma (1), conditions frequently encountered in dialysis patients. ACTZ is well absorbed through the gastrointestinal tract and is distributed in various tissues, including erythrocytes, kidneys, liver, muscles, eyes and the central nervous system (1). It is highly bound to albumin (>90%) and is mainly excreted unchanged in the urine (filtration and proximal tubular secretion) (1-3). Although the pharmacokinetics (PK) of ACTZ has been described in healthy volunteers, glaucoma patients and those suffering from transient elevation in intraocular pressure (IOP) (2, 4-6), little has been published about ACTZ PK in dialyzed patients besides a handful of case reports (7-10); from these we know that increased ACTZ serum concentrations may be associated with more side effects and that the dose should be adjusted accordingly in these patients (4,

9). This study was therefore conducted to better understand ACTZ PK and pharmacodynamics (PD) in this special population, comparing peritoneal dialysis patients and HV, and investigating the impact of covariates on PK/PD.

METHODS

Study design
Eight patients with chronic renal failure treated with continuous ambulatory peritoneal dialysis (CAPD) and seven healthy volunteers (HV) participated in the protocol (approved by the hospital's local Ethics Committee) after providing informed consent. HV were recruited if their renal function was normal (serum creatinine and estimated creatinine clearance).

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All participants had a baseline ophthalmologic examination with IOP measurement. Exclusion criteria were IOP > 20 mm Hg, hemoglobin < 70 g/L, serum bicarbonate < 20 mm/L, allergy to sulfa or local anesthetics, or regular administration of beta-blockers or corticosteroids.

After an 8 hour fast, all participants received ACTZ 500 mg (Novopharm, Montréal, Canada) intravenously over 2 minutes; breakfast was allowed one hour later. Serum urea, creatinine, glucose, electrolytes, CO_2 albumin, protein and complete blood count were measured using standard techniques. Heparinized blood samples were obtained before (0) and at 0.0833, 0.167, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6 hours after dosing. Dialysate and urine (if possible for patients) were collected over the next 24 hours. Samples were centrifuged and stored at -70°C until analysed.

IOP was measured with the Schiotz tonometer before (0) and 0.5, 1, 2, 4 and 8 hours after dosing. Each measurement was performed by the same person after a 5-minute rest in the supine position and local anesthesia with Alcaine 0.5% (proparacaïne).

Determination of ACTZ in plasma, urine and dialysate

The standard solution was ACTZ dissolved in methanol and the internal standard was sulfadiazine dissolved in methanol. As described by Chapron et al (11), ACTZ was measured with HPLC on a column μBondapak C_{18} (3.9 X 300mm), with a flow rate set at 2.5 ml/min. The mobile phase was made of acetate buffer, methanol and acetonitrile (95:2:3). The extraction was done with ammonium sulfamate and ethyl acetate. The intra-assay and inter-assay coefficient of variation (CV%) for ACTZ serum concentrations of 10-100 μg/ml were 2.6-5.2% and 2.8-6.3%, respectively.

Plasma protein binding

Plasma binding of ACTZ was measured by equilibrium dialysis at 37°C with a Teflon cell system (Spectrum) and a Spectapor 2 membrane (molecular weight 12,000-14,000). Each plasma sample was dialyzed against an equal volume of 0.067 M phosphate buffer pH 7.4 for 3 hours. The free fraction of ACTZ was calculated as: dialysate concentration/plasma concentration. The CV% for the determination of f_u was 2.8% at 20 ug/ml and 3.3% at 100 ug/ml.

Free fraction (f_u) was determined at different concentrations in spiked blank plasma: 10, 25, 50, 75 and 100 μg/ml. After this experiment showed that f_u was concentration dependent, protein binding was measured at 4 different concentrations, pooling the plasma of two consecutive (in time) samples, as there was a shortage of plasma samples. Hence total concentrations obtained after pooling were for HV 54, 36, 21 and 14 μg/ml; and for dialysis patients 44, 41, 32, 23 μg/ml.

Moreover, blood to plasma (B/P) ratio was measured in 3 HV and 3 CAPD. Whole blood and plasma samples were spiked with ACTZ 10, 50 and 100 μg/ml, and ACTZ concentration was determined after a 3–hour equilibration period.

Pharmacokinetics and Pharmacodynamics

Population PK/PD analyses were conducted using NONMEM VI (12). Total ACTZ ($ACTZ_{total}$) levels in plasma, urine and dialysate from all participants were simultaneously modeled, along with unbound ACTZ ($ACTZ_{free}$) concentrations in plasma. Standard model discrimination criteria (minimal objective function, residual figures, residual variability) were applied to select a structural PK model.

The impact of covariates on the base PK model was assessed graphically (13, 14). Forward stepwise addition followed by backward deletion was also used. After selecting the final PK model, individual PK parameters were fixed and used to determine the PD model, using the methods described for the PK model discrimination. Covariates that were tested for potential inclusion in both PK and PD models were age, weight and dialysis (categorical covariate).

RESULTS

Among the HV were 3 men and 4 women; there were 2 men and 6 women in the CAPD group. In HV vs CAPD: mean age was 29±7 vs 54±6, weight was 61 ± 14 kg vs 68 ± 16 kg, baseline IOP ($IOP_{baseline}$) was 12.2 ± 1.8 mm Hg vs 15.6 ± 3.4 mm Hg, and serum albumin was 42 ± 4 mg/mL vs 36 ± 6 mg/mL. The mean creatinine clearance in HV was 101±3 ml/min (estimated from Cockroft&Gault nomogram).

In all, 179, 23 and 22 concentrations of $ACTZ_{total}$ in plasma, urine and dialysate were simultaneously modeled. In addition, 60 $ACTZ_{free}$

plasma concentrations and 90 IOP measurements were analyzed. No adverse effects were observed in HV and CAPD during the study.

ACTZ PK in this population was best described by a multi-compartment model with central and peripheral compartments for $ACTZ_{total}$ and a peripheral compartment for $ACTZ_{free}$ (figure 1). Differential equations used to describe the model are presented in Appendix 1. Table 1 shows population parameter estimates for PK and PD of both healthy volunteers and CAPD patients. Figure 2 shows typical $ACTZ_{total}$ serum and urinary ACTZ concentration vs time curves, with their corresponding predicted curves. Significant covariates included in the PK model were dialysis on renal clearance and age on distributional clearance (Q1). According to this model, the mean terminal elimination half-life of total ACTZ was 3.4 ± 0.54 hours in HV and 20.6 ± 10.5 hours in CAPD patients. Appendix 2 provides examples of how covariates were coded in the model.

The % of unbound (fu) ACTZ was concentration-dependent: in HV it decreased from 5.3 to 3.3% over a range of 54 to 14 µm/l, and from 14.3 to 8.0% over a range of 44 to 23 µm/l in CAPD. The relation between $ACTZ_{total}$ and $ACTZ_{free}$ was described by a Michaelis-Menten function. On average, the predicted f_u of ACTZ with the model was greater in CAPD than in HV (8.6 vs 4.2%). Blood/plasma (B/P) ratio was higher in CAPD: for total ACTZ serum concentrations from 10 to 100 µg/ml, it increased from 0.77 to 0.89 in HV and from 0.96 to 1.25 in CAPD.

The final PD model was an inhibitory Emax (maximal change in IOP) model (with $IOP_{baseline}$) that was directly related to $ACTZ_{free}$ concentrations. Although indirect models linking IOP to ACTZ concentrations in the central compartment were also tested, the data was better explained by the direct model relating IOP to $ACTZ_{free}$ concentrations. Significant covariates for the PD model were dialysis on $IOP_{baseline}$ and Emax. $IOP_{baseline}$ was 12.6±0.4 in HV vs 15.5±1.6 mmHg in CAPD; Emax was 7.4±2.8 in HV vs 4.4±1.4 mmHg in CAPD. An average concentration-response curve for a healthy subject and dialysis patient is depicted in Figure 3.
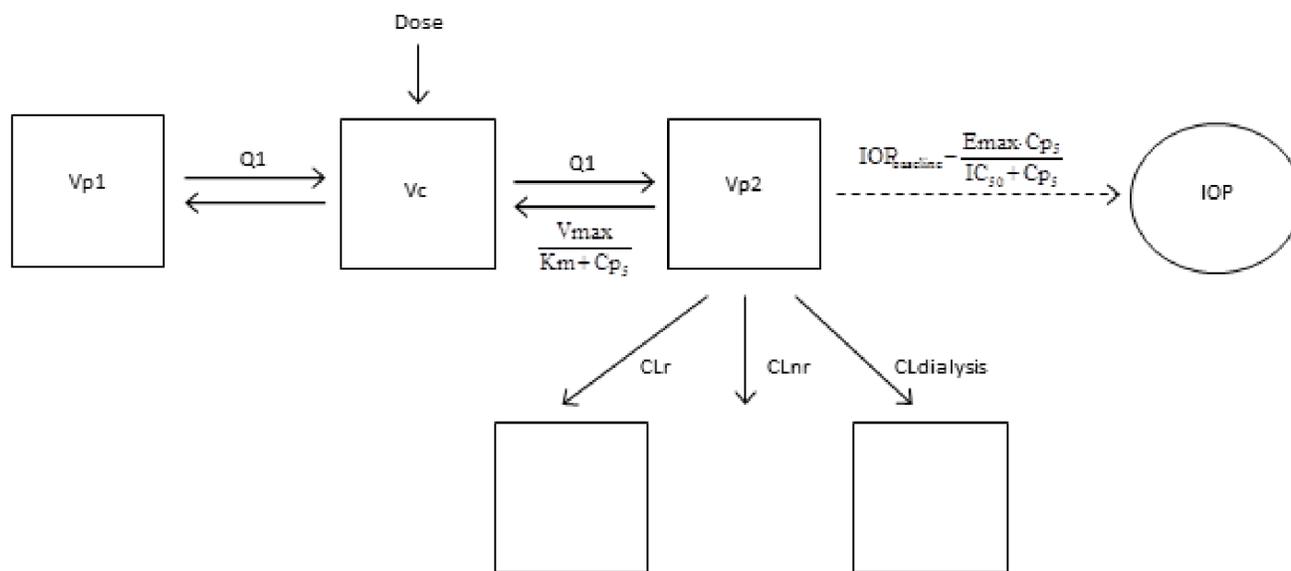

Figure 1. Multi-compartmental model for ACTZ PK. IOP$_{baseline}$: baseline intra-ocular pressure, **CLdialysis**: clearance mediated by dialysis, **CLnr**: non-renal clearance, **CLr**: renal clearance, **Cp5**: concentration of unbound ACTZ, **Emax**: Maximal level of inhibition of IOP, **IC$_{50}$**: concentration of unbound ACTZ associated with 50% of Emax, **IOP**: intra-ocular pressure, **Km**: unbound ACTZ concentration associated with 50% of Vmax, **Q1**: distributional clearance between central and peripheral volumes for total ACTZ, **Q2**: distributional clearance between central and peripheral volumes for unbound ACTZ, **Vc**: central volume of distribution for total ACTZ, **Vmax**: maximal rate,**Vp1**: peripheral volume of distribution for total ACTZ, **Vp2**: volume of distribution for unbound ACTZ.
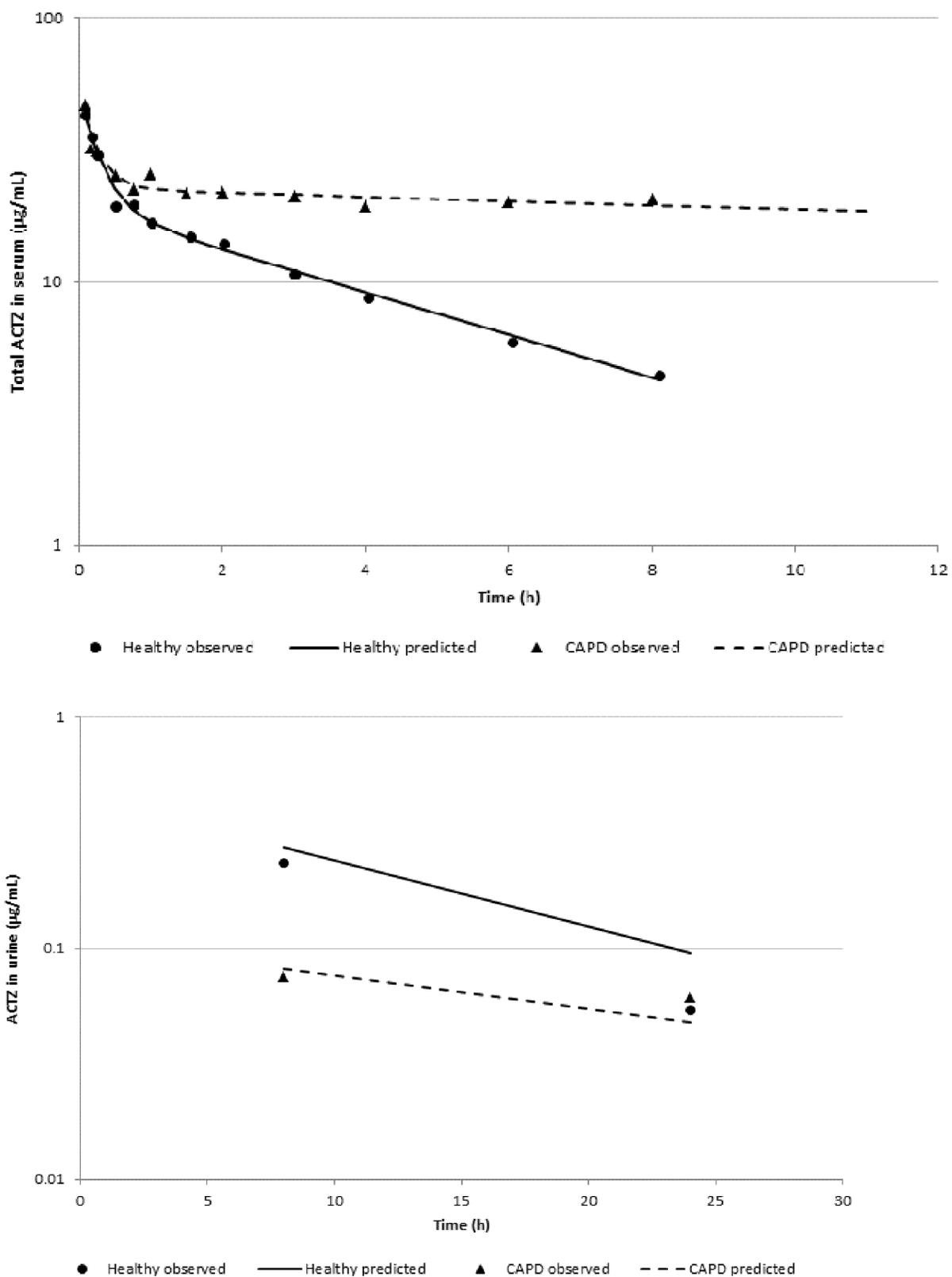
Figure 2. ACTZ$_{total}$ serum and urinary concentrations over time, observed and predicted, for Subjects #1 (HV) and #5 (CAPD)
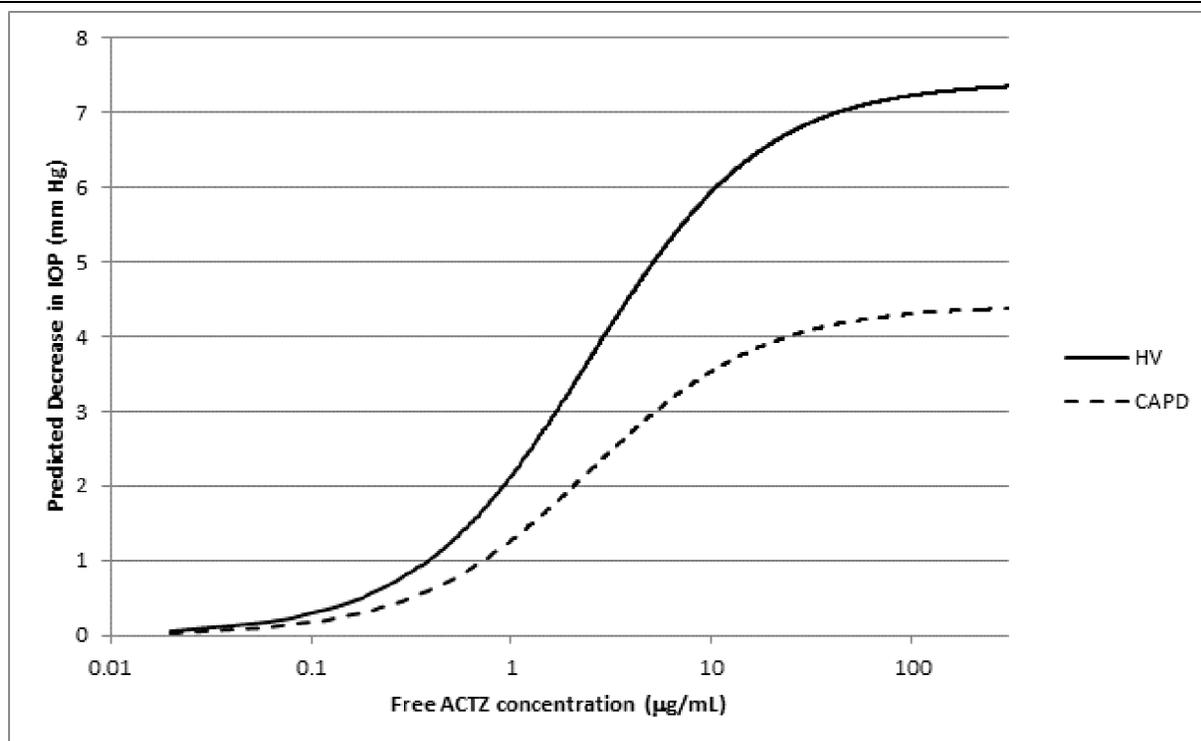
Figure 3. Predicted average ACTZ$_{free}$ **concentration-response curve for HV subjects and CAPD patients**

Residual variability (ranging from 10.5 to 39%) associated with the final model was acceptable. This represents variability not explained by the model, including intra-individual variability, model misspecification or variability in the analytical assay. In addition, goodness-of-fit plots did not indicate any trends or biases in predictions.

Inter-individual variability was assumed to be centered around a mean value of zero with a variance of ω^2. Intra-individual variability was modeled as a combination of additive and proportional error, except for ACTZ in urine and dialysate where the error model was simply proportional.

DISCUSSION

ACTZ PK in HV and glaucoma patients has been previously described (2, 4-7, 15); our study further elucidates the PK/PD relation in dialysis patients, using a population PK/PD approach. Although standard, noncompartmental analyses could have been used given the rich sampling scheme, the population PK/PD approach was adopted to gain a more mechanistic understanding of the PK/PD of

ACTZ in this population. In addition, the population approach has the potential to partition variability into inter-individual, intra-individual, inter-occasion and residual sources, as well as quantify the impact of covariates on variability (16). Thus, this approach was favored over the simpler noncompartmental approach.

The final PK/PD model was a multicompartment model describing the disposition of both ACTZ$_{total}$ and ACTZ$_{free}$, and the effects of the latter on IOP. The administration of ACTZ by the IV route allowed the model to accurately characterize the distribution phenomenon since it was not confounded with absorption processes. A key feature of this model is the non-linear function that links ACTZ$_{free}$ to ACTZ$_{total}$. During the model discrimination process, linear functions were also investigated but the function that best described this transfer remained a saturable one, as observed by others (2). Gomolin and colleagues reported a linear relationship between total and ACTZ$_{free}$, however their ACTZ$_{free}$ concentrations varied from 6 to 10 mcg/ml (6), while they ranged from 0.38 to 12 mcg/ml in our study, allowing us to capture the non-linearity over a larger span of serum

concentrations. Plasma drug binding to protein is generally a saturable process, depending on the dissociation constant, at higher concentrations (17), but sometimes it appears at therapeutic range concentrations (2, 17, 18) as shown in our study.

The terminal elimination half-life for total ACTZ estimated by compartmental analysis was compared to parameters estimated by noncompartmental methods (for information purposes). Terminal elimination half-life for total ACTZ estimated by noncompartmental methods was around 3 ± 0.6 hours for healthy volunteers and 24 ± 24 hours for CAPD patients, which was similar to what was estimated by the model.

The f_u remained greater in CAPD than in HV over the range of concentrations studied. This suggests that in this population, more $ACTZ_{free}$ was available to penetrate other compartments, for instance erythrocytes, as witnessed by higher B/P ratios. Indeed, severe renal failure alters protein binding, especially for acidic drugs binding to albumin (19). However, since our CAPD were generally older than the HV, this difference could partly be related to age. Actually, Chapron *et al.* (2) showed that age could be a factor influencing ACTZ distribution in plasma and erythrocytes; however the "age effect" (60% increase in f_u in their elderly subjects) was much smaller than the "dialysis effect" (105% increase in f_u in our CAPD mildly older patients). Our covariate analysis revealed that age influenced the transfer of $ACTZ_{total}$ between the central and peripheral compartments as older subjects had a greater Q1. Hence, both age and renal function could play a role independently from each other in the alteration of distribution.

End-stage renal disease (ESRD) was the other significant covariate in our model that influenced renal clearance, $IOP_{baseline}$ and Emax. $IOP_{baseline}$ was higher in CAPD compared to HV, which could be due partly to the fact that this population was older. Indeed, IOP is known to increase slightly with age in certain populations (20). Despite having a greater f_u, CAPD had a mean Emax, that was almost 50% lower compared to HV. This could be attributed to a possible competition with organic anions accumulating in renal dysfunction, for either uptake into the compartment (ciliary body) via an organic anion transporter (21), or for binding to the enzyme carbonic anhydrase (isoenzyme II) with an altered degree of inhibition of CA by ACTZ (17). The

increased risk of toxicity and side effects of ACTZ in ESRD when given a standard dose (9) is therefore probably due more to a decreased clearance and consequently higher serum concentration, than solely to a greater f_u that does not seem to enhance the PD response, at least at the ocular level. We observed a non-competitive pattern of concentration-response curve that could be explained by an irreversible modification of the enzyme in CAPD, as was described for the tertiary structure of albumin in uremic subjects (22).

Yano and colleagues (4) developed a PK/PD model for ACTZ in patients with transient IOP elevation and moderate to severe renal failure (estimated creatinine clearance 15-58 ml/min; no dialysis patients). A one-compartment model with first-order absorption and an inhibitory Emax model were used to describe PK and PD, respectively. In their analysis, the only significant covariate for ACTZ total clearance was creatinine clearance, while they found no significant covariate effect on the PD parameters. The estimated Emax and IC_{50} in our HV were similar to the values they reported (7.2 mm Hg and 1.64 mcg/ml), which suggests that dialysis patients have a response that is distinct from non-dialysis patients, whether the $IOP_{baseline}$ is normal or high. Furthermore, this suggests that the distinctive PD parameters that we estimated for our CAPD are not simply related to higher $IOP_{baseline}$ values.

The results from our analysis were comparable to those published in case reports involving CAPD patients. The elimination half-life estimated for CAPD patients in our study (21 hours) was similar to the values of 29 hours (7) and 26 hours (9) observed by others. Thus, our results also demonstrated that CAPD patients had a decreased clearance of ACTZ. In addition, our analysis was able to identify which PK and PD parameters were different in CAPD patients in comparison with healthy volunteers.

Some of the limitations of our analysis include the small sample size and the small number of men (n=5), which did not allow us to test sex as a covariate. The small sample size likely contributed to the elevated inter-subject variability associated with some PK/PD parameters. Furthermore, the CAPD were older than HV which could have some impact on the differences observed. In addition, ACTZ f_u at different concentrations was obtained by pooling samples taken at different timepoints.

Despite the limitations of this analysis, we have developed a model that describes ACTZ PK/PD in this special population, and revealed potential differences in comparison to HV. Our model suggests that not only are there differences in ACTZ PK in CAPD, but PD is altered as well: severely decreased total clearance (as it is eliminated almost solely by kidneys), decreased protein binding (which is saturable), and a reduced efficacy (decrease in Emax).

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APPENDIX 1

The PK of ACTZ was described by Equations 1 to 5, where PT is 0 for healthy volunteers and equal to 1 for CAPD. In these equations, A(1) represents the amount of ACTZ in the central compartment, A(2) is the amount of ACTZ in the first peripheral compartment, A(3) is the amount collected in urine, A(4) is the amount collected in dialysate and A(5) is the amount in the second peripheral compartment (representing the unbound fraction of ACTZ).

Equation 1
$$\frac{dA(1)}{dt} = -\left(\frac{Q1 + Q2}{V1}\right) \cdot A(1) + \frac{Q1}{V2} \cdot A(2) + \frac{VM \cdot (A(5)/V3)}{KM + (A(5)/V3)}$$

Equation 2
$$\frac{dA(2)}{dt} = \frac{Q1}{V1} \cdot A(1) + \frac{Q1}{V2} \cdot A(2)$$

Equation 3
$$\frac{dA(3)}{dt} = \frac{CLR}{V3} \cdot A(5)$$

Equation 4
$$\frac{dA(4)}{dt} = PT \cdot \frac{CLDI}{V3} \cdot A(5)$$

Equation 5
$$\frac{dA(5)}{dt} = \frac{Q2}{V1} \cdot A(1) - \frac{CLNR + CLR + PT \cdot CLDI}{V3} \cdot A(5) - \frac{VM \cdot (A(5)/V3)}{KM + (A(5)/V3)}$$

APPENDIX 2

Dialysis and age covariates were coded as per Equations 6 and 7, respectively.

Equation 6
$$\theta_{individual} = \left[\theta_{patient} \cdot PT + \theta_{healthy} \cdot (1 - PT)\right] \cdot e^{\eta}$$

Equation 7
$$\theta_{individual} = \theta_{population} \cdot \left(\frac{Age}{41.9}\right)^{\theta_{age}} \cdot e^{\eta}$$

Table 1a. Population PK Parameter Estimates RSE: relative standard error calculated with respect to the mean parameter value, **SE**: Standard error

Population Parameter	Parameter Description	Typical Value	SE	RSE%
Population Mean				
CLnr (L/h)	Non-renal clearance	1.53	0.69	44.9
Vc (L)	Central volume of distribution	5.77	0.79	13.7
Q1 (L/h)	Distributional clearance between central and peripheral volumes for total ACTZ	10.2	1.9	18.6
Exponent age	Exponent describing the effect of age on Q1	1.08	0.46	42.5
Vp1 (L)	Peripheral volume of distribution	6.46	0.87	13.5
CLr (L/h)	Renal clearance			
Healthy	Renal clearance in healthy subjects	80.3	8.7	10.8
Dialysis patient	Renal clearance in dialysis patients	1.2	0.9	72.8
CLdialysis (L/h)	Clearance mediated by dialysis	1.65	0.26	15.8
Q2 (L/h)	Distributional clearance between central and peripheral volumes for unbound ACTZ	7.97	0.69	8.7
Vp2 (L)	Volume of distribution for unbound ACTZ	6.14	1.33	21.7
Vmax (mg/h)	Maximal rate of transfer between compartments	1510	123	8.1
Km (mg/L)	Unbound ACTZ concentration associated with 50% of Vmax	12.4	2.8	22.3
Inter-subject variability				
CLnr (L/h)	Non-renal clearance	0.425 (72.8%)	0.648	152.5
Vc (L)	Central volume of distribution	0.225 (50.2%)	0.127	56.4
Q1 (L/h)	Distributional clearance between central and peripheral volumes for total ACTZ	0.234 (51.3%)	0.123	52.6
Vp1 (L)	Peripheral volume of distribution	0.209 (48.2%)	0.093	44.4
CLr (L/h)	Renal clearance			
Healthy	Renal clearance in healthy subjects	0.0518 (23.1%)	0.0257	49.6
Dialysis patient	Renal clearance in dialysis patients	4.32 (861.3%)	1.95	45.1
Vp2 (L)	Volume of distribution for unbound ACTZ	0.382 (68.2%)	0.145	38.0
Km (mg/L)	Maximal rate of transfer between compartments	0.0916 (31%)	0.0438	47.8
Error				
Proportional error plasma ACTZ	Proportional component of error model for plasma ACTZ	0.0111	0.0023	20.3
Additive error plasma ACTZ	Additive component of error model for plasma ACTZ	0.0203	0.0185	91.1
Proportional error urine & dialysate ACTZ	Proportional component of error model for ACTZ in urine and dialysate	0.152	0.040	26.0
Residual variability				
Total ACTZ in plasma		10.5%		

Population Parameter	Parameter Description	Typical Value	SE	RSE%
Unbound ACTZ in plasma		11.7%		
Total ACTZ in urine		39.0%		
Total ACTZ in dialysate		39.0%		

Table 1b. Population PD Parameter Estimates

Population Parameter	Parameter Description	Typical Value	SE	RSE%
Population Mean				
$IOP_{baseline}$ (mm Hg)	Baseline IOP			
Healthy	Baseline IOP in healthy subjects	12.4	0.4	2.8
Dialysis patient	Baseline IOP in dialysis patients	15.5	1.6	10.4
Emax (Δ IOP) (mm Hg)	Maximal level of inhibition of IOP			
Healthy	Maximal level of inhibition of IOP in healthy subjects	7.4	2.8	38.3
Dialysis patient	Maximal level of inhibition of IOP in dialysis patients	4.4	1.4	32.2
IC_{50} (mg/L)	Concentration of unbound ACTZ associated with 50% of Emax	2.47	1.27	51.4
Inter-subject variability				
$IOP_{baseline}$ (mm Hg)	Baseline IOP	0.0174 (13.2%)	0.0133	76.4
IC_{50} (mg/L)	Concentration of unbound ACTZ associated with 50% of Emax	1.38 (173%)	1.01	73.2
Error				
Proportional error IOP	Proportional component of error model for IOP	0.00968	0.0121	125.0
Additive error IOP	Additive component of error model for IOP	2.97	1.61	54.2
Residual variability				
IOP		17.0%		