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Chloramphenicol-induced Aplastic Anaemia – Should Its Topical Use Be Abandoned?

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Aplastic anaemia was first described by Paul Ehrlich in 1888. It is defined as peripheral pancytopenia occurring in the presence of a hypoplastic bone marrow with replacement of normal haemopoiesis by fat cells. It is a relatively rare disease and has an annual incidence of 2 per million in the Western population but is 2 to 3 times more common in the Oriental race. Exposure to radiation or chemotherapy results in a direct toxic effect on the bone marrow while viral agents or drug exposure may cause marrow aplasia through an immune-mediated mechanism. Idiosyncratic reactions to various pharmaceutical agents have also been implicated as one of the mechanism for marrow toxicity. Following chemotherapy or radiotherapy, bone marrow recovery is usually expected. In idiopathic aplastic anaemia, where there is no attributable cause, recovery of normal haemopoiesis is usually unpredictable.

Numerous drugs have been listed as causing aplastic anaemia and many of these associations have arisen following case reports. One such drug that has been implicated as causing aplastic anaemia is the use of chloramphenicol. Both the systemic and topical form appear to cause bone marrow depression. Two mechanisms are thought to be involved in causing marrow aplasia[1,2]. It may be due to a dose-dependent effect of chloramphenicol causing an inhibition of mitochondrial protein synthesis or it may result from an idiosyncratic reaction to chloramphenicol. DNA damage occurs in the haemopoietic stem cells which leads to marrow aplasia. It is thought that the associated aplastic anaemia seen with topical chloramphenicol use is an idiosyncratic reaction to the drug.

Chloramphenicol is the first broad spectrum antibacterial agent to be discovered and was introduced in 1948 in the United States. Shortly after its introduction, a case of fatal aplastic anaemia associated with its oral use was reported in 1950. The associated risk from systemic chloramphenicol has been estimated to be between 1:24000 to 1:40000 exposure[3]. Case reports of aplastic anaemia associated with topical chloramphenicol started to appear in the 1960s[4-8]. By the 1980s, sales in topical chloramphenicol fell drastically in the United States[8]. It now carries a warning that the drug should not be used unless there is no alternative. It would appear that the reservations in the use of the topical form have arisen mainly through case reportings and its adverse effects have not been fully substantiated.

Many other countries around the world have continued to use topical chloramphenicol eyedrops. In Great Britain, topical chloramphenicol is the drug of choice in superficial eye infections, It has a good spectrum of activity and the drug penetrates the cornea and the anterior chamber of the eye. The use of topical chloramphenicol has not fallen despite its association with aplastic anaemia. There has been no reported increase in the annual incidence of aplastic anaemia in the United Kingdom[9]. Similar findings are noted in the Netherlands. Three percent of its population is exposed to topical chloramphenicol. Despite this high incidence, no association with aplastic anaemia has been reported and the incidence of aplastic anaemia has remained constant[10]. On the other side of the globe, a review on the use of chloramphenicol in Hong Kong showed a 10 to 400 times increase as compared to several Western countries. Despite this high usage, the certified death from aplastic anaemia was found to be only 0.4 per 1000 deaths in Hong Kong as compared to 1 per 1000 deaths in England and Wales[11]. For many years, aplastic anaemia has been reported as being more common in Asia than in the West. One of the suggested explanation for this was drug exposure and its easy availability without prescription in Asia[12]. For a time, chloramphenicol was thought to be one of the common causes of aplastic anaemia. In a recent population-based, case-control study of aplastic anaemia conducted in Thailand, no significant association was seen with the use of this drug[13]. The overall proportion of drug-induced aplastic anaemia in this study group accounted for only 5% of the cases as compared to 25% in the Western population. In this study, the authors found a strong inverse association with socioeconomic status and an association with grain farming, occupational exposure to solvents and hepatitis A. In a Scottish study by Walker et al[14], high performance liquid chromatography was used to measure systemic detection of topical use of chloramphenicol. They failed to show a systemic accumulation of the drug from ocular use. They concluded that the use of topical

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chloramphenicol did not appear to be a justifiable risk in causing marrow aplasia. Topical chloramphenicol continues to be extensively prescribed in Scotland and there is no reported increase in the incidence of acquired aplastic anaemia from its use.

Most drugs incriminated to cause aplastic anaemia occur as a result of case reports. There appears to be a certain degree of personal biases. The best method of assessing drug association with aplastic anaemia is through epidemiological studies and large case-control studies. This allows the relative risk of a drug thought to cause bone marrow dyscrasias to be estimated in a more systemic method but such studies may be difficult to perform. Chloramphenicol is a useful drug in the treatment of superficial eye infections. It is a reliable drug and is relatively inexpensive. Data on its idiosyncratic effect on marrow toxicity are based mainly on case reports and does not justify its abandonment. Although the Americans may have reservations about its use, the British continue to support the use of topical chloramphenicol. Despite the toxic marrow effect of chloramphenicol, its prescription and sales continue in countries around the world. This has not resulted in an increase in the incidence of aplastic anaemia. Its topical use should not be abandoned until more substantial evidence is available to indicate its toxicity.

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