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Drug-Induced Lipid Changes

A Review of the Unintended Effects of Some Commonly Used Drugs on Serum Lipid Levels

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Contents

Abstract

Many drugs besides lipid-lowering drugs affect serum lipid levels in either a potentially harmful or beneficial way, and may therefore increase or decrease the risk of cardiovascular disease.

Diuretics, β-blocking agents, progestogens, combined oral contraceptives containing 'second generation' progestogens, danazol, immunosuppressive agents, protease inhibitors and enzyme-inducing anticonvulsants adversely affect the lipid profile. They increase total cholesterol, low density lipoprotein cholesterol and triglycerides by up to 40, 50 and 300%, respectively, and decrease high density lipoprotein cholesterol by a maximum of 50%. Conversely, α-blocking agents, estrogens, hormone replacement therapy, combined oral contraceptives containing 'third generation' progestogens, selective estrogen receptor modulators, growth hormone and valproic acid show mostly beneficial effects on the lipd profile. Some drugs, for example, isotretinoin, acitretin and antipsychotics, mainly elevate triglyceride levels.

Adverse or beneficial effects on serum cholesterol levels do not always translate into a higher or lower, respectively, incidence of cardiovascular disease, because these drugs may influence cardiovascular risk through multiple pathways. In some cases, excessive cholesterol levels occur, for example, with protease inhibitor therapy, and several cases of pancreatitis attributable to drug-induced hypertriglyceridaemia have been reported.

Some general guidelines on the management of drug-induced dyslipidaemia can be given. Replacement of the dyslipidaemia-inducing drug by an equivalent alternative therapy is preferred. However, such alternatives are often difficult to find. If there is no equivalent alternative and treatment with the dyslipidaemia-inducing drug must be initiated, monitoring of serum lipid levels is important. If drug use is expected to be long term, the existing guidelines for the management of dyslipidaemia in the general population can be applied to drug-induced dyslipidaemia. In cases of extreme hyperlipidaemia, medication use should be reassessed.

Hypercholesterolaemia is a well established risk factor for atherosclerosis, leading to cardiovascular, cerebrovascular and peripheral vascular morbidity and mortality. Serum lipid levels can be affected by many factors including drug therapy, both positively as well as negatively. These drugs may therefore also decrease or increase the risk of cardiovascular morbidity and mortality.

In this paper we review the effects of several important drug classes (besides lipid-lowering drugs) on serum lipid levels and the implications for clinical practice associated with their use. We describe the magnitude of their effects derived from data from randomised clinical studies and some observational studies (table I). The mechanisms of drug-induced dyslipidaemias are beyond the scope of this review and will not be discussed.

1. Cardiovascular Drugs

The effects of antihypertensive drug therapies on serum lipid levels are well documented by the results from randomised clinical trials and observational studies. Kasiske et al.[1] performed a meta-analysis of 474 studies (66% randomised, 25% observational) conducted between 1966 and 1993. A more recent editorial in the *Archives of Internal Medicine* shows that there is still much debate about antihypertensives, lipids and clinical implications.[2]

Thiazide diuretics increase serum total cholesterol and low density lipoprotein (LDL)-cholesterol levels by up to 5 to 10%.[1,3-7] High density lipoprotein (HDL)-cholesterol levels are not affected, whereas triglyceride concentrations are also elevated by 5 to 15%. All these effects were largest with higher dosages (50 to 100 mg/day).[1] In contrast with older studies,[4] Lakshman et al.[7] showed recently that these effects are short term; after 1 year of treatment, elevated serum lipid levels returned to their initial levels. Loop diuretics affect serum cholesterol levels in a similar way and magnitude as thiazide diuretics.[8-10] Weidmann et al.[4] reviewed the effects of potassium-sparing diuretics on the lipid profile. The effects of monotherapy with one of these agents are largely unknown. Combinations of a thiazide diuretic with a potassium-sparing diuretic show effects similar to the effects of monotherapy with a thiazide diuretic. This implies no effects of potassium-sparing diuretics on serum lipid levels. Indapamide does not significantly influence serum lipid levels.[1,5,11]

The effects of β-blocking agents on serum total cholesterol or LDL-cholesterol levels are negligible. However, they increase triglyceride levels (10 to 40%) and decrease HDL-cholesterol levels by about 5 to 20%.[1,3,6,12] One study showed that these effects on HDL-cholesterol lasted less than 1 year,[7] whereas others reported elevated levels even after several years of treatment.[1,12] Furthermore, increasing intrinsic sympathomimetic activity and β_1-selectivity are associated with a more neutral

Table I. Direction and magnitude of changes in serum lipid levels induced by different drug classes. Changes are percentage increases (↑) or decreases (↓)

Drug class	Total cholesterol	LDL-cholesterol	HDL-cholesterol	Triglycerides
Cardiovascular drugs				
Diuretics				
thiazide diuretics	↑ 5 to 10	↑ 5 to 10	NC	↑ 5 to 15
loop diuretics	↑ 5 to 10	↑ 5 to 10	NC	↑ 5 to 10
potassium-sparing diuretics	NC	NC	NC	NC
indapamide	NC	NC	NC	NC
β-Blockers	NC	NC	↓ 5 to 20	↑ 10 to 40
celiprolol	↓ 0 to 10	↓ 0 to 20	↑ 3 to 40	↓ 5 to 25
ACE inhibitors	NC	NC	NC	↑ (?)
Calcium antagonists	NC	NC	NC	NC
α-Blockers	↓ 5	↓ 5	↑ 2 to 5	↓ 4 to 14
Hormones				
Unopposed estrogens	↓ 2 to 10	↓ 7 to 20	↑ 5 to 20	↑ 40
Unopposed progestogens				
C_{21}-steroids	NA	↑	↓	↓
C_{19}-steroids	NA	↑ 6 to 13	↓15 to 30	↓ 20
Hormone replacement therapy	↓ 10	↓ 20	↑/NC/↓	↑/NC/↓
Combined oral contraceptives with:				
second generation progestogens	NA	↑ 10	↓ 0 to 15	↑ 50
third generation progestogens	NA	↓ 0 to 15	↑ 10 to 15	↑ 75
Selective estrogen receptor modulators				
tamoxifen	↓ 13	↓ 17	NC	↑ 0 to 30
raloxifene	↓ 5 to 10	↓ 10 to 20	NC	NC
Danazol	NA	↑ 10 to 40	↓ 50	NC
Growth hormone	↓ 5 to 15	↓ 10 to 25	↑ 7/↓ 20	NC
Retinoids				
Synthetic				
isotretinoin	↑ 15	↑ 15	NC/↓	↑ 35 to 144
acitretin	NC	NA	NC	↑ 60
Vitamin A	NC	NC	NC	NC
Immunosuppressive drugs	↑ 10 to 40	↑ 0 to 50	↑ 0 to 90	↑ 0 to 70
Protease inhibitors				
Ritonavir	↑ 30 to 40	NA	NC	↑ 200 to 300
Indinavir/nelfinavir	↑ 15 to 30	NA	NC	↑ 0 to 55
Saquinavir	NC	NC	NC	NC
Antipsychotics				
Clozapine	NC	NC	NC	↑ 35 to 48
Other	NC	NC	NC	↑ 0 to 51
Anticonvulsants				
Carbamazepine	↑ 0 to 15	NA	↑ 0 to 30/↓ 40	NC
Phenytoin/phenobarbital	↑ 5 to 15	NA	↑ 45/↓ 40	NC
Valproic acid	↓ 5 to 20	NA	NA	NC

HDL = high density lipoprotein; **LDL** = low density lipoprotein; **NA** = not available; **NC** = no change.

effect. Celiprolol, a selective β_1-blocker with weak β_2-sympathomimetic activity, even improves the lipid pattern.[3,13]

ACE inhibitors do not affect levels of the cholesterol fractions in patients without diabetes mellitus, but may decrease triglyceride levels,[1] although some reviews report no effect.[6,12] In patients with type 2 diabetes mellitus, Ravid et al.[14] observed a decrease in total cholesterol and LDL-cholesterol levels (5 and 7%, respectively) after ACE inhibitor therapy. HDL-cholesterol and triglyceride levels remained unchanged. These effects of ACE inhibitors may at least partly be attributed to the decline in albuminuria. Calcium antagonists do not affect the lipid profile.[1,6,12]

The only antihypertensive agents with beneficial effects on lipid levels are α_1-blocking agents. They lower total cholesterol and LDL-cholesterol levels (by approximately 5%) as well as triglyceride levels (by 4 to 14%).[1,6,7,12] Furthermore, they elevate the HDL-cholesterol level slightly (by 2 to 5%).

There are only a few population-based studies focusing on the effects of antihypertensive drug therapy on serum lipid levels.[15-17] These studies were mainly cross-sectional and showed no effects on total cholesterol levels and a decrease in HDL-cholesterol levels by 5 to 10%. However, in most studies, no distinction was made between the different antihypertensive drug classes[15,16] and some studies used patients with untreated hypertension and patients with normal blood pressure as a reference group.[15] This approach may lead to biased comparisons, since hypertension itself is associated with higher total cholesterol levels and lower HDL-cholesterol levels.[18]

Despite the potential negative effects of thiazide diuretics and β-blocking agents on the lipid profile, these drugs are effective in reducing cardiovascular morbidity and mortality. Both antihypertensives decrease the incidence of stroke and congestive heart failure. Low dose diuretic therapy also prevents coronary disease and reduces total mortality.[19] In patients with type 2 diabetes mellitus, atenolol proved to be as effective as captopril in reducing the risk of fatal and nonfatal macrovascular and microvascular complications despite its negative effects on bodyweight gain and higher glycated haemoglobin levels over the first 4 years.[20] In this study, serum lipid levels were not negatively affected by atenolol.

Recently, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), the doxazosin treatment arm was discontinued. Patients in the doxazosin group had a higher risk of congestive heart failure [4-year relative risk (RR) 2.04; 95% confidence interval (CI) 1.79 to 2.32], stroke (RR 1.19; 95% CI 1.01 to 1.40) and combined cardiovascular diseases (RR 1.25; 95% CI 1.17 to 1.33) compared with patients treated with the diuretic chlorthalidone.[21] These data suggest that beneficial effects on serum lipid levels from α_1-blocking agents do not translate into a lower incidence of cardiovascular diseases compared with thiazide diuretics.

2. Hormones

2.1 Unopposed Estrogens and Progestogens

Unopposed estrogens beneficially affect the lipid profile, mainly by lowering total cholesterol and LDL-cholesterol levels (by 2 to 10% and 7 to 20%, respectively) and elevating HDL-cholesterol levels (by 5 to 20%).[22-27] However, they also elevate triglyceride levels up to 40%. The effects on triglyceride levels are dose-dependent.[24] All effects depend on the type of estrogen: the synthetic estrogen ethinylestradiol has a stronger beneficial effect than do natural estrogens.[22] Estrogen implants show the same but weaker pattern on total cholesterol, LDL-cholesterol and HDL-cholesterol levels, although a reversal of the beneficial effect on HDL-cholesterol has also been reported.[27,28] Transdermal estrogens show almost no effects on serum lipid levels.[24,27,29]

Besides natural progesterone, several synthetic progestogens exist. These progestogens are either natural progestogen derivatives (C_{21} steroids) or testosterone derivatives (C_{19} steroids) with progestogenic activity. When used alone, high doses of

19-nortestosterone derivatives (e.g. norethisterone) decrease triglyceride levels by 20% and HDL-cholesterol levels by 25 to 30% and elevate LDL-cholesterol levels by 6 to 13%.[30,31] Low doses, as used in progestogen-only contraceptive pills, show no significant effects[32,33] and depot formulations only lower HDL-cholesterol (by 12 to 30%).[34,35]

Natural progesterone and its derivatives (medroxyprogesterone, medrogestone and dydrogesterone) show qualitatively similar, but weaker, effects on serum lipid levels.[30] Depot medroxyprogesterone mainly affects HDL-cholesterol, which is decreased by 15 to 30%.[34,36,37]

2.2 Combined Hormone Replacement Therapy

Hormone replacement therapy is mainly prescribed to relieve menopausal symptoms and prevent osteoporosis. The administration of unopposed estrogens to postmenopausal women has been shown to increase the risk of endometrial carcinoma. The addition of progestogens is therefore widespread, especially in women with an intact uterus. However, some of the beneficial effects of unopposed estrogens on the lipid profile might be diminished or even reversed by these progestogens.

Estrogen/progestogen regimens have similar effects on total cholesterol levels and LDL-cholesterol levels as unopposed estrogens.[22-24,26,27] The effects on HDL-cholesterol levels, however, are weakened (combinations with medroxyprogesterone or dydrogesterone) or even reversed (mainly combinations with norethisterone). Reports of their effects on triglyceride levels are inconsistent: increases,[22,23,25,26] no effects[23,27] and decreases[22] have been reported.

A meta-analysis of observational studies on the association between postmenopausal estrogens and coronary heart disease showed a protective effect of this therapy (RR 0.56, 95% CI 0.50 to 0.61).[38] However, this effect could be attributable to the 'healthy cohort effect'; women who receive a prescription for hormone replacement therapy might be healthier, or more determined to stay so, than women who forgo this therapy.[39] A recent randomised trial showed that treatment with hormone replacement therapy did not reduce the overall rate of coronary heart disease in postmenopausal women with established coronary disease (RR 0.99, 95% CI 0.80 to 1.22), despite positive effects on the lipid profile.[40] Moreover, more women in the hormone group experienced venous thromboembolic events (RR 2.89, 95% CI 1.50 to 5.58). Treatment for the purpose of secondary prevention of coronary heart disease alone is therefore not recommended by those investigators.

2.3 Combined Oral Contraceptives

Combined oral contraceptives consist of estrogens and 19-nortestosterone derivatives. Their safety has been reviewed extensively.[41-44] Their effects on serum lipid levels depend on the androgenicity of the progestogen. More androgenic progestogens such as levonorgestrel have larger effects than less androgenic progestogens such as desogestrel and gestodene. Oral contraceptives with 'second generation' progestogens (levonorgestrel, lynestrenol and norethisterone) show the most unfavourable effects. The androgenic and antiestrogenic properties of levonorgestrel result in the most pronounced effects. Formulations with levonorgestrel increase LDL-cholesterol levels (by 10%) and triglyceride levels (by up to 50%), whereas HDL-cholesterol levels are decreased (by 5 to 15%).[32,45] Preparations with other 'second generation' progestogens show similar effects on total-cholesterol, LDL-cholesterol and triglyceride levels. However, the effects on HDL-cholesterol may be more beneficial compared with formulations with levonorgestrel.[32,46]

'Third generation' progestogens (desogestrel and gestodene) were designed to reduce the risk of developing atherosclerosis. These formulations do show favourable effects on LDL-cholesterol levels (decreased by 0 to 15%) and HDL-cholesterol levels (increased by 10 to 15%), but they also increase triglyceride levels (by up to 75%).[32,41-43] The effects of desogestrel seem to be slightly more favourable than the effects of gestodene.

Despite these differences in effect on serum lipid levels, there is no convincing evidence that combined oral contraceptives containing 'second generation' progestogens lead to increased risk of cardiovascular disease compared with formulations containing 'third generation' progestogens. Studies of myocardial infarction yielded inconsistent results, which may be attributed to differences in the methodology of the observational studies. Research is also complicated by the low absolute cardiovascular risk in young women, and sound studies are rare.[47-49]

A number of studies, however, found an increased risk of venous thrombosis for formulations containing 'third generation' progestogens compared with formulations containing 'second generation' progestogens,[47,49] especially in the youngest women who use oral contraceptives for the first time.[50]

2.4 Selective Estrogen Receptor Modulators

Benshushan and Brzezinski[51] reviewed the effects of long term use of tamoxifen on the lipid profile. Tamoxifen beneficially affects both total cholesterol and LDL-cholesterol levels by decreasing them, on average by 13 and 17%, respectively. HDL-cholesterol levels do not change. The favourable effects are mediated by its partial estrogenic activity. Reported changes in triglyceride levels vary from no effect to a 30% increase. In 2 randomised trials of adjuvant tamoxifen therapy for breast cancer, the risk of cardiovascular morbidity and mortality was assessed.[52,53] These studies suggest a 25% reduction in cardiovascular mortality for women treated with tamoxifen. However, they included mostly premenopausal women and the effects of tamoxifen in postmenopausal women and healthy women remain to be established.

The effects of raloxifene on serum lipid levels bear a great resemblance to the pattern reported for tamoxifen. In postmenopausal women, raloxifene decreases total cholesterol (by 5 to 10%) and LDL-cholesterol (by 10 to 20%) levels.[54-58] HDL-cholesterol and triglyceride levels remain unchanged, the latter in contrast with tamoxifen therapy. The effect of raloxifene on the incidence of cardiovascular events is currently under investigation in the Raloxifene Use in The Heart (RUTH) trial.

2.5 Danazol

The main indication for danazol is treatment of endometriosis. Packard and Shepherd[59] reviewed published data on serum lipid levels during danazol therapy. Danazol induces an increase in LDL-cholesterol level by 10 to 40% and a decrease in HDL-cholesterol level by approximately 50%. These effects are not dose-dependent. Furthermore, they rapidly return to baseline levels, usually within 8 weeks after stopping therapy. Triglyceride levels are not altered.

2.6 Growth Hormone

Adults with growth hormone deficiency have lipid abnormalities, which may contribute to their increased risk of cardiovascular morbidity.[60] Treatment with recombinant human growth hormone (somatropin) results in decreased levels of total cholesterol (by 5 to 15%) and LDL-cholesterol (by 10 to 25%).[61-63] Triglyceride levels remain unchanged. Studies show inconsistent results regarding the effects on HDL-cholesterol; no effect[61,62] as well as an increase by 7%[63] or a decrease by approximately 20%[64] have been reported. These differences in response of HDL-cholesterol to somatropin are not fully understood, but apolipoprotein E phenotype may be a determining factor in this response.[65]

3. Retinoids

Retinoids include the natural compound vitamin A (retinol) and the synthetic derivatives of retinoic acid, isotretinoin and acitretin.

3.1 Synthetic Retinoids

Isotretinoin is a well established therapy for treatment-resistant acne vulgaris. Isotretinoin treatment increases total cholesterol and LDL-cholesterol levels by approximately 15% compared with pretreatment levels.[66-74] Reported effects on HDL-cholesterol are less consistent; nonsignificant ef-

fects[67,72,74] as well as decreases[66,68,69,73] have been reported. The most pronounced effects are however on triglyceride levels, with increases ranging from 35 to 144%. Barth et al.[71] assessed the need for routine measurements of plasma lipids in patients treated with isotretinoin. They found that the individuals with the highest levels of serum cholesterol after 16 weeks of treatment (>6.5 mmol/L) all had elevated cholesterol at the onset of therapy. Determination of the lipid profile prior to onset of therapy and measurement of triglyceride levels on 1 occasion after 4 weeks' therapy is recommended. More frequent determinations should be saved for patients predisposed to hypertriglyceridaemia and patients with diabetes mellitus.

Acitretin is primarily used for the treatment of severe and therapy-resistant psoriasis. The effects of acitretin on the lipid profile are less pronounced than the effects of isotretinoin.[75-79] Total cholesterol and HDL-cholesterol levels do not change and triglyceride levels increase by up to 60%. Measurement of lipid levels before onset of acitretin therapy and after a few weeks' treatment is also recommended. Hypertriglyceridaemia is a contraindication for both isotretinoin and acitretin treatment.

Dietary supplementation with fish oil in combination with acitretin therapy may improve the clinical features of psoriasis compared with acitretin therapy alone.[78] Moreover, there is a significant decrease (by 11%) in triglyceride levels after treatment with acitretin and fish oil. Further research is necessary to establish the potential benefit of this combination.

3.2 Vitamin A

The Carotene and Retinol Efficacy Lung Cancer Chemoprevention Trial (CARET) was designed to assess the effects of long term supplementation with β-carotene 30 mg/day and vitamin A 25 000 IU/day on lung cancer in smokers, former smokers and workers exposed to asbestos.[80] However, this trial ended prematurely because of the unexpected findings that the active treatment group had a 46% increased mortality from lung cancer and a 26% increased cardiovascular mortality compared with placebo.[81] Based on the knowledge that synthetic retinoids can affect serum lipid levels, it was hypothesised that the increased cardiovascular mortality in this trial was attributable to β-carotene–induced or vitamin A–induced dyslipidaemia. Analysis of the available data showed a small nonsignificant increase in triglyceride levels, but no differences in the other lipid levels after a mean follow-up of 5 years.[82] However, in the active treatment group more participants started lipid-lowering medication (RR 2.09) and developed diabetes mellitus (RR 2.58). The authors concluded that further research is warranted, especially because of the widespread use of vitamin A supplements and the use of high dose vitamin A in ongoing cancer prevention trials.

4. Immunosuppressive Drugs

Patients after successful transplantation show high cardiovascular morbidity and mortality because of the accumulation of cardiovascular risk factors such as hypertension and hyperlipidaemia. This hyperlipidaemia may be induced by immunosuppressive therapy following transplantation.

All lipid levels are increased and the magnitudes of the effects depend on the combination of immunosuppressive agents (cyclosporin, azathioprine and corticosteroids) and the gender of the patient.[83-87] Total cholesterol is increased by 10 to 40%, LDL-cholesterol by 0 to 50%, HDL-cholesterol by 0 to 90% and triglyceride levels by 0 to 70%. These effects seem to be larger in women than in men. Combinations with cyclosporin tend to have the largest effects, whereas the combination of azathioprine and prednisone shows the smallest increases.

Immunosuppressive therapy is not only associated with an increase in LDL-cholesterol levels, but also with accumulation of triglyceride-enriched LDL.[86] These are small dense LDL particles, which are known to be more atherogenic. Low dose cyclosporin (1.25 mg/kg) as used in the treatment of psoriasis did not significantly affect the lipid profile.[88]

Tacrolimus does not affect total cholesterol and LDL-cholesterol levels and shows a smaller effect

on triglyceride levels compared with cyclosporin (10 to 15% increase).[87] The effects on HDL-cholesterol are similar to the effects of cyclosporin. One of the newest immunosuppressive drugs, mycophenolate mofetil, does not cause adverse effects on the lipid profile.[89] However, sirolimus (rapamycin), another new immunosuppressant, seems to have an even more pronounced effect on both cholesterol and triglyceride levels than does cyclosporin.[90-92]

Kobashigawa et al.[83] showed that the addition of pravastatin, a HMG-CoA reductase inhibitor, after cardiac transplantation beneficially affected cholesterol levels and, more importantly, 1-year survival. Treatment with lipid-lowering medication after transplantation may be reasonable, especially in patients with multiple cardiovascular risk factors. HMG-CoA reductase inhibitors are the most valuable drugs to improve lipid profiles in transplant patients.[93] However, simultaneous use of cyclosporin and HMG-CoA reductase inhibitors may increase the risk of myopathy and rhabdomyolysis. The interaction between cyclosporin and HMG-CoA reductase inhibitors is not yet fully understood. Inhibition of the cytochrome P450 (CYP) enzyme CYP3A4 by cyclosporin and potential drug interactions between immunosuppressants and HMG-CoA reductase inhibitors in the small intestine may play an important role.[94] Pravastatin is not significantly metabolised by CYP enzymes and is the most hydrophilic HMG-CoA reductase inhibitor. Together with fluvastatin, which is a CYP2C9 substrate, pravastatin is a relatively safe choice in the treatment of transplant patients.

5. Protease Inhibitors

The lipodystrophy syndrome is a common complication in patients receiving HIV protease inhibitors.[95] The syndrome is characterised by peripheral fat wasting, central adiposity, dyslipidaemia and insulin resistance. The cause of the syndrome is unknown. All protease inhibitors cause the syndrome with similar severity after long term therapy. However, the onset seems to be more rapid with the combination of ritonavir and saquinavir.[96]

Ritonavir exhibits the most pronounced effects on serum lipid levels. Data from a randomised trial show that total cholesterol levels were increased by 30 to 40% and triglyceride levels were increased by 200 to 300% throughout the 32 weeks of the study.[97] In another trial, 61% of patients receiving ritonavir had at least a doubling of their triglyceride levels in the first 4 weeks, compared with 19% of patients receiving placebo.[98] These effects of ritonavir were confirmed in 2 observational studies.[96,99] Changes in serum lipid levels by indinavir and nelfinavir are smaller compared with those by ritonavir. Total cholesterol and LDL-cholesterol levels are increased by 15 to 30% and triglyceride levels increase by 0 to 55%.[96,99,100] HDL-cholesterol is unchanged after protease inhibitor therapy.[99-101] Combinations of saquinavir with ritonavir or nelfinavir do not further elevate serum lipid levels.[99]

Cases of extreme hyperlipidaemia, especially attributable to ritonavir, have been reported.[102,103] Total cholesterol reached levels of over 25 mmol/L and triglyceride levels were increased up to almost 10 mmol/L in 1 case and to over 60 mmol/L in the other case. After discontinuation of antiretroviral therapy and initiation of lipid-lowering medication, levels returned to normal. Cases of premature coronary artery disease and vascular complications after protease inhibitor therapy have also been reported.[104-106] However, 1 patient with acute angina pectoris had normal cholesterol and triglyceride levels[106] and another patient developed angina after only 4 weeks of protease inhibitor therapy,[104] suggesting a mechanism other than protease inhibitor–induced lipid abnormalities.

High serum triglyceride levels, especially >10 mmol/L, are known to be associated with an increased risk of pancreatitis. Pancreatitis has been reported after protease inhibitor therapy and this may well be related to protease inhibitor–induced hypertriglyceridaemia.[107-109]

Research on the pharmacological treatment of protease inhibitor–induced dyslipidaemia is limited. Treatment switching from triple therapy with the protease inhibitor to triple therapy without a protease inhibitor is one of the options. In patients not

previously treated with non-nucleoside reverse transcriptase inhibitors (NNRTIs), substituting nevirapine for protease inhibitor therapy improved the lipid profile.[110] Another option is adding lipid-lowering drugs, especially HMG-CoA reductase inhibitors or fibrates, to the ongoing protease inhibitor therapy. However, the use of HMG-CoA reductase inhibitors in patients receiving protease inhibitors could be problematic. Most HMG-CoA reductase inhibitors are metabolised in the liver by CYP3A4 and all protease inhibitors are known to inhibit this enzyme.[111] Elevated concentrations of HMG-CoA reductase inhibitors have been associated with increased risk of myopathy and rhabdomyolysis. Pravastatin and fluvastatin are again relatively safe choices because they are not, or not primarily, metabolised by the CYP3A4 enzyme.

So far, there are no studies comparing the effects of treatment switching to the effects of adding lipid-lowering drugs to successful antiretroviral therapy with a protease inhibitor. Since until very recently there were no guidelines available for the management of dyslipidaemia in patients with HIV,[112] individual physicians used to make their own judgements based on the beneficial effects of protease inhibitors on CD4+ lymphocyte count and viral load and on unfavourable effects on the lipid profile. In both cases, with or without existing guidelines, monitoring lipid levels is one of the key issues.

6. Antipsychotic Drugs

Treatment with antipsychotic drugs is associated with increased serum triglyceride levels. Gaulin et al.[113] determined serum lipid level changes after treatment with either clozapine or haloperidol. Changes were measured against baseline levels. Men and women treated with clozapine had significantly elevated triglyceride levels (increase by 48 and 35%, respectively), whereas only women treated with haloperidol showed increased triglyceride concentrations (51%). A cross-sectional study published in 1985 evaluated serum lipid levels in patients receiving either a phenothiazine (e.g. chlorpromazine) or a butyrophenone (e.g. haloperidol) for a long time (average 8 years).[114] There were no significant differences in cholesterol levels compared with the control group. Triglyceride levels in patients receiving phenothiazines were approximately 30% higher than in patients receiving butyrophenones, but levels were not higher than in the control group.

Studies of cardiovascular disease in patients with chronic schizophrenia are limited and outdated. The study by Hussar[115] in 1965 found no increased prevalence or incidence of cardiovascular disease in these patients. The more recent introduction of clozapine for the treatment of schizophrenia has led to several case reports of pancreatitis probably attributable to clozapine-induced hypertriglyceridaemia.[116]

7. Anticonvulsants

The effects of various anticonvulsants on serum lipid levels are the subject of controversy. Many observational studies have reported elevated levels of both LDL-cholesterol and HDL-cholesterol in patients receiving anticonvulsants compared with healthy control participants, whereas others reported no effects. This inconsistency has been observed in studies involving adults[117-119] and in paediatric studies.[120-123]

Carbamazepine elevates total cholesterol levels by 0 to 15% and HDL-cholesterol levels by 0 to 30% compared with healthy control participants. These effects seem to be more pronounced in women and they were independent of the dosage of carbamazepine and plasma concentrations.[119] One study showed levels of HDL-cholesterol decreased by almost 40%.[118] Phenytoin and phenobarbital have been studied less frequently, but studies indicate that both elevate total cholesterol levels by 5 to 15% compared with healthy control participants. Reported changes in HDL-cholesterol levels vary from a 40% decrease to a 45% increase. Valproic acid is the only anticonvulsant with a more favourable effect on the lipid profile. Total cholesterol levels with valproic acid tend to be 5 to 20% lower than those in control participants. Triglyceride levels are not affected by any of the anticonvulsants.

Anticonvulsants, except valproic acid, have enzyme-inducing effects on the hepatic microsomal CYP system, a system by which they are also principally metabolised. The same system is responsible for the breakdown of cholesterol to bile acids and competition between anticonvulsants and cholesterol for the enzyme may occur. The net effect of these 2 mechanisms, the inducing of the enzyme and the competition for the enzyme, is an increased total cholesterol level.[119,122]

The clinical relevance of the effects of anticonvulsants on the lipid profile is unclear. In a widely cited study by Muuronen et al.,[124] the risk of death from ischaemic heart disease in patients receiving phenytoin, carbamazepine or barbiturates (alone or in any combination) was 29% lower than in control participants. This difference was not caused by excess deaths attributable to any other cause. The HDL-increasing properties of the anticonvulsants may be an explanation for this phenomenon.

8. Implications for Clinical Practice

Many drugs besides lipid-lowering drugs affect serum lipid levels in either a beneficial or potential harmful way. These drugs differ in the magnitudes of their effects, varying from a small increase to more than doubling of levels, and from a small decrease to halving of levels.

Research on the impact of drug-induced dyslipidaemia is limited. However, it may be reasonable to extrapolate risk from the association between serum lipid levels and the risk of cardiovascular disease found in epidemiological studies. The Multiple Risk Factor Intervention Trial (MRFIT) showed that the relationship between serum total cholesterol and coronary heart disease is continuously graded without any threshold.[125] A 1% increase in serum total cholesterol was associated with an almost 2% higher 6-year risk of coronary heart disease. However, drugs may influence the risk of cardiovascular disease through multiple pathways. This could result in a net effect on risk different from what would be expected based on the effects of these drugs on serum lipid levels alone. A clear example is the antihypertensive drugs; despite their unfavourable effects on the lipid profile, thiazide diuretics and β-blocking agents do decrease cardiovascular morbidity and mortality.

Some general guidelines on the management of drug-induced dyslipidaemia in daily clinical practice can be given. An equivalent alternative therapy for the dyslipidaemia-inducing agent would be preferred. However, such alternatives are often difficult to find. Combined oral contraceptives with progestogens of the 'third generation' may not be an equivalent alternative for formulations containing 'second generation' progestogens, because they increase the risk of venous thrombosis. ACE inhibitors may be an alternative for the treatment of hypertension instead of thiazide diuretics and β-blocking agents. It was recently confirmed that there is no significant difference in efficacy in preventing cardiovascular morbidity and mortality between these classes of antihypertensive drugs.[126,127] However, thiazide diuretics and β-blocking agents are still considered to be first-line agents in most treatment guidelines because of the long term experience with these agents and the low treatment costs.

If there is no equivalent alternative available, risks of the treatment should be weighed against the possible benefit. Although protease inhibitors strongly influence the lipid profile, their utilisation in the treatment of HIV is often necessary. In those situations, the lipid profile should be determined before onset of therapy and monitored during treatment. Initiation of lipid-lowering medication can be considered if increased lipid levels fall within the ranges indicated by current guidelines for the management of hyperlipidaemia in the general population. These guidelines also take additional risk factors for cardiovascular disease into account in their decision whether to start lipid-lowering medication. If the dyslipidaemia-inducing drug is only prescribed for a short period of time, use of a lipid-lowering drug may not be advisable.

Treatment with a dyslipidaemia-inducing drug should be reassessed in cases of extreme hypercholesterolaemia or extreme hypertriglyceridaemia that could lead to pancreatitis.

9. Conclusion

Many drugs affect the lipid profile. However, the overall effect on cardiovascular morbidity and mortality not only depends on changes in lipid levels, but also on other drug effects. The existing guidelines for the management of dyslipidaemia in the general population can also be applied to iatrogenic dyslipidaemia if drug use is long term. In cases of extreme drug-induced hyperlipidaemia, medication use should be reassessed.

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