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Leading Article

Thalidomide – the way forward

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In the 1950s thalidomide was a novel therapeutic agent that failed to control epileptic fits as anticipated from animal studies. However, it caused such drowsiness that it was ultimately marketed in 1958 as a sedative.[1] Its promotion ironically emphasized its safety as overdoses in animal tests failed to cause death.[2]

In 1959 a single case report of a rare congenital abnormality, namely phocomelia, in a female infant born to a young primigravida was published.[3] There followed a burst of similar reports in the medical literature and, in 1961, the connection between thalidomide and teratogenesis, particularly phocomelia, was established.[4,5] Other recognized thalidomide birth defects include duodenal stenosis, oesophageal fistulae, neural tube abnormalities, micro-opthalmia, deformities of the pinna of the ears and mid-line haemangiomas.[6] These abnormalities occurred following ingestion of thalidomide during the 35th–50th day of pregnancy,[7] affecting an estimated 12,000 babies worldwide in the late 1950s to early 1960s.

Peripheral neuropathy is the other major side effect of thalidomide and has received far less publicity. Three case reports appeared between 1960 and 1961[8–10] suggesting that peripheral neuritis was associated with thalidomide therapy and, in 1961, Fullerton[11] described 13 patients who had developed a predominantly sensory peripheral neuropathy with mild proximal muscle weakness whilst taking thalidomide as a night sedative.

The teratogenic potential of thalidomide led to its withdrawal in the UK. The impact of the catastrophe on the public was considerable and thalidomide remains a household name some 30 years later, attracting media attention whenever related scientific information is published.

In Israel an astute observation by Sheskin published in 1965[12,13] resurrected interest in thalidomide. He noted that a patient with mania and co-incidental erythema nodosum leprosum (lepra reaction (ENL)) in whom thalidomide was used for sedation demonstrated a dramatic improvement in the skin lesion within 12 hours. Thalidomide has since been used for ENL in more than 5,000 reported cases with an impressive efficacy of 99%.[14] In addition thalidomide has been used successfully in a large number of conditions including severe oral and genital ulceration[15–18] often associated with Behçet's disease[19–21] and in actinic prurigo,[22,23] chronic discoid lupus erythematosus,[24,25] prurigo nodularis,[26] ulcerative colitis,[27] erythema multiforme,[28] pyoderma gangrenosum,[29] postherpetic neuralgia[30] and Weber–Christian disease.[31] Most recently thalidomide has proved valuable in the management of graft versus host disease (GVHD),[32–36] in the mucosal ulcers of human immunodeficiency virus (HIV)[37–39] and is currently under investigation as a possible antiviral agent, particularly against HIV.[40]

The therapeutic benefits of thalidomide must be weighed against the tragedy of the 1960s. Currently in the UK thalidomide is being prescribed in hospitals on a 'named patient' basis, in accordance with Section 9(1) of the Medicines Act[41] to a small number of patients who have exhausted other therapeutic options. Guidelines are presented to enable the highest standards of safety to be adopted in the use of thalidomide, and these recommendations will require revision and modification as further clinical experience with thalidomide is gained. Clearly in each individual patient the risks of teratogenicity and peripheral neuropathy must be carefully addressed both before and during treatment.

The use of thalidomide in fertile women remains controversial and must be restricted to small numbers in highly controlled situations, where both patients and doctors fully comprehend and accept the responsibilities and risks, which must include the possibility of contraceptive failure.[42] In the USA attempts at controlling the prescription of drugs with teratogenic risk, such as the extreme efforts of Roche over the use of isotretinoin in pregnant women in the USA, has been notable for its lack of success.[43] In the UK the use of isotretinoin is restricted to prescribing by hospital consultants only. The risk of peripheral

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neuropathy remains, particularly with chronic treatment, but with regular monitoring of the amplitude of sensory nerve action potentials, subclinical neuropathic changes can be detected.[44] Provided the recommendations for the use of thalidomide are closely followed then this drug can be used safely.

Thalidomide provides an important therapeutic option in patients with a number of conditions whose disease cannot be as satisfactorily controlled by other means, and potentially may be increasingly prescribed because of its value in the growing fields of GVHD[16] and HIV.[17] The effective dose of thalidomide is not known, but experience in oral and genital ulceration suggests that small doses are effective. Although there are no product licences for thalidomide in this country, its use on a 'named patient' basis will allow its continued use for those patients for whom it remains an important therapeutic option by clinicians with the necessary expertise. The guideline is designed to promote the safest possible use of thalidomide.

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