Research / Recherche

Safety of one 52-µmol (50 000 IU) oral dose of vitamin A administered to neonates

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A placebo-controlled trial was carried out among 2067 Indonesian neonates to assess the safety of administering one oral 52-µmol (50 000 IU) dose of vitamin A. Infants were assessed for potential acute side-effects before and throughout 48 hours after the dose. The first 965 infants were examined by cranial ultrasound before and at 24 hours after dosing to rule out intracranial haemorrhage and determine the resistive index (RI) of the anterior cerebral artery using duplex Doppler.

Groups were comparable at the baseline. A bulging fontanelle occurred in the control and vitamin A groups, respectively, among 2.7% and 4.6% of the infants at 24 hours, and 2.4% and 4.5% of the infants at 48 hours. The groups did not differ in any other sign or symptom assessed. No infant developed intracranial haemorrhage. Mean RI values were normal and not different between groups at baseline or at 24 hours. Mean RI fell during the 24 hours, as normally occurs; the mean decrease was nearly identical in the two groups. A bulging fontanelle was not associated with increased rates of any sign or symptom or with an increase in RI.

The 52-µmol dose of oral vitamin A may cause a small increase in intracranial volume in a small proportion of infants, but no increase in intracranial pressure. Acute side-effects following this intervention were rare and mild.

Vitamin A deficiency is the leading cause of blindness (*1*) and a major cause of severe morbidity and mortality among young children throughout the developing world (*2*). A recent meta-analysis of eight controlled trials estimated that community-wide vitamin A supplementation resulted in a 23% average reduction in child mortality rates (*3*). Accordingly, signatory nations of the 1992 World Declaration and Plan of Action for Nutrition have pledged to eliminate vitamin A deficiency by the year 2000 (*4*).

Periodic vitamin A supplementation of preschool children has been the most widely used intervention in controlling deficiency. The current WHO recommendation for universal prophylactic dosing in areas of prevalent vitamin A deficiency is 210 µmol (200 000 IU) every 3 to 6 months for children aged 1 to 6 years and half this dose for children aged 3 to 12 months (*5*). This intervention reduces xerophthalmia (*6*) and mortality (*7–10*) rates, and is associated with low rates of mostly mild, transient side-effects. In the only placebo-controlled trial investigating side-effects following the 210-µmol dose, 3–7% excess rates of transient nausea, vomiting, headache, and fever were reported; there was no excess risk of diarrhoea (*11*).

Supplementation of neonates with 52 µmol (50 000 IU) vitamin A (*12*) and young infants during immunization contacts with 26 µmol (25 000 IU) has been recommended.[a] While the impact of such supplementation during the first six months of life on

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Reprint No. **5542**

[a] **World Health Organization, International Vitamin A Consultative Group.** *Using immunization contacts to combat vitamin A deficiency. Report of an informal consultation. 30 June – 1 July 1992.* Geneva, 1992.

mortality has been inconclusive (*3*), it may promote accrual of vitamin A stores for the latter half of infancy when improved vitamin A status clearly reduces the risk of death (*8, 10, 13*).

A major constraint to establishing vitamin A supplementation programmes for infants has been the paucity of data demonstrating safety. The present trial was conducted to detect potential acute side-effects occurring at rates as low as 0.5–1.0% among newborn infants given one 52-µmol oral dose of vitamin A.

Materials and methods

All studies were carried out at Hasan Sadikin Hospital in Bandung, Indonesia, a large public referral hospital serving the urban and surrounding rural area.

Pilot study

Prior to beginning the safety trial, we studied the absorption curve of a 52-µmol oral dose of vitamin A among nine full-term neonates. Before dosing and at 6 and 24 hours after dosing, blood samples were drawn and analysed for retinol and retinyl esters by HPLC. Ester concentrations at the baseline were not measured, but assumed to be nil (*14*). Median retinol concentration at baseline was 0.53 µmol/l (range, 0.23 µmol/l to 0.74 µmol/l). Six hours after dosing, retinol concentrations rose (median, 1.08 µmol/l; range, 0.55 µmol/l to 1.83 µmol/l), and then stabilized or fell slightly by 24 hours (median, 0.85 µmol/l; range, 0.58 µmol/l to 1.20 µmol/l). Retinyl esters rose dramatically at six hours, (median, 3.85 µmol/l; range; 1.79 µmol/l to 12.32 µmol/l), and then fell quickly at 24 hours (median, 0.57 µmol/l; range, 0.0 µmol/l to 1.08 µmol/l). These results are consistent with those of Marie & See, who dosed infants with 367 µmol (350 000 IU) vitamin A, a dose large enough to produce clinical symptoms of acute toxicity in all infants studied (*15*). These authors observed that bulging of the fontanelle developed in parallel (but later by a few hours) with the increase in total serum vitamin A (retinol + ester) concentration, and that other side-effects such as vomiting, fever, irritability and diarrhoea occurred within 12 to 24 hours after dosing. We concluded that surveillance throughout the 48 hours after ingestion would detect any acute signs and symptoms which may occur.

Safety trial

All infants born at Hasan Sadikin Hospital from 18 June 1992 to 2 June 1993 were considered for enrolment. To aid in interpretation, infants unlikely to survive in the absence of medical care were excluded. These included infants with birth weight <1500 g, severe respiratory distress syndrome, major congenital anomalies, paralysis, hypoglycaemia (<1.66 mmol/l), hypocalcaemia (<2.0 mmol/l), clinical evidence of ischaemic hypoxia (5-minute APGAR scores <7, which did not improve by 24 hours), or clinical evidence of sepsis (hypothermia which did not resolve within 24 hours). The first 808 infants were restricted to infants >2500 g. Following an interim review by a Data Safety and Monitoring Committee, smaller infants were enrolled in two stages: infants with birth weights between 2000 and 2500 g were included beginning 7 December 1992; infants with birth weights between 1500 and 2000 g were included beginning 25 January 1993. Fever (temperature >37.5 °C) was initially an exclusion criterion, but was dropped on 25 January 1993. Similarly, a 5-minute APGAR score <7 was initially an exclusion criterion, but on 25 January we began enrolling these infants if their status had improved by 24 hours. Enrolment was limited to infants of birth weights 1500 to 2500 g between 15 May and 3 June 1993, to increase the sample size of that birth weight stratum. Of the 2844 live births occurring between 18 June 1992 and 2 June 1993 which met the birth weight criteria in force at the time, 2067 infants (73%) were successfully enrolled. Those not enrolled either met one or more medical exclusion criteria or did not give consent.

Following written informed parental consent, baseline examination was carried out by one of 12 nurse-midwives and one of four paediatricians. Physician and nurse examinations were carried out independently. A unique identifying number was assigned to each infant and written on a bracelet worn by the infant throughout the study.

Nurse-midwives elicited a history of mild and forceful vomiting, irritability, and loose stools experienced by the infant since birth, measured the infant's axillary temperature using the same digital thermometer for all infants, and palpated the anterior fontanelle. The history was obtained from the caregiver for the infant during the period between birth and the baseline; this person was either the mother or the staff nurse in charge of infants in the nursery. The fontanelle was graded as normal, or with a bulge (slight, moderate, or severe). The infant was classified as irritable if it was reported that irritability persisted after changing the diaper, feeding, and covering or uncovering with a blanket. Demographic data, obstetric information, APGAR scores, and the birth weight and length were gathered from medical records.

The physician also palpated the anterior fontanelle, grading it as normal or having a slight, moderate, or severe bulge, assessed the level of irritability,

and made three repeated measurements of head circumference. Midway through the trial inter- and intra-physician error in head circumference measurement was assessed among the four paediatricians. Each paediatrician independently measured the head of the same 20 babies three times on the same day. Of the total variability, 0.03% was due to intra-physician differences, 0.3% to differences between physicians, and 99.6% to differences between infants.

The first 973 infants underwent a cranial ultrasound study to rule out intracranial haemorrhage, and a duplex Doppler examination of the anterior cerebral artery to determine the resistive index (RI), an indirect indicator of intracranial pressure. Each infant was examined in standard coronal projection through the anterior fontanelle using a high-resolution unit equipped with a 5 MHz sector transducer for imaging, and Doppler studies (ACUSON 128 XP, Mountainview, CA, USA). Every infant was examined with the head in midline position in order to avoid alterations in intracranial venous drainage and intracranial pressure (ICP). The pericallosal artery (a branch of the anterior cerebral) was identified with colour Doppler and the range gate was placed over the artery as it coursed anterior to the genu of the corpus callosum. The RI is a relative measure of cerebral vascular resistance (*16*) and was calculated automatically by the ultrasound unit as follows:

[(Peak systolic velocity – End diastolic velocity)/Peak systolic velocity] × 100.

The RI was determined on three representative Doppler waveforms using a built-in spectrum analyser. The mean of the three values is reported. All examinations were performed at power output settings less than those recommended in current FDA guidelines (≤94mW/cm^2) (*17*). The estimated maximum *in situ* SPTA (spatial peak temporal average) intensities in water were ≤94mW/cm^2 during colour and pulsed Doppler mode.

All ultrasound studies were recorded on video cassette tape. Examinations for the first 295 infants and a randomly selected 82 additional infants were reviewed by one of us (GAT), a specialized paediatric radiologist, who was unaware of the treatment group, interpretation of the ultrasound study by the study paediatricians, or clinical signs and symptoms experienced by the infant. The purpose of the review was to determine if the correct artery (the anterior cerebral) had been studied; to confirm the presence or absence of intracranial haemorrhage; to detect ventricular dilatation; to evaluate the quality of the sonographic images (good, poor, or none obtained); to evaluate the quality of the wave forms achieved by the duplex Doppler for calculation of the RI (acceptable or poor); and to confirm the representativeness of the three wave forms selected for RI determination.

Following the baseline examination, the infants were randomly allocated to receive one oral dose of 52 µmol vitamin A (as retinyl palmitate) + 23 µmol vitamin E (as dl-α-tocopherol), or placebo (<0.10 µmol vitamin A + 23 µmol vitamin E). The supplement was administered directly into the infant's mouth by a nurse. Capsules were analysed throughout the study. The dose administered to the first 383 of the 1034 infants in the vitamin A group averaged 62 ± 6 µmol (59 449 ± 5700 IU). Contents of the second batch of capsules given to the remaining 651 infants averaged 53.7 ± 0.08 µmol (51 234 ± 78 IU).

Morbidity histories were repeated by the nurses at the end of each nursing shift and at 12, 24, and 48 hours post-dosing from the care-giver of the infant for the respective period. Measurement of temperature and examination of the anterior fontanelle was also repeated by the nurse 12, 24, and 48 hours after dosing. Physicians' examinations were repeated 24 and 48 hours post-dosing. Our protocol stipulated that ultrasound examinations should be repeated at 48 hours if the 24-hour examination was abnormal; no infant required a 48-hour examination.

Three weeks after discharge, a home visit to the first 234 infants enrolled was attempted to rule out significant longer-term side-effects. Vital status and weight were assessed.

Group differences were tested by *t*-test for continuous variables; differences in proportions were tested by χ^2 or Fisher's exact test as appropriate. ANOVA was used to compare means of more than two groups (*18*). Agreement between nurse and physician fontanelle examinations was evaluated by the Kappa statistic (*18*).

The trial was reviewed and approved by the Joint Committee on Clinical Investigation at The Johns Hopkins University School of Medicine, Baltimore, MD, USA; the Ethical Review Committee of Hasan Sadikin Hospital, Bandung, Indonesia; and the Indonesian Ministry of Health in Jakarta.

Results

Groups were comparable in all baseline characteristics (Table 1). The mean age at dosing was 16.1 hours and 16.4 hours in the control and vitamin A groups, respectively; 88% of infants were dosed within the first 24 hours of life. In both groups, >98% of infants were breast-fed during the 48-hour period of observation. Groups were similar in maternal age and parity.

There were no treatment group differences in mild or forceful vomiting at baseline or throughout the 48-hour period of follow-up (Table 2). Similarly, the rates of irritability did not differ between groups

Table 1: **Baseline characteristics by treatment group (n = 2067 cases)**[a]

Characteristic	Control group (n=1033)	Vitamin A group (n=1034)
No. of males	532 (51.5)[b]	543 (52.5)
Mean birth weight (g)	3007.0 (*430.3*)[b]	3002.1 (*436.6*)
Mean birth length (cm)	48.3 (*1.9*)	48.4 (*1.9*)
Gestational age:		
<38 weeks	56 (5.4)	66 (6.4)
38–42 weeks	977 (94.6)	967 (93.5)
>42 weeks	0	1 (0.1)
Appropriateness of weight for gestational age:		
AGA (appropriate)	951 (92.1)	950 (91.9)
SGA (small)	56 (5.4)	51 (4.9)
LGA (large)	26 (2.5)	33 (3.2)
Mean 5-minute APGAR score	9.0 (*0.5*)	9.0 (*0.4*)
Mean maternal age (years)	27.3 (5.5)	27.4 (*5.9*)
Mean maternal parity	2.4 (*1.8*)	2.4 (*1.8*)

[a] Groups not different in any baseline characteristic at $P<0.05$ level.
[b] Figures in parentheses are percentages, or standard deviations (in italics).

at any time during the study. The mean temperature of the vitamin A group was 0.05 °C (37.24 °C (±0.46) versus 37.29 °C (±0.45)) and 0.06 °C (37.08 °C (±0.48) verus 37.14 °C (±0.46)) higher at 12 and 24 hours, respectively, compared to the control group; given the large sample size, these differences reached statistical significance. By 48 hours this small difference had disappeared. There was no difference in the proportion of infants who were febrile (>38 °C) at any time during the study.

There were no differences in the rates of loose stools between the treatment groups at baseline or during the first 12 hours post-dosing. Between 12 and 24 hours there was a low but excess rate of loose stools in the vitamin A group, confined to the 1–2 episodes category (17 (1.6%) versus 6 (0.6%)). Only four infants experienced three or more episodes of loose stools during this interval and all were in the control group. Similarly, between 24 and 48 hours, a slightly higher proportion of infants experienced 1 or 2 loose stools during the 24-hour period in the vitamin A group compared to the control group (69 (6.7%) versus 55 (5.3%)), though the proportions having 3 or more loose stools during the interval were not different (36 (3.5%) versus 37 (3.5%) in the vitamin A and control groups, respectively).

At baseline, the nurses identified only one infant (in the control group) with a slightly bulging fontanelle while the doctors identified 13 such cases in the control group and 3 cases in the vitamin A group (Table 3). At 12 hours, the rates of slightly bulging fontanelle (as assessed by the nurses) did not differ between the two groups (6 (0.6%) versus 7 (0.7%) in the vitamin A and control groups, respectively). However, at 24 and 48 hours there were excess rates of slightly bulging fontanelle in the vitamin A group by both the nurses' and doctors' examinations, and at 24 hours one infant in the vitamin A group had a moderately bulging fontanelle. By the nurses' examination, there were excess rates of bulging fontanelle (slight and moderate) in the vitamin A group of 0.9% and 1.7% at 24 and 48 hours, respectively. By the doctors' examination, there were excess rates of 1.8% and 2.1% at 24 and 48 hours, respectively.

Agreement between physicians and nurses in their follow-up fontanelle examinations was good (Kappa= 0.46 and 0.42 at 24 and 48 hours, respectively). At both follow-up examinations, the physicians identified more bulging fontanelles than did the nurses; most of the cases identified by the nurses were also identified by the physicians. The one case of moderately bulging fontanelle was identified by both nurses and physicians. Therefore, further analysis of fontanelle status is based on the physicians' examination.

Among infants in the vitamin A group, all 46 cases with bulging fontanelle at 24 hours represented incident cases; none had been bulging at baseline. Of the 46 cases at 48 hours, 15 (32.6%) were persistent from 24 hours and 31 (67.4%) were incident. Among infants in the control group, 25 (89.3%) of the 28 cases with bulging fontanelle at 24 hours were incident cases; 8 (17.4%) persisted to 48 hours. Thus, 17 of the 25 cases at 48 hours (68.0%) were incident.

Mean head circumference in the two groups was virtually identical at each examination (Table 3). Differences in the proportions of infants with an enlarged head circumference (≥0.5 cm) within each 24-hour period were small and insignificant: 3.8%

Table 2: **Signs and symptoms of morbidity at baseline, 12, 24, and 48 hours after dosing in vitamin-A and control groups (*n*=2067)**

Sign or symptom	Baseline		12 Hours		24 Hours		48 Hours	
	Control (*n*=1033)	Vitamin A (*n*=1034)	Control (*n*=1033)	Vitamin A (*n*=1034)	Control (*n*=1033)[a]	Vitamin A (*n*=1034)	Control (*n*=1027)[b]	Vitamin A (*n*=1031)[c]
No. of vomiting episodes:								
Mild: 1–2	13 (1.3)[d]	8 (0.8)	92 (8.9)	76 (7.4)	61 (5.9)	55 (5.3)	94 (9.1)	83 (8.0)
≥3	0	0	11 (1.1)	16 (1.6)	2 (0.2)	5 (0.5)	16 (1.6)	9 (0.9)
Forceful: 1–2	0	2 (0.2)	4 (0.4)	3 (0.3)	2 (0.2)	3 (0.3)	2 (0.2)	2 (0.2)
≥3	0	0	0	2 (0.2)	1 (0.1)	0	0	0
No. with irritability (by history):								
1–2 times	0	0	9 (0.9)	5 (0.5)	11 (1.1)	7 (0.7)	9 (0.9)	10 (1.0)
Sometimes	1 (0.1)	0	26 (2.5)	25 (2.4)	21 (2.0)	20 (1.9)	10 (1.0)	7 (0.7)
Often	0	0	8 (0.8)	10 (1.0)	5 (0.5)	15 (1.4)	4 (0.4)	5 (0.5)
No. with fever (>38 °C)	6 (0.6)	3 (0.3)	34 (3.3)	40 (3.9)	29 (2.8)	32 (3.1)	55 (5.3)	45 (4.4)
No. with loose stools:								
1–2	0	0	1 (0.1)	0	6 (0.6)	17 (1.6)	55 (5.3)	69 (6.7)
3–5	0	0	1 (0.1)	1 (0.1)	3 (0.3)	0	22 (2.1)	32 (3.1)
≥6	0	0	0	0	1 (0.1)	0[e]	15 (1.4)	4 (0.4)[e]

[a] Missing 1 case for vomiting, irritability, and loose stools.
[b] Six cases discharged before 48-hour follow-up.
[c] Three cases discharged before 48-hour follow-up; one additional case missing for irritability and fever.
[d] Figures in parentheses are percentages.
[e] Groups significantly different, $P<0.03$.

versus 5.0% ($P=0.22$) between baseline and 24 hours; 5.7% versus 6.8% ($P=0.35$) between 24 and 48 hours, for the control and vitamin A groups, respectively. During both 24-hour intervals, the slight excess in enlarged head circumference in the vitamin A group was confined to the 0.5 to 1.0 cm increase category. The two treatment groups had nearly identical rates in the more severe category of >1.0 cm increase. Fewer than 10 infants were judged to be irritable by the paediatricians at any examination and there were no differences between treatment groups (data not shown).

Haemorrhage was not detected by ultrasound examination in any infant at baseline or 24 hours after dosing (Table 3). One infant had a haemorrhage at baseline, and was excluded from the trial. The mean RI at baseline was 70.6% and 70.4% in the control and vitamin A groups, respectively; reported RI values for healthy term infants are around 70% (range, 60–80%) (*16, 19*). At 24 hours, the mean RI value had fallen to 68.4% and 68.3% in the control and vitamin A groups, respectively. There was no treatment group difference in the mean change between baseline and 24 hours (–2.2% (7.9) versus –2.2% (8.1)). No infant had an RI over 87% at either examination.

Of the 375 infants whose baseline and 24-hour ultrasound studies were reviewed by the paediatric radiologist, 184 were in the vitamin A group, and 191 in the control group. Three of these infants had a bulging fontanelle at baseline and 6 had a bulging fontanelle at 24 hours. The anterior cerebral artery was correctly studied in 353 (94%) of the baseline studies. The errors made were balanced between treatment groups ($P=0.54$). Among the 24-hour ultrasound studies which were reviewed, the anterior cerebral artery was correctly studied in 90% of the cases. There was again no difference between the treatment groups in which this artery was studied ($P=0.47$). The arteries studied in error were the internal and middle carotid and a branch of the anterior cerebral. These arteries have been demonstrated to have very similar RI values compared to the anterior cerebral (*16, 19*). The quality of the wave forms was graded as acceptable in 98% of the baseline studies and in 97% of the 24-hour studies. The quality of the sonographic images obtained for ruling out haemorrhage was graded as good in 97% of the baseline and 24-hour studies. The absence of intracranial haemorrhage was confirmed in all studies. No ventricular dilatation was observed in any infant, including those with bulging fontanelles. The reviewer agreed with all wave forms selected for calculation of the RI in all ultrasound studies from both groups at both examinations.

A bulging fontanelle suggests an increase in intracranial fluid volume which is not necessarily associated with an increase in intracranial pressure

Table 3: **Indicators of intracranial volume and pressure, as determined by physicians and nurses, at baseline, 12, 24 and 48 hours, by treatment group**

Indicator	Baseline		24 Hours		48 Hours	
	Control (*n*=1033)	Vitamin A (*n*=1034)	Control (*n*=1033)	Vitamin A (*n*=1034)	Control (*n*=1027)[a]	Vitamin A (*n*=1030)[b]
No. with bulging fontanelle (physicians):						
Slight	13 (1.3)[c]	3 (0.3)	28 (2.7)	45 (4.4)	25 (2.4)	46 (4.5)
Moderate	0	0	0	1 (0.1)	0	0
Severe	0	0[d]	0	0[e]	0	0[d]
No. with bulging fontanelle (nurses):						
Slight	1 (0.1)	0	13 (1.3)	22 (2.1)	6 (0.6)	24 (2.3)
Moderate	0	0	0	1 (0.1)	0	0
Severe	0	0	0	0	0	0[e]
Resistive index:[f]						
Mean %	70.6 (*7.1*)[c]	70.4 (*6.8*)	68.4 (*6.4*)	68.3 (*6.8*)		
Mean change (baseline to 24 hours)			−2.2 (*7.9*)	−2.2 (*8.1*)		
Intracranial haemorrhage:[f]						
Absent:	489 (100)	484 (100)	482 (100)	483 (100)		
Present:	0	0	0	0		
Mean head circumference (cm)	33.3 (*1.3*)	33.2 (*1.3*)	33.2 (*1.3*)	33.3 (*1.3*)	33.3 (*1.3*)	33.3 (*1.3*)
Change in head circumference:	Baseline to 24 hours		24 to 48 hours[g]		Baseline to 48 hours	
≥0.5–1.0 cm	21 (2.0)	37 (3.6)	41 (4.0)	54 (5.2)	59 (5.7)	70 (6.8)
>1.0 cm	18 (1.7)	14 (1.4)	18 (1.7)	16 (1.6)	19 (1.8)	20 (1.9)

[a] Six cases discharged before 48-hour follow-up.
[b] Three cases discharged before 48-hour follow-up; one additional case missing fontanelle data.
[c] Figures in parentheses are percentages, or standard deviations (in italics).
[d] Groups significantly different, $P \leq 0.02$.
[e] Groups significantly different, $P = 0.05$.
[f] Ultrasound studies were limited to 489 and 484 infants at baseline and 482 and 483 infants at 24 hours in the control and vitamin A groups, respectively.
[g] $n = 1027$ for control group; $n = 1030$ for vitamin A group due to cases discharged before 48 hours or missing data.

(ICP) (*20*). To assess the relationship between the clinical findings of the fontanelle and intracranial pressure, we compared the RI values and rates of clinical signs and symptoms for infants who did and did not develop a bulging fontanelle (Table 4). Resistive index data were available on 33 of the 74 infants with bulging fontanelles at 24 hours. The mean reduction in RI during the 24 hours after dosing was slightly less (but not significant) among infants in the vitamin A group who developed a bulging fontanelle compared to infants with normal fontanelle examinations at 24 hours in the vitamin A and placebo groups. The proportion of infants with an increase in RI at 24 hours after dosing was not different among infants who developed a bulging fontanelle 24 hours following vitamin A, compared with infants who had normal fontanelles following either vitamin A or placebo. Similarly, the presence of a bulging fontanelle was not associated with higher rates of any sign or symptom assessed at any time during the 48-hour period after dosing. Odds ratios were not different from 1.0 for irritability, vomiting, loose stools, or fever among infants who developed a bulging fontanelle at 24 or 48 hours, compared to infants whose fontanelle examinations were normal (data not shown).

A total of 199 low-birth-weight (<2500 g) infants (98 controls and 101 in the vitamin A group) were included in the study and evaluated separately. There were no treatment group differences in rates of vomiting, irritability, fever, loose stools, mean head circumference or change in head circumference during follow-up (data not shown). Three infants (one control and two in the vitamin A group) had slightly bulging fontanelles at 24 hours; at 48 hours one infant in the control group and none in the vitamin A group had a bulging fontanelle. Within the sample size constraints there was no evidence that low-birth-weight or premature infants were at any greater risk of developing a bulging fontanelle. Ultrasound data were available for only 18 low-birth-weight infants at the baseline, and for 16 at 24 hours. Mean RI val-

Table 4: **Mean resistive index (RI) and change at 24 hours, and the proportion of infants with increased resistive index by treatment group and fontanelle status at 24 hours**

Treatment group and fontanelle status at 24 hours	Resistive index (mean value)			No. with 24-hr RI more than baseline RI
	Baseline	At 24 hours	Difference[a]	
Placebo:				
Normal (*n*=471)	70.5 (*7.1*)[b]	68.4 (*6.4*)	−2.1 (*7.9*)	185 (39.3)[b]
Tense (*n*=11)	75.3 (*6.7*)	68.6 (*6.1*)	−6.7 (*8.7*)	2 (18.2)
Vitamin A:				
Normal (*n*=461)	70.3 (*6.8*)	68.2 (*6.8*)	−2.2 (*8.1*)	190 (41.2)
Tense ((*n*=22)	72.7 (*6.2*)	71.1 (*6.1*)	−1.6 (*7.3*)	9 (40.9)

[a] *P* value (ANOVA) = 0.3.
[b] Figures in parentheses are percentages; those in italics are standard deviations.

ues did not differ between groups at the baseline (73.1% versus 70.8%, $P = 0.46$) or at 24 hours (71.7% versus 72.2%, $P=0.92$) for the control and vitamin A groups, respectively. Compared to term infants, the reported RI values for low-birth-weight infants are higher and more variable (about 78%; range, 50–100%) (*16, 19*).

Of the 234 infants who were visited at home three weeks after dosing, 228 (97.4%) were successfully examined. Mean weight gain over the period did not differ between the groups (22.3 versus 23.8 g/day for the control and vitamin A groups, respectively, $P=0.45$). This approximates the 25th percentile rate of growth of a reference sample of American children (*21*). All infants were alive at the time of the visit.

Discussion

Bulging of the anterior fontanelle was the only side-effect which occurred at a significantly higher rate following a 52-µmol oral dose of vitamin A compared to placebo. Bulging fontanelles have been commonly reported in infants following large doses of vitamin A (*15, 22–25*), but the mechanism is poorly understood. Ironically, in pigs (*26*), calves (*27*), rats (*28*) and dogs (*26*) vitamin A toxicity results in decreased intracranial pressure. None the less, these animal models provide clues to the human process. Free vitamin A (not bound to RBP, retinol-binding protein) can penetrate the central nervous system (CNS) (*29*) where it apparently alters the capillary permeability of the arachnoid villi (the site of cerebral spinal fluid resorption) (*28*). Others have speculated that changes in the cellular integrity of the choroid plexus tissue (the site of CSF formation) may result in an overproduction of CSF (*30*). Interestingly, in humans, increased intracranial pressure can also result from vitamin A deficiency (*31*).

While the details remain obscure, vitamin A apparently affects the integrity of the membranes responsible for resorption and/or formation of CSF, so that the CSF volume increases in humans during both deficiency and toxicity of vitamin A. The human cranium can accommodate within a range of CSF volumes without changing the intracranial pressure (*20, 32*). In infants, perhaps because the sutures and fontanelles are open, even larger increases in volume can be accommodated in the cranium before the pressure increases (*33*). An increase in intracranial pressure leads to symptoms such as vomiting and irritability.

In our study, the presence of a bulging fontanelle was not associated with increased rates of any morbidity assessed at any time throughout the period of follow-up. In addition, we used duplex Doppler cranial sonography as a noninvasive indicator of intracranial pressure. Several authors have shown a strong linear correlation between RI and increasing intracranial pressure (*16, 34–36*). Mean RI values were remarkably similar for infants in the control and vitamin A groups and were consistent with reported values of normal infants. RI values over 100% represent a backflow of arterial blood during diastole, often as a result of increased cerebrovascular resistance. No infant in our study had an RI value over 87%, not even those who developed bulging fontanelles or those with low birth weight. In addition, RI values normally fall quickly as the infants mature (*37*). We observed this fall in RI between the infants' first and second days of life, and the mean decrease was nearly identical for the vitamin A and placebo groups. Even among infants who developed a bulging fontanelle by 24 hours after dosing, the mean change in RI for this same time period was negative.

These findings suggest that while intracranial volume may have increased due to the vitamin A, the compliance of the neonatal cranium was sufficient to prevent an increase in pressure. Furthermore, even the increased intracranial volume experienced by the infants following 52 µmol of vitamin A was rare and

modest. All but one of the bulging fontanelles were graded as "slight" and the proportions of infants with increases in head circumference of >0.5 cm in a 24-hour period were similar following vitamin A or placebo.

The literature contains reports of at least 13 infants who were 4 months of age or less at the time of exposure to total doses of vitamin A ranging from 314 µmol (300 000 IU) to 7078 µmol (6.75 million IU) administered over periods of 1 day to 9 months (*15, 22, 24, 25*). All presented with bulging fontanelles and all but one (*22*) had concomitant neurological and other toxic signs and symptoms including vomiting (*15, 23, 25*), irritability (*23, 25*), skin lesions (*23, 24*), and skeletal lesions (*23, 24*). In all infants the symptoms resolved completely on cessation of the vitamin. Five of these infants were developmentally assessed at 3.5 to 5 years of age and found to be normal (*23, 24*). Two underwent psychological testing at 4 years of age and were found to have above-average intelligence with no evidence of organic brain disease (*24*). Though not conclusive, the apparent absence of long-term neurological sequelae in cases of severe vitamin A toxicity with a clearly increased ICP is reassuring because the cases with bulging fontanelles in this study showed no evidence of increased ICP.

Acute side-effects among neonates following a 52-µmol oral dose of vitamin A were rare in this study, and those that occurred were mild. Our findings confirm those of two smaller studies. In Nepal, infants less that one month of age experienced no excess risk of irritability, vomiting, fever, loose stools, or bulging fontanelle following one 52-µmol oral dose compared to similar infants given placebo (*38*). Similarly, no side-effects were observed among 52 Thai neonates following the same oral dose.[b]

Neonatal dosing may offer several benefits. Infants normally accrue stores of vitamin A during lactation (*39*). However, the milk of women living in areas where vitamin A deficiency is endemic, while sufficient to prevent xerophthalmia during lactation, may be insufficient to allow the infant to build the necessary stores (*39*). Infants who are not breast-fed are at greatest risk of developing severe vitamin A deficiency (*40*). Accordingly, supplementation of neonates consuming vitamin A-poor breast milk, or not breast-fed at all, may promote accrual of vitamin A stores in preparation for weaning when an adequate vitamin A-rich diet is often lacking. Our safety findings are directly applicable to breast-fed infants since nearly all the infants (99%) in this study were breast-fed during the first two days of life. Risk of acute side-effects following this dose is probably even lower among infants who do not receive vitamin A-rich colostrum.

Thanangkul demonstrated that provision of a 52-µmol dose at birth maintained higher circulating retinol concentrations for 7.5 months compared to placebo controls.[b] She also reported that provision of one 314 µmol (300 000 IU) dose to mothers immediately post-partum had a similar affect on breast-fed infant serum retinol concentrations over the same period of follow-up, a finding which was recently confirmed in another study using a more rigorous study design (*41*). Thus, perhaps the most efficacious intervention would be for birth attendants to give supplements to both mothers and infants, an idea first suggested in 1978 (*42*). Delivery of vitamin A supplements by birth attendants may be efficient and cost-effective. At the World Summit for Children in 1990, the world's political leaders agreed that all deliveries should be carried out by trained personnel by the year 2000 as a global priority and a technically and financially feasible goal (*43*).

Finally, it is impossible to prove the absence of a finding. In an attempt to identify the presence of any longer-term adverse effects and benefits of dosing neonates with vitamin A, we are currently following all 2067 infants for one year. Endpoints include vital status, growth, morbidity, and vitamin A status.

[b] **Thanangkul O et al.** Comparison of the effects of a single high dose of vitamin A given to mother and infant upon plasma levels of vitamin A in the infants. In: *Joint WHO/USAID Meeting on Vitamin A Deficiency: Priorities for Research and Action Programmes, Jakarta, Indonesia 25–29 November 1974.* Jakarta, 1974 (unpublished WHO document NUT/WP/74.14, 1974).

Acknowledgements

This research was supported by Cooperative Agreement No. DAN-0045-A-5094 between the Dana Center for Preventive Ophthalmology, the Johns Hopkins University; the Bureau of Research and Development, Office of Nutrition, U.S. Agency for International Development, Washington DC; and NIH grant #S10-RR04060, with assistance from Task Force Sight and Life, Hoffmann La Roche, Basle, Switzerland.

We are grateful to Dr Muhilal (Nutrition Research and Development Centre, Bogor, Indonesia) and Dr S. Tanumidhardjo (Iowa State University) for analysing the pilot study serum specimens, the members of the Data Safety and Monitoring Committee (Dr F. Jalal, National Development Planning Agency, Jakarta; Dr Yati Sunarto, Gadjah Mada University, Yogyakarta; Dr F. Davidson, USAID, Washington DC; and Dr J. Tielsch and Dr R. Ichord, The Johns Hopkins University), and Ms D. Garrett for preparing the manuscript.

Résumé

Innocuité de l'administration d'une dose orale de 52 µmol (50 000 UI) de vitamine A chez le nouveau-né

La supplémentation périodique en vitamine A chez les enfants d'âge préscolaire est l'intervention la plus répandue pour lutter contre l'avitaminose A. Pour le traitement prophylactique généralisé dans les régions fortement touchées par la carence en vitamine A, l'OMS recommande actuellement une dose orale de 210 µmol (200 000 UI) tous les 3 à 6 mois chez les enfants de 1 à 6 ans et la moitié de cette dose chez les enfants de 3 à 12 mois. Chez les nourrissons de moins de 3 mois, la supplémentation a été recommandée mais n'a jamais été mise en pratique faute de données démontrant son innocuité. L'essai décrit dans cet article visait à détecter d'éventuels effets secondaires aigus chez des nouveaux-nés ayant reçu une dose orale de 52 µmol (50 000 UI) de vitamine A.

Au total, 2067 nouveau-nés indonésiens nés dans un hôpital public à Bandung (Indonésie) ont été inclus dans l'essai, après obtention du consentement éclairé écrit des parents. Les nouveau-nés ont été répartis par tirage au sort en deux groupes, l'un recevant une dose orale de 52 µmol de vitamine A + 23 µmol (40 UI) de vitamine E, et l'autre un placebo (<0,10 µmol de vitamine A + 23 µmol de vitamine E). Les nourrissons ont été suivis par une équipe de 12 infirmières-sage-femmes et 4 pédiatres avant et pendant la période de 48 heures suivant l'administration, à la recherche de signes tels que vomissements, irritabilité, diarrhée, fièvre, modification du périmètre crânien, et bombement de la fontanelle antérieure. Les fontanelles ont été notées comme normales ou présentant un bombement léger, modéré ou sévère. Les 965 premiers nourrissons traités ont été soumis à une échographie crânienne avant l'administration et 24 heures après, pour rechercher des signes d'hémorragie intracrânienne, et à un Doppler en duplex de l'artère cérébrale antérieure pour déterminer l'index de résistance (IR). L'IR donne une mesure relative de la résistance circulatoire cérébrale et est un indicateur indirect de l'hypertension intracrânienne. Il a été déterminé sur 3 formes d'ondes représentatives et la moyenne des valeurs a été notée. Un échantillon aléatoire d'échographies a été examiné et les résultats ont été confirmés par un radiologue spécialisé en pédiatrie.

En ce qui concerne les données de référence (avant l'administration), les groupes étaient comparables. Un bombement de la fontanelle a été observé chez 2,7% et 4,6% des nourrissons au bout de 24 heures, et chez 2,4% et 4,5% des nourrissons au bout de 48 heures, dans le groupe témoin et dans le groupe traité respectivement. Aucune différence entre les groupes n'a été observée pour les autres signes. Aucun nourrisson n'a présenté d'hémorragie intracrânienne. Les valeurs moyennes de l'IR étaient normales et ne différaient pas entre les groupes, que ce soit avant l'administration ou 24 heures après. L'IR moyen diminuait au cours des 24 heures, de façon pratiquement identique dans les deux groupes. Le bombement de la fontanelle n'était associé à aucune augmentation de l'un quelconque des signes et symptômes recherchés ni à une augmentation de l'IR.

L'administration d'une dose orale de vitamine A peut provoquer une légère augmentation du volume intracrânien chez une petite proportion de nourrissons, mais sans augmentation de la tension intracrânienne. Les effets secondaires aigus chez les nouveau-nés à la suite de ce traitement sont rares et bénins.

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