Drugs for lipid disorders, antiplatelet drugs and fibrinolytics

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Abstract

Drugs used to treat hyperlipidaemias, to reduce platelet aggregation and to achieve thrombolysis are discussed here. 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; MRCP; nicotinic acid; omega-3 fatty acids; statins

Key points

- Proprotein convertase subtilisin/kexin type 9 inhibitors are subcutaneously injected monoclonal antibodies that inhibit low-density lipoprotein (LDL) receptor breakdown on liver cells and can reduce circulating LDL-cholesterol by 45—70%. They reduce cardiovascular events in people with cardiovascular disease who are taking a statin
- Statins remain the cornerstone of LDL-cholesterol reduction, with decreases in circulating LDL-cholesterol of up to 50%. Myalgia can be an issue. They are recommended for both primary and secondary prevention of cardiovascular disease
- Fibrates are of particular use in circulating triglyceride (triacylglycerol) reduction
- Fibrinolytic agents are predominantly used in the acute management of ischaemic stroke when patients present early. They are still used in ST segment elevation myocardial infarction when there is no access to primary percutaneous coronary intervention
- Clopidogrel, prasugrel and ticagrelor bind irreversibly to P2 receptors on platelets, inhibiting platelet activation. They are used in acute coronary syndromes in conjunction with aspirin when specific criteria are met

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 (triacylglycerols).

Statins

Mechanism: drugs such as simvastatin, atorvastatin and rosuvastatin limit cholesterol formation in the liver. They inhibit the enzyme HMG CoA reductase, which catalyses 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%. There is usually a modest rise in HDL-cholesterol of about 5%. The LDL-cholesterol reduction is up to 50%, and depends on the dose and efficacy of the drug used. Non-lipid effects of statins, including stabilization of atherosclerotic plaques and a decrease in inflammatory cell infiltrate, are increasingly recognized.[1,2]

Adverse effects: gastrointestinal upset is well recognized. Liver function tests can become abnormal in the first few weeks of use, and a rise to >3 times the upper limit of normal should lead to drug withdrawal. Myalgia, myositis and, rarely, rhabdomyolysis are important adverse effects, more common when statins are taken with fibrates or nicotinic acid. They may be caused by a lack of an intermediary in the cholesterol synthesis pathway needed for muscle protein function. A different statin can sometimes be used without symptom recurrence, and low-dose intermittent rosuvastatin can be effective in patients who experience muscle symptoms while taking other statins. 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-α (PPAR-α)), 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. Plasma triglycerides fall by up to 50%, with a more modest 15% reduction in LDL-cholesterol. Increased hepatic synthesis of apolipoproteins A1 and A2 raises circulating HDL by up to 20%.[1,2]

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

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Drugs for lipid disorders

Drug	$t_{½}$ (hours)	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

Dose reduction: avoid in active or severe liver (L) impairment; reduce dose or avoid in renal (R) impairment. Pregnancy: avoid (A); caution (C) as it can cause fat-soluble vitamin deficiency. Breastfeeding: manufacturer advises avoid (A); caution (C) as it can cause fat-soluble vitamin deficiency.
$t_{½}$, plasma half-life.

Table 1

into the gut. Nearly all 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. Plasma LDL-cholesterol is reduced by 15—20%, and a small rise in both HDL cholesterol and triglycerides can be seen.[1,2]

Adverse effects: the most common reason for discontinuation of therapy is the unpalatable taste and texture of the medication; it 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, so these 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 into the liver, and shifts the subfraction from HDL3 to the more protective HDL2. A 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.[1,2]

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 gradually increasing the dose, taking the drug with food or the concurrent use of low-dose aspirin. 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. There are now data to suggest that it reduces cardiovascular events when taken with a statin after an acute coronary syndrome.[1,2]

Adverse effects: these include diarrhoea, headache and angioedema.

Omega-3-acid ethyl esters

Mechanism: omega-3-acid ethyl esters are long-chain polyunsaturated acids, such as eicosapentaenoic acid and docosahexaenoic acid. 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 to treat severe hypertriglyceridaemia. Omega-3-acid ethyl esters also decrease plasma fibrinogen, which limits thrombogenesis, and alter prostanoid synthesis in platelets, which inhibits platelet aggregation. They also enhance nitric oxide-mediated vasodilatation, and have a membrane-stabilizing effect in the heart, which gives them an antiarrhythmic action. However, there is no evidence that they help to prevent cardiovascular disease.[1,2]

Adverse effects: the most common effects are gastrointestinal disturbance and prolonged bleeding time.

Proprotein convertase subtilisin/kexin (PCSK) type 9 inhibitors

Mechanism: evolocumab and alirocumab are subcutaneously injected monoclonal antibodies. They have half-lives of 11—20 days and are injected every 2 weeks. They inhibit the enzyme PCSK type 9, which degrades LDL receptor expression on liver cell surfaces. This increases LDL receptor expression and decreases circulating LDL-cholesterol by 45—70%. Data on evolocumab and alirocumab suggest a reduction in cardiovascular events when used with a statin in patients with cardiovascular disease.[3] They are currently recommended for use as primary or secondary prevention in familial hypercholesterolaemia when an adequate reduction in LDL-cholesterol is not achieved by statin therapy alone. They are recommended for use as secondary prevention in non-familial hypercholesterolaemia when LDL-cholesterol is above recommended limits despite stain therapy.

Adverse effects: irritation and pain can occur at the injection site. Nasopharyngitis, arthralgia and back pain are also seen.

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