

Protein Deficiency and Treatment of Xerophthalmia

Alfred Sommer, MD; Muhilal, PhD; Ignatius Tarwotjo, MPH

• In a controlled clinical trial of massive-dose vitamin A therapy for xerophthalmia, holo-retinol-binding protein (holo-RBP) response was related to baseline protein status. Corneal healing was more commonly delayed or transient in children with protein-energy malnutrition (PEM), despite the vast majority achieving holo-RBP levels incompatible with severe corneal destruction. Correction of PEM is essential to ensuring a sustained clinical cure, and repeated massive vitamin A therapy is advisable until that occurs.

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Data suggest that xerophthalmia develops in 5 million children every year.¹ Effective therapy should drastically reduce the number going blind. We recently demonstrated that oral administration of 200,000 IU of vitamin A on two successive days is at least as safe and effective as less practical regimens employing water-miscible parenteral preparations.^{2,3} In the present study we demonstrate that protein-energy malnutrition (PEM) affects the clinical and biochemical response to vitamin A, requiring modification of routine treatment schedules.

BACKGROUND AND METHODS

As already described in detail,^{1,2} these studies were conducted in an area of Indonesia with a known high incidence of xerophthalmia. Between June 1977 and September 1978, 50 children with vitamin A-responsive conjunctival xerosis,⁴ 162 children with active corneal xerophthalmia,⁵ and 51 matched controls (clinically normal children of the same age and sex, and living in the same neighborhood, as a representative sample of the patients with corneal involvement)¹ underwent detailed ophthalmic and pediatric examination and follow-up.² Patients with pure conjunctival xerosis were designated X1. Patients with corneal involvement were broadly categorized by the severest lesion in the worst affected eye^{1,4}: X2 (xerosis), ranging from mild haziness of the inferior cornea

through thickened keratinized corneal plaques; X3A, classic punched-out, non-infiltrated cylindrical ulceration; and X3B, localized through generalized full-thickness corneal necrosis. Patients with corneal involvement were offered free hospitalization. The vast majority accepted and received high-protein diets and appropriate treatment of systemic infections.

After receiving informed consent from an accompanying parent or guardian, all patients with corneal involvement were randomly enrolled in one of several treatment regimens: initially 200,000 IU of oil-miscible vitamin A orally (PO) or 100,000 IU of water-miscible vitamin A intramuscularly (IM). For reasons cited later, both regimens were soon changed by the addition of an oral dose the following day. Whenever possible, the children were reexamined daily until corneal healing was complete, and monthly thereafter. Venous blood (3 mL) was obtained⁶ prior to therapy and again at four hours, and 1, 3, and 7 days and then monthly after their initial dose. Clinical examinations and biochemi-

cal analyses were conducted in masked fashion. Vitamin A levels were usually determined within one week and never more than two weeks following collection⁶; holo-retinol-binding protein (holo-RBP) responses were usually determined within two months and never more than eight months after collection.⁷ Transferrin levels were determined by the Mancini technique.⁸

Because of equipment failure, vitamin A determinations are not available for the period between July 16, 1977, and Jan 14, 1978, or holo-RBP determinations after May 15, 1978. When supplies of water-miscible vitamin A were exhausted, masking was maintained by substituting oil-miscible parenteral vitamin A, then the accepted therapy in Indonesia. These patients are excluded from the analyses, accounting for the greater number of PO-PO than IM-PO subjects.

Oral and parenteral recipient groups were comparable for all major variables expected to influence outcome.^{1,2} Initial serum levels of vitamin A, albumin, and transferrin were inversely related to the severity of corneal involvement.^{1,3}

RESULTS

Holo-RBP Response in Corneal Xerophthalmia

The effect of baseline protein status on holo-RBP response to a massive vitamin A dose is shown in Table 1. Data are limited to patients with cor-

Table 1.—Holo-Retinol-Binding Protein Response in Patients With Corneal Xerophthalmia

Time Since Dose, hr	Serum Albumin, g/dL			
	≥ 3.5	3.4-3.0	2.9-2.5	< 2.5
Oral Dose				
0				
n	9	6	6	6
\bar{u} (mean)	1.7	1.3	0.3	1.3
SD	1.4	1.2	0.5	1.0
0-4				
n	9	6	6	4
$\bar{u}\Delta$ †	+26.2‡	+14.5‡	+8.7‡	+5.8‡
SD	17.2	3.4	5.0	1.7
4-24				
n	10	4	7	3
$\bar{u}\Delta$	-10.7§	-8.0§	-3.6	+0.3
SD	15.2	4.2	6.0	3.2
Intramuscular (IM) Dose				
0				
n	2	6	9	...
\bar{u}	0.0	1.3	0.9	...
SD	0.0	0.8	0.9	...
0-4				
n	2	6	9	...
$\bar{u}\Delta$	+26.5‡	+12.3‡	+6.7§	...
SD	7.8	6.3	8.2	...
4-24				
n	1	8	6	...
$\bar{u}\Delta$	-3.0	+1.1	+9.2§	...
SD	...	7.0	8.9	...

* Oral dose was 200,000 IU of oil-miscible vitamin A at zero hours; IM dose, 100,000 IU of water-miscible vitamin A intramuscularly at zero hours.

† The $\bar{u}\Delta$ values are paired comparisons. Cases at zero hours are those available for paired comparison at four hours. The $\bar{u}\Delta$ values correlated with serum albumin category as follows: Oral: change at zero to four hours, $r = .9586$, $P < .02$; change at four to 24 hours, $r = .9957$, $P < .001$; IM: change at zero to four hours, $r = .9700$, $P < .01$; change at four to 24 hours, $r = .9826$, $P < .05$.

‡ Net change ($\bar{u}\Delta$), $P < .01$.

§ Net change ($\bar{u}\Delta$), $P < .05$.

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From the International Center for Epidemiologic and Preventive Ophthalmology, The Johns Hopkins Medical Institutions, Baltimore (Dr Sommer); the Helen Keller International, New York (Dr Sommer); the Nutritional Blindness Prevention Project, Bandung, Indonesia (Drs Sommer and Muhilal and Mr Tarwotjo); and the National Institute of Nutrition Research, Bogor, Indonesia (Dr Muhilal).

Reprint requests to Witmer Institute, 600 N Wolfe St, Baltimore, MD 21205 (Dr Sommer).

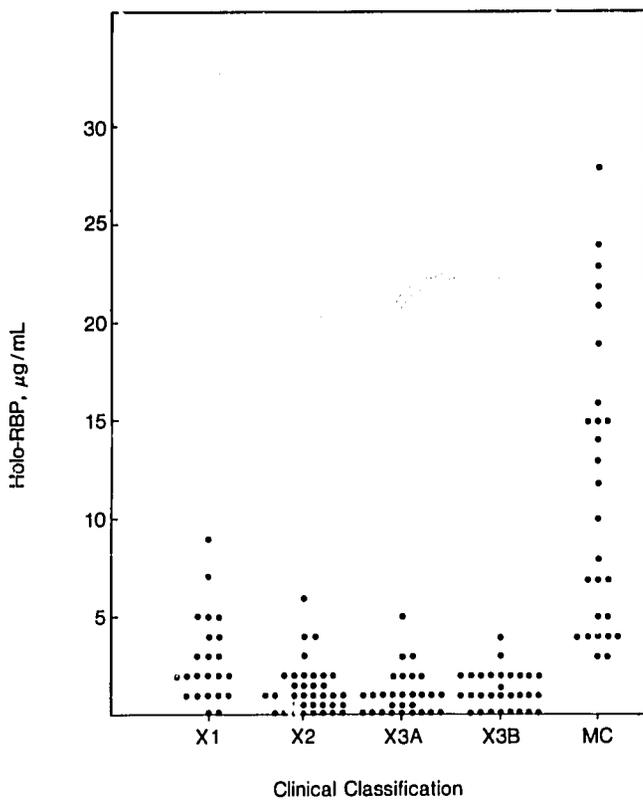


Fig 1.—Initial serum holo-retinol-binding protein (holo-RBP) levels in children with Bitot's spots (X1)^a, corneal xerosis (X2), corneal ulceration (X3A), corneal necrosis (X3B), and matched controls (MC) of representative subsample¹ of patients with corneal involvement.

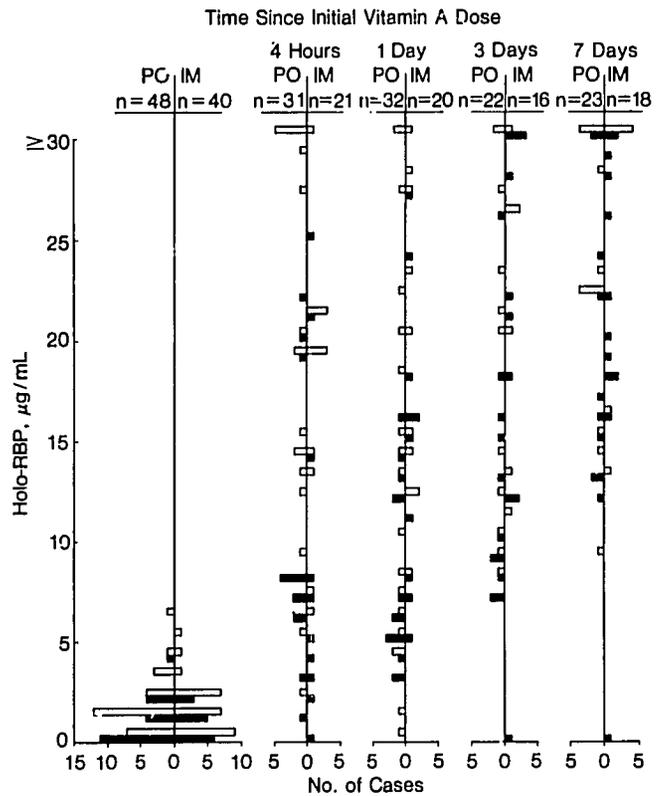


Fig 2.—Holo-retinol-binding protein levels in patients with corneal xerophthalmia. Levels at 0, 4, and 24 hours following therapy include all patients receiving 200,000 IU of oil-miscible vitamin A orally (PO) or 100,000 IU of water-miscible vitamin A intramuscularly (IM). Levels at three and seven days include only patients who received second, oral dose at 24 hours. Severe protein-energy malnutrition (PEM) (indicated by solid rectangles) is defined as initial serum albumin level less than 3.0 g/dL or transferrin level less than 50 mg/dL. No PEM to moderate PEM is indicated by open rectangles.

Clinical Category*	Total No. of Cases	PEM,† No.(%)
X2		
Deterioration	9	7(78)
Relapse	3	3(100)
Total reverses	12	10(83)‡
Uneventful cure	52	18(35)‡
X3		
Clinical reverse	5	5(100)
Uneventful cure	45	25(56)
Total (X2 plus X3)		
Clinical reverse	17	15(88)‡
Uneventful cure	97	43(44)‡

* Deterioration, initial deterioration followed by recovery; relapse, cure followed within two months by deterioration; cure, uneventful healing without relapse within two months. X2 indicates corneal xerosis; X3, corneal ulceration/necrosis.

† PEM is defined as one or more of the following: (1) serum albumin level less than 3.0 g/dL or transferrin level less than 50 mg/dL; (2) weight for height less than 70% of standard; (3) presence of pedal edema.

‡ Difference between those with and without clinical reverse, $P < .01$.

neal involvement included in the clinical study² for whom paired values were available at zero (T_0) and four (T_4) hours, and/or four and 24 (T_{24}) hours. Initial mean holo-RBP levels (among patients for which paired values were available at zero and four hours) were similar, and severely

depressed in all groups.

A statistically significant elevation in holo-RBP occurred between T_0 and T_4 . The magnitude of the response was independent of the mode of vitamin A administration, but it was directly related to the initial level of serum albumin (oral recipients, $r = .959$,

$P < .02$; IM recipients, $r = .970$, $P < .1$).

The holo-RBP response between T_4 and T_{24} was quite the reverse, net change being inversely related to initial albumin level (oral recipients, $r = -.983$, $P < .05$), and dependent on the route of administration. Oral recipients in the three highest albumin categories suffered net declines of holo-RBP equivalent to 41% to 55% of their initial rise, while parenteral recipients either maintained their T_4 level or experienced a slight, further rise.

Initial holo-RBP levels of all patients with corneal involvement (whether or not they were eligible for analysis of clinical response²), their normal controls, and children with vitamin A-responsive Bitot's spots are plotted in Fig 1, as a means of defining a "safe" level. Values among controls were all above 3 µg/mL, and in 74% were 5 µg/mL or higher. Only 8% of patients with corneal involvement had values above 3 µg/mL; among the subgroup with severe disease (X3B), none had values above 5 µg/mL and only 3% (1/29) had values above 3 µg/mL. A holo-RBP level of 3

to 5 µg/mL appears to provide a minimal degree of safety, at least transiently, from severe disease.

The vast majority of patients with corneal involvement achieved safe levels within 24 hours of receiving a single massive dose of vitamin A (Fig 2). By four hours, 79% of patients with and 96% without significant PEM had levels above 3 µg/mL, the difference between the two groups being statistically significant ($P < .05$). By 24 hours the rates were 92% and 93%, respectively.

Clinical Response of Corneal Xerophthalmia

Two of 20 patients who received single massive doses of vitamin A (one oral, the other parenteral water-miscible) had relapses within three weeks of treatment and initial healing. Serum albumin level was less than 3 g/dL and transferrin level was 20 mg/dL or less in both. Double-dose therapy was then instituted, but failed to eliminate the problem. In the therapeutic series already reported,² nine of 52 patients with corneal xerosis (X2) suffered initial, transient deterioration of their corneal status, and three other patients had relapses within two months of initial therapy. Seventy-eight percent of the former and all of the latter had severe PEM, percentages significantly higher than for patients with X2 suffering neither of these reverses ($P < .01$) (Table 2).

The same was true of patients with stromal loss (X3): those who did poorly suffered initial deterioration, and either received additional vitamin A, died, or suffered a relapse. Severe PEM was initially present in all, a rate twice that of X3 patients who did well (five of five vs 25 of 45). The difference just misses statistical significance.

The relapse rate among patients presenting with PEM who received only a single dose of vitamin A was significantly higher than among those enrolled in the double-dose regimen (38% [3/8] vs 10% [6/58]) ($P < .05$).

The effect of severe PEM on isolated vitamin A therapy is well illustrated by the following case report.

A 2-year-old boy with pedal edema had corneal xerosis in both eyes and an ulcer (X3A) in the left eye. His mother refused to permit hospitalization and the child received only a single oral dose of vitamin A. Despite severe persistent protein deficiency (albumin level consistently ≤ 1.7 g/dL and transferrin level ≤ 20 mg/dL), both corneas healed by day 9. During the interval, holo-RBP level rose to 12 µg/dL. Serum vitamin A levels peaked at 31 µg/dL (day 4), falling to 11 µg/dL by day 8. By day 15, punctate keratopathy had returned. When he was next seen, on day 23, both

corneas were severely xerotic and ulcerated (X3A). The holo-RBP level was 0 µg/mL. He received a second oral dose of vitamin A and by the next day both corneas had improved. He died two days later.

COMMENT

The vast majority of patients with corneal xerophthalmia respond rapidly to vitamin A therapy.^{2,3} But as the present analysis makes clear, in a small proportion, almost exclusively children with severe PEM, the clinical response is either delayed or, more worrisome, transient.

In rats deprived of vitamin A, serum RBP levels fall^{10,11} and apo-retinol-binding protein (apo-RBP) accumulates in the liver.¹⁰ When vitamin A is administered it combines with available apo-RBP, holo-RBP levels rising to a peak at two to five hours.^{10,11} Among rats suffering combined deficiencies of protein and vitamin A, the magnitude of the holo-RBP response is reduced.¹¹ This same pattern was observed in our patients with xerophthalmia. The initial (T_0 to T_4) holo-RBP response was directly related to the adequacy of baseline protein status. Presumably children of better protein status had accumulated more apo-RBP in their liver. Among protein-deficient children without xerophthalmia with adequate vitamin A stores, a high-protein diet can raise serum vitamin A and RBP levels.^{12,13}

The subsequent decline in serum holo-RBP levels (T_4 to T_{24}) among our oral recipients suggests that apo-RBP synthesis was inadequate to support the peak rate of holo-RBP release. This was most apparent among better-nourished individuals, presumably because their peak release had been greatest. Decreased holo-RBP utilization in more protein-deficient subjects, as has been observed in protein-deficient rats,^{11,14} may have contributed to this difference. The T_4 to T_{24} response among parenteral recipients displayed the same protein-dependent pattern, but without any groups suffering a net decline. The route of administration had no sustained effect, however, on either the clinical^{2,3} or holo-RBP response.

Protein deficiency probably interferes with clinical recovery through a variety of mechanisms. Delayed clinical response may be related to depression of peak holo-RBP release or direct interference with target cell metabolism.¹ In any case, the short-term effects are limited. Within 24 hours essentially all patients achieved "safe" holo-RBP levels, and, as with the case described in detail, isolated vitamin A therapy ordinarily initiates corneal healing in even severely pro-

tein-deficient children.¹ Of greater concern is the transient nature of the response. Severely protein-deficient children appear incapable of adequately assimilating a massive vitamin A dose: holo-RBP levels may decline, and corneal status may deteriorate, after one to three weeks. This occurred more frequently among single- than double-dose recipients.

Although relapses respond to further dosing, children often receive only initial therapy, with little if any follow-up therapy. The data suggest that adequate, sustained healing of severe xerophthalmia requires correction of underlying protein deficiency. It appears that repeated, massive vitamin A therapy every one to two weeks is advisable until that occurs.

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