TOTAL AGRANULOCYTOSIS CAUSED BY DAPSONE THERAPY FOR TUBERCULOID LEPROSY – AN UNAPPRECIATED SERIOUS SIDE EFFECT OF ANTI-LEPROSY TREATMENT WITH CLINICAL IMPLICATIONS

R.L. Satarasinghe, M.A.R. Jayawardana*, G.V.T.S.K. De Silva, S. Murugathas, A.A.A. Riyaaz, U.D.U.K. Wickrmasingha and R. Wijesinghe

Department of Medicine, Sri Jayewardenepura General Hospital and Postgraduate Training Center, Thalapathpitiya, Nugegoda, Sri Lanka

SUMMARY

Dapsone-induced agranulocytosis is a rare but potentially fatal adverse effect of treatment for tuberculoid leprosy. Publications distributed by the WHO Leprosy Elimination Campaign for patient information on leprosy do not contain any advice or guidelines for post-dapsone therapy follow-up. As a result of this major deficiency, the local anti-leprosy campaign in Sri Lanka has no such guidelines on dapsone therapy for leprosy patients. We report two patients with total agranulocytosis caused by dapsone therapy for tuberculoid leprosy including one fatality. As leprosy is more prevalent in developing countries such as Sri Lanka, we recommend that WHO publications on patient information should include post-dapsone therapy follow-up guidelines to avoid such catastrophes which are undetected until the patients are critically ill.

* Author for correspondence:
Dr. M.A.R. Jayawardana
Department of Medicine, Ward 6,
Sri Jayewardenepura General Hospital and Postgraduate Training Center
Thalapathpitiya, Nugegoda, Sri Lanka
e-mail: marjayawardana@yahoo.com

KEY WORDS

dapsone, agranulocytosis, guidelines, WHO

INTRODUCTION

Literature review revealed that dapsone-induced neutropenia is a rarity during treatment for tuberculoid leprosy. Even at the national level in Sri Lanka, no guidelines have been formulated for prescribing physicians to monitor therapy. We report two patients with dapsone-induced total agranulocytosis, leading to death in one of them.

PATIENT REPORTS

Patient 1

A 35 year-old female who had been on dapsone therapy for two months for tuberculoid leprosy presented with an acute febrile illness of one week duration. Investigations showed a total white cell count of 500/mm^3 with a zero neutrophil count, evidence of haemolysis and fungi-like hyphae with a hypocellular marrow in trephine bone marrow biopsy. She was managed with a combination of broad spectrum intravenous antibiotics and antifungal agents. As a supportive measure granulocyte colony stimulating factor (GCSF) was administered. She made a complete recovery.

Patient 2

A 28 year-old female presented with a history of an acute febrile illness of three days duration and with evidence of otitis media. She had been on dapsone therapy for two months for tuberculoid leprosy. Investigation revealed leucopenia with a white cell count of 500/mm^3, zero neutrophil count and evidence of haemolysis. She succumbed to the illness within 72 hours of admission despite treatment with broad spectrum antibiotics, antifungal agents and GCSF. A computerized axial tomography (CT scan) of the head following admission was normal. The postmortem findings revealed filamentous organisms in the lungs while the rest of the organs were unremarkable except for mild congestion.

Both patients were on standard paucibacillary treatment regimen for tuberculoid leprosy with dapsone 100 mg daily and rifampicin 600 mg monthly for six months, as recommended by the World Health Organization (WHO).

DISCUSSION

Agranulocytosis is a rare, potentially life-threatening medical emergency occurring as a result of an idiosyncratic reaction associated with drug therapy. Aminopyrine, clozapine, dapsone and anti-thyroid drugs are the best documented. Agranulocytosis is generally associated with older individuals, above 60 years, and those of non-Caucasian origin[1]. In patients with leprosy, dapsone-related agranulocytosis is said to be minimal.

Nevertheless, when dapsone is prescribed for dermatitis herpitiformis, the risk of agranulocytosis increases 25-fold reaching 1:400. Typically patients present with fever and evidence of infection during the first 3 months of initiating therapy with dapsone.

The frequency of agranulocytosis when dapsone was used for malaria prophylaxis in United States servicemen in Vietnam was sufficient for its withdrawal[2]. A literature survey revealed two reports of agranulocytosis related to dapsone therapy in patients with leprosy from India[3,4]. There have been no further reports to our knowledge. Over the last 18 years, the global prevalence of leprosy has been reduced and the leprosy burden is now centralized in the following endemic countries: Brazil, India, Madagascar, Mozambique and Nepal - according to WHO reports.

The mechanism of dapsone-induced agranulocytosis is unclear but may involve erythrocytes[5]. After absorption from the intestines, dapsone is transported through the portal circulation to the liver, where it is metabolized via acetylation or *N*-hydroxylation. The latter yields hydroxylamine, a potentially toxic metabolite produced by cytochrome P-450 enzymes, whereas acetylation by *N*-acetyltransferase yields the non-toxic metabolites, mono- and di-acetyl dapsones[6]. Erythrocytes exposed to hydroxylamine even when repeatedly washed may still release this metabolite in sufficient concentration to kill mononuclear leucocytes *in vitro*. The erythrocytes may be a conduit for hydroxylamine to reach the bone marrow, where it can covalently

bind to granulocyte precursors initiating an immune reaction in certain individuals leading to potentially fatal agranulocytosis.

Dapsone toxicity may be related to increased plasma levels or being more immunocompromised, but in both patients there were no other features to suggest immunocompromised state in comparison to other patients with tuberculoid leprosy who have received such therapy. Measurement of plasma levels of dapsone to monitor therapy to recognize patients who develop agranulocytosis has never been recommended in guidelines on the treatment of leprosy, as in developing countries where leprosy is more prevalent, and it will never be cost-effective. Studies are needed to examine the relationship between the risk of development of agranulocytosis and plasma dapsone levels to recommend such monitoring as a preventive measure, as there are no data available in a literature search.

In the "Guide to Eliminate Leprosy as a Public Health Problem" produced by the WHO Leprosy Elimination Group, this potentially lethal adverse effect of dapsone is not mentioned under the subtitle "Information for the patient" or elsewhere. Similarly, the publication "The Final Push Strategy to Eliminate Leprosy as a Public Health Problem–Questions & Answers" produced by the same group once again fails to warn patients with regard to dapsone-induced agranulocytosis, and it even stipulates that multi-drug therapy (MDT) in leprosy has negligible side effects[7]. Hence we believe that the awareness of this serious side effect of dapsone is not truly appreciated by patients and prescribing physicians in developing countries where leprosy still exists in abundance.

The filamentous structures seen in the bone marrow and lungs of our patients illustrate fungaemia which could occur in agranulocytosis. The absence of macroscopic changes in the viscera of the fatal case probably depicts the failure to initiate an acute inflammatory response in the absence of neutrophils.

CONCLUSIONS

The two patients described here are to our knowledge the first reported cases of total agranulocytosis due to dapsone therapy in patients with tuberculoid leprosy from Sri Lanka. The available WHO publications and guidelines followed locally have not adequately addressed this potentially lethal complication of dapsone therapy and

there are no follow-up national guidelines in Sri Lanka for dapsone recipients. Hence there may be many such cases suffering fatalities due to undetected agranulocytosis and other related complications. Therefore we strongly recommend that there should be uniformly adopted international guidelines on dapsone therapy, and the WHO should take appropriate action to warn the anti-leprosy campaigns and the patients with regard to this potentially lethal adverse effect.

The measurement of plasma dapsone levels to identify high risk patients who could develop agranulocytosis has still not been recommended for developing countries due to the lack of sufficient data in benefit and risk involved, although it remains a viable option.

REFERENCES

1. Coleman MD. Dapsone mediated agranulocytosis: risks, possible mechanisms and prevention. Toxicology 2001; 162: 53-60.
2. Firkin FC, Mariani AF. Agranulocytosis due to dapsone. Med J Aust 1977; 2: 247-251.
3. Hiran S, Pande TK, Pani S, Vishwanathan KA. Dapsone agranulocytosis in a leprosy patient. Lepr Rev 1994; 65: 279-281.
4. Bhat RM, Radhakrishnan K. A case report of fatal dapsone induced agranulocytosis in an Indian mid borderline leprosy patient. Lepr Rev 2003; 74: 167-170.
5. Coleman MD. Dapsone toxicity: some current perspectives. Gen Pharmacol 1995; 26: 461-467.
6. Zuidoma J, Hibers-Modderman EJ, Merkees F. Clinical pharmacokinetics of dapsone. Clin Pharmacokinet 1986; 11: 299-315.
7. World Health Organization Leprosy Elimination Group. The Final Push Strategy to Eliminate Leprosy as a Public Health Problem–Questions & Answers, 2nd Ed. Geneva: WHO, 2003; 1-41.
8. www.who.int/lep