



Oral isotretinoin

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Summary

Oral isotretinoin is listed on the Australian Pharmaceutical Benefits Scheme for patients with severe cystic acne that has failed to respond adequately to other therapy. A single course of isotretinoin induces a long-term remission in over 80% of these patients. A minority, usually after a prolonged remission, benefit from a subsequent course. Pregnancy prevention is of paramount importance for women taking isotretinoin as it is highly teratogenic. Extra caution is also needed if the patient has diabetes, hyperlipidaemia or a mood disorder, drinks heavily or has a very physically active lifestyle.

Key words: acne, adverse effects, birth defects.

(*Aust Prescr* 2005;28:59–61)

Introduction

Cystic acne is characterised by numerous painful nodules that if inadequately controlled result in permanent scars. The natural duration of severe cystic acne is at least 10 years. Sufferers often become increasingly self-conscious, and many even isolate themselves to avoid social interactions. The impact of severe acne and its scars can be psychologically devastating in our increasingly appearance-conscious society. This is not just a disease of youth. Employers are less likely to recruit people with severe cystic acne and if working, these individuals are less likely to apply for and get promotions.

Severe acne can erode a person's self-confidence and may diminish their chances of finding a partner because of fear of rejection due to their appearance.

Isotretinoin, a retinoid related to vitamin A, is an effective oral treatment for patients with severe cystic acne. Isotretinoin reduces sebum production, unblocks pores and stops formation of new comedones. By opening up the hair follicle, it also reduces the anaerobic bacteria that contribute to the inflammation seen in acne. It is not effective on pre-existing scars and should ideally be started before scarring has begun. As isotretinoin has some serious adverse effects, it can only be prescribed by dermatologists. Early referral to a dermatologist should be considered for patients with progressively

worsening, moderately severe acne or a family history of severe cystic scarring acne.

Dosing, duration of therapy and total dose

Australian dermatologists usually prescribe a low starting dose then slowly escalate it over a few months (usually to 0.5–1 mg/kg/day but varying with patient tolerance and response). This reduces the risk and severity of adverse reactions including most mucocutaneous adverse effects, severe acne flares, and transient increases in liver enzyme concentrations. The incidence and severity of most adverse effects appear to be dose related, peak within weeks of dose increments and then generally improve as the body adapts and patients get used to taking extra skin and mucosal care, and other precautions.

Facial acne generally improves first, then the neck, back and finally buttocks. In Australia the total dose of isotretinoin given over 5–8 months is approximately 120 mg/kg. A longer course and higher total dose might be prescribed for clearing and inducing a remission in particularly severe cases of acne conglobata that extend to the lower back, buttocks or thighs. The product information recommends a 16-week course. Most Australian dermatologists prefer to give a longer course at a lower dose to improve tolerance and the outcomes for patients.

Isotretinoin is a potent teratogen

In most pregnancies exposure to oral isotretinoin causes severe birth defects. Even babies born without obvious central nervous system abnormalities may be mentally retarded. Every reasonable precaution must be taken to ensure female patients are not, nor become, pregnant while taking isotretinoin. Although isotretinoin and its metabolites are not stored in the body and are eliminated within a week of stopping therapy, effective birth control is necessary

from one month before the start of treatment until one month after the end of treatment. Patients cannot donate blood during, and until a month after, treatment because of this risk. There are no risks to the fetus however if the father is taking isotretinoin.

There are important implications for the patient, their family, general practitioner, prescribing dermatologist, and pharmacist. Female patients should be using at least one effective contraceptive measure reliably and have a recent negative pregnancy test before starting therapy. Isotretinoin is then started on the second or third day of the next menstrual period.

Oral isotretinoin causes severe birth defects

Regular reviews of females of childbearing potential taking isotretinoin may include pregnancy testing along with further counselling about the importance and adequacy of contraception. The frequency of these reviews is tailored according to the perceived risk of pregnancy, the precautions in place and the patient's reliability in using them. Teenagers and young adults may require extensive counselling to correct misbeliefs on the effectiveness of and the best and safest ways to use contraception.

I discourage patients from purchasing isotretinoin via internet or mail order pharmacies as there is no opportunity for regular extra face-to-face reminders about the damaging effects of isotretinoin in pregnancy.

If a female taking isotretinoin suspects that she might have become pregnant, she should stop the medication immediately and seek urgent medical advice and pregnancy testing along with expert counselling.

Common adverse effects

Most adverse effects are dose related and due to the inhibition of sebaceous and meibomium gland function and/or the premature desquamation of epidermal cells. This leads to drying of the skin and mucous membranes and their increased sensitivity to irritation. Before starting isotretinoin, the patient should be given a long list of recommended changes to make in their personal care and lifestyle to minimise the risk of the drug causing symptoms or adverse effects (Table 1). Some patients are excellent at following recommendations while others wait until they have problems before taking corrective measures.

A flare of acne several weeks into therapy unfortunately does occur in a minority of patients. This is less common and less severe if the dose is started low then slowly escalated. A patient with an acne flare worse than their usual flares in the first weeks or months after starting isotretinoin should be seen urgently by their dermatologist. A short course of prednisolone might be prescribed, possibly in conjunction with oral erythromycin and triamcinolone injections into cysts.

Isotretinoin and the liver

Unlike vitamin A, isotretinoin is not stored in the liver. Isotretinoin is probably not directly hepatotoxic. When isotretinoin is started at higher doses (for example 1 mg/kg/day) 'transient leaky hepatocyte membranes' are thought to be responsible for the asymptomatic rise in liver enzymes in a small proportion of patients. This is uncommonly seen in Australia when a lower starting dose is used. If liver enzymes rise more than two and a half fold above normal or they fail to normalise when rechecked 3–4 weeks later, investigations for other causes (such as viral hepatitis, alcohol) are indicated. Consideration should still be given to stopping isotretinoin, because it can exacerbate liver enzyme rises due to other causes. Patients need counselling regarding alcohol intake and

Table 1

Recommended methods of minimising the adverse effects of isotretinoin

Problem	Solution
Common problems	
Dry cracked lips	Lip balm always in pocket, pawpaw ointment at night if very dry
Dry skin (especially face)	Soap-free wash, non-fragranced, plus non-acneogenic moisturiser
Sun sensitivity	SPF 30 broadspectrum sunscreen, a hat and appropriate clothing if outdoors (10 am to 3 pm)
Dry or irritable eyes	Artificial tears
Contact lens intolerance	Wear glasses
Eczema	Moisturise regularly, intermittent topical corticosteroids
Dry cracked nose/nose bleeds	Petrolatum or vitamin E lotion twice a day applied using cotton tip
Less common/occasional but more significant problems	
Angular cheilitis	Mupirocin ointment or povidone-iodine qid (usually due to <i>Staphylococcus aureus</i> infection)
Impaired night vision	Avoid night driving or check adequacy of vision before driving at night
Visual disturbance	Refer for ophthalmological examination and consider ceasing treatment
Paronychia	Nails should extend beyond lateral fold and not have sharp edges. Topical povidone-iodine, anti-staphylococcal antibiotics
Skin fragility and delay in wound healing	Avoid waxing, avoid and/or take extra protective precautions for activities associated with significant hand trauma e.g. manual labour tasks
Tiredness, tenderness or stiffness of bones, joints and muscles	These vary greatly between patients, and are dose- and activity-related (improve or resolve with activity modification and/or dose reduction over days to weeks). Avoid extremely strenuous activities; exercise to maintain conditioning, use isotretinoin in the off-season for serious sports enthusiasts/professional athletes. May also unmask underlying problems e.g. lower backache.

the avoidance of other hepatotoxins while taking isotretinoin and for several weeks after its cessation.

Isotretinoin and blood lipids

There is a small increase in triglyceride concentrations in 25% of patients and 7% have an increase in their cholesterol concentrations. These changes resolve on stopping therapy. Extra caution needs to be taken in patients with high baseline lipid concentrations, a family history of hyperlipidaemia,

diabetes, or who drink large amounts of alcohol. These patients may have larger increases in their triglyceride concentrations when taking isotretinoin and require monitoring of their lipids with each dose increase.

There are a number of reports of a large rise in triglycerides (for example, greater than 10 mg/L) being associated with symptomatic steatohepatitis and acute pancreatitis. Many of these reactions may have been prevented by measuring baseline lipids and then repeating them on at least one occasion several weeks into therapy. These tests should be repeated regularly during therapy and appropriate action taken if a significant rise occurs.

Isotretinoin can reveal individuals who have an increased risk of developing early onset hyperlipidaemia, insulin resistance, obesity and accelerated atherosclerosis. Those at greatest risk are teenagers and young adults whose triglyceride and cholesterol increase significantly while on isotretinoin. After completing a course of isotretinoin these people will benefit from regular monitoring of their metabolism, education about healthy living and early preventative health interventions.

Rare idiosyncratic but important reactions

People starting isotretinoin often have a few minor, transient headaches during the first few weeks of therapy. However, if these headaches occur on waking and are persistent or severe, or are associated with nausea and vomiting or blurred vision, suspect pseudotumour cerebri. Isotretinoin needs to be promptly stopped and the patient should be examined for papilloedema. An urgent referral to a neurologist for further assessment and management is indicated.

There are rare reports of reversible cytopenias occurring in people taking isotretinoin. Check for cytopenia if a patient presents with high fever, sore throat, petechiae or easy or unusually severe bruising.

Acne, isotretinoin and depression

Severe cystic acne is associated with an increased risk of depression. It occurs relatively commonly in males in their late teens and early twenties – a group known to be at relatively high risk of depression, suicide and first developing schizophrenia. If acne flares after several weeks of taking a drug described as the last resort for severe acne or if the adverse effects of a dry, red face with cracked lips are particularly severe, patients may have justifiable reasons for feeling down about their acne and its therapy. All patients being seen for acne and particularly more severe forms of acne should therefore be routinely screened for symptoms of depression whenever seen by a health professional.

While there are a number of media reports, there is no proven link between isotretinoin and depression, suicide or psychotic symptoms. So far, studies and analysis of spontaneous reports suggest that, overall, isotretinoin may have a protective effect

against depression. There is a tendency for patients' mood to elevate as their acne improves and clears. However, these reports cannot exclude a rare idiosyncratic susceptibility to psychiatric illness and this issue should be discussed when patients give informed consent to treatment.

If a patient with severe cystic acne has a past history of depression or is suspected or diagnosed as depressed, they should be closely monitored and managed in conjunction with their general practitioner or psychiatrist before starting isotretinoin. Depression does not preclude the prescribing of isotretinoin particularly if the patient's acne is responsible for their lowered mood. Their mood will not necessarily worsen while on isotretinoin and may even elevate with successful control of their acne.

Conclusion

Isotretinoin is the gold standard treatment for severe cystic acne, but there is a major risk of harm associated with its use. This risk can be reduced by careful assessment of the patients before and during treatment. Patients, particularly women, need to be informed about the adverse effects of isotretinoin and how to avoid them.

Further reading

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Conflict of interest: none declared

Self-test questions

The following statements are either true or false (answers on page 79)

1. Women taking isotretinoin should avoid pregnancy until at least one month after stopping treatment.
2. Patients taking isotretinoin require regular testing of their liver function.