Drugs for lipid disorders, antiplatelet drugs and fibrinolytics

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Abstract

Drugs used for the treatment of hyperlipidaemias, to reduce platelet aggregation and to achieve thrombolysis are discussed. Their major mechanisms of action, key pharmacokinetic principles essential for their safe use, and important adverse effects are explained. Each class of drug is also given context for effective clinical use.

Keywords Antiplatelet therapy; aspirin; fibrates; fibrinolytics; hyperlipidaemia; lipid disorders; nicotinic acid; omega-3 fatty acids; statins

What's new?

- The non-lipid effects of statins are increasingly recognized to include the stabilization of atherosclerotic plaques, decreased inflammatory cell infiltration and improved function of damaged vascular endothelium
- A small randomized study has shown that once weekly low-dose rosuvastatin significantly lowers LDL cholesterol in patients previously unable to take statins because of myalgia
- A recent large randomized study failed to show a reduction in heart attack or stroke in patients treated with niacin and simvastatin compared with simvastatin alone
- Ticagrelor is an ADP receptor antagonist that has a more predictable platelet inhibition and less resistance than clopidogrel and may be used in acute coronary syndromes
- There has been no consistent evidence that clopidogrel taken with omeprazole results in a worse clinical outcome

Lipid disorders

Drugs for treating lipid disorders (Table 1) have different effects on the plasma concentrations of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides.

Statins

Mechanism: drugs such as simvastatin, atorvastatin and rosuvastatin limit cholesterol formation in the liver. They inhibit HMG CoA reductase, the rate-limiting step in hepatic cholesterol synthesis. A feedback mechanism resulting from reduced intrahepatic cholesterol increases the number of LDL receptors on hepatic cells. Liver uptake of cholesterol increases and circulating LDL cholesterol falls. Very low-density lipoprotein (VLDL) synthesis in the liver is also reduced, which in turn reduces circulating triglycerides by up to 15%.[1] There is usually a modest rise in HDL cholesterol of about 5%. The LDL-cholesterol reduction can be as much as 50% and is dependent on the dose and the efficacy of the drug used.[2,3] Non-lipid effects of statins, including the stabilization of atherosclerotic plaques and a decrease in inflammatory cell infiltrate, are becoming increasingly recognized.[4,5]

Adverse effects: gastrointestinal upset is well recognized. Liver function tests may become deranged in the first few weeks of use, and a rise to more than three times the upper limit of normal should result in drug withdrawal. Myalgia, myositis and, rarely, rhabdomyolysis are important adverse effects, more common when statins are taken with fibrates or nicotinic acid.[6,7] They are possibly caused by a lack of an intermediary in the cholesterol synthesis pathway needed for muscle protein function.[8] A different statin can sometimes be used without recurrence of symptoms, and use of low-dose intermittent rosuvastatin has shown promise in patients who experience muscle symptoms while taking other statins.[9] Simvastatin and fluvastatin can enhance the effect of warfarin.

Fibrates

Mechanism: drugs such as bezafibrate, gemfibrozil and fenofibrate activate a gene transcription factor (peroxisome proliferator-activated receptor alpha, PPAR-alpha), which encodes proteins that control lipoprotein metabolism. Fibrates increase the uptake of fatty acids into the liver, heart and skeletal muscle, where they are altered to limit their availability for triglyceride synthesis. Plasma triglyceride clearance is also increased by enhanced lipoprotein lipase activity.[1] Plasma triglycerides fall by up to 50%, with a more modest 15% reduction in LDL cholesterol. Increased hepatic synthesis of apolipoprotein AI and AII raises circulating HDL by up to 20%.[10]

Adverse effects: fibrates can cause gastrointestinal disturbance, rashes, pruritus, dizziness and headache. Myalgia and myositis are uncommon but more likely to occur in combination with a statin or with renal impairment. Fibrates can enhance the effect of warfarin.

Bile acid-binding (anion exchange) resins

Mechanism: cholesterol synthesized in the liver is either passed into the circulation or incorporated into bile salts and secreted into the gut. Nearly all of the cholesterol from bile salts is then reabsorbed. The resins, colestyramine, colesevelam and colestipol, limit this reabsorption by binding bile salts in the gut. The liver compensates by upregulating LDL receptors to remove LDL cholesterol from the circulation and maintain bile salt synthesis.

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Drugs for lipid disorders

Drug	T1/2 (h)	Dose reduction?	Pregnancy?	Breastfeeding?
Statins				
Atorvastatin	30	L	A	A
Fluvastatin	1	L	A	A
Pravastatin	1	L, R	A	A
Rosuvastatin	20	L, R	A	A
Simvastatin	2	L, R	A	A
Fibrates				
Bezafibrate	1—5	L, R	A	A
Ciprofibrate	27—28	L, R	A	A
Fenofibrate	20—27	L, R	A	A
Gemfibrozil	1—2	L, R	A	A
Resins/absorption inhibitors				
Colesevelam	—		C	C
Colestipol	—		C	C
Colestyramine	—		C	C
Ezetimibe	22	L	A	A
Nicotinic acid				
Acipimox	1	R	A	A
Nicotinic acid	1—2	L	A	A

T1/2, plasma half-life. Dose reduction: avoid in active or severe liver (L) impairment; reduce dose or avoid in renal (R) impairment. Pregnancy: avoid (A); caution (C) since may cause fat-soluble vitamin deficiency. Breastfeeding: manufacturer advises avoid (A); caution (C) since may cause fat-soluble vitamin deficiency.

Table 1

Plasma LDL cholesterol is reduced by 15—20%, and a small rise in both HDL cholesterol and triglycerides may be seen.[10]

Adverse effects: the most common reason for discontinuation of therapy is the unpalatable taste and texture of the medication, which can also cause constipation. Resins are insoluble and non-absorbable polymers that interfere with the absorption of several drugs, such as digoxin, warfarin and levothyroxine, which should be taken 1 hour before or 4 hours after the resin.

Nicotinic acid and derivatives

Mechanisms: triglycerides are largely stored in adipocytes after ingestion, or synthesized in hepatocytes. Nicotinic acid, a B vitamin, and its synthetic derivative, acipimox, act via hepatocyte receptors to reduce lipolysis and the availability of free fatty acids. This limits hepatic triglyceride and VLDL synthesis. Nicotinic acid can reduce plasma triglycerides by 35% and LDL by 15%. It also increases HDL by up to 25%, by decreasing its uptake onto the liver and shifts the subfractions from HDL3 to the more protective HDL2.[10] A recent large randomized study failed to show a reduction in myocardial infarction or stroke in patients taking nicotinic acid with simvastatin compared with those taking simvastatin alone.

Adverse effects: nicotinic acid has many effects that limit its use, the most troublesome being cutaneous vasodilatation with flushing and itching. This can be reduced by a gradual increase in dose, taking the drug with food, or concurrent use of low-dose aspirin. A modified-release formulation of nicotinic acid can improve tolerability. Gastrointestinal disturbance, headache and dizziness are also frequent. Nicotinic acid can cause glucose intolerance at higher doses and potential hepatotoxicity requires monitoring of liver enzymes during treatment.

Specific cholesterol absorption inhibitor

Mechanism: ezetimibe decreases cholesterol absorption in the small intestine and, when taken alone, reduces plasma cholesterol by 15% and LDL cholesterol by 20%. When given with a statin, it produces an additive reduction of LDL cholesterol. However, there are no studies to show that ezetimibe, alone or with a statin, reduces cardiovascular events.

Adverse effects include diarrhoea, headache and angioedema.

Omega-3 fatty acid compounds

Mechanism: omega-3 fatty acids are long-chained polyunsaturated acids, such as alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. They have multiple cardioprotective effects that extend beyond lipid control. All are poor substrates for the enzymes that produce triglycerides but they competitively block triglyceride synthesis. The result is decreased circulating triglycerides and VLDL, with increased HDL. LDL cholesterol is, however, also increased. Their main use is for treatment of severe hypertriglyceridaemia. Omega-3 fatty acids also decrease plasma fibrinogen, which limits thrombogenesis, and alter prostanoid synthesis in platelets, which inhibits platelet aggregation. They have an anti-inflammatory action that decreases the expression of endothelial adhesion molecules and may inhibit the growth of atherosclerotic plaques. Omega-3 fatty acids also enhance nitric