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Pharmacokinetics of an elexacaftor/tezacaftor/ivacaftor formulation in pediatric cystic fibrosis: Comparison with published parameters of the reference drug

Paulo Cáceres Guido[1], *Guillermo F. Taboada*[1], *Adriana Sassone*[1], *Andrea Saulo*[1], *Silvana Agostini*[1], *Matías Cruz*[1], *María C. Nogueira*[1], *Sara Rodríguez*[1], *Anabella Boto*[1], *Hilda Giugno*[1], *Carolina Crespo*[1], *Luis P. Gravina*[1], *Claudio Castaños*[1]

ABSTRACT

The combination of elexacaftor, tezacaftor, and ivacaftor (ETI) has substantially improved the prognosis for cystic fibrosis. The pharmacokinetics of an Argentine-manufactured ETI formulation were evaluated in 10 patients aged 12-18 years using serial plasma samples collected between 0 and 8 hours. We estimated Cmax, Tmax, and AUC, and quantified the metabolites Ele-M23 and Tez-M1. We indirectly compared the parameters with published values for the reference drug. For elexacaftor, tezacaftor, and ivacaftor, Cmax values were 10.6 ± 4.3, 5.5 ± 2.4, and 1.5 ± 0.8 µg/ml, and AUC values were 182 ± 67, 78 ± 33, and 14 ± 4 µg/h/ml, respectively. Both metabolites were quantifiable in all patients.

In this exploratory cohort, the observed pharmacokinetic parameters were close to the published values for the reference drug. These findings do not establish bioequivalence and require confirmation through comparative studies.

Keywords: *cystic fibrosis; pharmacokinetics; pediatrics; cystic fibrosis transmembrane conductance regulator; elexacaftor, ivacaftor, tezacaftor.*

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[1] *Hospital de Pediatría S.A.M.I.C. Prof. Dr. Juan P. Garrahan, Autonomous City of Buenos Aires, Argentina.*

Correspondence to *Paulo Cáceres Guido: caceresguido@gmail.com*

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INTRODUCTION

Cystic fibrosis (CF) is an autosomal recessive, multisystemic, progressive genetic disorder caused by variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene, which encodes a chloride channel that transports bicarbonate across the apical membrane of epithelial cells. Its dysfunction leads to inflammation, infection, and irreversible lung damage.[1] The F508del variant is present in at least one allele in approximately 85% of CF patients worldwide; in Argentina, the incidence is about 1 in 7000 live births, with 70% carrying at least one F508del allele.[1,2]

Treatment, historically symptomatic (mucociliary clearance, nutritional support, antibiotic therapy, and pancreatic enzyme replacement), has been radically transformed by CFTR modulators that target the molecular defect. Since 2019, triple therapy with elexacaftor, tezacaftor, and ivacaftor (ETI) has become the new standard of care.[3-5] Elexacaftor and tezacaftor are correctors (they promote the folding and trafficking of CFTR to the membrane), while ivacaftor is an enhancer (it increases channel opening). Pivotal clinical trials demonstrated increases in forced expiratory volume in the first second (FEV1) of up to 14% and significant reductions in sweat chloride levels, consistent with partial restoration of CFTR function.[3-5]

Proper interpretation of these benefits requires knowledge of the systemic exposure achieved. Pharmacokinetic (PK) characterization is essential; it requires methods that quantify the drugs and, if possible, their active metabolites, M23 of elexacaftor (Ele-M23) and M1 of tezacaftor (Tez-M1).[6] In pediatrics, the PK of these modulators presents a complex challenge: lipid malabsorption due to pancreatic insufficiency, genetic variations in hepatic metabolism via cytochrome P450, and the ontogenetic maturation of CYP3A4/CYP3A5 influence exposure and result in considerable interindividual variability.[7-9] Similar published findings include observational studies, population-based models of ETI in children and adults, and assessments of the impact of diet on ETI concentrations.[7,8,10,11]

In Argentina, domestically produced, non-innovative formulations can promote sustainable and equitable treatment, but PK studies are needed to determine whether exposure matches that of the international reference drug.[7] There are no published PK studies of the Argentine formulation of ETI in the pediatric population. The primary objective was to estimate the maximum concentration (Cmax), the time to reach it (Tmax), and the area under the curve versus time (AUC) of the Argentine formulation Trixacar® (drug A, DA) in pediatric patients with cystic fibrosis, comparing them indirectly with published values for Trikafta® (drug B, DB). The secondary objective was to describe the PK profiles of Ele-M23 and Tez-M1.[7,8]

POPULATION AND METHODS

A prospective, observational, single-cohort study without a concurrent control group (December 2024 through September 2025). The results are compared with published values; this does not constitute a formal bioequivalence assessment. The Research Review and Ethics Committee at Hospital Garrahan approved the protocol (ID #1650), with the corresponding informed consent and assent forms.

Patients aged 12-18 years with confirmed cystic fibrosis (CF) who were clinically stable were included; those with hepatic or renal dysfunction were excluded. All had at least one F508del allele. The L467F;F508del allele complex, associated with a poor response to ETI, was evaluated by Sanger sequencing of *CFTR* exon 11 when DNA was available.[12] Patient selection was performed using non-probabilistic convenience sampling, based on the treating specialist's clinical assessment of high treatment adherence, to ensure that the measurements reflected a steady state.

Patients received DA according to the dosage regimen approved by the national regulatory agency (National Administration of Medicines, Food, and Medical Technology, ANMAT, by its Spanish acronym): a morning dose of 200 mg of elexacaftor, 100 mg of tezacaftor, and 150 mg of ivacaftor, and an evening dose of 150 mg of ivacaftor, administered 12 hours apart, with high-fat meals under the supervision of the hospital's Nutrition Department. Each patient had a single visit with 1.5-ml blood draws at seven time points (pre-dose, 2, 4, 5, 6, 7, and 8 hours post-dose), totaling 70 samples, equivalent to 350 determinations of elexacaftor, tezacaftor, ivacaftor, Ele-M23, and Tez-M1. Quantification was performed by ultrafast liquid chromatography with photodiode array detection (UFLC-PDA), using a C18 column and acetonitrile/water (65:35) as the mobile phase, itraconazole as an internal standard; purity standards >98%, stock solutions in HPLC-grade methanol stored at

-80 °C; validation of selectivity, linearity, precision, accuracy, matrix effect, and stability.[6]

Cmax and Tmax were obtained by direct measurement. The AUC was estimated using a noncompartmental analysis: the linear trapezoidal method for 0-8 h, extrapolated to the dosing interval (24 h for elexacaftor/tezacaftor, 12 h for ivacaftor) assuming first-order elimination, consistent with pediatric population models and based on the terminal elimination constant, a procedure validated for CFTR modulators with limited sampling.[7,8,13,14] AUC0-24 and AUC0-12 are estimates derived from the profile up to 8 h. We obtained the DB values from the prescribing information.[15]

Continuous variables were expressed as mean ± standard deviation (SD) and coefficient of variation (CV), and Tmax as median with range; categorical variables were expressed as frequencies. We calculated percentage differences and 95% confidence intervals (95%CI) and performed a sensitivity analysis using mean ± SD (*Table 1*). Given the observational design and sample size, no formal hypothesis tests were conducted.

RESULTS

Ten patients were included: age 15 (13-17) years, weight 52 (43-56) kg; 6 were female. Standardized doses: elexacaftor 3.5 mg/kg, tezacaftor 1.8 mg/kg, ivacaftor 5.5 mg/kg. F508del was homozygous in 8 of 10 patients and heterozygous in 2 (one with R553X; the second variant was not identified). We analyzed the L467F variant in 7 of the 10 patients and did not detect it in any.

The 95% CI for the Cmax and AUC estimates of DA were, respectively: for elexacaftor, 7.5-13.7 µg/ml and 134-230 µg/h/ml; for tezacaftor, 3.8-7.2 µg/ml and 54-102 µg/h/ml; and for ivacaftor, 0.9-2.1 µg/ml and 11-17 µg/h/ml. *Table 1* presents the PK parameters of DA and compares them descriptively with published DB values.

The average profiles of the parent drugs showed interindividual variability (CV 28.6-53.3%) (*Figure 1*), which is also evident in the individual curves (*Figure 2*). Quantifiable concentrations of Ele-M23 and Tez-M1 were detected in all patients (*Figure 3*).

DISCUSSION

To the best of our knowledge, this is the first study to describe the PK of a formulation of non-innovative Argentine-manufactured ETI in pediatric patients. DA achieved exposures

Table 1. Pharmacokinetic parameters of drug A and an indirect comparison with published values for drug B

Parameter	DA (mean ± SD; CV%)	DB (mean ± SD; CV%)	Arithmetic difference DA vs. DB (%)
Elexacaftor			
Cmax (µg/ml)	10.6 ± 4.3; CV 40.6%	8.7 ± 2.1	+21.8
AUC0-24 µg/h/ml)	182 ± 67; CV 36.8%	162 ± 48	+12.3
Tmax (H)	6 (2-8)	6 (4-12)	-
Tezacaftor			
Cmax (µg/ml)	5.5 ± 2.4; CV 43.6%	6.8 ± 1.5	-19.1
AUC0-24 µg/h/ml)	78 ± 33;	95 ± 24	-17.9
Tmax (H)	4 (2-7)	3 (2-4)	-
Ivacaftor			
Cmax (µg/ml)	1.5 ± 0.8; CV 53.3%	1.2 ± 0.3	+25.0
AUC0-12 µg/h/ml)	14 ± 4; CV 28.6%	12 ± 4	+16.7
Tmax (H)	5 (2-7)	4	-

DA: drug A, Trixacar®, manufactured in Argentina; DB: drug B, Trikafta®, the international reference product. The values for DB are taken from the reference product's prescribing information.[15]

DA values are expressed as mean ± standard deviation with coefficient of variation (CV), except for Tmax, which is expressed as median (range). The "Arithmetic difference" column represents the percentage difference between the observed mean values and the published values, without formal statistical analysis.

Sensitivity analysis: when recalculating the differences using the mean ± standard deviation, the ranges were as follows: for elexacaftor, Cmax −1.9% to +60.6% and AUC0-24 −13.3% to +59.6%; for tezacaftor, Cmax −33.7% to +3.8% and AUC0-24 −34.5% to +9.9%; ivacaftor: Cmax 0% to +66.7% and AUC0-12 −12.5% to +75.0%.

Figure 1. Plasma concentration-time curves for the three unchanged drugs: elexacaftor, tezacaftor, and ivacaftor (mean ± standard deviation)

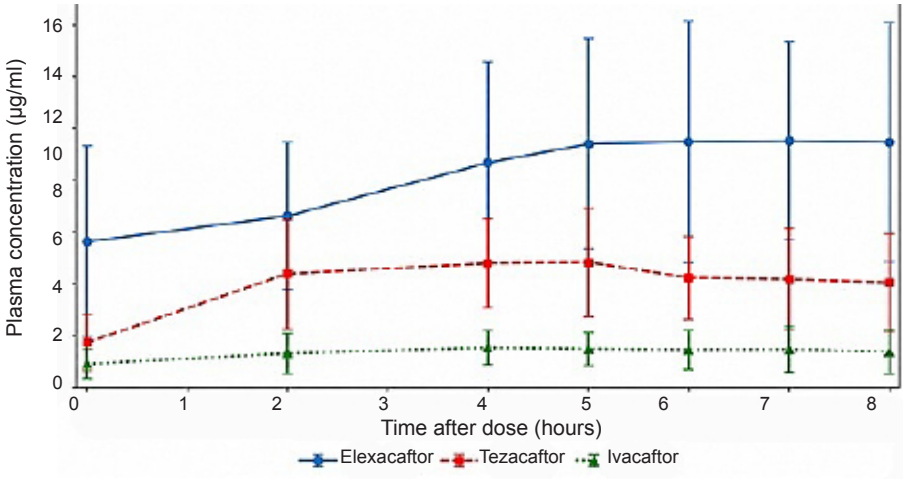


Figure 2. Individual plasma concentration-time curves (0-8 h) for the parent drugs: (A) elexacaftor, (B) tezacaftor, and (C) ivacaftor

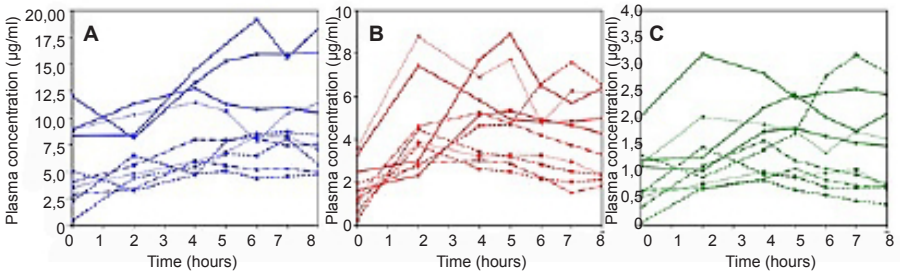
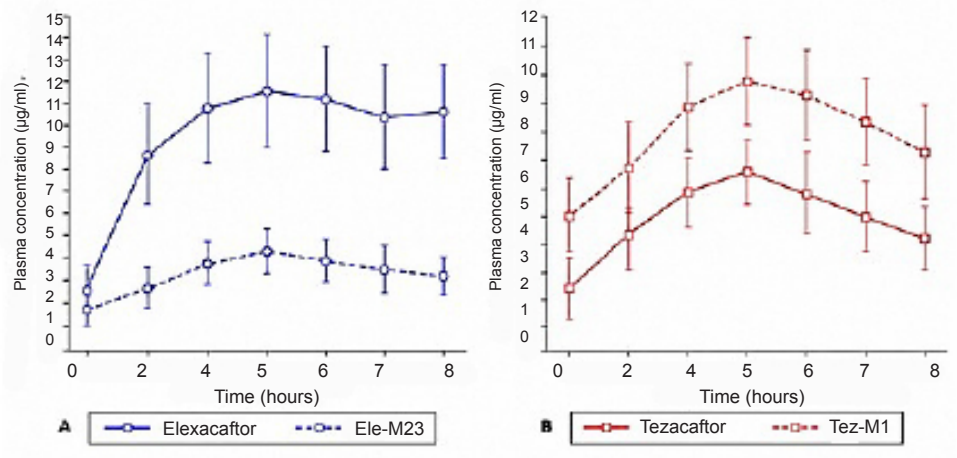


Figure 3. Plasma concentration-time curves (0-8 h) for the parent drugs and their metabolites: (A) elexacaftor and Ele-M23, (B) tezacaftor and Tez-M1



consistent with those published for DB, particularly for elexacaftor and tezacaftor.[7,8,15] These findings do not demonstrate formal bioequivalence and suggest the need for confirmatory studies.

Interindividual variability (CV 28.6-53.3%) falls within the reported range, possibly due to CYP3A4/CYP3A5 polymorphisms, disease-related alterations in intestinal absorption, and dietary fat content.[7-9,11] The L467F variant was not detected in the seven patients evaluated. Because this variant is in the *CFTR* gene and not involved in ETI metabolism, its absence does not explain the observed pharmacokinetic variability.[12]

For ivacaftor, the differences were greater (Cmax +25%, AUC +16.7%), although no biochemical or clinical signs of intolerance were observed; these findings require confirmation with a larger sample size and follow-up.[3-5,15] The similarity in Tmax suggests an absorption pattern consistent with DB, although it does not establish absorption equivalence.

Quantification of Ele-M23 and Tez-M1 confirms systemic exposure to active metabolites; their contribution to the overall effect requires specific studies.[15] The study design does not allow for an assessment of the C0-AUC correlation; the usefulness of trough levels as a simplified monitoring method is a potentially useful hypothesis, but one that requires evaluation. Quantifying drugs and metabolites could help monitor adherence in at-risk populations; previous studies reinforce the value of individualized PK monitoring.[7,8,10] These results provide useful information for the development of population-based models and personalized dosing.[7,8]

Limitations include: sample size (n = 10, consistent with exploratory studies on low-prevalence diseases); convenience sampling based on perceived adherence without objective quantification; sampling up to 8 hours (AUC0-24 and AUC0-12 are estimates, even though the procedure is validated); and comparison with published parameters without a contemporary evaluation.[7,8,13,14] Future studies with larger sample sizes, extended sampling periods, objective measures of adherence, and comparative designs are needed to confirm these findings.

CONCLUSION

This pharmacokinetic study in pediatric patients with CF showed that the Argentine-manufactured formulation has exposure parameters for elexacaftor and tezacaftor close to the previously published values for the international reference standard, and ivacaftor values near those ranges, though with greater differences. Because of the study design, these results do not establish formal bioequivalence or replace larger-scale confirmatory studies; however, they provide relevant pharmacokinetic evidence for an Argentine formulation that may be more accessible to public health systems and the pediatric population with CF. ■

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