FIXED DRUG ERUPTIONS TO MALOPRIM

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SYNOPSIS

Eleven men who developed fixed drug eruptions were studied. All have positive challenge tests to dapsone or Maloprim*. As little as 1 mg of dapsone can provoke a positive reaction on challenge. Of 7 patients who were additionally challenged to pyrimethamine, 2 reacted positively indicating polysensitivity. This finding is of importance as Fansidar which is the alternative drug used for prophylaxis/therapy of chloroquine-resistant Plasmodium falciparum malaria in endemic areas also contains pyrimethamine.**

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Maloprim has been in use as a prophylaxis against malaria caused by Plasmodium falciparum in particular in countries where chloroquine-resistant strains are prevalent. It is a compound tablet each containing dapsone (diaminodiphenyl-sulphone) 100 mg and pyrimethamine (2, 4-diamino-pyrimidine) 12.5 mg. Talwat(1) reported 12 cases of fixed drug eruptions due to dapsone presenting with "black spots" among Papua New Guinea defence force personnel. He concluded that the fixed eruptions were caused by dapsone as evidenced by a positive provocation test in 5 of his patients to dapsone (50 mg) and a negative response to pyrimethamine (12.5 mg) in 3 of these patients.

We report our observations in 11 patients who developed fixed eruptions to Maloprim.

PATIENTS AND METHODS

Between April 1985 and May 1986, 11 patients with fixed eruptions to Malprim were seen. These were young men from the Singapore Armed Forces taking Maloprim for malaria prophylaxis during field training.

A careful history was obtained to determine the time relationship between the ingestion of tablets and onset of the eruption. Other medications, if any, administered at the same time were noted. The sites affected by the fixed eruptions were recorded. After the acute lesions had completely subsided, challenge tests were performed with informed consent of the patients.

The protocol as shown in Table 1 was used whenever possible.

If a reaction should occur at any stage the patient was advised to report immediately for confirmation of the reaction. Further testing was not done until at least 4 weeks later, when the acute reaction would have settled completely. Fansidar** was used as one of the test items because this was used as the alternative prophylactic drug for malaria in someone who has reacted adversely to Maloprim.

A "variable" dapsone dose was used for 8 of the patients. Doses ranged from 1 to 100 mg. Dosage started as low as 1 mg and increases through 12.5 mg, 25 mg, 50 mg to 100 mg. The objective was to determine the threshold of reaction to dapsone.

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RESULTS

The 11 patients studied were Singapore Armed Forces men. They aged between 19 and 25 years. Ten of them were Chinese and 1 Indian (Sikh).

All 11 patients had a positive response on provocation.

Eight patients reacted to challenge with dapsone alone (figure 1). The dose of dapsone given to these 8 patients were 1 mg (1), 12.5 mg (1), 25 mg (2), 50 mg (3) and 100 mg (1). The onset of reaction ranged from half an hour to 5 hours after consuming the dapsone.

Seven patients completed oral challenge to pyrimethamine. One patient refused after recording a positive reaction to dapsone (given earlier in this case). Of these 7 patients, 2 had a positive reaction, which appeared 1 and 4 hours after administration of the tablets (figure 2). These reactions appeared in the **same sites** as those reacting to dapsone. One of these 2 patients developed a severe reaction with reactivation of old lesions and and the appearance of several new lesions with oral ulceration, fever and chills. Many of the lesions were clinically 'iris' lesions with bullae in the center. The eruption required oral corticosteroid therapy and took 3 weeks to subside. This was also the patient who react to 1 mg of dapsone subsequently.

Of those patients who had a negative reaction to pyrimethamine 4 were challenged to Fansidar. None showed a positive response.

In 3 other patients it was only possible to record a positive reaction to Maloprim, 2 to the whole tablet and 1 to half a tablet of Maloprim. These reactions occurred within 10 hours after oral challenge.

DISCUSSION

Maloprim, taken in a once weekly dose, is used for prophylaxis against malaria caused by Plasmodium falciparum in endemic areas. The occurrence of 11 cases in a year where approximately 50,000 tablets are consumed indicates the incidence of fixed eruptions due to Maloprim is very low, approximately 1 in 4,500 exposures. Browne reported 254 dapsone-induced fixed eruptions in deeply pigmented subjects and estimated the frequency to be up to 3% of leprosy patients treated. However, like Talwat, we have found that leprosy patients rarely develop fixed eruptions to dapsone. In Singapore there are about 1,900 patients, most of them Chinese, currently on dapsone for

TABLE 1
PROVOCATION TESTS

Drug	Reaction	
	Positive/Negative	**Onset (hrs)**
Day 1 — pyrimathamine 25 mg Day 2 — pyrimathamine 50 mg Day 4 — Fansidar ** Day 7 — dapsone 50 mg Day 8 — dapsone 100 mg		

* MALOPRIM (Wellcome)
Each tablet contains:
(a) pyrimethamine 12.5 mg
(b) dapsone 100 mg

** FANSIDAR (Roche)
Each tablet contains :
(a) sulfadoxine 500 mg
(b) pyrimethamine 25 mg

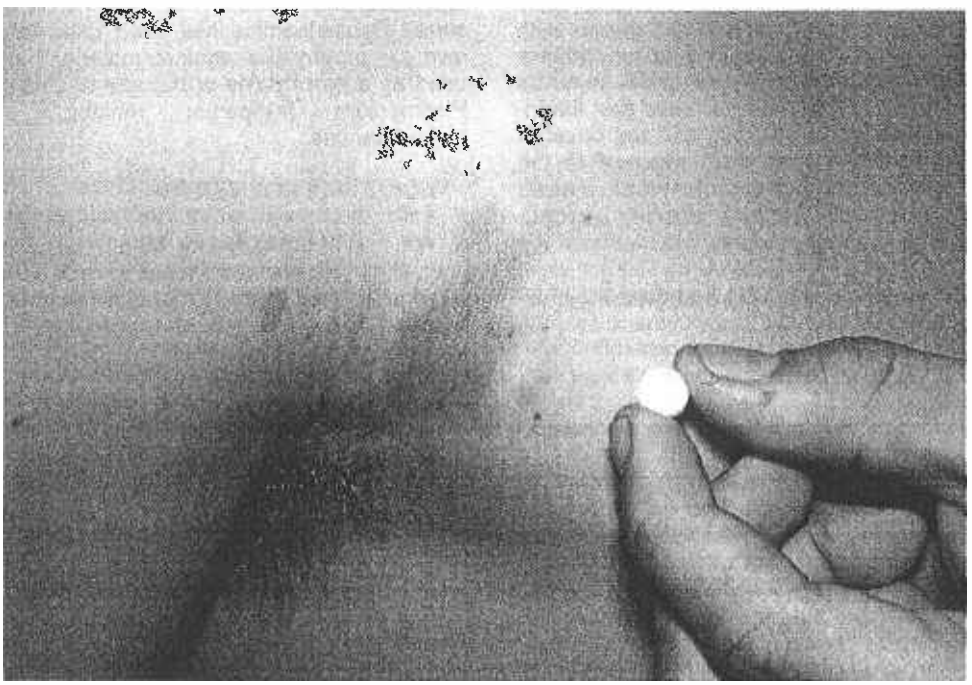

Figure 1: Positive challenge to dapsone 50 mg showing the reactivation of the fixed drug eruption 2 hours after challenge.

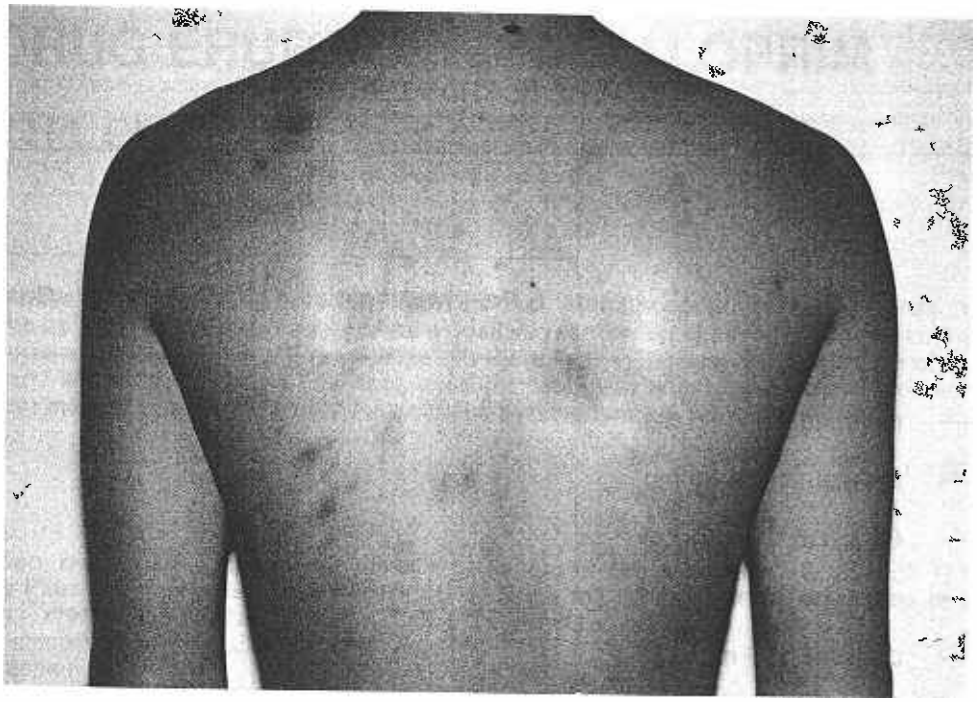

Figure 2: Positive reaction 4 hours following an oral challenge to 25 mg of pyrimethamine. In this patient, in addition to the reactivation of the previous lesions, there were many new lesions, oral ulceration, fever and chills.

leprosy and there were no reported cases of fixed eruptions. Although the minimum provocation dose was not performed in all cases, we observed that the full dose is frequently not required for provocation. As with our experience with tetracycline-induced fixed eruptions(3), very small doses can bring on a reaction. One patient was provoked with only 1 mg of dapsone.

On challenge, it is expected that the reaction would appear within 10 hours. Our patients reported the onset of activity from half-an-hour to 5 hours after drug ingestion except for 2 patients who took the tablets in the evening and noticed the lesions in the morning. The activity could have started in the night during sleep. This concurs with previous reports that fixed drug eruptions occur within a few hours although occasionally the interval may be longer with other drugs(4). Two patients noted that the interval between the ingestion of the drug and the onset of activity shortened each time they were exposed to the drug. Therefore, when provoking a patient with a fixed drug eruption, it is expected that a positive reaction should appear no later than the interval obtained from the history.

This study showed all patients who had dapsone challenge reacted positively. In contrast to Talwat's study, 2 of 7 patients also reacted with pyrimethamine challenge. The reaction appeared on the same sites as those which developed subsequently to dapsone. Fixed eruptions caused by 2 chemically unrelated drugs have been reported previously(5,6). This polysensitivity may manifest on the same or different sites. To our knowledge there have been no previous report of fixed eruptions to pyrimethamine nor polysensitivity of this drug and dapsone.

What is the importance of knowing the concommitant existence of pyrimethamine reactivity in addition to dapsone? Pyrimethamine has been used in the past on its own for prophylaxis against malaria. Fansidar currently used as a prophylaxis or therapy of chloroquine-resistant Plasmodium falciparum malaria, also contains pyrimethamine.

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