

Reinstatement of Dapsone Following Hypersensitivity

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Sir,

Dapsone therapy can cause severe adverse reactions known as the sulphone or dapsone hypersensitivity syndrome (DS). The most common presenting symptom is a maculopapular or exfoliative rash confined to either the upper limbs or the forehead, but it can also be disseminated. The sequence of symptoms – dermatitis, lymphadenopathy notably along the posterior border of the sternomastoid muscles and hepatitis – forms a particular pattern.

Opinions vary on desensitization after DS. In 1963, Browne (1) reported 52 leprosy patients in whom desensitization was attempted; only 2 cases had severe dermatitis after every dose of dapsone. Since then there have only been two reports of successful attempts to reintroduce dapsone in HIV patients (2, 3). This is the first report of the reintroduction of dapsone after DS in a patient with dermatitis herpetiformis.

CASE REPORT

An otherwise healthy 16-year-old girl developed pruritic papules and vesicles on the scalp, face, upper back, buttocks and knees. Immunohistological findings were characteristic of dermatitis herpetiformis. After normal routine blood and urine analyses, including G6PD, she was started on dapsone 50 mg once daily and a gluten-free diet. After 7 days the dose was increased to 100 mg once daily because of the slow improvement of her disease. On day 16, reddish, desquamating patches appeared on the patient's forehead (Fig. 1). On day 18, she was afebrile and had no general malaise, but the desquamating lesions had spread to the rest of the face and upper limbs, and purple maculopapular lesions affected the distal third of the lower extremities. Further physical examination revealed painless lateral cervical adenopathy, and a blood sample showed increased erythrocyte sedimentation rate (ESR), moderate haemolysis and leucocyte count of $5100/\text{mm}^3$ with 13% eosinophils.

Faced with the onset of exfoliative dermatitis on the forehead, cervical lymphadenopathy, eosinophilia and increased ESR, dapsone hypersensitivity was diagnosed, and the drug was withdrawn. The clinical and laboratory alterations resolved within 4 days. Since the syndrome had been mild and late, and there was no effective alternative therapy, we reviewed the previous series of 67 patients in whom the drug had been

reintroduced after DS, and one week after withdrawal we started treatment under daily close observation at the initially tolerated dosage of 50 mg each morning. After 2 weeks, during which no signs of intolerance were observed, another 100 mg per week was added in two 50 mg doses taken at night at least 48 h apart. Further evening doses were added at 2-week intervals, reaching 50 mg every 12 h in week 8; the same approach was employed to reach the therapeutic dosage, 100 mg every 12 h, in week 18. There have been no side effects other than moderate haemolysis during the entire reintroduction period. The patient's dermatitis is now being controlled with a gluten-free diet.

DISCUSSION

Historically, following the introduction of dapsone to clinical practice in the 1950s, cases of DS were related to high dosages (> 50 mg/day) in the first 6–8 weeks of treatment (1, 4). As a result, low initial dosages and a longer introductory phase became the standard practice (5), and between 1956 and 1980 virtually no new cases



Fig. 1. The patient 16 days after the start of therapy and with the first sign of dapsone syndrome (erythematous, desquamating macules on the forehead). Former papules and excoriated vesicles of dermatitis herpetiformis are still present.

Table II. Reports of hypersensitivity reactions in diseases treated with dapsone 1956–2000

Year	Leprosy	DH	PP in HIV disease	Other diseases
1956–1979	1 ¹	2 ^{7,8}		1 EED ⁶
1980–1986 ⁹	10	2		1 Acne, 1 Vasculitis, 1 Psoriasis
1987–1993	4 ^{11,a}		2 ^{2,b}	1 Malaria, ^c 1 Bite of spider ^c
1994–2000	7 ^d	1 ^e	2 ^{3,f}	1 PG, ^g 1 Pemphigoid, ^g 1 Pemphigus, ^g 1 Asthma, ^g 1 PAN, ^g 2 Lupus, ^g 1 Acne ^g

DH, dermatitis herpetiformis; PP, prophylaxis of *Pneumocystis pneumonia*; EED, erythema elevatum diutinum; PG, pyoderma gangrenosum; PAN, polyarteritis nodosa. ^{1–11}Refers to numbers in reference list. ^aPatki et al., *Lepr Rev* 1989; 60: 274–277; Richardus et al., *Lepr Rev* 1989; 60: 267–273; Singal et al., *Indian J Lepr* 1993; 65: 443–445. ^bMohle-Boetani et al., *West J Med* 1992; 156: 303–306. ^cGrayson et al., *Lancet* 1988; 1: 531; Wille et al., *Am J Med Sci* 1988; 296: 270–271. ^dRege et al., *Indian J Lepr* 1994; 66: 59–64; Hortaleza et al., *Lepr Rev* 1995; 66: 307–313; Lau, *Forensic Sci Int* 1995; 73: 109–115; Arunthathi et al., *Acta Leprol* 1998; 11: 3–5; Ng et al., *J Am Acad Dermatol* 1998; 39: 646–648; Kumar et al., *Indian J Lepr* 1998; 70: 271–276; Jaswal et al., *Indian J Lepr* 1998; 70: 229–230. ^eMcKenna et al., *Br J Dermatol* 1997; 137: 657–658. ^fChalasani et al., *South Med J* 1994; 87: 1145–1146. ^gSaito et al., *Clin Exp Dermatol* 1994; 19: 152–156; Risse et al., *Ann Derm Venereol* 1994; 121: 242–244; Barnard et al., *Am J Gastroenterol* 1994; 89: 2057–2059; Bocquet et al., *Ann Dermatol Venereol* 1995; 122: 514–516; Prussick et al., *J Am Acad Dermatol* 1996; 35: 346–349; Mok et al., *J Rheumatol* 1996; 23: 766–768; Christiansen et al., *Acta Derm Venereol* 1999; 79: 482; Corp et al., *J Pediatr Gastroenterol Nutr* 1998; 26: 103–105.

were reported (1, 6–8) (see also 9, 10). In the early 1980s, full-dosage initial treatments returned to prevent bacteriological resistance in leprosy patients, and this new practice became the standard also for other diseases treated with dapsone. As indicated in Table I, of the 45 DS reports in the literature since 1956, only 4 are reported in the first 23 years, the rest are from 1980, 18 of them in the last 7 years, especially among HIV patients where dapsone is used as prophylaxis of *Pneumocystis pneumonia*.

It is concluded from the published reports that the initial dosage is the crucial point in the increase of DS (1, 4, 5, 9–12). Dapsone is metabolized in a time-dependent manner and the balance between oxidation to its toxic metabolites and their reduction is an important protective cellular mechanism. If an imbalance exists, binding of toxic metabolites to proteins may occur and result in drug hypersensitivity (13), as in the so-called antiepileptic drug hypersensitivity syndrome (14).

In our opinion, the tolerance observed previously in 67 patients (1–3) and in this case following gradual reintroduction is likely to have been a result of adaptation of the patient's capacity to detoxify the drug rather than true immunological desensitization. In Browne's series of 52 patients (1), the maximum tolerated dose on resumption was found to be at most one-half the dose given immediately before the recurrence. In view of the long half-life of dapsone (14–83 h), we did not increase the dosage from very low levels by small increments, as recommended previously (1–3), but instead restarted treatment at the dosage tolerated initially (50 mg), which was also one-half the dose given before the DS appeared and increased the dosage over a longer induction period.

In summary, the available data suggest that >50 mg/day in the first 6–8 weeks of treatment is inadvisable in

patients who do not have leprosy, and that in cases of DS the careful reintroduction of dapsone could be a valid therapeutic option.

REFERENCES

- Browne SG. Desensitization for dapsone dermatitis. *BMJ* 1963; 2: 664–667.
- Metroka CE, Lewis NJ, Jacobus DP. Desensitization to dapsone in HIV-positive patients (Letter). *JAMA* 1992; 267: 512.
- Cook DE, Kossey JL. Successful desensitization to dapsone for *Pneumocystis carinii* prophylaxis in an HIV-positive patient. *Ann Pharmacother* 1998; 12: 1302–1305.
- Lowe J. Diaminodiphenylsulphone in the treatment of leprosy. *Lancet* 1951; 1: 18–21.
- Trautman JR. The management of leprosy and its complications. *N Engl J Med* 1965; 273: 756–758.
- Potter B, Szymanski FJ, Fretzin D. Erythema elevatum diutinum and sulfone hypersensitivity. *Arch Dermatol* 1967; 95: 436–440.
- Millikan LE, Harrell ER. Drug reactions to the sulfones. *Arch Dermatol* 1970; 102: 220–224.
- Kingham JGC, Swain P, Swarbrick ET, Walker JG, Dawson AM. Dapsone and severe hypoalbuminemia: a report of two cases. *Lancet* 1979; 2: 662–664.
- Smith WCS. Are hypersensitivity reactions to dapsone becoming more frequent? *Lepr Rev* 1988; 59: 53–58.
- Frey HM, Gershon AA, Borkowsky W, Bullock WE. Fatal reaction to dapsone during treatment of leprosy. *Ann Intern Med* 1981; 94: 777–779.
- Reeve PA, Ala J, Hall JJ. Dapsone syndrome in Vanuatu: a high incidence during multidrug treatment of leprosy. *J Trop Med Hyg* 1992; 95: 266–270.
- de Soldenhoff R. Are dapsone hypersensitivity reactions dose related? (Letter). *Lepr Rev* 1990; 61: 391–392.
- Shear NH, Spielberg SP, Grant DM, et al. Differences in metabolism of sulfonamides predisposing to idiosyncratic toxicity. *Ann Intern Med* 1986; 105: 179–184.
- Schlienger RG, Shear NH. Antiepileptic drug hypersensitivity syndrome. *Epilepsia* 1998; 39 Suppl. 7: S3–7.