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Topical Ketoconazole for Infantile Seborrhoeic Dermatitis

A. Taieb, V. Legrain, C. Palmier, S. Lejean, M. Six, J. Maleville

Service de Dermatologie Pédiatrique, Hôpital des Enfants, Bordeaux, France

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Abstract. In an open study, 19 infants with a bipolar seborrhoeic rash were treated with ketoconazole 2% in cream once a day and evaluated over 10 days of treatment. At day 10, 78.9% of patients were almost cleared. Percutaneous absorption peaked 1–3 h after topical treatment, and was minimal. No plasma ketoconazole accumulation over the 10-day treatment was detected. Treatment failures corresponded to histologically psoriasiform eruptions and probable atopic dermatitis.

For most paediatric dermatologists infantile 'seborrhoeic' dermatitis (SD) represents more a cutaneous response pattern in the first months of life than a separate disease entity. Whether designations like Leiner's disease – Leiner-Moussous disease in France, because the same cutaneous findings were simultaneously described in Bordeaux at our institution by Moussous [1] – and napkin psoriasis [2] deserve to be maintained remains a matter of debate [3]. Therapeutic empiricism with the common use of antimicrobials, topical steroids or both, reflects the lack of basic understanding of this group of diseases.

On the basis of its excellent therapeutic index in adults with seborrhoeic dermatitis [4], we decided to use topical ketoconazole 2% in cream in an open study. The aims of this study were: (1) to study the efficacy and tolerance of topical ketoconazole used alone in infantile SD, and (2) to correlate clinicopathologic findings with therapeutic response.

Patients and Methods

Nineteen patients (M = 11, F = 8) were included. The clinical criteria for inclusion were similar to those of Atherton and Rook for infantile SD [6]: bipolar involvement of scalp and napkin area, with secondary *'idic'* erythematosquamous lesions in proximal folds and on the trunk and face.

All infants were treated as inpatients during the first 5 days. Ketoconazole was applied once daily after bathing and only white soap was used. A lubricant (Diprobase ointment) was used as topical treatment at night. A clinical, photographic, and microbiological assessment was carried out before treatment and at day 5. Samples for assessment of cutaneous microflora were obtained from the lesions situated on the trunk, and never on the perineum. Cotton swabs were used for culture of bacteria and fungi, and an adhesive tape mounted on a glass slide was used for *Pityrosporum ovale* direct examination after staining. Clinical and photographic follow-up was established on an outpatient basis at day 10 and later on if necessary. A biopsy was obtained when possible in case of poor response at day 5. The quantity of drug used (number of tubes) was monitored at days 5 and 10.

The response was judged according to a global score taking into account the surface involved and the intensity of the dermatosis (redness, scaliness, oozing): +++ = excellent; ++ = good; + = fair; +/– = poor; 0 = absent.

Plasma Ketoconazole Determinations

In 7 patients (5 included in table 1 and 2 others) with extensive lesions, plasma ketoconazole was measured using high-performance liquid chromatography (Mr. Levron, Janssen Laboratories, Aubervilliers, France).

Results

Table 1 summarizes the clinical, therapeutic and pathologic data.

Table 1. Clinical, bacteriological, histological features and therapeutic response

Patient No., sex, age (months)	Cutaneous surface[a] m^2	% surface involved	SPB		Efficacy		Histopathology	Plasma[b] ketoconazole ng/ml
			day 0	day 5	day 5	day 10		
1 M 4	0.33	80	absence	absence	+++	+++	ND	ND
2 M 1.5	0.25	40	absence	*S. aureus* SB	+	++	ND	ND
3 M 2.5	0.26	50	absence	*S. aureus* SB	+/– stop day 5	–	psoriasis	ND
4 M 2.5	0.29	20	–	*S. aureus*	++	++	ND	ND
5 F 2	0.24	70	*S. aureus*	*S. aureus* SB	++	+++	SD	ND
6 M 11	–	15	*S. aureus* SB	*S. aureus* SB	0 stop day 6	–	psoriasiform changes	ND
7 F 2.5	0.25	60	absence	*S. aureus* SB	++	++	SD	133
8 F 1	0.24	50	absence	*S. aureus* SB	+++	+++	ND	63
9 F 1.5	0.23	20	absence	absence	+/–	++	ND	32
10 M 3	0.32	40	absence	*S. aureus*	0	0	ND	40
11 M 1	0.24	70	–	*S. aureus*	0 stop day 8	–	pustular psoriasis	ND
12 M 2	0.28	60	*S. aureus*	*S. aureus*	++	+++	ND	ND
13 M 1	0.26	40	absence	absence	++	++	ND	ND
14 M 3	0.32	30	*S. aureus*	*S. aureus*	++	++	ND	ND
15 F 2	0.23	20	*S. aureus*	*S. aureus*	+	++	ND	ND
16 F 4	0.34	50	absence	absence	++	++	ND	ND
17 F 1	0.25	40	absence	*S. aureus*	++	+++	ND	ND
18 F 2	–	40	*S. aureus*	–	+++	++	ND	ND
19 M 5	0.32	40	absence	*S. aureus*	+	++	SD	54

ND = Not done; SD = consistent with seborrhoeic dermatitis; SB = group B hemolytic Streptococcus; SPB = skin pathogen bacteria.

[a] According to a nomogram computed from Du Bois and Du Bois (Arch Intern Med 1916;17:863); in Tables scientifiques, Documenta Geigy, Ed 6. Basle, Geigy, 1963, p 643.

[b] Three hours after topical treatment between days 1 and 5.

Mean age at inclusion was 2.8 months (1 to 11 months). Most patients had a severe bipolar seborrhoeic rash (mean percent surface involved: 48%) lasting from 1 to 9 weeks (mean 3 weeks).

An excellent or good response was noted in 11 of 19 (57.9%) patients at day 5. At day 10, 15 (78.9%) patients were almost cleared – good and excellent scores (fig. 1). Face and scalp lesions faded more rapidly (fig. 2).

A patient (No. 10) with no response had a sister with asthma and developed lesions consistent with atopic dermatitis (fig. 3). A biopsy could not be performed; serum IgE were not elevated (<5 kIu/l). A biopsy was obtained in the other 3 poor or nonresponders and showed changes typical for psoriasis vulgaris (patient 3; fig. 4a, b), consistent with psoriasis vulgaris (patient 6), or evoking pustular psoriasis (patient 11). In 2 of these patients, a positive family history for psoriasis was elicited (No. 6 and 11).

In 3 responders (patients 5, 7 and 19), a biopsy showed subacute dermatitis with epidermal spongiotic changes and mononuclear cell exocytosis, consistent with SD (fig. 4c).

Candida albicans was found in 1 of 19 cases before treatment on the skin and never at day 5. No *P. ovale* was detected at direct examination. More carriage for pathogen bacteria (*Staphylococcus aureus* and *Streptococcus pyogenes* group B mostly) was noted at day 5 (13 patients vs. 6 before treatment), without worsening of clinical findings (table 1).

Cutaneous tolerance to ketoconazole 2% in cream was judged good by physicians, nurses and parents. In cases

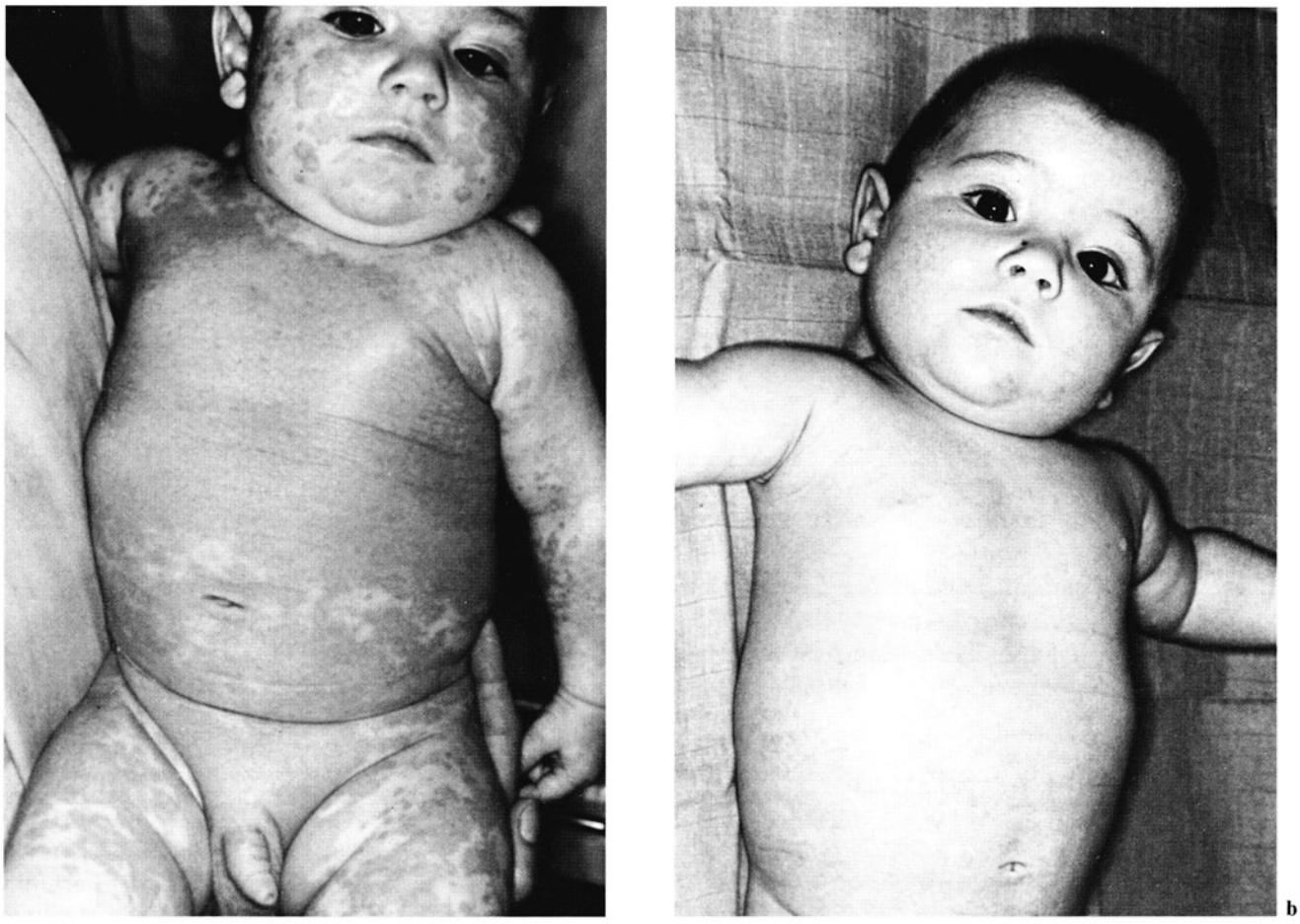


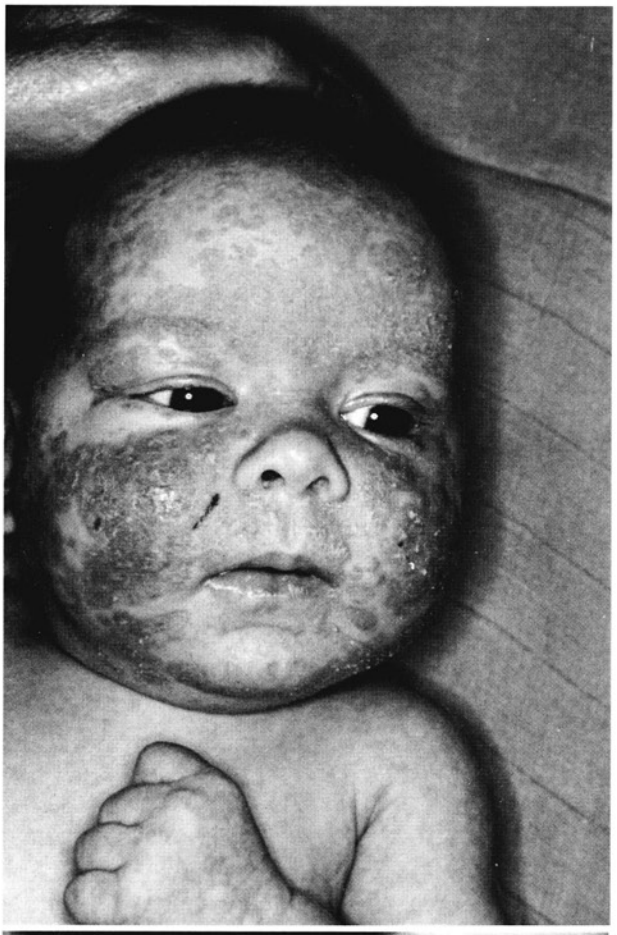
Fig. 1. Case 1, a 5-month-old male baby with dramatic improvement over 10 days of treatment; classified as excellent responder. **a** Day 1. **b** Day 10.

with poor or absent response to treatment, we did not notice an increase in the inflammatory component of the dermatosis, except for patient 11, in whom a subcorneal pustule was demonstrated histologically.

Plasma ketoconazole concentration peaked between 1 and 3 h after topical treatment. No evidence of serum ketoconazole accumulation over time was found over the 10-day treatment course (table 2). An average 84 mg of ketoconazole was used daily (corresponding to 42 ± 12 g of cream for 10 days of treatment) and mean plasma ketoconazole level 3 h after treatment was 64 ± 40 ng/ml.

Among the 4 patients with absent or poor response to treatment, 2 (No. 3 and 10) were lost to follow-up over the 6 months following the trial. Patient 11, who presented initially with a psoriasiform rash developed a relapse 4 months later. Patient 6 is free of lesions. Among responders, an early (3–6 months) follow-up was obtained in only 7 cases. All were free of cutaneous lesions, except for patient 14 who had recurrent erythematous patches in the neck fold, and had had two attacks of asthmatic bronchitis. It should be noted that patient 1, an excellent responder, relapsed immediately after discontinuation of therapy, but responded again very well to the same treatment which had to be tapered down gradually over 2 months.

Fig. 2. Case 2, a 1.5-month-old female classified as a good responder: the cephalic lesions are almost cleared at day 10, the napkin area shows improvement but remains erythematous. The rash cleared completely over the next week with the same regimen. **a, b** Day 1. **c, d** Day 10.



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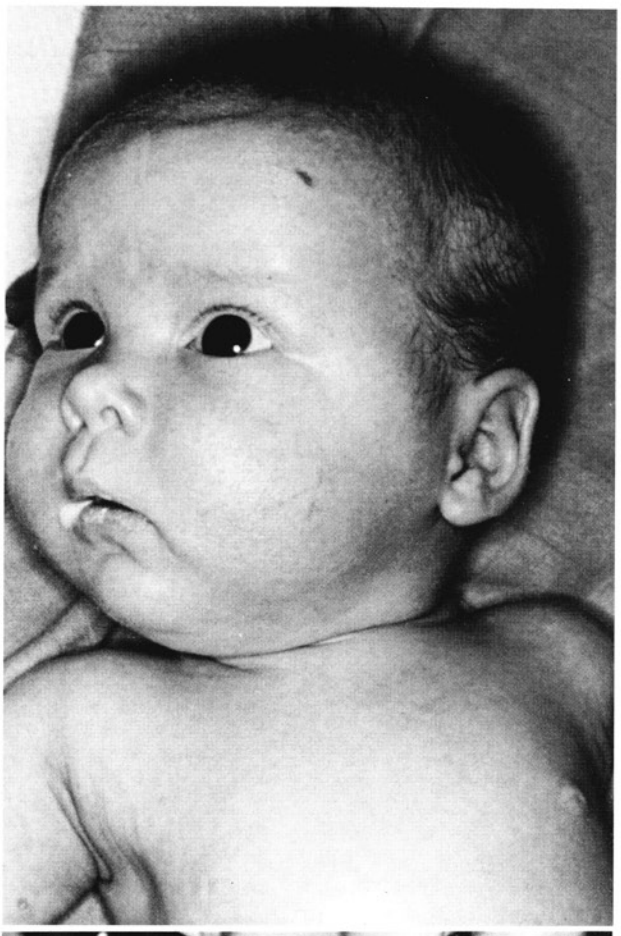

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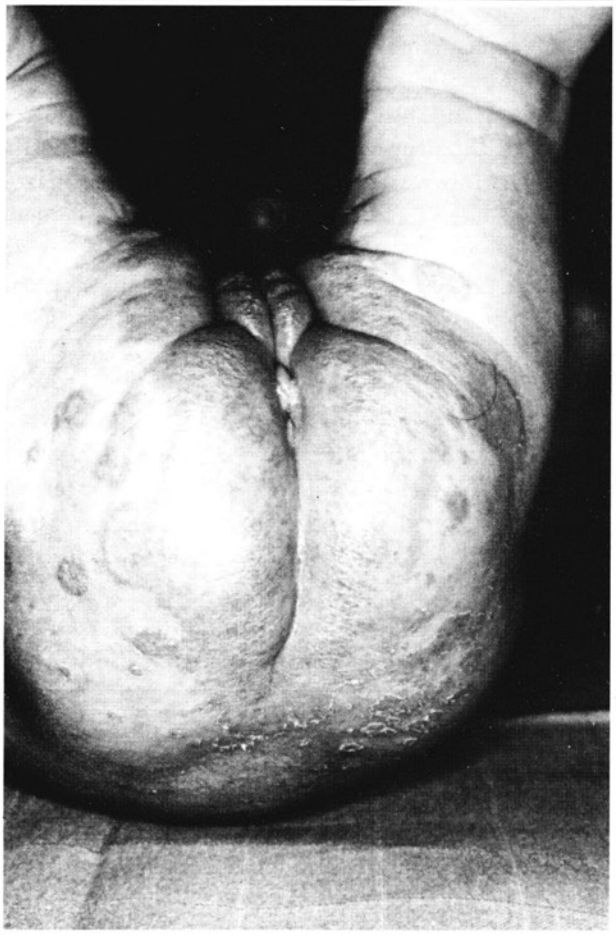

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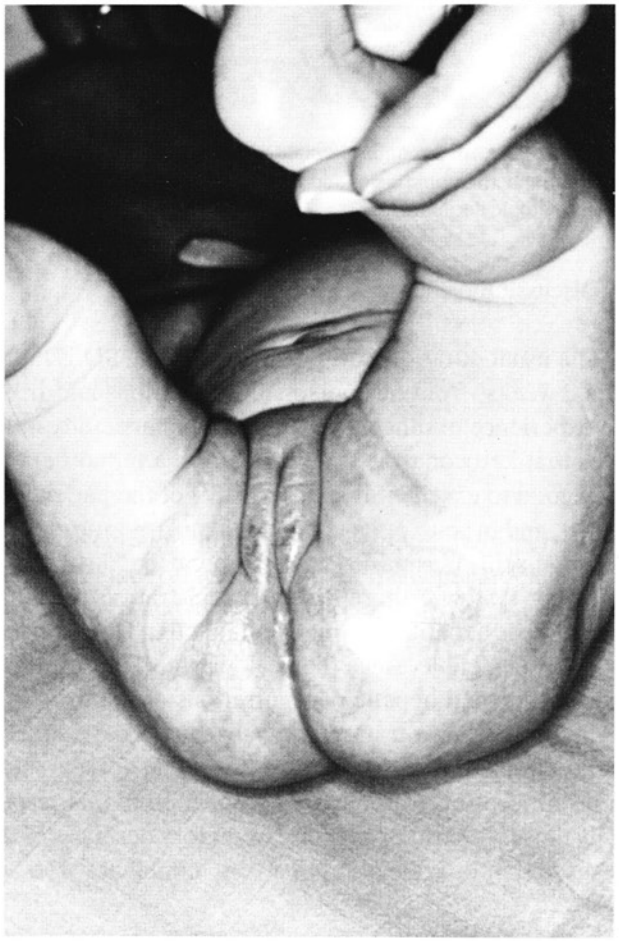

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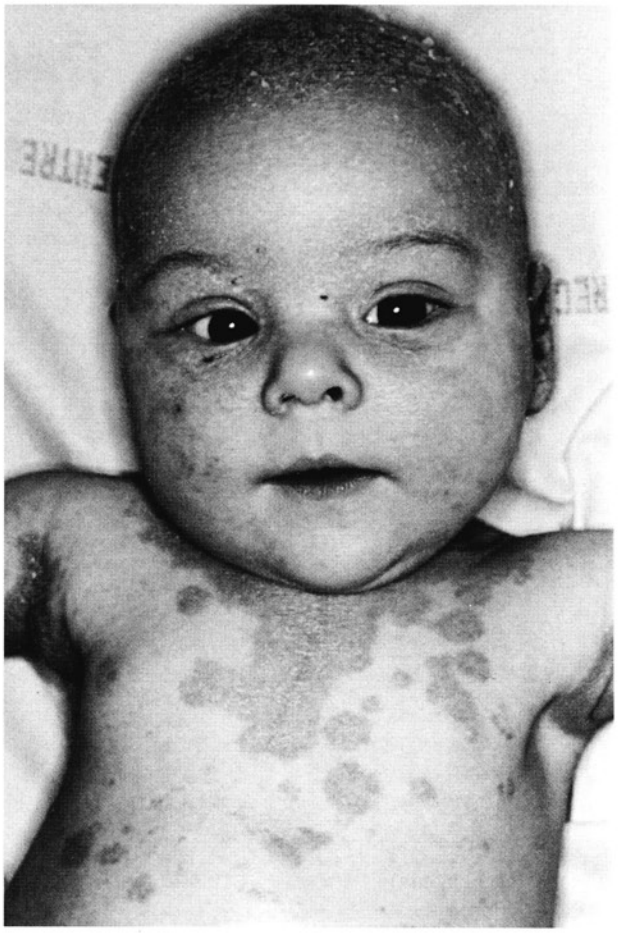


Fig. 3. Case 10, 3-month-old male, day 10. No response over 10 days of treatment: atopic facies and family history suggest of probable switch to atopic dermatitis.

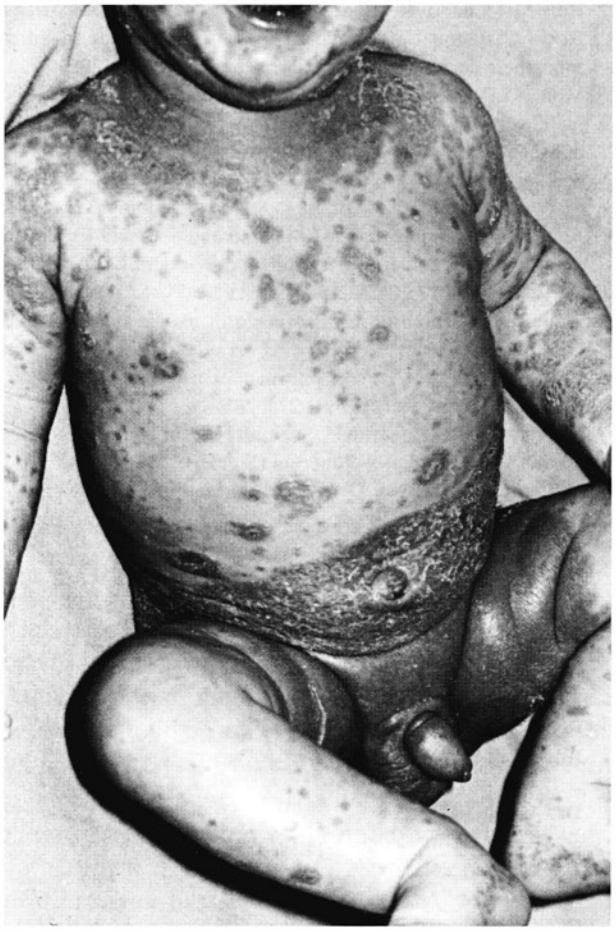
Discussion

The usual duration of the rash in infantile SD is more than 3 weeks, from our personal observations and from the experience of others [5]. This preliminary study indicates that ketoconazole 2% in cream as a monotherapy gives good to excellent responses in 3/4 of the patients at day 10, and in spite of its application on large surfaces of inflamed skin, plasma levels are around 1–2% of those following systemic therapeutic administration [6]. The risks of toxic hepatitis due to percutaneous absorption are probably negligible, since the peak plasma concentration is far lower than hepatic concentrations of the drug following oral administration and subsequent entry in the portal circulation. Few data are available for percutaneous absorption of topical imidazoles in infants, especially those with widespread inflammatory dermatoses. It seems that bifonazole also has a very limited absorption.

The antiinflammatory (anti-LTB4) [7] activity of ketoconazole seems a valuable adjunct to its antimicrobial role for the treatment of infantile SD. Our study shows that the actual role of microorganisms in the rash of SD is at best controversial, since the carriage of pathogens did not correlate with the therapeutic response, especially for *S. aureus* and group B streptococci. *Candida albicans* was found in only 1 patient, and the antifungal action of ketoconazole could clearly not account for its efficacy. As concerns pityrosporum yeast infection, which for some [4, 8, 9] could be the immediate cause of adult SD, direct examination in the trunk area was negative for all specimens in our series. However, since the completion of this study, Broberg and Faergemann [10] have reported a high figure for carriage of *P. ovale* in this condition, using direct microscopy and cultures in the forehead and temporal areas. A pioneering work presented in abstract form in 1985 showed the presence of *P. ovale* in infants with seborrhoeic dermatitis [11]. Ruiz-Maldonado et al. [12] have further shown that *P. ovale* was significantly more frequent in infants with seborrhoeic dermatitis than those with atopic dermatitis or other dermatoses. The low incidence of carriage of *C. albicans* and *S. aureus* at day 1 of the study is surprisingly low as compared with other studies [13–14], but may correspond to previously administered treatments, and to the site of sampling outside of the perineum.

The nonspecific part of the treatment included vigorous scrubbing and subsequent bathing. This, and the possible role of the drug vehicle, was not evaluated in this open study. However, the effect of the 2% ketoconazole cream was indeed dramatic in most cases of cephalic lesions. The recent report of increased carriage of *P. ovale* in this area [10, 12] may give a clue to this therapeutic response. Ruiz-Maldonado et al. [12] also mention that 11 of their 15 patients were cleared after 2 weeks of 2% topical ketoconazole cream without further detail. However, a controlled study is needed for confirmation.

The prognosis of infantile SD is still puzzling. Follow-up studies of bipolar infantile SD are rare and not truly prospective but cross-sectional [15–17], and are therefore difficult to interpret. They generally indicate that a subgroup of patients with mostly psoriasiform rashes are at risk of developing later atopic dermatitis or psoriasis. Clinical and biological markers are not yet firmly established to determine the outcome of such patients [3, 18–19]. Only 4 of 19 of our patients were nonresponders or poor responders, and treatment had to be changed to topical steroids or tars. Three had histological changes consistent with psoriasis, and the fourth probably had atopic dermatitis. Whether or not the response to ketoco-



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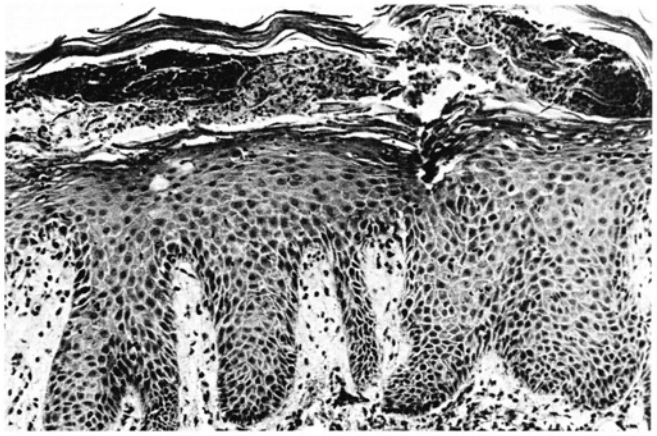

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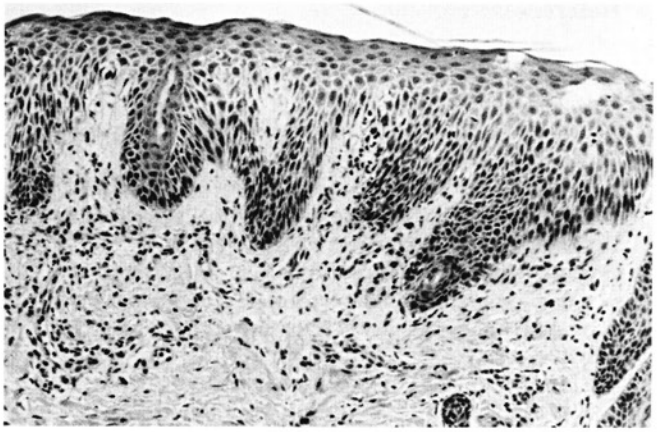

c

Fig. 4. Case 3, 2.5-month-old male, day 5 (**a**). Classified as poor response. Psoriasis in the father. Improvement with tar treatment over 1 week. **b** Histopathologic changes diagnostic of psoriasis. HE-saffron. x 250. PAS stain negative for fungi. **c** For comparison, histopathology consistent with SD (case 7); no significant acanthosis or papillomatosis, spongiosis, mild mononuclear cell exocytosis, moderate papillary dermis infiltrate with capillary dilatation. PAS stain negative. Biopsy matched for site (lower abdomen) and magnification (x 250).

Table 2. Plasma ketoconazole concentrations following daily application of 4.5 g of a 2% ketoconazole cream

	Plasma ketoconazole, ng/ml		
	day 1	day 5/6	day 10
Patient 19 (age: 5 months)			
1 h[a]	37	51	60
3 h	54	43	36
6 h	18	33	44
12 h	13	ND	ND
Patient 20 (age: 1 month)			
1 h	40	125	–
3 h	103	35	–
6 h	32	ND	–
12 h	123	69	–
Patient 21 (age: 2 months)			
1 h	20	14	18
3 h	37	79	21
6 h	18	24	ND
12 h	14	11	ND

[a] Delay between application and blood sampling.

nazole treatment might sort out potentially persistent, endogenous dermatoses – like psoriasis and atopic dermatitis – and 'reactive' dermatoses among the spectrum of infantile SD remains to be confirmed in larger series and by further follow-up.

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Dr. A. Taieb
Service de Dermatologie Pédiatrique
Hôpital des Enfants
168, cours de l'Argonne
F–33077 Bordeaux Cédex (France)