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Thioguanine Treatment in Psoriasis

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The efficacy of thioguanine in the treatment of severe cases of psoriasis is demonstrated. This treatment is valuable in selected cases of severe psoriasis in whom other treatment is ineffective or impossible due to side effects. The effect of thioguanine on psoriasis lesions appears to run parallel with depression of the bone marrow. The bone marrow toxicity has to be considered. Patients previously treated with methotrexate are very sensitive to thioguanine and close follow up is mandatory with adjustment of the thioguanine dose according to blood white cell and thrombocyte levels. *Key word: Bone marrow depression.*
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Thioguanine, which is closely related to 6-mercaptopurine, is an antimetabolite in the synthesis of purine, chiefly guanine. The mechanism of action is, however, not fully defined. Thioguanine is administered orally and maximal plasma concentration is reached in 8 to 10 hours. It is metabolized in the liver and 35% of a given dose is excreted in the urine within 24 hours (1). The main indication for thioguanine is acute leukemia where it usually is used at initial dosages of 400 mg a day as part of a chemotherapeutic regimen.

Demis et al. (2) reported that thioguanine had an effect in two cases of psoriasis, one of whom also suffered from an active arthritis. A good response was obtained on both the skin and joint lesions. Since that thiogunanine was used in isolated cases of severe psoriasis with good effect, but the drug has not gained wide use.

Zackheim et al. (3, 4) recently presented 20 years of experience with thioguanine therapy for psoriasis mostly in cases, in whom methotrexate was contraindicated due to liver damage or gastrointestinal intolerance. Their results prompted us to use thioguanine in similar cases of severe psoriasis, in whom the use of methotrexate or retinoids had been associated with problems.

MATERIALS AND METHODS

Nine patients were treated with thioguanine (Table I). One patient had widespread plaque type of psoriasis combined with chronic active psoriatic arthritis, five patients had total or subtotal involvement of the body surface by psoriasis lesions, two patients had widespread pustular psoriasis and one patient pustular psoriasis mainly on palms and soles. The duration of psoriasis varied between 10 and 34 years. All of the patients had been treated with methotrexate, some of them with etretinate and PUVA.

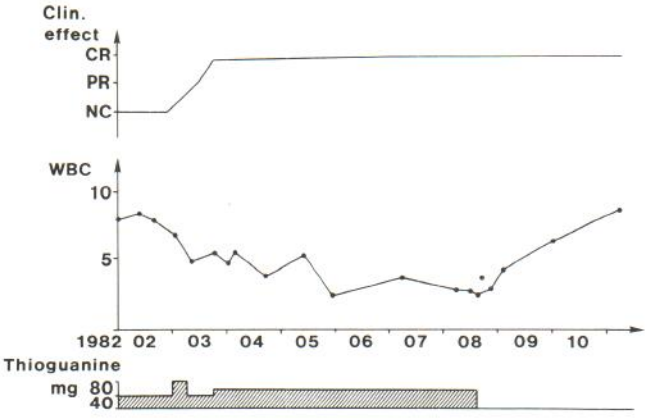

Fig. 1. The therapeutic response of thioguanine in a male patient, 36 years of age, with longstanding widespread plaque-type psoriasis and psoriatic arthritis (case 1). CR =complete remission, PR=partial remission to more than 50%, NC=no change or remission less than 50% as compared with the situation at the start of treatment. White blood cell (WCB) count in 10^9/litre.

Thioguanine treatment was instituted either because of insufficient effect or unacceptable toxicity of previous treatment regimes.

Initially the dosage of thioguanine was usually 40 mg per day for some weeks and then increased to 60 or 80 mg per day. In most cases a clear regression was seen after 3 to 4 weeks. After clearing of the skin lesions, the dose has been reduced and in some cases a maintenance dose of 40 mg every other day or twice a week had maintained the remission.

RESULTS

The good effect of thioguanine can be illustrated by case 1 (Fig. 1) with longstanding severe psoriasis and psoriatic arthritis. He was treated with methotrexate for nearly 9 years with a total dose of more than 7 grams but the drug could not be used any longer due to liver toxicity. With thioguanine 40 mg and later 60 mg per day, the lesions cleared completely within 2 months with the exception of a single plaque on one leg which also cleared after another month of treatment. The joint complaints diminished and nail changes gradually cleared.

After withdrawal of thioguanine, psoriasis relapsed after 3 to 4 months. Thioguanine was reinstituted and again caused complete clearing of the lesions within 2 months and after that a maintenance dose of 40 mg twice weekly has kept the patient completely free of lesions for more than 1 ½ years. Similar good therapeutic results have been seen in other cases of longstanding severe prosirasis including pustular psoriasis (Table I).

Thioguanine therapy is, however, not always without problems. In two cases on low doses of thioguanine (cases 5 and 6), a severe bone marrow depression occurred with white blood cell counts less than 1 000 and platelet counts less than 10 000. One patient (case 6) had psoriasis covering the whole body surface. A severe bone marrow depression occurred within three weeks of treatment (Fig. 2). All psoriasis lesions disappeared rapidly, when the bone marrow was depressed, and he was free from psoriasis for the first time in 20 years. Parallel with the returning bone marrow activity the psoriasis lesions reappeared.

DISCUSSION

Like 6-mercaptopurine, thioguanine as an antimetabolite inhibits DNA synthesis via an inhibition of purine ring biosynthesis. It is, however, unlikely that thioguanine in the doses used in our patients could directly influence the growth of the keratinocytes in such a way

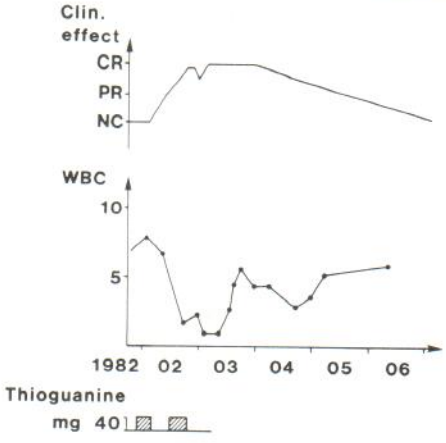

Fig. 2. The rapid effect on psoriatic lesions and on white blood count of small doses of thioguanine in a male patient, 53 years of age, with erythroderma (case 6). The bone marrow was restituted without additional therapy.

Table I. *Effect of thioguanine in therapy-resistant psoriasis*

Patients age, sex	Psoriasis Dur. (yrs)	Psoriasis Type	Previous treatment	Thioguanine treatment Initial dose (mg/d)	Effect (%)	Within (months)	Maintenance dose (mg)	Total duration (months)	Reduction of WBC (%)	Side effect
1 39 M	10	Plaque + pso arth	MTX 7 g	40–60	100	2	40×2/w	30	40	No
2 40 M	33	General	MTX 1 g PUVA Tigason	40–80	90	2	40/d	14	25	No
3 66 M	34	General	MTX 8 g	80–120	95	3	40×2/w	13	35	No
4 36 M	15	General	MTX 3 g PUVA Tigason	40–80	100	6	40×2/w	16	20	Slight G–I complaints
5 60 F	14	General	MTX 1 g	40×3/w	50	3	40×3/w	7	30	
			PUVA	40–80	95			1	90	Severe bone marrow depression
6 53 M	25	General	MTX 4 g PUVA	40	100	1	–	3 w	90	Severe bone marrow depression
7 70 F	18	General	MTX 1 g	40–120	No			5	10	No
		Pustulos		40	90	2	40×2/w	16	10	No
8 72 M	15	General Pustulos	MTX 3 g Hydrea Tigason	40–80	0		–	2 w	0	Liver+ renal toxicity
9 59 M	8	Pustular palms, soles	MTX 4 g	40–80	50	1	40/d	6	30	Thrombopenia

as to explain the observed therapeutic effect. On the other hand, the effect of thioguanine in the psoriasis patients apparently runs parallel to the depression of the bone marrow and the clearing of the psoriatic lesions therefore might be explained by suppression of the inflammatory component of the psoriasis lesions caused by the decreased number of peripheral neutrophils.

Another possible mechanism of action is that thioguanine acts by an inhibition of neutrophil function, such as the chemotactic mobility of the cells, in the same way as is suggested to be the effect of methotrexate and hydroxyurea (5, 6).

The main toxicity of thioguanine is hematopoietic. The peripheral blood white cell count can therefore be used as a monitor of treatment. The therapeutic range,however, seems to be narrow since an effect upon the skin is only seen if bone marrow toxicity also occurs.

The toxicity of such low doses of thioguanine as were used in our psoriatic patients is surprising. There are two theoretical explanations for the high sensitivity of the drug. First, the bone marrow might have been damaged to some extent by the previous treatment, as our patients had been treated with considerable amounts of methotrexate and/or PUVA, why the marrow cells have became more vulnerable. Alternatively, as thioguanine is metabolized in the liver, it is possible that a moderate liver damage caused by methotrexate or psoralen may decrease the metabolization of thioguanine leading to elevated tissue concentrations. Thioguanine is not hepatotoxic in laboratory animals (7). It has been reported to cause some liver toxicity in man but certainly to a lesser degree than methotrexate (3). Patients with liver toxicity after methotrexate usually tolerate thioguanine well. However, acute cholestatis occurred in one of our cases of generalized pustular psoriasis already after only a few weeks treatment of thioguanine in low dose and a similar case has also been reported by Zackheim (3).

Despite the narrow therapeutic range with increased risk of bone marrow and perhaps also liver toxicity, we consider thioguanine to be a valuable alternative when other forms of treatment for severe psoriasis have failed.

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