Annales de l'Unité de recherche en pratique pharmaceutique – 16 May 2013, p.1-9
http://urppchusj.com - doi : 10.18163/urppchusj2013051601

Original article

Use of Fenofibrate in Asparaginase-Induced Hypertriglyceridemia in Children with ALL: a Case Series

Therrien R, Barret P, Robitaille M, Moghrabi A

Roxane Therrien, B.Pharm., M.Sc., Pharmacist, Pharmacy department and Pharmacy practice research unit, CHU Sainte-Justine, Montreal (Qc)

Pierre Barret, D.Pharm, Research assistant, Pharmacy practice research unit, CHU Sainte-Justine, Montreal (Qc) at the time of the study

Marthe Robitaille, B.Sc., Nutritionist, CHU Sainte-Justine, Montreal (Qc)

Albert Moghrabi, MD, CHU Sainte-Justine, Montreal (Qc) at the time of the study

Correspondence: Roxane Therrien, CHU Sainte-Justine, Montreal, Qc, Canada, H3T1C5 – 514.345.4865 – roxane.therrien.hsj@ssss.gouv.qc.ca

Abstract

Leukemia patients receiving asparaginase sometime develop hypertriglyceridemia requiring delays in therapy despite severe hypolipidic diet. This paper reports on the use of fenofibrate in ten pediatric patients with ALL. Fenofibrate was tried in order to improve quality of life, avoid delays in therapy and pursue optimal treatment of ALL despite the lack of information on this treatment. Before adding the fenofibrate, the average triglyceridemia for these patients was a median 4.60 mmol/L, and it was reduced to 3.07 mmol/L after fenofibrate. The average reduction was of 31%. This response is comparable to other studies using fenofibrate in the treatment of hypertriglyceridemia in children in general. Our results shows the efficacy of fenofibrate in reducing hypertriglyceridemia secondary to asparaginase in pediatric ALL patients.

Introduction

Asparaginase, an essential component of the treatment of acute lymphoblastic leukemia (ALL), is well known for its side effects, the most frequent of which are allergies (20%), thromboembolic events (2-11%) and severe pancreatitis (4-7%) [1-5]. It has also been reported that asparaginase causes abnormalities in lipid metabolism, particularly hypertriglyceridemia [2, 4-5]. Hypertriglyceridemia has been observed since this drug was first introduced in clinical trials 40 years ago [6]. The first studies on the effect of asparaginase on lipid metabolism showed a decrease in total cholesterol along with a rise in triglycerides (TGs) in most patients [7-8]. Two studies of childhood ALL showed a temporal association between asparaginase administration and hypertriglyceridemia [2,4]. In one of these studies, the incidence of hypertriglyceridemia (> 200 mg/dL or 2.26 mmol/L) was estimated to be 67% during asparaginase-containing regimens with 19% exceeding 1000 mg/dL (11.3 mmol/L) [4]. No association between hypertriglyceridemia and pancreatitis was detected [4]. In the general population, hypertriglyceridemia is also a rare cause of pancreatitis, although the risk is increased with TGs levels > 1000 mg/dL (11.3 mmol/L) [1,3,5,9]. Hypertriglyceridemia due to asparaginase is reversible after drug discontinuation and is rarely associated with severe complications, but it has been reported to be life-threatening in certain cases [1,3,5,10]. The most significant consequence of hyperlipidemia is hyperviscosity syndrome with CNS involvement [1].

The pathogenetic mechanism seems to be due to an increase in the endogenous synthesis of very-low-density lipoprotein (VLDL) during asparaginase administration and a decrease in lipoprotein lipase (LPL) activity with a consequent decrease in the removal of TGs from plasma [3-6, 11-12]. LPL is the rate-limiting enzyme for the removal of TGs from the circulation; the fasting plasma concentration of TGs correlates with LPL activity [10]. Lipoprotein A has been shown to be reduced in patients treated with asparaginase [13]. While Apo-A1 usually reflects the HDL fraction, it is reported to be slightly decreased during asparaginase therapy, whereas there is a shift from higher density lipoprotein particles to lower density lipoprotein particles due to an altered ratio of lipid to protein.1 Apo-B100, the principal protein of TG-rich particles also increases. The molecular mechanism behind increased Apo-B synthesis is not clear.1

In addition to the effects of asparaginase on lipid metabolism, both the diagnosis of ALL and the use of other chemotherapeutic agents, notably corticosteroids, have been associated with alterations in lipid synthesis and clearance [4-5,12,14]. During treatment with corticosteroids, an extensive production of TG-rich lipoproteins occurs [11-12]. On the other hand, corticosteroid treatment results in increased LPL activity, which is thought to be sufficient to prevent extreme hypertriglyceridemia in patients treated with corticosteroids alone [11].

Treatment of hypertriglyceridemia secondary to asparaginase ranges from simple follow-up and dietary restrictions to lipid pheresis and drug discontinuation [3,14]. Plasmapheresis has also been used to treat very severe cases of hypertriglyceridemia (up to 5620 mg/dL or 63.5 mmol/L) secondary to asparaginase [1,3]. The use of bezafibrate has been reported in a severe case of hypertriglyceridemia associated with a cerebral sinus occlusion in a teenage boy who received PEG-asparaginase for the treatment of ALL [10]. Reports on the use of hypolipemic medication are otherwise rare in this particular situation. Given the serious nature of ALL and the important value of asparaginase in its treatment, delays and changes in the antileukemic regimen need to be minimized [14]. It is, therefore, important to identify therapeutic options to treat this complication of asparaginase.

The use of fibrates is the mainstay treatment of hypertriglyceridemia. Fibrates can reduce plasma TGs levels by up to 50% and raise HDL-C concentrations by as much as 20% [9]. Fibrate therapy is generally very well tolerated [9,15]. The most frequently reported adverse reactions have been gastrointestinal disturbances, which account for approximately one-half of the adverse effects. Other common reactions include headache, muscle pain and rash [15]. Published reports of hepatitis or myositis have been very rare [9,15]. The use of fibrates as prophylaxis against pancreatitis when plasma TGs exceed 10 mmol/L is well established [9]. The major effect of fenofibrate is the enhancement of TG-rich lipoprotein catabolism by increasing lipoprotein lipase activity. Fenofibrate is then a logical option considering that asparaginase probably decreases lipoprotein lipase activity. In addition, fenofibrate appears to decrease cholesterol biosynthesis, which may in turn enhance LDL clearance through increased hepatic LDL receptor activity [15]. As with other lipid-regulating drugs, fenofibrate therapy should only be instituted after dietary restrictions and other nonpharmacologic interventions have been proven inadequate for controlling lipid abnormalities [15]. In clinical studies of patients with type IIa hypercholesterolemia, fenofibrate consistently reduced total plasma TG levels by 16% to 34% after two to six months of treatment [15]. In a large multicenter study of hyperlipoproteinemia type IIa and IIb, a six-month treatment with fenofibrate reduced total TGs by 38% [15].

In our cohort of patients with ALL, hypertriglyceridemia has caused delays in asparaginase administration. During asparaginase therapy, patients experienced fatigue and tiredeness and needed to come to the hospital more frequently. Delay in treatment because of hypertriglyceridemia is not desirable. Therefore, we decided to try fenofibrate to improve their quality of life and pursue an optimal treatment of ALL in pediatric patients.

Methods

Review of fenofibrate and asparaginase utilization

An electronic pharmacy file search was conducted to find all the patients who started fenofibrate and asparaginase between July 1st, 2004, and May 30th, 2008. While the exact starting date of fenobibrate was known, the end of treatment date was unknown because it was not documented by the community pharmacy. For all patients, fenofibrate was stopped after asparaginase was stopped.

Retrospective data collection (age, weight, sex, ALL protocol, asparaginase doses, TGs, concomittant medications, side effects, diet) was carried out using patient files and electronic records. TG values did not necessarily correspond to fasting values. TG levels were routinely dosed on all patients receiving asparaginase. Treatment was held if the TG level was > 1000 mg/dL (11 mmol/L), considering the higher risk of pancreatitis with TG levels above that value. Patients were all treated according to the Dana-Farber Cancer Consortium protocols for pediatric ALL. Between 2000 and 2005, DFCI00001 protocol was used, with *Escherichia coli* asparaginase administered every week for a total of 30 doses during the intensification phase. Between 2005 and 2008, DFCI05001 protocol was used with asparaginase administration randomized to 30 doses of *Escherichia coli* asparaginase every week or to 15 doses of PEG-asparaginase every two weeks during the consolidation II phase. Erwinia asparaginase was not available at the time of the study.

The impact of the timing, dose and type of corticosteroids on TG levels was evaluated. The proportion of TG levels was compared with Fishers' exact test and the median TG values were compared with a Mann-Whitney.

Results

Ten ALL patients receiving fenofibrate for asparaginase-induced hypertriglyceridemia were included. Three of these patients were girls. The average age was ten years (range: 1-18).

Asparaginase administration

Table I presents the ALL protocol, asparaginase doses, serum TGs levels and the timing of the introduction of fenofibrate for each patient. Three patients were on DFCI00001 protocol (1,2 and 3) and seven on DFCI05001 protocol. According to these protocols the recurrence risk was considered standard for two patients (2 and 5), high for seven patients (1,3,6,7,8,9,10) and very high for one patient (4). Six patients (1, 2, 3, 8, 9, 10) received *Escherichia coli* asparaginase and four patients (4, 5, 6, 7) received PEG-asparaginase.

Ten doses of asparaginase were given in five patients even though TGs were > 11 mmol/L. Patients received all their doses over an average in of 33 weeks. A total of 47% of asparaginase doses were given before the addition of fenofibrate and 53% after. On average, fenofibrate was added at the 13th week of treatment with asparaginase. Two patients changed from *Escherichia coli* asparaginase to PEG-asparaginase because of allergy (patient 1 had a local reaction consisting of redness and soreness for two doses in a row. Patient 9 had an anaphylactic reaction.

Fenofibrate administration

Table II presents the fenofibrate doses. The average dose used was 3.7 mg/kg/day (range: 1.3-7.6) in micronized or microcoated formulation. The average dose used for patients younger than 12 years old (n=5 patients), was 5.1 mg/kg/day (range 2.4-7.6). Compliance with treatment could not be evaluated. No severe side effects were reported.

Table III presents the efficacy of fenofibrate in lowering TG levels. Before the addition of fenofibrate, the median triglyceridemia was 4.60 mmol/L. After the addition of fenofibrate, the average TG decreased to a median 3.07 mmol/L. The average reduction in the median TG levels was of 31%. Twenty-three doses of asparaginase were delayed because of hypertriglyceridemia before the addition of fenofibrate compared to only eight doses after.

Diet

Patient 1 was put on a very severe low-lipid diet of 6 g of lipids per day for two months before fenofibrate was initiated. The patient had to be put on tube-feeding and a Tolerex® solution (0.2g of carthame oil/100 ml) for two and a half months (starting one and a half months before fenofibrate) because of weight loss related to the diet. While on tube-feeding, he was allowed three additional grams of lipids per day. Three weeks after fenofibrate was started, the lipid allowance was raised to 15 g per day. The patient was highly compliant with the diet. Patient 2, started a low-lipid diet at the same time as he started taking fenofibrate. He was restricted to 6 to 8 g of lipids per day during the weeks of prednisone and 10 to 16 g for the other weeks. This patient was also compliant with his diet. Three patients (4, 5, 9) were put on a low-lipid diet where the quantity of allowed lipids was not found. Patient 4, eight days before starting fenofibrate; Patient 5, seven days before starting fenofibrate; and Patient 9 on the same day as fenofibrate was started. No data were found on the diets of four patients (3, 6, 7, 8 and 10).

Effect of corticosteroids on TG levels

The proportion of TG levels > 11 mmol/L was higher 7 to 13 days after the start of corticosteroids (31/51 TG levels, 91%) than on any other moment in the cycle (20/51, 39%) (Fishers' exact test, $p < 0.001$). TG values were also higher 7 to 13 days after the start of corticosteroids (median[min-max] 6.49[0.27-24.29] mmol/L) than on any other moment in the cycle (3.07[0.44-38.87]) (Mann Whitney test, $p < 0.001$).

Six patients received high dose dexamethasone (4, 6, 8, 7, 9, 10), two patients received high dose prednisone (1, 3), one patient received low dose dexamethasone (5) and one patient received low dose prednisone (2). No impact of the type (prednisone vs dexamethasone) or of the dose of corticosteroids (high dose vs low dose) was found on TG levels.

Concomitant medication

Patients also received mercaptopurine 50 mg/m^2 for 14 consecutive days in a 21 days cycle, vincristine 2 mg/m^2 every 3 weeks, methotrexate 30 mg/m^2 every week (for patients deemed at a standard recurrence risk) or doxorubicine 30 mg/m^2 with dexrazozane 300 mg/m^2 every 3 weeks (for patients deemed at a high recurrence risk). Patients that received asparaginase with the DCFI0001 protocol were randomized to receiving either dexamethasone (6 mg/m^2 for standard risk and 18 mg/m^2 for high risk) or prednisone (40 mg/m^2 for standard risk and 120 mg/m^2 for high risk) for 5 consecutive days every 3 weeks. Patients that received asparaginase with the DFCI05001 protocol received dexamethasone (6 mg/m^2 for standard risk and 18 mg/m^2 for high risk and very high risk) for 5 consecutive days every 3 weeks.

Table I Asparaginase Administration and Triglycerides levels

	Patient 1 (n=30 asparaginase doses)		Patient 2 (n=30 asparaginase doses)		Patient 3 (n=30 asparaginase doses)		Patient 4 (n=15 asparaginase doses)		Patient 5 (n=15 asparaginase doses)	
Wk	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG
1	44000 U (E)	1.04	20500 U(E)	1.37	40250 U (E)	2.01	1875 U(P)	1.7	1500 U (P)	0.62
2	44000 U (E)	1.30	20500 U(E)	4.06	40250 U (E)	3.63				
3	44000 U (E)	2.13	20500 U(E)	0.60	40250 U (E)	1.35	1875 U(P)	3.8	1500 U (P)	1.20
4	44000 U (E)	1.50	20800 U(E)	1.14	40250 U (E)	1.93				
5	44000 U (E)	5.12	20800 U(E)	9.04	40250 U (E)	7.61	1875 U(P)	2.4	1500 U (P)	6.02
6	Cancelled*	3.60	20800 U(E)	1.24	40250 U (E)	4.95				
7	44000 U (E)	2.22	20800 U(E)	1.77	40250 U (E)	11.8	1800 U(P)	2.1	1500 U (P)	2.18
8	42000 U (E)	3.02	20800 U(E)	10.8	40250 U (E)	4.74				
9	4200 U (P)	2.95	20800 U(E)	n/a	40000 U (E)	3.96	1800 U(P)	11.3	1500 U (P)	5.12
10	4200 U (P)	2.41	20800 U(E)	4.11	40000 U (E)	10.1				
11	4200 U (P)	9.54	Cancelled	15	40000 U (E)	8.33	Cancelled F	24	1500 U (P)	21.9
12	4200 U (P)	7.83	20800 U(E)	0.6	40000 U (E)	7.76	1800 U(P)	5.7		
13	4200 U (P)	4.0	21000 U(E)	0.93	40000 U (E)	10.1			1500 U (P)	2.4
14	4200 U (P)	11.5	21000 U(E)	2.6	40000 U (E)	6.97	1800 U(P)	5.2		
15	4200 U (P)	13.7	21000 U(E)	14.7	40000 U (E)	6.75			1500 U (P)	1.3
16	4200 U (P)	7.5	21000 U(E)	2.18	40000 U (E)	13.3	1800 U(P)	8.5		
17	Cancelled	25.1	21000 U(E)	3.57	40000 U (E)	5.39			Cancelled	16.5
18	4200 U (P)	8.79	Cancelled F	23.8	40000 U (E)	6.72	1800 U(P)	4.8	1500 U (P)	1.49
19	4200 U (P)	11.7	21000 U(E)	1.3	40000 U (E)	7.05				
20	4200 U (P)	7.94	21000 U(E)	0.72	40000 U (E)	2.55	Cancelled	12.9	Cancelled F	18
21	Cancelled	14.5	Cancelled	16.1	40000 U (E)	3.30	1800 U(P)	2.4	1500 U (P)	0.63
22	4200 U (P)	6.7	21000 U(E)	1.24	40000 U (E)	1.47				
23	4200 U (P)	11.2	21000 U(E)	0.52	40000 U (E)	1.29	1800 U(P)	1.6	1500 U (P)	5.4
24	Cancelled	17	21000 U(E)	9.3	Cancelled F	14.9				
25	Cancelled	14.4	21000 U(E)	2.6	40000 U (E)	0.93	1800 U(P)	11.8	1500 U (P)	1.3
26	Cancelled	19.9	21000 U(E)	2.47	40000 U (E)	1.17				
27	Cancelled F	14	Cancelled	21.9	40000 U (E)	5.67	1800 U(P)	2.99	1500 U (P)	0.52
28	4200 U (P)	2.6	21000 U(E)	2.6	40000 U (E)	0.61				
29	4200 U (P)	2.9	21000 U(E)	0.6	40000 U (E)	1.48	1800 U(P)	4.41	1500 U (P)	3.89
30	4200 U (P)	4.5	21000 U(E)	9.3	40000 U (E)	7.39				
31	4200 U (P)	3.7	21000 U(E)	2.4	40000 U (E)	0.80	1800 U(P)	1.57	1500 U (P)	0.80
32	4200 U (P)	10.6	Cancelled*							
33	4200 U (P)	8.2	21000 U(E)	2.0						
34	4200 U (P)	2.9	21000 U(E)	2.0						
35	4200 U (P)	7.3	21000 U(E)	2.2						
36	4200 U (P)	1.82								
37	4200 U (P)	3.07								

Table I continued

	Patient 6 (n=15 asparaginase doses)		Patient 7 (n=15 asparaginase doses)		Patient 8 (n=30 asparaginase doses)		Patient 9 (n=30 asparaginase doses)		Patient 10 (n=30 asparaginase doses)	
Wk	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG	Asparaginase dose	TG
1	4200 U(P)	1.80	1250 U (P)	0.78	50000 U (E)	0.61	26000 U (E)	2.29	37500 U (E)	1.19
2					50000 U (E)	3.81	26000 U (E)	5.54	37500 U (E)	2.76
3	4200 U(P)	3.56	1250 U (P)	n/a	50000 U (E)	3.22	26000 U (E)	8.83	37000 U (E)	3.65
4					50000 U (E)	3.74	26000 U (E)	2.45	37000 U (E)	6.92
5	Cancelled F	13.9	1250 U (P)	0.89	50000 U (E)	5.77	26000 U (E)	10.4	Cancelled*	
6	4200 U(P)	4.9			Cancelled*		Cancelled	23.7	38750 U (E)	1.85
7			1250 U (P)	7.29	50000 U (E)	1.43	27750 U (E)	2.08	37500 U (E)	8.61
8	4200 U(P)	4.5			Cancelled	14.4	27750 U (E)	4.15	38750 U (E)	7.20
9			1250 U (P)	2.57	50000 U (E)	2.73	Cancelled F	22.1	Cancelled	13.31
10	4200 U(P)	5.5			50000 U (E)	9.0	27750 U (E)	3.11	37000 U (E)	2.42
11			Cancelled	19.5	Cancelled	12.5	27750 U (E)	1.82	Cancelled*	
12	4200 U(P)	3.17	1250 U (P)	0.95	50000 U (E)	5.6	27750 U (E)	3.18	37500 U (E)	2.06
13					50000 U (E)	5.21	27750 U (E)	5.27	37000 U (E) F	6.22
14	4200 U(P)	0.88	Cancelled	28.8	50000 U (E)	3.78	27750 U (E)	8.60	Cancelled*	
15			1250 U (P)	1.61	50000 U (E)	4.72	2575 U(P)	3.48	Cancelled*	
16	4200 U(P)	2.56			50000 U (E)	7.12	2500 U(P)	0.73	37000 U (E)	1.33
17			Cancelled	42.9	Cancelled	18.9	2500 U(P)	1.76	37000 U (E)	3.66
18	4200 U(P)	1.38	1250 U (P)	1.85	50000 U (E)	1.41	2500 U(P)	0.81	37500 U (E)	3.96
19					50000 U (E)	7.41	2500 U(P)	3.5	37500 U (E)	4.78
20	4200 U(P)	2.57	Cancelled	32.8	Cancelled F	15.3	2500 U(P)	2.86	37500 U (E)	6.49
21			1250 U (P)	3.4	50000 U (E)	2.58	2500 U(P)	5.75	37500 U (E)	3.29
22	4200 U(P)	2.93			50000 U (E)	5.81	2500 U(P)	5.9	37500 U (E)	4.81
23			1250 U (P) F	4.02	50000 U (E)	10.2	2500 U(P)	n/a	37500 U (E)	4.30
24	4200 U(P)	1.57			50000 U (E)	4.74	2500 U(P)	4.07	37500 U (E)	3.59
25			1275 U (P)	2.29	50000 U (E)	6.72	Cancelled	19.1	37500 U (E)	3.61
26	4200 U(P)	2.13			50000 U (E)	7.67	2500 U(P)	7.31	37500 U (E)	5.18
27			1275 U (P)	1.14	Cancelled	16.1	2500 U(P)	4.75	37500 U (E)	3.22
28	4200 U(P)	2.53			50000 U (E)	2.31	2500 U(P)	6.51	37500 U (E)	2.79
29			Cancelled	23.7	50000 U (E)	2.97	2500 U(P)	3.64	37500 U (E)	3.23
30	4200 U(P)	4.34	1300 U (P)	3.27	Cancelled	13.0	2500 U(P)	2.11	37500 U (E)	1.35
31					50000 U (E)	2.75	2500 U(P)	5.28	37500 U (E)	2.19
32			1300 U (P)	0.4	50000 U (E)	1.8	2500 U(P)	5.64	37500 U (E)	4.72
33					50000 U (E)	4.66	2500 U(P)	1.67	37500 U (E)	2.23
34			1300 U (P)	0.94	50000 U (E)	6.73			37500 U (E)	3.23
35					50000 U (E)	6.12			37500 U (E)	2.52
36					50000 U (E)	7.59				
37					50000 U (E)	7.78				

Table I Legend

* = asparaginase cancelled for a reason other than hypertriglyceridemia
n/a= not available
x = asparaginase given even if TG >11 mmol/L
F = Start of fenofibrate
(P) = PEG-asparaginase
(E) = e.coli asparaginase
TG = triglyceride levels in mmol/L

Table II Fenofibrate Doses

Patients	Sex	Age (years)	Weight (kg)	Fenofibrate Posology	Fenofibrate Dose (mg/kg/day)
1	Male	18	56	160 mg PO once a day (microcoated)	2.9
2	Male	6	21.4	100 mg PO once a day (microcoated)	4.7
3	Female	14	50.9	160 mg PO once a day (microcoated)	3.1
4	Male	5	17.7	100 mg PO once a day (microcoated)	5.6
5	Male	2	14.8	100 mg PO once a day (microcoated)	6.8
6	Female	13	63	160 mg PO once a day (microcoated)	2.5
7	Male	1	13.2	100 mg PO once a day (microcoated)	7.6
8	Male	16	78.5	160 mg PO once a day (microcoated) X 2 months	2
				100 mg PO once a day (microcoated) X 1 month	1.3
				200 mg PO once a day (micronized)	2.6
9	Female	11	28.4	100 mg PO once a day X 3 months (microcoated)and then	3.5
				67 mg PO once a day (micronized)	2.4
10	Male	14	48.9	160 mg PO once a day (microcoated)	3.3

Table III. Efficacy of Fenofibrate on Triglyceridemia

Patients	Before the addition of fenofibrate		After the addition of fenofibrate		Variation
	Doses (n)	Median TG (mmol/L)	Doses (n)	Median TG (mmol/L)	Variation on median TG (%)
1	25	7.50	11	3.70	-50.67
2	17	2.60	16	2.30	-11.54
3	24	6.06	7	1.17	-80.68
4	6	3.10	11	4.80	+54.84
5	11	2.40	6	1.05	-56.25
6	3	3.56	13	2.57	-27.81
7	13	3.40	6	1.72	-49.56
8	19	5.21	17	6.12	+17.47
9	9	5.54	23	3.64	-34.30
10	11	6.65	19	3.59	-1.64

TG = triglyceride levels in mmol/L

Patients also received a multitude of other medication during asparaginase therapy, that was not required by the protocol and that we list here for completion. All patients received either trimethoprim/sulfamethoxazole or inhaled pentamidine for pneumocystis jiroveci prophylaxis. Patient 1 received amitriptyline, dimenhydrinate, fluconazole, metoclopramide, morphine, ranitidine and zopiclone. Patient 2 received amitriptyline and codeine. Patient 3 received no other medication. Patient 4 received codeine, methotrimeprazine and mineral oil. Patient 5 received codeine and mineral oil. Patient 6 received docusate, famciclovir, insuline, lorazepam, pyridoxine and ranitidine. Patient 7 received dimenhydrinate, mineral oil, potassium and ranitidine. Patient 8 received amlodipine, amitriptyline, codeine, docusate, hydromorphone, lactulose, lorazepam, metronidazole, morphine, nabilone, naproxen and posaconazole. Patient 9 received amitriptyline, clarithromycine, codeine, docusate, fluconazole, gabapentine, lactulose, lorazepam, morphine and oseltamivir. Patient 10 received amlodipine, clobazam, diphenhydramine, docusate, enoxaparin, lansoprazole, magnesium and pyridoxine.

Discussion

To our knowledge this is the first report of fenofibrate administration in pediatric patients with hypertriglyceridemia secondary to asparaginase.

Our results show a 31% reduction in plasma TGs with fenofibrate for this population in the clinical setting. These results are comparable to a pediatric study done by Steinmetz et al. on the effect of fenofibrate in seventeen hyperlipimic patients between the ages of 4 and 19 years [16]. Before treatment they were all put on a low-lipid diet. Cholesterol intake was limited to no more than 300 mg/day and at least two-thirds of the daily lipid ration was polyunsaturated. After three to six months of dieting, the lipid levels still remained too high. Fenofibrate was started at 200 mg/day with a readjustment of the dose to 100 or 300 mg. The mean decrease in serum TGs level was 39% after three months of treatment. They also found that the higher the TGs concentration before treatment, the more pronounced the TG-lowering effects. We could not highlight such an association in our report. Temporary interruptions or irregularities in taking the drug accounted for most of the temporary increases in the lipid parameters, which were corrected rapidly when the patient showed greater discipline with regard to complying with the prescription. Again, since we had no precise data on the patients' medication compliance, we could not find such an association.

In our patient population, asparaginase therapy delays because of hypertriglyceridemia were important. The consolidation phase of the protocol with asparaginase is quite difficult for the patients' quality of life and prolonging this phase is not desirable. We observed that 23 doses of asparaginase were cancelled because of hypertriglyceridemia in our 10 patients before fenofibrate was added compared to eight doses after it was introduced. Considering that almost half of all the doses of asparaginase were given after fenofibrate was initiated, we consider this as sign of efficacy, i.e., a 65% reduction in dose cancellations.

In the five children under 12 years of age, the average dose of fenofibrate was 5.1 mg/kg/day, but the range varied from 2.4 to 7.6. Even though fenofibrate is not approved in pediatrics, the recommended dose for children is 5 mg/kg/day (fenofibrate or micronized fenofibrate). Fenofibrate administration has been reported in children aged four and over. 17 As the recommended dosing in pediatrics is 5 mg/kg/day (micronized), this level was for the most part respected. However, for the two younger patients (one and two years old), the dose was higher. Patients who were 12 years or older received adult doses. In the adult population, the recommended daily dose of film-coated fenofibrate (Lipidil Supra®) is 160 mg once a day up to a maximal dose of 200 mg.18

In our patients, the average age was ten years and seven out of ten patients were boys. This is not representative of the usual ALL population (based on DFCI 95-01) that was 56% male with a mean age of 4.6 years.19

Unfortunately, we obtained data on the diet of only half of the patients. For the patients for whom we did not have any data, it is not known whether it was because they were not put on a low-lipid diet or because the diet was simply not noted.

Considering that hypertriglyceridemia secondary to asparaginase requires a very restrictive diet that is very difficult to follow by patients and that has serious consequences on the quality of life, fenofibrate is now more rapidly introduced for these patients before waiting for the results of a lipid lowering diet. Fenofibrate in addition to a low-lipid diet may help improve the efficacy of the diet.

Of all the concurrent medications patients were taking, only dexrazoxane and corticosteroids were associated with hypertriglyceridemia. Altought hypertriglyceridemia associated with dexrazoxane is anectodal [20], corticosteroids, are a well known cause of lipid abnormalities and notably hypertriglyceridemia [4,13-14,21-23]. Steroids are catabolic and cause fatty acid mobilization from adipose tissue, leading to an increase in free fatty acid (FFA) levels in serum [21-23]. Elevated FFA levels increase triglyceride synthesis and secretion [21]. It is noteworthy that 8/10 patients were on high-dose corticosteroids (prednisone 120 mg/m^2 or dexamethasone 18 mg/m^2). We found higher TG levels on the week following the five days of corticosteroids.

Conclusion

Fenofibrate can be an effective way to reduce hypertriglyceridemia secondary to asparaginase in pediatric ALL patients. It should be used after a nonpharmacologic treatment has been tried such as a hypolipidic diet but should not be delayed if the diet required is too restrictive for patients and if doses of asparaginase are delayed or cancelled because of hypertriglyceridemia. We recommend that fenofibrate treatment be initiated at 5 mg/kg/day (micronized) for children under 12 years old and 160 to 200 mg/day (microcoated) for children 12 years old and older. Prospective studies will help document this effect.

Reviewer: None.

Funding: None.

Conflict of interest: Authors declare that they have no conflict of interest.

Références

1. Ridola V, Buonuomo PS, Maurizi P, et al. Severe acute hypertriglyceridemia during acute lymphoblastic leukemia induction successfully treated with plasmapheresis. Pediatr Blood Cancer 2008;50:378-80.
2. Cremer P, Lakomek M, Beck W, et al. The effect of L-asparaginase on lipid metabolism during induction chemotherapy of childhood lymphoblastic leukaemia. Eur J Pediatr 1988;147:64-7.
3. Kfoury-Baz EM, Nassar RA, Tanios RF, et al. Plasmapheresis in asparaginase-induced hypertriglyceridemia. Transfusion 2008;48:1227-30.
4. Parsons SK, Skapek SX, Neufeld EJ, et al. Asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Blood 1997;89:1886-95.
5. Cohen H, Bielorai B, Harats D, et al. Conservative treatment of L-asparaginase-associated lipid abnormalities in children with acute lymphoblastic leukemia. Pediatr Blood Cancer 2010;54:703-6.
6. Keung YK, Rizk R, Wu XY, et al. Drug-induced hypertriglyceridemia with and without pancreatitis. South Med J 1999;92:912-4.
7. Zollner N, Heimstadt P. Effects of a single administration of L-asparaginase on serum lipids. Nutr Metab 1971;13:344-8.
8. Astaldi G, Micu D, Micu M. Effect of L-asparaginase on serum-cholesterol. Lancet 1970;1:1113-4.
9. Yuan G, Al-Shali KZ, Hegele RA. Hypertriglyceridemia: its etiology, effects and treatment. CMAJ 2007;176:1113-20.
10. Dietel V, Buhrdel P, Hirsch W, et al. Cerebral sinus occlusion in a boy presenting with asparaginase-induced hypertriglyceridemia. Klin Padiatr 2007;219:95-6.
11. Hoogerbrugge N, Jansen H, Hoogerbrugge PM. Transient hyperlipidemia during treatment of ALL with L-asparaginase is related to decreased lipoprotein lipase activity. Leukemia 1997;11:1377-9.
12. Tozuka M, Yamauchi K, Hidaka H, et al. Characterization of hypertriglyceridemia induced by L-asparaginase therapy for acute lymphoblastic leukemia and malignant lymphoma. Ann Clin Lab Sci 1997;27:351-7.
13. Halton JM, Nazir DJ, McQueen MJ, et al. Blood lipid profiles in children with acute lymphoblastic leukemia. Cancer 1998;83:379-84.
14. Steinherz PG. Transient, severe hyperlipidemia in patients with acute lymphoblastic leukemia treated with prednisone and asparaginase. Cancer 1994;74:3234-9.
15. Balfour JA, McTavish D, Heel RC. Fenofibrate. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic use in dyslipidaemia. Drugs 1990;40:260-90.
16. Steinmetz J, Morin C, Panek E, et al. Biological variations in hyperlipidemic children and adolescents treated with fenofibrate. Clin Chim Acta 1981;112:43-53.
17. Micromedex® Healthcare Series [database online]. Greenwood Village Colorado. Thomson Reuters (Healthcare) Inc. Updated periodically.
18. Canadian Pharmacists Association. Compendium of pharmaceuticals and specialties. Canadian Pharmacists Association. Edition 2009. Ottawa, Canada.
19. Moghrabi A, Levy DE, Asselin B, et al. Results of the Dana-Farber Cancer Institute ALL Consortium Protocol 95-01 for children with acute lymphoblastic leukemia. Blood 2007;109:896-904.
20. Holcenberg JS, Tutsch KD, Earhart RH, et al. Phase I study of ICRF-187 in pediatric cancer patients and comparison of its pharmacokinetics in children and adults. Cancer Treat Rep 1986;70:703-9.
21. Amin SB, Sinkin RA, McDermott MP, et al. Lipid intolerance in neonates receiving dexamethasone for bronchopulmonary dysplasia. Arch Pediatr Adolesc Med 1999;153:795-800.
22. Dullaart RP, Schols JL, van der Steege G, et al. Glucocorticoid replacement is associated with hypertriglyceridaemia, elevated glucose and higher non-HDL cholesterol and may diminish the association of HDL cholesterol with the -629C>A CETP promoter

polymorphism in GH-receiving hypopituitary patients. Clin Endocrinol 2008;69:359-66.

23. El-Shaboury AH, Hayes TM. Hyperlipidaemia in asthmatic patients receiving long-term steroid therapy. Br Med J. 1973;2:85-6.