CHAPTER 35

THALIDOMIDE THERAPY IN DERMATOLOGY

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INTRODUCTION

Thalidomide was first synthesized in 1954 by the CIBA pharmaceutical company and marketed as an over-the-counter sedative, antiemetic and tranquilizer medication under the label of Contergan in West Germany in 1956.[1,2] It was used in Europe and Canada as a sedative and antiemetic particularly for pregnant women.[3] Although Contergan rapidly became popular and widely prescribed with its efficacy in many countries, tragic reports demonstrating the association between thalidomide use in pregnancy and limb defects (phocomelia) in infants began to be published soon. In 1960s, it was reported that fifty percent of the mothers with deformed children had taken thalidomide during the first trimester of pregnancy and approximately 12,000 children worldwide developed phocomelia related to in utero thalidomide exposure.[4] The drug was subsequently withdrawn world-wide completely by 1962 and its use was prohibited until its revival for the treatment of erythema nodosum leprosum (ENL).

PHARMACOLOGY

Thalidomide is an α-N-phthalimidoglutarimide, a synthetic derivate of glutamic acid with two-ring structure. The left-sided pthalidimide ring is thought to be responsible for the teratogenic effects of the drug.[2,5,6] The right-sided glutarimide ring is structurally similar to other sedatives. The drug exits as optically active L- and R- isomers.[2] Thalidomide is absorbed rapidly and the plasma concentration is peaked within 2-6 hours.[7] The half-life of the drug is between 8 to 12 hours and total clearance is approximately 10 L/h.[8,9] The major way of metabolization is still obscure and it is mostly eliminated by non-enzymatic hydrolytic cleavage.[2] Its excretion is non-renal and lower than one percent of the total dose can be found unchanged in the urine after 24 hours.[7,10]

MECHANISM OF ACTION

Although the action mechanism of thalidomide has not been exactly clarified yet several possible effects have been proposed.

Anti-inflammatory antipruritic effects

Thalidomide has been found to be act as a potent inhibitor of tumor necrosis factor (TNF)-α by activating the degradation of mRNA. The main anti-inflammatory effect of thalidomide has been related to inhibition of TNF-α produced by stimulated monocytes.[11] It has observed been to decrease interferon production, polymorphonuclear leukocyte (PMN) chemotaxis, monocyte phagocytosis and CD_4 to CD_8 cell ratio.[12] Anti-inflammatory effect of the drug was first demonstrated by Faure et al. in 1980.[13] The authors showed a marked, dose-independent inhibition of chemotaxis of pre-incubation of PMNs caused with thalidomide in vitro. A marked decrease of CD_4 / CD_8 ratio was found after thalidomide administration in the patients with ENL.[14] McHugh et al. demonstrated that thalidomide upregulated IL-4 (Th_2) initially peaking at 48 hours while it inhibited IFN-γ (Th_1).[15] On the contrary Verbon et al. found an increase of the production of IFN-γ (Th_1) in vivo and a decrease of the levels of IL-5 (Th_2).[16] Recent studies have focused on IL-12, a potent activator of Th_1 response and thalidomide has been shown to suppress the production of IL-12 and potently inhibit development of cellular immune response although contrary results were also found.[17,18] Criado et al. showed that a single dose thalidomide decreased UVB-induced erythema. The authors suggested that thalidomide acted as antagonist of soluble inflammatory mediators such as prostaglandin E, prostaglandin F2, and histamine.[19]

Hypnosedative effect

Thalidomide easily penetrates the central nervous system and its hypnosedative effect is most likely mediated by its right-sided glutarimide ring.[6] Its hypnosedative effect is high enough compared with barbiturates.[20] Its sedating and neural effect may explain its role and efficacy in the management of pruritic conditions of dermatology such as prurigo nodularis, actinic prurigo and uremic pruritus.

Anti-angiogenic effect

The antiangiogenic effect of thalidomide was hypothesized to be controlled in part through the transcrip-

with prednisolone and thalidomide.[59] However, as a contradictory result, Jacob et al. Reported three cases of PG treated with adalimumab after a failed course of thalidomide treatment.[60]

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a frequent complication of allogeneic bone marrow transplantation. Thalidomide has been reported to be an effective drug for treatment of chronic graft-versus-host disease (cGVHD).[61] Vogelsang et al. reported complete therapeutic response to thalidomide in 14 of 44 patients with GVHD and the response was partial in 12 patients. Eight (38%) of 21 patients with high-risk cGVHD improved after primary treatment with thalidomide. In this preliminary phase-II trial, they found that thalidomide appeared to be safe and effective for the treatment of cGVHD.[62] In a subsequent study, 16 (20%) of 80 patients with refractory cGVHD showed improvement after treatment with thalidomide.[63]

Langerhans cell histiocytosis

Broekaert et al. reported a 57-year-old woman with Langerhans cell histiocytosis presented with a one-year history of non-healing inguinal and perianal ulcers undergoing thalidomide treatment. The patient received thalidomide at a dosage of 50 mg/d and showed a prompt response with total regression of the lesions after two months.[64]

ADVERSE EFFECTS

The most common side-effect is sedation and it may diminish over time.

Teratogenicity

Although the teratogenicity effect caused by thalidomide has been well known and established after the great tragedy, the exact mechanism of thalidomide's teratogenic potential remains still obscure.[20] The most sensitive period has been estimated to be 34 to 50 days after conception.[6] Even a single dose of 100 mg during this period is sufficient to produce teratogenic malformations.[10] Neurotoxic and anti-angiogenic effect of the drug have been accused. Electron microscopic trials disclosed the inhibition corneal neovascularization in thalidomide-treated rabbits.[65] The most common embryogenic defect caused by thalidomide is phocomelia which may be accompanied by ear malformation and renal, urogenital and gastrointestinal system malformations.[20] McBride reported 40% mortality immediately after birth caused by thalidomide teratogenicity.[66]

Peripheral neuropathy

Thalidomide-induced neuropathy has occurred in up to 50% of some series of patients, and can be irreversible. It is not related to the total cumulative dose.[67] The most common presentation is mild proximal muscle weakness with symmetric painful paresthesia of the hands and feet.[20] In a prospective cohort including 135 dermatologic patients receiving thalidomide therapy thalidomide-induced neuropathy were detected in 25.2% of the patients.[68]

Drug interactions

Thalidomide enhances the activity of alcohol, barbiturates, reserpine and chlorpromazine.[6] It increases serum levels of acetaminophen and raises the activity of histamine, serotonin and prostaglandins.[10]

CONCLUSION

Although thalidomide has been used successfully in treating of many other dermatological conditions that are refractory to standard therapy it is approved by the FDA only for ENL. It is expensive and inconvenient to obtain the medication. Physicians should be informed about possible side effects, especially peripheral neuropathy. Optimal maintenance doses are recommended with control of adverse reactions. A negative pregnancy test should be obtained in 24 hours of the onset of therapy. Birth control should be started at least one month before therapy and fertile men should wear condom during sexual intercourse because the drug has been detected in semen.[69,70]

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