

Drug interactions in HIV-infected children undergoing treatment with antiretrovirals

Interacciones farmacológicas en niños con infección por VIH en tratamiento con antirretrovirales

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What do we know about the subject matter of this study?

Pharmacological interactions with the different antiretroviral drugs available for the treatment of HIV have been described and analyzed mainly in the adult population due to the greater use of these drugs in this age group, some of which are potentially serious.

What does this study contribute to what is already known?

It presented a pediatric case of drug interaction between an antiretroviral and a frequently used drug, in addition to a review of interactions of the different antiretrovirals with drugs commonly used in pediatrics, grouped according to their potential risk.

Abstract

Drug interactions are undesirable events observed in clinical practice. In patients with HIV infection on antiretroviral therapy (ART), it is particularly important to bear in mind that many drugs commonly used in pediatrics can cause such interactions. **Objective:** to report a case of drug interaction between an antiretroviral drug (lopinavir/ritonavir) and inhaled corticosteroid in a child with HIV infection, and to review more frequent drug interactions in children on ART. **Clinical Case:** 5-year-old male with history of stage N1 vertical transmitted HIV infection (1994 CDC classification), on ART from 8 months of age with zidovudine, lamivudine, and lopinavir/ritonavir, with successful virological and immunological outcome. Due to symptoms of allergic rhinitis (congestion, itchy nose, and nocturnal snoring) treatment with intranasal fluticasone was started. After 1 month of treatment,

Keywords:

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he developed cushingoid facies, weight gain, mixed dyslipidemia, insulin resistance, morning basal cortisol levels $< 1 \mu\text{g/dL}$, and Adrenocorticotrophic hormone (ACTH) $< 2 \text{ pg/ml}$, presenting ACTH stimulation test compatible with central adrenal insufficiency, attributed to a drug interaction with lopinavir/ritonavir due to known interaction. He started hydrocortisone replacement treatment, recovering hypothalamic-pituitary-adrenal axis function after 18 months. **Conclusion:** Knowledge of this and other drug interactions between ART and drugs commonly used in pediatrics is essential for the comprehensive management of patients with HIV infection, especially in the prevention of unwanted adverse effects.

Introduction

Drug interactions are events that cause an alteration of the expected effect of a drug due to the recent or simultaneous use of other drugs, dietary supplements, medicinal herbs, and even food. Within drug-drug interactions, the desired effect can be increased or decreased, so it is very important to be aware of them in clinical practice¹.

HIV is one of the most relevant current public health problems. Globally, according to UNAIDS data as of 2019, 37.9 million people were living with HIV, and 1.7 million of them were children under 15 years of age².

In Chile, from the first pediatric case diagnosed in 1987 to December 2019, the Public Health Institute (ISP) had studied more than 4,200 children under 13 years of age, confirming HIV infection in 460 of them, identifying vertical transmission identified in 426 of these cases³. Of the children with HIV infection, about 90% are on antiretroviral therapy (ART) according to unpublished data from the Pediatric HIV/AIDS Committee of the Chilean Pediatric Society.

ART has allowed children who have access to it to have a life expectancy and quality of life very similar to the general population. As these drugs are rarely used in pediatrics, it is especially relevant to inform about the main drug interactions in order to avoid undesired effects when prescribing other drugs in this group of patients.

The objective of this report is to present a case of a clinically relevant drug interaction between an antiretroviral drug (lopinavir/ritonavir) and inhaled corticosteroids in a child with HIV infection and to review more frequent drug interactions in children on ART.

Clinical Case

5-year-old male patient with history of vertical HIV infection stage N1 (CDC classification 1994)⁴, diagnosed by maternal pathology, who started ART at 8 months of life with zidovudine (240 mg/m²/dose every 12 hours), lamivudine (5 mg/kg/dose every 12 hours), and lopinavir/ritonavir (Kaletra®) (300 mg/m²/dose

every 12 hours based on lopinavir), which he maintains to date, with good virological and immunological control; HIV viral load undetectable since the eighth month after initiation of therapy and CD4+ cell count in immunological stage 1.

He was evaluated in otorhinolaryngology due to months of clinical symptoms characterized by congestion and itchy nose, associated with nocturnal snoring. He was diagnosed with allergic rhinitis and started treatment with cetirizine 5 mg per day and nebulized fluticasone propionate (Flixonase®) 50 $\mu\text{g/spray}$, one application in each nostril every 12 hours.

In evaluation at the infectious disease polyclinic one month after starting treatment with intranasal corticosteroids, the physical examination revealed cushingoid facies and 1-kg weight gain in one month; laboratory tests showed altered lipid profile, with mixed dyslipidemia (total cholesterol 235 mg/dL, LDL 133.5 mg/dL, HDL 67 mg/dL, triglycerides 172 mg/dL), and mild insulin resistance (insulinemia 14.4 mU/L, glycemia 87 mg/dL, HOMA-IR index 3.1 (normal value < 2). It should be noted that the previous routine metabolic tests performed every six months had always been in normal ranges. It was decided to reduce the dose of Flixonase® to 50% due to knowledge of the interaction between lopinavir/ritonavir and inhaled corticosteroids.

The patient presented a gradual decrease of the cushingoid facies and without weight gain. The second month after decreasing the dose of corticosteroid, he presented a normal facial appearance, without weight variations and maintaining eutrophy. Due to persistent metabolic alterations, nutritional support was requested for the management of dyslipidemia and insulin resistance, indicating a low-fat diet, restriction of carbohydrates and rich in omega 3, change of eating habits, and daily aerobic exercise.

He was evaluated by endocrinology 5 months after the decrease of corticosteroid treatment after finding AM cortisol levels $< 0.054 \mu\text{g/dL}$. On physical examination, the patient was in very good general condition, active, asymptomatic, without clinical signs of adrenal insufficiency, eutrophic, with normal height, and without alteration in growth velocity.

Tests were requested to evaluate the HPA axis, finding basal AM cortisol $< 1 \mu\text{g/dL}$, adrenocorticotrophic hormone (ACTH) $< 2 \text{ pg/ml}$, ACTH test with basal AM cortisol $< 1 \mu\text{g/dL}$ and post ACTH cortisol $< 1 \mu\text{g/dL}$, which indicated severe inhibition of the HPA axis, interpreted as a secondary central adrenal insufficiency associated with the interaction between lopinavir/ritonavir of ART and inhaled corticosteroid therapy, probably transient, so he started substitution therapy with hydrocortisone at a dose of $14\text{mg/m}^2/\text{day}$. The study was completed with the evaluation of the function of the rest of the neuroendocrine axes, showing no alteration, both at the time of diagnosis and during the evolution of the clinical picture.

The corticosteroid nasal spray was definitively discontinued 3 months after starting the substitution treatment, maintaining only with cetirizine, without exacerbation of his allergic rhinitis. ART was maintained without changes and the response of metabolic alterations associated with nutritional management and change of habits was evaluated over time, considering that the use of lopinavir/ritonavir can be associated by itself to the presence of dyslipidemia. Subsequent controls showed a gradual improvement in the lipid profile, insulin resistance was resolved, normalizing insulin and HOMA index values, and always with normal glycemia levels, so it was decided to maintain the first-line ART regimen.

Six months after initiation of hydrocortisone substitution therapy, the first significant increase in basal cortisol levels was detected ($6.04 \mu\text{g/dL}$). It was maintained with minimal substitution doses controlling cortisol levels every 3 months, achieving definitive discontinuation 18 months after starting treatment, with basal cortisol of $8.02 \mu\text{g/dL}$ and post ACTH of $17 \mu\text{g/dL}$, demonstrating basal and adrenal sufficiency under stress. Table 1 summarizes the evolution of cortisol and ACTH levels. It is noteworthy that, during the entire time the patient was on substitution treatment,

he never required the use of stress doses. The patient evolved satisfactorily, maintaining his first-line ART regimen, without dyslipidemia or other endocrine-metabolic disorders.

Discussion

This clinical case shows an example of potentially lethal drug interaction, by combining an antiretroviral, in this case, lopinavir/ritonavir, with an intranasal corticosteroid, a drug widely used in clinical practice, causing secondary adrenal insufficiency.

In general, adverse reactions involving the endocrine system, including Cushing's syndrome secondary to prolonged administration of exogenous corticosteroids, are among the least frequently reported for intranasal or inhaled administered fluticasone⁵, because this drug has a systemic absorption of less than 2% when administered by these routes. However, coadministration with an antiretroviral such as lopinavir/ritonavir, a protease⁶, can significantly increase the systemic absorption of fluticasone after intranasal or inhaled administration, which mechanism of interaction is the inhibition of fluticasone metabolism via hepatic and intestinal routes by the CYP450 3A4 (CYP3A4) enzyme^{7,8}. Fluticasone is metabolized by the CYP3A4 enzyme system and, when co-administered with ritonavir, which acts as an inhibitor of this enzyme system, results in an accumulation of the steroid, adrenal suppression, and Cushing's syndrome.

In a literature review by Epperla and McKiernan, they described 11 pediatric and 26 adult patients who presented with iatrogenic Cushing's syndrome and adrenal suppression with therapy including fluticasone and ritonavir. Three adult cases were secondary to the use of intranasal and inhalation fluticasone, while the remaining patients had only used inhaled fluticasone. The total daily administered dose of fluticasone ranged

Table 1. Baseline and post ACTH Cortisol blood levels

	At diagnosis	Replacement treatment initiation	1 month	3 months	6 months	9 months	12 months	15 months	18 months. End of treatment
Basal Cortisol $\mu\text{g/dL}$ (RV: 6.02-18.40)	< 0.054	< 0.1	0.23	0.08	6.04	4.8	9.86	6.09	8.01
ACTH pg/ml (RV: 9 - 69)		< 2.00							
Cortisol 30' after ACTH test $\mu\text{g/dL}$ (RV: > 18)		< 1.00						11.9	17

RV: reference value.

from 200 to 2000 µg/day in adult patients and 200 to 1000 µg/day in pediatric patients, and ritonavir was used in low doses as a booster and in high doses⁹.

In our case, the patient received a dose of 200 µg/day of fluticasone, and adverse effects were already observed after one month of use. The speed and potency in causing clinical manifestations and inhibition of the HPA axis stand out since the first effects were observed one month after the initiation of fluticasone and total recovery of the axis occurred one and a half years after the initiation of substitution therapy.

In previously reported cases, it has been observed that the onset of Cushing's syndrome can vary between 2 weeks and 3 months in pediatric cases, with an average onset of 2.1 months^{9,10}. Therefore, the use of intranasal or inhaled fluticasone in combination with ritonavir is not recommended unless the potential benefit outweighs the risk of systemic side effects¹¹. Alternatives to fluticasone should be considered whenever possible if ritonavir is to be used. Less potent, less lipophilic, and/or shorter-acting agents, such as

beclomethasone, may be appropriate as alternatives, although most, if not all, inhaled corticosteroids are likely to interact with ritonavir to some extent¹². If it is not possible to forego their use, it is suggested to use the lowest possible effective dose of the corticosteroid and adjust as necessary, according to therapeutic response, patient tolerance, and laboratory tests assessing adrenal axis function.

Patients should be monitored for signs and symptoms of hypercortisolism, in addition to performing anthropometry, since among the earliest findings, rapid weight gain is described, which can be evidenced from the first month of co-administration⁹, as in our patient. Another option in patients with allergic rhinitis or bronchial asthma is to evaluate the use of other medications, such as leukotriene receptor antagonists, antihistamines, non-pharmacological measures, among others.

After prolonged use of fluticasone with ritonavir, a progressive reduction of the fluticasone dose may be necessary if use is to be discontinued, since there is a

Table 2. Drug interactions between Nucleoside Reverse Transcriptase Inhibitors (NRTI) and drugs commonly used in pediatrics¹³

ARV	Do not co-administrate*	Potential interaction**	Precaution***
NRTI	AZT	- Antimicrobials: albendazole, chloramphenicol, rifampicin, trimethoprim/sulfamethoxazole, vancomycin, sulfadiazine, amphotericin B, fluconazole - Neuropsychiatric: ethosuximide, phenobarbital, valproic acid, chlorpromazine, clozapine, quetiapine - Others: acetazolamide	- Analgesics and anesthetics: ibuprofen, methadone, naproxen - Antimicrobials: clarithromycin, ganciclovir - Immunological: azathioprine, mycophenolate - Neuropsychiatric: carbamazepine, phenytoin
	3TC	Antimicrobials: sulfadiazine	- Antimicrobials: ampicillin, penicillin, trimethoprim/sulfamethoxazole - Cardiovascular: atenolol
	TDF	Antimicrobials: TAF - Analgesics y anesthetics: aspirin, celecoxib, ibuprofen, mefenamic acid, naproxen, piroxicam - Antimicrobials: amikacin, clarithromycin, gentamicin, piperacillin, sulfadiazine, vancomycin, amphotericin B, itraconazole, ketoconazole, acyclovir, ganciclovir - Cardiovascular: hydralazine, amiodarone - Immunological: ciclosporin y mycophenolate - Neuropsychiatric: topiramate, lithium - Others: acetazolamide	- Antimicrobials: ampicillin, flucloxacillin, penicillin - Immunological: sirolimus, tacrolimus
	ABC	- Antimicrobials: flucloxacillin - Hematological: clopidogrel	- Analgesics y anesthetics: methadone - Antimicrobials: metronidazole, rifampicin - Immunological: mycophenolate - Neuropsychiatric: phenobarbital, phenytoin, carbamazepine - Others: isotretinoin

ARV: antiretroviral. NRTI: Nucleoside Reverse Transcriptase Inhibitors. AZT: zidovudine. 3TC: lamivudine. TDF: tenofovir disoproxil fumarate. TAF: tenofovir alafenamide. ABC: abacavir. *co-administration is not recommended unless the benefit outweighs the risk. **it can be clinically significant. May require additional monitoring, adequacy of drug dose or timing of administration. ***it is unlikely that further action, monitoring, or dose adjustment will be required.

Table 3. Drug interactions between Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and drugs commonly used in pediatrics¹³

ARV	Do not co-administrate*	Potential interaction**	Precaution***
NNRTI	NVP	- Analgesics y anesthetics: fentanyl, bupivacaine, ketamine, propofol - Antimicrobials: clarithromycin, clindamycin, doxycycline, erythromycin, caspofungin, fluconazole, voriconazole - Neuropsychiatric: phenobarbital	- Analgesics y anesthetics: methadone, tramadol - Antimicrobials: albendazole, mebendazole, rifabutin, chloramphenicol, terbinafine - Respiratory: montelukast - Cardiovascular: isosorbide dinitrate - Metabolic endocrine: atorvastatin - Neuropsychiatric: escitalopram, sertraline, venlafaxine, haloperidol - Others: colchicine, isotretinoin
		- Respiratory: salmeterol - Cardiovascular: amiodarone, lidocaine, amlodipine, diltiazem, nifedipine, nitrendipine, verapamil, sildenafil - Steroids: betamethasone, budesonide, dexamethasone, fludrocortisone, fluticasone, oral hydrocortisone, methylprednisolone, mometasone, prednisolone, prednisone, testosterone, triamcinolone - Gastrointestinal: domperidone - Hematological: acenocoumarin, clopidogrel - Immunological: ciclosporin, mycophenolate, sirolimus, tacrolimus - Metabolic endocrine: lovastatin, levothyroxine - Neuropsychiatric: carbamazepine, clonazepam, ethosuximide, phenytoin, imipramine, trazodone, aripiprazole, clozapine, quetiapine, risperidone, alprazolam, clobazam, diazepam, oral midazolam, zolpidem, zopiclone - Others: modafinil, oxybutynin	
EFV	- Antimicrobials: sofosbuvir - Neuropsychiatric: IV and oral midazolam	- Analgesics y anesthetics: celecoxib, diclofenac, fentanyl, ibuprofen, mefenamic acid, methadone, morphine, naproxen, piroxicam, bupivacaine, ketamine, propofol, - Antimicrobials: clarithromycin, clindamycin, doxycycline, erythromycin, moxifloxacin, rifabutin, caspofungin, itraconazole, voriconazole - Respiratory: salmeterol - Cardiovascular: amiodarone, amlodipine, diltiazem, nifedipine, verapamil, labetalol, sildenafil - Steroids: betamethasone, budesonide, dexamethasone, fludrocortisone, fluticasone, oral hydrocortisone, methylprednisolone, mometasone, prednisolone, prednisone, testosterone, triamcinolone - Gastrointestinal: domperidone - Hematological: acenocoumarin, clopidogrel - Immunological: ciclosporin, mycophenolate, sirolimus, tacrolimus - Metabolic endocrine: atorvastatin, lovastatin - Neuropsychiatric: carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital, phenytoin, imipramine, trazodone, aripiprazole, clozapine, olanzapine, quetiapine, risperidone, alprazolam, clobazam, diazepam, zolpidem, zopiclone - Others: modafinil, rocuronium, oxybutynin	- Analgesics y anesthetics: tramadol - Antimicrobials: albendazole, mebendazole, chloramphenicol, rifampicin, sulfadiazine, terbinafina - Respiratory: montelukast - Cardiovascular: carvedilol, lidocaine, isosorbide dinitrate, losartan - Neuropsychiatric: escitalopram, sertraline, venlafaxine, haloperidol - Others: colchicine

ARV: antiretroviral. NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitors. NVP: nevirapine. EFV: efavirenz. *: co-administration is not recommended unless the benefit outweighs the risk. **: it can be clinically significant. May require additional monitoring, adequacy of drug dose or timing of administration. ***: it is unlikely that further action, monitoring, or dose adjustment will be required.

Table 4. Drug interactions between Protease Inhibitors (PI) and drugs commonly used in pediatrics¹³

ARV	Do not co-administrate*	Potential interaction**	Precaution***
IP	- Antimicrobials: rifampicin - Cardiovascular: amiodarone, sildenafil - Steroids: budesonide, fluticasone, mometasone, triamcinolone - Gastrointestinal: domperidone - Hematological: clopidogrel - Immunological: sirolimus - Metabolic endocrine: lovastatin, simvastatin - Neuropsychiatric: quetiapine, oral midazolam	- Analgesics y anesthetics: buprenorphine, fentanyl, methadone, morphine, bupivacaine, ketamine, propofol - Antimicrobials: albendazole, mebendazole, azithromycin, ciprofloxacin, clarithromycin, clindamycin, erythromycin, levofloxacin, metronidazole, moxifloxacin, rifabutin, itraconazole, voriconazole, tenofovir - Respiratory: aminophylline, salmeterol - Cardiovascular: digoxin, isosorbide dinitrate, labetalol, lidocaine, atenolol, carvedilol, propranolol, amlodipine, diltiazem, nifedipine, verapamil - Steroids: betamethasone, clobetasol, dexamethasone, fludrocortisone, oral hydrocortisone, methylprednisolone, prednisolone, prednisone, testosterone - Gastrointestinal: loperamide, ondansetron - Hematological: acenocoumarin, aspirin - Immunological: ciclosporin, mycophenolate, tacrolimus - Metabolic endocrine: estradiol, levonorgestrel, oral medroxyprogesterone, atorvastatin - Neuropsychiatric: carbamazepine, clonazepam, ethosuximide, lamotrigine, phenobarbital, phenytoin, valproate, amitriptyline, imipramine, escitalopram, fluoxetine, lithium, paroxetine, sertraline, trazodone, venlafaxine, aripiprazole, chlorpromazine, clozapine, haloperidol, olanzapine, risperidone, alprazolam, chlordiazepoxide, clobazam, diazepam, hydroxyzine, IV midazolam, zolpidem, zopiclone - Others: colchicine, isotretinoin, modafinil, naloxone, oxybutynin, rocuronium	- Analgesics y anesthetics: tramadol - Antihistaminic: chlorphenamine, loratadine - Antimicrobials: chloramphenicol, sulfadiazine, terbinafine - Respiratory: montelukast - Metabolic endocrine: etonogestrel implant
DRV/r	- Antimicrobials: rifampicin - Cardiovascular: amiodarone, sildenafil - Steroids: budesonide, fluticasone, mometasone, triamcinolone - Gastrointestinal: domperidone - Hematological: clopidogrel - Immunological: sirolimus - Metabolic endocrine: lovastatin, simvastatin - Neuropsychiatric: phenobarbital, phenytoin, quetiapine, oral midazolam	- Analgesics y anesthetics: buprenorphine, fentanyl, methadone, morphine, bupivacaine, ketamine, propofol - Antimicrobials: albendazole, mebendazole, clarithromycin, clindamycin, erythromycin, metronidazole, moxifloxacin, rifabutin, itraconazole, voriconazole, tenofovir - Respiratory: aminophylline, salmeterol - Cardiovascular: digoxin, isosorbide dinitrate, labetalol, lidocaine, amlodipine, diltiazem, nifedipine, verapamil - Steroids: betamethasone, clobetasol, dexamethasone, fludrocortisone, oral hydrocortisone, methylprednisolone, prednisolone, prednisone, testosterone - Gastrointestinal: loperamide, ondansetron - Hematological: acenocoumarin, aspirin - Immunological: ciclosporin, mycophenolate, tacrolimus - Metabolic endocrine: estradiol, levonorgestrel, oral medroxyprogesterone, atorvastatin - Neuropsychiatric: carbamazepine, clonazepam, ethosuximide, lamotrigine, valproate, imipramine, sertraline, trazodone, aripiprazole, clozapine, olanzapine, risperidone, alprazolam, chlordiazepoxide, clobazam, diazepam, midazolam, zolpidem, zopiclone - Others: colchicine, isotretinoin, modafinil, naloxone, oxybutynin, rocuronium	- Analgesics y anesthetics: pethidine, piroxicam, tramadol - Antihistaminic: chlorphenamine, loratadine - Antimicrobials: chloramphenicol, sulfadiazine, terbinafine - Respiratory: montelukast - Cardiovascular: carvedilol, propranolol - Neuropsychiatric: amitriptyline, escitalopram, fluoxetine, paroxetine, venlafaxine, chlorpromazine, haloperidol

ARV: antiretroviral. IP: protease inhibitors. LPV/r: lopinavir/ritonavir. DRV/r: darunavir/ritonavir. *co-administration is not recommended unless the benefit outweighs the risk. **it can be clinically significant. May require additional monitoring, adequacy of drug dose or timing of administration. ***it is unlikely that further action, monitoring, or dose adjustment will be required.

Table 5. Drug interactions between Integrase Inhibitors (II) and drugs commonly used in pediatrics¹³

ARV	Do not co-administrate*	Potential interaction**	Precaution***
II	RTG	– Antimicrobials: rifampicin – Gastrointestinal: antacids – Neuropsychiatric: carbamazepine, phenobarbital, phenytoin – Supplements and vitamins: multivitamins that contain one or more of the following: ascorbic acid, cholecalciferol, cyanocobalamin, folic acid, iodine, nicotinamide, retinol, riboflavin, thiamine, and/or tocopherol; calcium supplements, iron or magnesium; ferrous fumarate.	
	DTG	– Antimicrobials: rifampicin – Cardiovascular: atenolol – Gastrointestinal: antacids – Neuropsychiatric: carbamazepine, phenobarbital, phenytoin – Others: ephedrine – Supplements and vitamins: multivitamins that contain one or more of the following: ascorbic acid, cholecalciferol, cyanocobalamin, folic acid, iodine, nicotinamide, retinol, riboflavin, thiamine, and/or tocopherol; calcium supplements, iron or magnesium; ferrous fumarate.	– Neuropsychiatric: clobazam – Others: pyridostigmine

ARV: antiretroviral. II: integrase inhibitors. RTG: raltegravir. DTG: dolutegravir. *co-administration is not recommended unless the benefit outweighs the risk. **it can be clinically significant. May require additional monitoring, adequacy of drug dose or timing of administration. ***it is unlikely that further action, monitoring, or dose adjustment will be required.

significant risk of suppression of adrenal axis function, and the use of systemic corticosteroids in replacement doses may be necessary until recovery of axis function, as occurred in this patient.

Although this clinical case is only an example of drug interactions, it is important to know those associated with the most used antiretrovirals in pediatrics from the family of Nucleoside Reverse Transcriptase Inhibitors (NRTIs), Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease Inhibitors (PIs), and Integrase Inhibitors (INIs). It is important to note that clinicians should consider the potential interactions of antiretrovirals when prescribing other drugs, which will be specific to each drug depending on its pharmacodynamic and pharmacokinetic characteristics. ARTs that are metabolized in the liver (NNRTIs, PIs, maraviroc, and elvitegravir II) are the ones that can have the most interactions with other drugs.

Tables 2, 3, 4, and 5 list the main drug interactions between the families of antiretrovirals most used in patients in the Chilean pediatric cohort and drugs commonly used in children. For the preparation of these tables, all the interactions of the included antiretrovirals were extracted from the HIV-Drug Interactions website of the University of Liverpool¹³. Then, they

were filtered according to the health registries in force in Chile and availability in the pharmacological arsenal of the *Hospital Dr. Exequiel González Cortés*. Frequently used drugs were selected, as well as those of occasional use, but with potentially severe interactions.

Physicians who manage non-HIV pathologies in these children, whether asthma, allergies, neuropsychiatric pathology, intercurrent infections, arrhythmias, or others, must verify possible drug interactions between ART and the treatment they are going to prescribe, where the support and joint work with a clinical pharmaceutical scientist is essential. In addition, numerous digital resources allow a quick review of drug interactions. Among the free consultation websites, the aforementioned HIV-Drug Interactions of the University of Liverpool¹³ and others such as Drugs.com¹¹ or Medscape.com are available. Among paid subscription tools, some mobile applications such as IBM Micromedex® or Lexicomp® are recommended.

Conclusion

As a result of this clinical case and subsequent review of the most frequent drug interactions between

antiretrovirals and drugs frequently used in pediatrics, the number of drugs involved, and the associated adverse drug reactions are relevant. Therefore, given the relative increase in the use of ART, whether in the context of the vertical transmission protocol, pediatric HIV treatment, or post-exposure prophylaxis, it is essential for pediatricians caring for these patients to be aware of these interactions in order to prevent adverse events such as the one described in this review.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have

followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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