

ORAL VERSUS INTRAMUSCULAR VITAMIN A IN THE TREATMENT OF XEROPHTHALMIA

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Summary In a controlled trial 69 children with corneal xerophthalmia were given 200 000 IU oil-miscible vitamin A by mouth and a matched group of 45 children were given 100 000 IU water-miscible vitamin A intramuscularly. Both groups received an additional oral dose the next day. There was no detectable difference in the clinical response to the two regimens, even when analysis was limited to patients with concomitant diarrhoea or protein-energy malnutrition. Although serum-vitamin-A levels were significantly higher after parenteral than oral therapy, holoretinol-binding-protein levels were not. Oral administration of vitamin A is not only more practical but appears to be just as effective as parenteral administration in the treatment of severe xerophthalmia.

Introduction

EACH year an estimated quarter million Asian children develop potentially blinding corneal xerophthalmia.¹ The treatment recommended² is immediate intramuscular administration of 100 000 IU water-miscible vitamin A followed by a further 100 000 IU orally the next day. In the absence of comparative clinical data, injectable rather than oral vitamin A was favoured as the initial dose for two reasons: (1) serum-vitamin-A levels rise faster after parenteral than oral administration;³ and (2) there was concern that diarrhoea and protein-energy malnutrition (PEM), common in these children, would significantly impair absorption, rendering the oral dose even less effective.

Unfortunately, water-miscible parenteral preparations of vitamin A are more costly and less readily available than oral preparations, and their administration requires needles, syringes, and highly trained personnel. Given these practical constraints to the use of parenteral therapy and the lack of evidence of its clinical superiority, we carried out a controlled trial of the efficacy of

purely oral versus parenteral plus oral vitamin A in the treatment of corneal xerophthalmia.

Background and Methods

Xerophthalmia has long been a serious public-health problem in Indonesia. In September, 1976, the Ministry of Health, in cooperation with Helen Keller International, launched a 3-year applied research programme, including an intensive hospital-based study of children with xerophthalmia of varying severity.

All children presenting to the Cicendo Eye Hospital, Bandung, between June, 1977, and August, 1978, with evidence of corneal xerophthalmia were enrolled in the clinical trial. Each was examined by an ophthalmologist and paediatrician. Height, weight, and dietary history were recorded by a nutritionist. After informed consent had been obtained from the accompanying parent or guardian, 2 ml of blood was taken and the children were allocated at random to receive either an oral or an intramuscular dose of vitamin A. Both groups received an additional, oral, dose the next day. For the oral dose the contents of a standard UNICEF capsule containing 200 000 IU oil-miscible retinyl palmitate and 40 IU vitamin E were expressed into the child's mouth. The intramuscular dose contained 100 000 IU water-miscible retinyl palmitate. When supplies of the water-miscible preparation were exhausted oil-miscible injectable vitamin A was substituted. These cases are not included, which accounts for the larger number of oral than parenteral+oral treatments in this report.

Ocular diagnosis was based on standard clinical criteria⁴ and the WHO classification of xerophthalmia—X2, dry hazy corneal xerosis; X3A, corneal xerosis with ulceration; and X3B, keratomalacia. Eyes with total limbus to limbus necrosis, lacking viable cornea, are excluded. All subjects were encouraged to accept free inpatient treatment. Significant illnesses, such as gastroenteritis, respiratory-tract infections, and tuberculosis were treated. Patients refusing to be admitted to hospital were encouraged to return daily until healing was complete. All observations were made by the same ophthalmologist using a Haag-Streit 900 slit lamp, and all abnormalities were drawn and photographed. In a concurrently running protocol introduced mid-way through the present study, topical retinoic acid was applied to one eye of each child. Eyes receiving retinoic acid are excluded from the analysis.

Whenever possible, blood samples were collected at the time of diagnosis and 4 h, 1 day, 3 days, and 7 days after the start of therapy. The 24 h blood was collected before the second dose was given. All bloods were spun immediately after collection, and the supernatant was stored at -20°C. Vitamin-A determinations were carried out with the method of Neeld and Pearson,⁵ usually within a week and never more than 2 weeks after collection. Holoretinol-binding protein (holo-RBP) levels were determined with the method of Glover et al.,⁶ usually within 2 months and never more than 8 months after collection. All biochemical determinations were done without knowledge of the patient's clinical condition or treatment. Because of equipment failure, vitamin-A determinations are

* The Nutritional Blindness Prevention Project is a joint undertaking of the Ministry of Health, Government of Indonesia, and Helen Keller International.

not available for the period July 16, 1977, to Jan. 14, 1978, nor holo-RBP determinations after May 15, 1978.

Results

The oral group consisted of 88 eyes of 69 patients, the parenteral group 58 eyes of 45 patients. The age-range was 3 months to 10 years, with a peak in both treatment groups at 2–3 years. The two groups were also comparable in the proportion admitted to hospital, mortality, severity of corneal involvement, prevalence of diarrhoea (four or more loose stools a day), and prevalence of severe protein-energy malnutrition (presence of one or more of the following: serum albumin <3.0 g/dl; serum transferrin <50 mg/dl; weight-for-height <70% of the Harvard standard;⁷ and foot oedema) (table I).

The clinical response to the two therapeutic regimens was similar (table II). Approximately a quarter of all eyes examined 1 day, two-thirds examined 2–4 days, and 95% examined 6–8 days after the start of therapy had either improved or healed.

There was no evidence that patients with diarrhoea or protein-energy malnutrition who received parenteral vitamin A fared any better than those who received oral vitamin A. In each comparison recipients of oral and parenteral doses were comparable for all variables listed in table I.

Serum-vitamin-A levels, initially extremely depressed, rose dramatically within 4 h of administration of either

TABLE I—COMPARABILITY OF TREATMENT GROUPS

—	Oral therapy		Parenteral therapy	
	No.	%	No.	%
Total eyes	88	100	58	100
Hospitalised	67	76	45	78
Clinical diagnosis				
X2	50	57	38	66
X3A	26	30	9	16
X3B	12	14	11	19
Diarrhoea	35	40	20	34
Protein-energy malnutrition*	47	53	30	52
Mortality	8	9	3	5

* Defined by the presence of one or more of the following: serum albumin <3.0 g/dl; serum transferrin <50 mg/dl; weight for height <70% of standard; foot oedema.

TABLE II—CLINICAL RESPONSE OF CORNEAL LESION IN ALL CASES

Days since therapy	Clinical condition				
	Worse	Static	Improved	Cured	Total
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)*
1:					
Oral	3 (6)	29 (62)	15 (32)	...	47 (53)
IM	7 (23)	16 (53)	7 (23)	...	30 (52)
2–4:					
Oral	7 (10)	11 (16)	39 (57)	12 (17)	69 (78)
IM	3 (7)	14 (30)	23 (50)	6 (13)	46 (79)
6–8:					
Oral	— (—)	4 (6)	34 (51)	29 (43)	67 (76)
IM	2 (4)	— (—)	29 (55)	22 (42)	53 (91)
12–16:					
Oral	— (—)	1 (2)	12 (24)	36 (73)	49 (56)
IM	2 (5)	0 (0)	11 (27)	28 (68)	41 (71)

* Percentage of all eyes in series examined in the interval.

TABLE III—SERUM VITAMIN-A AND HOLO-RBP LEVELS

Time since initial dose	Serum vitamin A (μg/dl)		Serum holo-RBP (μg/ml)	
	Oral	IM	Oral	IM
0 h:				
Mean	6.8	6.1	1.2	1.3
SD	3.9	3.8	1.4	1.8
N	35	16	35	29
4 h:				
Mean	33.6	47.6	19.5	15.1
SD	26.9	36.4	15.1	10.2
N	36	16	23	11
1 day:				
Mean	22.1†	107.7	12.1*	20.0
SD	24.2	46.2	10.0	9.8
N	35	10	22	13
3 days:				
Mean	28.4†	152.8	18.6	21.6
SD	34.1	86.5	12.4	9.8
N	37	17	18	15
7 days:				
Mean	22.9†	53.0	24.7	27.4
SD	8.0	39.8	10.1	16.3
N	37	18	20	16

Difference between oral and parenteral (IM) group statistically significant at: * $p < 0.05$; † $p < 0.001$.

oral or parenteral vitamin A ($p < 0.001$) (table III). At 1, 3, and 7 days, however, the level in recipients of parenteral vitamin A was statistically significantly greater than that in patients on the oral regimen ($p < 0.001$). By day 7 this difference had diminished.

As with serum vitamin-A, initial holo-RBP levels were very low and rose dramatically within 4 h of the start of either form of therapy ($p < 0.001$). Unlike the vitamin-A response, however, there was never a consistently significant difference between the two treatment groups. Only at day 1 did this difference approach statistical significance ($t = 2.27$, for which $p < 0.05$ in a single comparison, whereas these were multiple sequential comparisons). From 4 h onwards holo-RBP levels in both groups were within normal limits.

Nonetheless, the pattern of the holo-RBP response was not the same in the two treatment groups. In patients on oral treatment there was a statistically significant fall in holo-RBP between 4 h and 24 h ($p < 0.02$), followed by a progressive rise between days 1–3 and 3–7 (statistically significant at $p < 0.05$ and $p < 0.001$ respectively as paired comparisons). In contrast, the level among patients on parenteral treatment rose slowly and steadily between 4 h and 7 days (only the overall, and none of the interval, changes being statistically significant). There was a distinct plateau between days 1 and 3.

Discussion

This study confirms our preliminary findings¹ that corneal xerophthalmia responds just as rapidly to double-dose oral as to parenteral + oral vitamin A. Fears that oral therapy alone would delay healing, especially in children with diarrhoea or protein-energy malnutrition, appear to have been unfounded.

As reported by others,³ serum vitamin A reached higher levels in patients receiving intramuscular therapy. But this reflects the presence, in varying proportions, of at least two substances—retinyl ester—the form in which the vitamin A is administered; and

retinol bound to retinol-binding protein (holo-RBP), the physiologically active entity. In contrast to total serum-vitamin-A levels, holo-RBP levels were virtually identical at every interval except day 1, when the difference between the two groups was of only borderline statistical significance and the levels in both were within the normal range. The holo-RBP response therefore supports the clinical observations.

The rapid rise in holo-RBP 4 h after the first vitamin-A dose indicates that enough retinol was made available, by both routes, to support an initial outpouring of RBP synthesised and stored by the liver during the period of vitamin-A deficiency.⁸ The subsequent fall in holo-RBP among patients on oral treatment, although of no clinical importance, suggests that even though serum vitamin A had reached a normal level this may have been less effective in maintaining RBP release than the supranormal levels achieved through the parenteral route. The further rise in serum holo-RBP, observed in both groups, probably reflects a subsequent increase in the rate of RBP synthesis.

Corneal xerophthalmia is a medical emergency requiring prompt administration of vitamin A. Since oral therapy is as effective as parenteral, treatment need not be delayed for lack of water-miscible parenteral preparations, needles, syringes, or medical personnel skilled in their use. High-potency oral preparations of oil-miscible vitamin A, already widely used for prophylaxis, can be administered by teachers and mothers as well as by medical workers. This does not mean that children with severe xerophthalmia should do without medical attention. Many have systemic illnesses and protein-energy malnutrition (PEM). Severe PEM, in particular, interferes with storage and handling of vitamin A and may lead to early relapse after either parenteral or oral treatment.

We did not encounter any evidence of toxicity except for occasional asymptomatic papilloedema. Although oral therapy consisted of two doses of 200 000 IU oil-miscible vitamin A given on successive days, a third dose, 1-2 weeks later, would probably improve liver stores even further and delay or reduce the risk of clinical relapse.

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NEURAL AND HORMONAL PEPTIDES IN RECTAL BIOPSY SPECIMENS FROM PATIENTS WITH CHAGAS' DISEASE AND CHRONIC AUTONOMIC FAILURE

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Summary The neural and hormonal peptide content of rectal biopsy specimens from 10 patients with chronic autonomic failure, 10 patients with chronic gastrointestinal Chagas' disease, and 13 controls was studied with radioimmunoassay and immunocytochemistry. In the patients with Chagas' disease the mean concentrations of rectal vasoactive intestinal polypeptide, enteroglucagon, substance P, and somatostatin were all less than half of those in controls and in patients with chronic autonomic failure. Immunocytochemistry revealed a considerable reduction in the number and immunostaining of the peptide-containing cells and nerves. Concentrations of regulatory peptides in the rectum are thus reduced in association with intrinsic but not extrinsic autonomic neuropathy.

Introduction

CHRONIC gastrointestinal Chagas' disease is manifested many years after infection with the flagellate protozoan, *Trypanosoma cruzi*. Periganglionitis and degeneration of intrinsic-cell bodies are the main histological features. These lead to severe denervation of the corresponding gut segment and subsequent megaoesophagus, megacolon, and megaduodenum without clinical involvement of the rectum.¹ In contrast, chronic autonomic failure is characterised by widespread sympathetic and parasympathetic dysfunction, including postural hypotension, bladder dysfunction, and anhidrosis; but the bowel is rarely involved. Chronic autonomic failure may occur alone or with multiple-system atrophy, with the Shy-Drager syndrome, or with parkinsonism. The lesions of chronic autonomic failure vary in degree and site but predominantly affect brainstem nuclei and intermediolateral-column cells which necropsy studies have shown are reduced to 20% of normal.²⁻⁴ Thus, Chagas' disease represents a peripheral intrinsic lesion, whereas chronic autonomic failure is a preganglionic extrinsic nerve abnormality.

A number of peptides have been found in the colon and rectum in mucosal endocrine cells and/or in autonomic nerves. These include enteroglucagon, substances P, vasoactive intestinal polypeptide (VIP), and somatostatin. The precise physiological roles of these rectal peptides are unknown, but they appear to have powerful biological effects. We have studied their concentrations and sites of origin with radioimmunoassay and immunocytochemistry in patients with Chagas' disease and patients with chronic autonomic failure.