Thalidomide is probably the most infamous drug ever to have been brought to market. Its devastating teratogenic effects led to its withdrawal. However, it has been found to be effective and safe for a number of conditions, if carefully used.

This article describes them first trimester of pregnancy. Thalidomide's subsequent revival has been clinically led, driven by observation (mostly anecdotal but cumulatively overwhelming) of significant improvement in certain clearly defined disorders.

Interest in thalidomide was initially rekindled in the mid-1960s by its effect on type II reactions in leprosy. However, it is now apparent that it has anti-inflammatory properties in other diseases, such as severe aphthous stomatitis, Behçet's disease, graft-versus-host disease (GVHD), some manifestations of HIV infection and, possibly, malignancies. If this had not been the case, it is likely that thalidomide would have passed into the annals of history un lamented but not forgotten.

MODE OF ACTION

The efficacy of thalidomide as a hypnotic and sedative was the reason for its introduction and popularity in the 1950s. These effects are probably a result of the glutarimide moiety substituted in the 3 position with an inert group, the structure of which is not critical. This configuration exists in a number of sedative and hypnotic drugs such as glutethimide. Thalidomide has no narcotic, antiepileptic or analgesic activity, and it has no effect on motor co-ordination.

Although the clinical effects of thalidomide are in many cases clear, its mode of action is less so. Thalidomide has two distinct pharmacological activities: a potent depressant effect on the central nervous system and a less clearly understood immunomodulato-
ry effect in some inflammatory diseases. Thalidomide can down-regulate the cytokine tumour necrosis factor-alpha (TNF-\(\alpha\)), leading to a partial reduction in its synthesis and a shortening of its half-life. The assumption has been that because TNF-\(\alpha\) levels are elevated in patients with erythema nodosum leprosum (ENL) and lowered by thalidomide therapy, this was the mode of action of the drug. However, the ability of thalidomide to lower TNF-\(\alpha\) levels in different models is not consistent, and other strategies to reduce TNF-\(\alpha\) (e.g., with receptor antagonists) do not mimic the effects of thalidomide. Other pharmacological actions of thalidomide have been noted in animal studies. These include stimulation of prolactin and adrenocorticotropic hormone production and inhibition of the secretion of follicle stimulating hormone and thyroid stimulating hormone. The drug's reported inhibitory effects on angiogenesis could also be important.

For most therapeutic indications, it is customary to start treatment with 400mg thalidomide daily given orally in two divided doses. When symptoms are controlled, usually within five to 10 days, the dose is progressively reduced to a single night-time administration of 50 or 100mg. This is then continued for a maintenance period, which may last from one to six months or more. In view of the risk of neuroopathy, doses should always be as low as possible and frequent attempts should be made to withdraw the drug, if symptoms allow. Pharmacokinetic studies seem to indicate that there is no advantage in giving doses greater than 200mg four times daily.

**ADVERSE REACTIONS**

**Neuropathy** From early 1960 onwards, isolated reports of polyneuropathy linked to the use of thalidomide have not been reported. Thalidomide is now known to cause axonal neuropathy, which predominantly affects sensory nerves, although there is some evidence to suggest that the drug has more widespread effects on the nervous system. The clinical symptoms reported and reviewed by Gunzler include hypo- and hyperaesthesia, impaired temperature sensitivity and impaired autonomic function. These symptoms can resolve slowly but usually persist.

Reports of motor disturbances are rare but the most useful objective measurement of thalidomide-induced peripheral neuropathy is decreased sensory nerve action potential amplitude, measured in the sural and median nerves.

Conflicting estimates of the incidence of thalidomide-induced neurological disturbances range from less than 1 per cent to 50 per cent. This adverse reaction might be related to the total dose of thalidomide but this is far from clear. Cases of neurological disturbances have been reported with cumulative doses of just 15g, whereas others, particularly those of patients with ENL reactions, have been treated continuously for years without overt problems. Thus, sensory nerve conduction studies should be performed, using standard techniques and surface electrodes, at regular intervals throughout therapy. This will permit early detection of reduced amplitudes before symptoms occur.

**Limb defects** The history of the realisation that thalidomide could cause limb defects and associated abnormalities has been fully described by Mellin and Katzenstein.

Before the link was recognised, the frequency of phocomelia in Germany ranged from four cases in 1958 to eight in 1959, 70 in 1960 and 222 in 1961, paralleling the increased use of thalidomide. The critical period for embryopathy occurs in the period between 20 and 40 days of gestation. The intact phthalimide or phthalimidine groups appear to be responsible for thalidomide's teratogenic activity but the mechanism has not been conclusively demonstrated.

Hypotheses about thalidomide's teratogenicity include antagonism of the action of vitamins or amino acids, acylation of biogenic amines, interaction with enzymes that release or metabolise, and interference with hydroxyproline biosynthesis.

**Other adverse effects** Other serious reactions to thalidomide are rare. Somers reported that there had been 20 cases of overdose reported in humans, with no adverse effects. This corresponds with the lack of acute toxicity seen in animals.

In view of the nature of the original indications for the drug, it is not surprising that drowsiness is an almost universal side effect in patients treated for inflammatory disease. Rashes have been reported frequently in individual patients.

Other frequent adverse experiences include constipation (which can be profound), xerostomia (dryness of the mouth), increased appetite, nausea and loss of libido. Endocrine abnormalities, which experimental evidence suggests might be the result of an effect on the hypothalamus, include menstrual abnormalities, normalisation of hyperthyroidism, myxoedema and increased urinary secretion of hydrocorticosteroids.

**THERAPEUTIC USES**

**Sedation** The use of thalidomide as a sedative is obsolete but its efficacy is indisputable. In the initial report of a trial involving 300 patients the results were graded as excellent in all types of "vegetative dys-tonia" and improvement was also noted in mild hyperthyroidism, nervous gastric troubles, labile hypertension, and bronchial asthma. In a study of 200 psychotic patients treated with 100mg thalidomide at bedtime for over a year, the results were regarded as satisfactory, although severe constipation was a problem in some. There were only 11 cases of intolerance to the drug.

Clinical trials have also been conducted in children aged two weeks to 12 years with brain damage or various disorders of affect. No problems were encountered and the drug seemed beneficial. Kunstmann gave thalidomide to 110 paediatric patients, of whom 98 were under the age of one year. The children had various medical problems but, when treated with thalidomide, seemed to sleep naturally and were alert when awakened. No harmful effects were recorded, there was no tendency to addiction and no alteration of biochemical parameters was noted.

**Erythema nodosum leprosum** Patients with lepromatous leprosy can suffer sudden flares either spontaneously or, more usually, as a result of therapy. About 15–20 per cent of multibacillary leprosy patients develop ENL (or type II lepra reaction) within the first year of therapy. Clinically, it is characterised by the appearance of painful erythematous subcutaneous nodules, not related to former leprosy lesions. These occur with or without systemic manifestations, such as pyrexia, malaise, lymphadenopathy, neuritis, arthralgia, and weight loss.

The drugs used to control this reaction and which allow antilepromatous chemotherapy to continue, include clofazimine, dapsone and rifampicin. However, since the mid-1960s, the use of thalidomide in ENL has exceeded its use for any other purpose and it is now the drug of choice. The advantage of thalidomide is that it shortens and ameliorates the ENL reaction, thus allowing antilepromatous treatment to continue.

Sheskin in 1965 first reported six patients with ENL who responded to treatment with thalidomide but many subsequent trials have confirmed its usefulness. A statistically controlled, double-blind trial was performed in 1966 that involved 58 patients who were divided into two equal groups. In the thalidomide group, 91.76 per cent of patients experienced complete remission of symptoms and 8.24 per cent remained unchanged. In the placebo group, 27.25 per cent of patients improved, 50 per cent were unchanged, and 22.75 per cent became worse. About 10 years after his initial report, Sheskin reviewed 4,522 cases of lepromatous leprosy from 62 institutions and concluded that the response to treatment with thalidomide was satisfactory in 99 per cent.

Thalidomide acts quickly, with the earliest improvement being seen after eight hours. However, 48 hours are usually required before the patient becomes afebrile. Although no relapse is seen in milder cases of lepromatous leprosy, in severe cases, relapse can occur when the drug is stopped. Recurrences are usually delayed for five to 10 days or even for one month after stopping therapy. Unlike clofazimine, thalidomide gives no benefit in type I (borderline or reversal) lepra reactions.

**Oral and genital ulceration** The value of thalidomide in the management of severe oral and genital ulceration has now been established. It is effective regardless of whether or not the ulcers occur as an isolated symptom, as part of Behçet's
disease, in combination with genital ulceration, or in association with HIV infection (see later).17–19

The response to treatment is rapid. In 22 patients who had suffered from Behçet’s disease for over 10 years, healing occurred in seven to 10 days after treatment with thalidomide. There was no improvement in eye symptoms.20 Similarly, in a series of patients with severe oral ulceration with or without genital ulceration, 14 out of 15 patients given thalidomide (who had a mean duration of symptoms of 6.5 years) had achieved complete resolution at day 11 and one was rated as having improved significantly.19

**Graft-versus-host disease** GVHD occurs after bone marrow transplantation when donor lymphocytes attack the recipient’s body, causing a chronic sclerosderma-like condition. It is steadily destructive and often fatal.

Saurat et al described a 28-year-old man who developed severe GVHD after a bone marrow transplant for aplastic anaemia. Ciclosporin, prednisolone, and azathioprine did not control the condition but after the addition of thalidomide 300mg daily he improved dramatically. There was no reactivation of the reaction after the drug’s withdrawal.20 Lim et al similarly described a patient who had GVHD that relapsed while he was receiving prednisolone 40mg daily and ciclosporin. Improvement was noted within three days of starting thalidomide, which was continued at a dose of 800mg daily.21 Rovelli et al reported a complete response in six out of 14 children.22 However, Ringden et al recorded three patients who failed to respond to thalidomide but, in contrast to most of the positive reports, none was receiving ciclosporin.23 This indicates that the two drugs could have a synergistic effect.

**Actinic prurigo** Actinic prurigo is an uncommon, light-sensitive dermatosis that starts in childhood, runs a chronic course, and is resistant to treatment. Londoño24 first reported the use of thalidomide in 34 patients given 300mg daily. A favourable response was obtained in 32 patients between three weeks and three months after starting treatment. All relapsed when treatment was stopped. These results have subsequently been confirmed by other studies.

**Discoid lupus erythematosus** As in actinic prurigo, patients with discoid lupus erythematosus suffer, to a certain degree, from photosensitivity. Rubio and Gonzalez25 reported 19 patients who responded within three days of starting thalidomide. The somewhat bizarre reasoning was that if it could impair the growth of a “physiological neoplasm” in the form of a foetus, then why not a true neoplasm?21 Thalidomide has proved to be ineffective as a cytostatic agent and most trials of its use for a variety of tumours have given unconvincing results. Interest in this use has been rekindled by the demonstration that thalidomide has anti-angiogenic properties.4 Solid tumours rely on their ability to cause neovascularisation in order to grow, and inhibition of this process can delay growth.

Multiple myeloma is another malignancy where treatment with thalidomide has shown some evidence of benefit. One trial showed that 30 out of 89 patients treated with the drug had some degree of lowering of their monoclonal protein levels.29 In 11 out of 24 patients evaluated, there was also a decrease in bone marrow plasmacytosis. Other studies have given similar results.30,31 In a further investigation that looked at 23 patients who had undergone extensive previous therapy, it was judged that, in seven, the response was better than with any preceding therapy.32

**Disorders associated with HIV** Patients with advanced HIV infection can develop persistent oral and oesophageal ulcers of the aphthous type. Satisfactory results have been achieved with thalidomide in these patients.33–35 In a prospective, controlled trial, Jacobson et al showed complete healing of oral ulcers in 16 out of 29 patients, compared with two out of 26 taking placebo.36 In a similar study of oesophageal ulcers, eight out of 11 patients taking the drug improved, compared with three out of 13 on placebo.37

In a study of 20 patients with AIDS-related Kaposi’s sarcoma, a partial response was seen in eight,38 and, in another study, six out of 17 responded.39

TNF-α is believed to play a role in cachexia associated with malignancy and with HIV infection. In a prospective, randomised, placebo-controlled trial, wasting progressed in three out of 14 patients on thalidomide compared with 10 out of 14 given placebo.40

In an open study of 12 males with diarrhoea caused by refractory microsporidiosis, bowel movements were reduced from a mean of six to three per day.41

**CONCLUSIONS**

The use of thalidomide for any condition remains contentious. It must only be given with extreme caution, under close supervision and with full knowledge of the potential hazards. Nevertheless, its unequivocal effect in leprosy and Behçet’s disease has stimulated exploration of its action in other diseases, and research continues. Recent reports indicate benefit in uraemic pruritus,42 Crohn’s disease,43,44 and possibly in sarcoidosis.45

At the same time, research into derivatives and analogues of the drug which might have increased efficacy and reduced toxicity is also under way. These would offer new therapeutic options in a range of distressing disorders that can otherwise be difficult to manage.1,46

The past might have been devastating but the future for thalidomide is looking promising.
REFERENCES


