Nephrol Dial Transplant (2000) 15: 1993–1999

Nephrology
Dialysis
Transplantation

Original Article

Fibrate-induced increase in blood urea and creatinine: is gemfibrozil the only innocuous agent?

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Abstract

Background. Some reports indicate that fibrates can induce renal dysfunction. However, the clinical characteristics of these episodes, and the respective nephrotoxicity of the four main fibrates used—namely, fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil—remain ill defined.

Methods. To better characterize this side-effect, we first reviewed the charts of 27 patients from our institution who developed an impairment of renal function during fibrate therapy. We next analysed the articles ($n=24$) that contained data on renal function in patients taking fibrates ($n=2676$).

Results. Among our 27 patients, 25 were on fenofibrate therapy, one was taking bezafibrate, and one ciprofibrate. Nineteen were recipients of solid-organ transplants (kidney recipients, $n=15$; heart or heart-lung recipients, $n=4$), and eight were non-transplanted patients with some impairment of renal function. Baseline plasma creatinine ranged from 0.9 to 2.9 mg/dl. It increased by a mean of 40% after the start of fibrate therapy. There was a concomitant increase of blood urea values (mean 36%) in most of the patients. Renal function returned to baseline in 18/24 patients after fibrate discontinuation. However, six patients, all transplant recipients, experienced a permanent increase in plasma creatinine. The incidence of fibrate-induced renal dysfunction among our series of kidney transplant recipients was 60%, as it occurred in 15 of the 25 patients who had ever taken fibrates. An increase of mean creatinine values during therapy was described in all papers on fenofibrate ($n=7$) and bezafibrate ($n=8$) (range 8–18% and 8–40% respectively), and in three of four papers dealing with ciprofibrate (range 6–16%). No significant renal impairment was described in any of the eight articles reporting data on gemfibrozil therapy.

Conclusion. Therapy with fenofibrate, bezafibrate, and ciprofibrate may induce renal dysfunction. Gemfibrozil appears to be devoid of this side-effect.

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Keywords: creatinine; fibrate; gemfibrozil; literature review; transplantation; urea

Introduction

Hypercholesterolaemia and hypertriglyceridaemia are important risk factors for the development of atherosclerosis [1–3]. Lipid-lowering drugs are therefore frequently prescribed among the general population. Hypolipaemic agents are also often administered to patients suffering from chronic nephropathies [4], as well as in transplanted patients treated by cyclosporin or corticosteroids. Indeed, these conditions are associated with an increased incidence of hyperlipidaemia [5,6]. While the statins are mainly effective in decreasing cholesterol levels, the fibrates are more potent in reducing serum triglyceride levels [7]. The main side-effects of fibrates are gastrointestinal and muscular [8]. Some reports also indicate that these drugs may lead to a decrease in renal function [9–24]. The clinical characteristics of these episodes, and the respective nephrotoxicity of the four main fibrates used, namely, fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil, remain however, ill-defined. The occurrence of several episodes of significant renal dysfunction in patients under fibrate therapy at our institution led us to review our experience as well as the literature on this topic.

Subjects and methods

We reviewed retrospectively the charts of the 27 patients from our centre who had experienced an episode of renal dysfunction attributed to fibrate therapy. This complication occurred in non-transplanted patients ($n=8$); in patients transplanted with a heart or a combined heart-lung graft ($n=4$); and in 15 recipients of renal allografts. In order to evaluate the incidence of fibrate-induced rise in plasma creatinine, and in an effort to identify risk factors for this complication, we searched within our renal transplant database for patients who took fibrates without renal side-effects. Ten such patients were identified in addition to the 15 described above. The diagnosis of fibrate-induced renal dys-

Table 1. Non-transplant patients

	1	2	3	4	5	6	7	8
Age/gender	56/F	55/M	71/F	55/M	36/M	66/M	58/M	63/M
P creat (mg/dl)								
before fibrate	1.1	1.2	1.4	1.5	1.5	1.5	1.7	1.8
during fibrate	1.4	1.6	1.9	2.0	2.2	1.8	2.3	2.6
Δ P creat (%)	27	33	36	33	50	20	35	44
Δ P urea (%)	45	100	NA[a]	36	NA	0	47	NA
Dose of fibrate (mg/day)	100	200	200	200	UNK[b]	200	UNK	200
Fibrate used	Ciprofibrate	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate	Fenofibrate
Time to renal dysfunction	3 months	1 month	1 month	4 months	3 months	3 months	UNK	4 months
Reversibility	Complete	Treatment ongoing	Complete	Complete	Complete	Complete	Complete	Treatment ongoing

[a]NA, not available; [b]UNK, unknown.

function was made when the following conditions were met: (i) plasma creatinine increased by at least 0.2 mg/dl over basal values; (ii) the renal dysfunction was temporally related to the initiation of fibrate therapy; (iii) no new nephrotoxic agents such as non-steroidal anti-inflammatory drugs, angiotensin-converting enzyme inhibitors, angiotensin-II receptor antagonists, or nephrotoxic antibiotics had been initiated during that period; (iv) there was no other obvious cause of renal dysfunction; and (v) renal dysfunction improved after fibrate discontinuation. Patients meeting these criterias ($n=27$) were referred by the clinics of nephrology, as well as from the renal, cardiac, or lung transplant departments. Blood creatinine and urea determinations were performed by Jaffe kinetics and urease pseudokinetics respectively.

For the literature review, we screened the US National Library of Medicine (Medline) from 1975 until November 1999 with the following keywords in various combinations: fibrate, fenofibrate, bezafibrate, ciprofibrate, gemfibrozil, renal (or kidney) failure, and transplantation. In addition, any relevant reference quoted in the papers retrieved was also examined.

Results

Patients with fibrate-induced nephrotoxicity seen at our institution

The eight non-transplant patients had normal or only mildly impaired renal function at baseline (range of plasma creatinine 1.1–1.8 mg/dl) (Table 1). Seven received fenofibrate and one ciprofibrate. Plasma creatinine increased by a mean of 35% (range 20–50%) during fibrate therapy. Plasma urea increased in four of five patients in whom it was measured. Renal dysfunction was noted 1–4 months after the initiation of fibrate therapy. It was fully reversible in the six patients in whom it was discontinued.

The nephrotoxic effect of fenofibrate has been observed in three heart and one heart-lung transplant recipients (Table 2). They had been transplanted 2–9 years previously. They were on CsA therapy, and all exhibited some degree of CsA-induced chronic renal dysfunction. The mean plasma creatinine level at baseline was 2.4 mg/dl (range 1.6–2.9). It increased by a mean of 88% (range 58–150%) during fibrate therapy. All patients also experienced an increase of plasma urea. The renal dysfunction was noted 1–3 months after the start of fenofibrate treatment. One patient developed acute renal failure that required haemodialysis for 10 days. He recovered completely after fibrate discontinuation. However, two patients experienced a persistent decrease of renal function. CsA blood concentrations showed a decrease during fenofibrate therapy (Table 2).

Table 2. Heart or heart-lung transplant recipients

	9	10	11	12
Age/gender	62/M	35/M	71/M	63/M
P creat (mg/dl)				
before FNF[a]	1.6	2.5	2.6	2.9
during FNF	4.0	HD[d]	4.1	4.7
Δ P creat (%)	150	80	58	62
Δ P urea (%)	160	22	37	19
Dose of FNF (mg/day)	200	200	200	200
Time to renal dysfunction (months)	3	1	1	1
Transplant	Heart	Heart + Lung	Heart	Heart
Primary immunosuppression	CsA[b]	CsA	CsA	CsA
Mean CsA level (ng/ml)				
1 month before FNF	118	252	62	120
during FNF	66	131	NA[c]	84
Time from transplantation to FNF treatment (years)	7	2	9	9
Reversibility	Partial	Complete	Partial	Complete
If partial, P creat (mg/dl)	2.6		3.7	

[a]FNF, fenofibrate; [b]CsA, cyclosporin A; [c]NA, not available; [d]HD, haemodialysis was needed for 10 days. Dialysis was started when P creat was 4.5 mg/dl; therefore this value was taken into account for the calculations of the means.

Fifteen kidney transplant recipients developed fibrate-induced nephrotoxicity (Table 3). One was taking bezafibrate; the 14 other patients were on fenofibrate therapy. The number of patients taking azathioprine, sirolimus, and CsA as the primary immunosuppressive drug was two, two, and 11 respectively. Mean plasma creatinine before fibrate therapy was 1.5 mg/dl (range 0.9–2.2). It increased during fibrate administration up to a mean of 1.9 mg/dl (mean increase 31%; range 14–67%). Among the 14 patients who received

Table 3. Kidney transplant recipients

	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27
Age/gender	57/F	48/F	59/M	52/F	59/F	51/F	49/F	40/M	50/F	37/M	51/M	36/M	51/F	33/M	44/M
P creat (mg/dl)															
before fibrate	0.9	1.1	1.2	1.2	1.2	1.3	1.4	1.4	1.4	1.5	1.7	1.7	1.8	1.9	2.2
during fibrate	1.2	1.4	1.5	1.8	1.9	1.5	1.6	1.6	1.9	2.3	2.0	2.2	3.0	2.2	2.6
Δ P creat (%)	33	21	25	50	58	15	14	14	36	53	18	30	67	14	18
Δ P urea (%)	9	16	32	38	67	18	4	39	20	0	7	26	85	10	32
Fibrate used	FNF	FNF	FNF	FNF	FNF	FNF	FNF	FNF	FNF	FNF	FNF	FNF	BZF	FNF	FNF
Dose of fibrate (mg/day)	100	200	200	200	200	100	200	200	100	200	200	200	200	200	100
Primary IS	CsA	CsA	CsA	AZA	CsA	CsA	CsA	CsA	CsA	SRL	CsA	SRL	AZA	CsA	CsA
Mean CsA level (ng/ml)															
1 month before fibrate	146	125	157		195	170	131	120	160		170			183	122
during fibrate	190	104	139	—	165	145	106	170	131	—	70	—	—	185	119
Time from transplantation to fibrate treatment	6 m	4 y	1 y	23 y	2 y	1 y	8 m	6 m	6 m	6 m	1 y	2 m	18 y	10 m	2 y
Time to renal dysfunction	15 days	2 m	1 m	5 m	3 m	UNK	3 m	UNK	1 m	1 m	15 days	15 days	2 m	7 days	1 m
Reversibility	Compl	Compl	Compl	Partial	Partial	Compl	Compl	TO	Compl	Partial	Compl	Compl	Partial	Compl	Compl
if partial, P creat (mg/dl)				1.4	1.5					2.0			2.5		
Time to reversibility	2 m	3 m	1 m	15 d	1 m	1 m	15 d	NA	21 d	1 m	1 m	1 m	3 m	1 m	15 d

TO, treatment ongoing; FNF, fenofibrate; BZF, bezafibrate; IS, immunosuppression; CsA, cyclosporin A; SRL, sirolimus; AZA, azathioprine; UNK, unknown; Compl, complete.

fenofibrate, four were on 100 mg/day and 10 were on 200 mg/day dosage. Both baseline mean plasma creatinine (mg/dl) (1.45 ± 0.54, 100 mg/day; *vs* 1.43 ± 0.27, 200 mg/day) as well as values observed during therapy (1.80 ± 0.61, 100 mg/day; *vs* 1.85 ± 0.32, 200 mg/day) were not significantly different between the groups. Blood urea increased by 20% or more in 8/15 patients. Renal dysfunction was observed 15 days to 5 months after the initiation of fibrate therapy. In 10 patients, plasma creatinine returned to baseline values, attained between 15 days and 3 months after fibrate discontinuation. Plasma creatinine remained permanently increased after the withdrawal of the drug in four patients. CsA levels decreased during fibrate therapy in eight of 11 patients (Table 3). A renal biopsy was performed during fibrate therapy in two of the 15 renal transplant recipients (patients No. 15 and 17); there was no lesion on histology.

In order to evaluate the incidence of fibrate-induced rise in plasma creatinine, we searched within our renal transplant database for patients who had ever taken fibrates. Ten such patients were identified in addition to the 15 described above. All were taking fenofibrate, and none developed increases of urea or creatinine (mean plasma urea (mg/dl) 53.2 ± 16.8 before *vs* 49.9 ± 17.9 during fibrate therapy, $P = \text{NS}$; mean plasma creatinine (mg/dl) 1.32 ± 0.30 before *vs* 1.32 ± 0.32 during fibrate therapy, $P = \text{NS}$). A comparison between these 10 patients and the 15 patients in whom an increase in urea or creatinine occurred revealed no difference in age, sex ratio, plasma creatinine at the initiation of fibrate therapy, type and dose of the fibrate used, proportion of patients on CsA, mean CsA levels before and during fibrate therapy, or time from transplantation to fibrate therapy (Table 4).

When data from heart, heart-lung, and kidney transplant recipients on CsA therapy were pooled ($n = 14$), it appeared that CsA levels decreased during fibrate therapy (mean levels: 129 ± 40 ng/ml (SD) *vs* 155 ± 38 before; $P = 0.045$ by unpaired Student's *t*-test). This was previously observed by others [10,12,25], and is related to the induction of cytochrome P 450 activity by fibrates [26].

Analysis of data from all 27 patients (non-transplant and those with a heart, heart-lung, or kidney transplant) revealed a strong correlation between the increases in plasma creatinine and urea ($n = 24$; $r = 0.7$, $P = 0.0001$). There was no correlation between baseline plasma creatinine and the percentage increase of plasma creatinine that occurred during fibrate therapy ($n = 27$; $r = 0.29$; $P = 0.14$).

No patient had symptoms of myositis or displayed increased creatine-phosphokinase levels.

Table 4. Kidney transplant recipients

Patient characteristics	Rise of plasma creatinine after fibrate therapy		*P*
	Yes	No	
n	15	10	—
Mean age[a]	48 ± 8	42 ± 11	NS
Gender	7 M/8 F	5 M/5 F	NS
Mean Pcreat before fibrate (mg/dl)	1.46 ± 0.34	1.32 ± 0.30	NS
Mean Pcreat during fibrate (mg/dl)	1.91 ± 0.49	1.32 ± 0.32	0.0025
Fibrate used (fenofibrate/bezafibrate[b])	14/1	10/0	NS
Patients receiving 100/200 mg/day fenofibrate (*n*)	4/10	6/3[c]	NS
Primary immunosuppression[d]	11 CsA/2 Srl/2 Aza	6 CsA/4 Aza	NS
Mean CsA level (ng/ml)			
1 month before fibrate	153 ± 26	144 ± 51	NS
during fibrate	139 ± 37	144 ± 51	NS
Mean time from transplantation to fibrate treatment	3.7 ± 6.9 years	8.3 ± 6.1 years	NS

[a]Data are mean $\pm$ SD; [b]dose of bezafibrate, 200 mg/day; [c]dose of fenofibrate was unknown in one patient; [d]CsA, cyclosporin A; Srl, sirolimus; Aza, azathioprine.

Review of the literature (Table 5)

We examined papers giving data about plasma creatinine and urea in patients treated with either fenofibrate, bezafibrate, ciprofibrate, and gemfibrozil. Glomerular filtration rate and creatinine clearance was mentioned in only one of these papers [24]. Some articles gave only qualitative estimations, reporting plasma creatinine or urea as showing 'no increase' or 'slight increase' during therapy [7,18,27–31]. The majority of papers gave quantitative data on the mean values for creatinine and sometimes urea at baseline and during therapy. For clarity, we calculated the percentage increase in creatinine and urea that occurred during therapy. The statistical significance of these changes was given in the articles and is indicated in Table 5. The primary aim of these papers was either efficacy at reducing blood lipids [7,10,12–15,17–22,27–29,31–33] or albuminuria [30], or the report of adverse events occurring during therapy [9,16,23,24]. The articles dealt with hyperlipaemic patients belonging to either the general population, which had normal renal function [7,9,13,14,17–23,30,31]; patients with various degree of renal impairment, as defined by plasma creatinine $\geqslant 1.3$ mg/dl (referred here as chronic renal failure (CRF)) [15,24,27,28,32]; or patients transplanted with kidneys or hearts. In the latter two groups, the mean plasma creatinine at baseline was always elevated [9–12,16,29,33]. An increase of creatinine was observed in the 14 studies reporting the effects of either fenofibrate or bezafibrate, and in three of four papers dealing with ciprofibrate. The range of the mean creatinine increase was 8–18% with fenofibrate, 8–40% with bezafibrate, and 6–16% with ciprofibrate. The increase of creatinine was observed in patients with normal function [13,14,17–23], in patients with impaired renal function [15,24], and in transplant recipients [9–12,16]. When reported, the increase of urea paralleled that of creatinine. When mentioned, the alteration of renal function was reversible in all studies after withdrawal of the drug.

Table 5. Review of the literature and this study

Fibrate used	Reference	Aim of the study	Daily dose of fibrate (mg/day)	Transplant status	Baseline renal function[a]	Patients (*n*)	CsA[b]	Initial P creat (mg/dl)	Variation during fibrate therapy		Reversibility
									Creat (%)	Urea (%)	
Fenofibrate	23	Adverse event	200	—	NL	10	—	0.87	+16**	NR[c]	NR
	22	Efficacy	300	—	NL	21	—	0.88	+8**	+9***	NR
	13	Efficacy-safety	200	—	NL	56	—	0.99	+11***	NR	Yes
	19	Efficacy-safety	300	—	NL	41	—	1.10	+12***	NR	NR
	Present cases	Adverse event	200	—	NL/CRF	7	—	1.51	+36***	NR	Yes
	24	Adverse event	200	—	CRF	13	—	1.66	+16*	+13*	NR
	Present cases	Adverse event	200[d]	RT	CRF	24	+[e]	1.39	+17****	+16	Partial[f]
	11	Pharmacokin.	200	HT	CRF	10	+	1.64	+8**	NR	NR
	10	Efficacy-safety	200	HT	CRF	43	+	1.93	+18**	NR	Yes
	Present cases	Adverse event	200	HT or HLT	CRF	4	+	2.40	+88	+60	Partial[g]
Bezafibrate	23	Adverse event	400	—	NL	10	—	0.87	+8 (NS)	NR	NR
	14	Efficacy	600	—	NL	26	—	0.95	+9***	+15**	NR
	18	Efficacy	600	—	NL	14	—	NR	Slight increase[h]	NR	NR
	17	Efficacy	600	—	NL	22	—	1.07	+21*	+20*	Yes
	15	Efficacy	200	—	CRF	9	—	5.92	+17**	+39**	Yes
	9	Adverse event	400	RT	NL	2	+	1.19	+32	+22	Yes
	16	Adverse event	800	RT	CRF	1	+	2.50	+40	+43	Yes
	Present case	Adverse event	200	RT	CRF	1	—	1.80	+67	+85	Partial
	12	Efficacy-safety	400	HT	CRF	43	+	1.58	+26***	No increase[h]	NR
Ciprofibrate	31	Efficacy	50–100	—	NL	16	—	NR	No increase[h]	No increase[h]	—
	22	Efficacy	100	—	NL	20	—	0.87	+16***	+5*	NR
	20	Efficacy-safety	100–200	—	NL	102	—	1.01	+6**	NR	NR
	21	Efficacy	100	—	NL	30	—	1.01	+9*	NR	Yes
	Present case	Adverse event	100	—	NL	1	—	1.10	+27	+45	Yes
Gemfibrozil	7	Efficacy	1200	—	NL	2051	—	NR	No increase[h]	NR	—
	30	Other[i]	1200	—	NL	7	—	0.94	No increase[h]	NR	—
	27	Efficacy	1200	—	CRF	11	—	1.54	No increase[h]	NR	—
	32	Efficacy	600	—	CRF	28	—	2.12	−10 (NS)	NR	—
	28	Efficacy	1200	—	CRF	18	—	3.96	No increase[h]	NR	—
	9	Adverse event	600	RT	CRF	22	+	1.63	−3 (NS)	NR	—
	33	Efficacy	NR	RT	CRF	12	NR	1.80	+11 (NS)	NR	—
	29	Efficacy	300–1200	RT	CRF	38	+	1.82	No increase[h]	NR	—

HT, heart transplant; HLT, heart–lung transplant; RT, renal transplant; [a]NL: normal renal function; CRF, chronic renal failure; [b]Patients were (+) or were not (—) on CsA therapy. [c]NR, not reported. [d]Ten patients received 100 mg of fenofibrate; the dose was unknown in one patient. [e]17 of the 24 patients were on CsA. [f]The reversibility was partial in four patients and complete in the others. [g]The reversibility was partial in two patients. [h]Values are said to show 'no' or 'slight' increases but data are not given. [i]This paper investigated the efficacy on microalbuminuria of diabetes. *$P<0.05$; **$P<0.01$; ***$P<0.001$; ****$P<0.0001$.

In contrast, none of the eight papers dealing with gemfibrozil reported a significant alteration of renal function, whether the patients had normal or impaired renal function at baseline, and whether they were transplanted or not [7,9,27–30,32,33].

Discussion

The first conclusion from this work is that fenofibrate, bezafibrate, and ciprofibrate may lead to an increase of serum creatinine. The increase in blood urea, when reported in the articles reviewed, was in the same range as that of creatinine. Similarly, in our patients, we observed a close correlation between the increases of creatinine and urea. Likewise, other molecules that are excreted by the kidneys, such as cystatine C and homocysteine, were also found to increase after fibrate therapy [23]. This suggests that these fibrates induce a reduction in glomerular filtration rate. Fibrates impair the generation of vasodilatory prostaglandins both *in vitro* and *in vivo*, a process which may obviously contribute to renal function impairment [34,35]. Notably, however, isotopic measures of renal blood flow and glomerular filtration rate remained unchanged after 2 weeks of treatment with fenofibrate [24], so that the definitive pathophysiology of fibrate-induced increase of urea and creatinine remains to be fully elucidated.

Our literature search revealed that all papers examining serum creatinine in patients given either fenofibrate or bezafibrate reported an increase of mean creatinine values during therapy. Likewise, ciprofibrate therapy also led to increased serum creatinine in three of four articles. The increased creatinine levels were observed in patients with normal as well as in those with impaired basal renal function, and in transplanted as well as in non-transplanted patients. The range of mean plasma creatinine increase reported was 8–18% with fenofibrate, 8–40% with bezafibrate, and 6–16% with ciprofibrate. As these figures represent only the mean increase observed for the whole patient population in each paper, it is likely that some patients experienced a much greater creatinine increase. Indeed, about one-third of our cases under fibrate therapy experienced an increase of creatinine greater than 50%. Moreover, one patient of our series required transient haemodialysis.

Like others [10,12,25], we observed a decrease in cyclosporin blood levels during fibrate therapy. It is, however, unlikely that the rise of urea and creatinine values in our series of renal transplant recipients was due to rejection triggered by low CsA concentrations. Firstly, the degree of CsA trough level reduction was small. Second, a kidney graft biopsy was performed in two patients. Histological examination was essentially normal.

In our series, the mean time period before the occurrence of fibrate-induced renal dysfunction was 1.9 months. However, part of this delay might be related to the interval at which creatinine was measured. Indeed, in some patients, the increase of serum creatinine was observed within 1 week after the initiation of fibrate therapy. While reversibility always occurred after fibrate discontinuation in non-transplanted patients, both in our series and in the literature, some of our transplanted patients experienced a persistent renal impairment. At present, the incidence of fibrate-associated nephrotoxicity among non-transplanted patients with normal renal function at baseline is still unknown. Indeed, none of the cohort studies mention the percentages of patients in whom creatinine increased to abnormal levels. This event, however, appears to be frequent in kidney-transplant recipients as it developed in more than half of the patients on fibrate therapy in our series. Why nephrotoxicity developed in some patients but not in others is unclear at present; there was no influence of the dose of fenofibrate taken (100 or 200 mg/day) on either the risk or the magnitude of the fibrate-induced rise in creatinine. Most of these patients were on cyclosporin therapy, and one could speculate that cyclosporin may enhance the susceptibility to develop fibrate-induced increase of urea and creatinine.

It appears from the literature review that gemfibrozil, in contrast to fenofibrate, bezafibrate, and ciprofibrate, has not been reported to cause renal dysfunction. This favourable profile was observed in all categories of patients, whether they had normal or impaired renal function, and whether they were recipients of a kidney transplant or not. One of the hypotheses that may account for the absence of nephrotoxic effects of gemfibrozil might be the fact that this molecule, in contrast to the other fibrates, fails to bind and activate peroxisome proliferator-activated receptors [36]. Indeed, these nuclear receptors, once bound by fibrates, down-regulate the expression of the inducible COX-2 enzyme [34,35], which may be critical for the maintenance of vasodilatory prostaglandins within the kidneys. In support of this hypothesis, clofibrate and ciprofibrate, but not gemfibrozil, did inhibit the production of vasodilatory prostaglandins [35,37].

On practical grounds, what attitude could be proposed for patients who need fibrate therapy? In patients with normal renal function, it is probably wise to check plasma urea and creatinine concentrations some weeks after the initiation of fibrate therapy. If renal dysfunction occurs, and is considered troublesome, changing the patient from fenofibrate, bezafibrate, or ciprofibrate to gemfibrozil seems worth the trial. In patients with various degrees of renal dysfunction, gemfibrozil might be the fibrate of choice, in order to avoid a possible worrying further increase of urea and creatinine. Finally, it seems reasonable to discourage the administration of fenofibrate, bezafibrate, or ciprofibrate to kidney-transplant recipients. Firstly, a decrease in renal function in these patients always raises the suspicion of a rejection episode, often leading to diagnostic procedures that may culminate in a renal biopsy. Second, some kidney-transplant recipients may experience an irreversible impairment of graft function after fenofibrate or bezafibrate therapy.

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Received for publication: 14.12.99
Accepted in revised form: 22.6.00