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0031-3998/85/1905-0441$02.00/0
PEDIATRIC RESEARCH
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Vol. 19, No. 5, 1985
*Printed in U.S.A.*

# Effect of Infant Age on Aminopyrine Breath Test Results

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**ABSTRACT. The aminopyrine breath test has been used in adults as a measure of hepatic N-demethylase activity. In order to study maturational changes in enzyme function, $^{13}C$ aminopyrine (2 mg/kg) was administered orally to infants ($n = 16$) between the ages of 1 and 38 wk. Breath samples were collected for 6 h after administration of the labeled aminopyrine for the measurement of $^{13}CO_2$ enrichment. Using a number of different scoring methods to quantitate $^{13}CO_2$ elimination of breath, demethylation of aminopyrine was found to be positively correlated to age. By 20 wk of age, some infants had rates of elimination similar to those measured in adults. Absorption was excluded as a limiting variable, because no improvement in oxidation rates was found when the aminopyrine was readministered as an intravenous bolus. Changes in nutritional status and route of feeding (enteral *versus* parenteral) did not prevent the effect of maturation on aminopyrine elimination. Conclusions: 1) maturational differences are seen in the metabolism of aminopyrine; 2) these differences may reflect immaturity of N-demethylase activity or diversion of the liberated formaldehyde into biosynthetic rather than oxidative pathways. (*Pediatr Res* 19: 441–445, 1985)**

Received August 27, 1984; accepted December 31, 1984.

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This work is a publication of the USDA/ARS Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine, and Texas Children's Hospital, Houston, TX and is supported by Grant AM28129 from NIAMDDK.

The hepatic P 450 cytochrome monooxygenase enzyme complex is responsible for the metabolism of a myriad of xenobiotics. Available information suggests that the P 450 system undergoes maturational increases in activity (1, 2). One of the *in vivo* markers that has been used to measure P 450 activity has been the capacity of hepatocytes to demethylate aminopyrine (3–5). By labeling the methyl group with $^{14}C$ or the nonradioactive isotope, $^{13}C$, an *in vivo* assessment of demethylating capacity can be made. After demethylation, the labeled methyl group is converted to formaldehyde, formate, and eventually the carbon is excreted in breath carbon dioxide (6).

Although the aminopyrine breath test has been used for a number of years in adults, there is little experience with the application of the test in infants and children (7). Because demethylation is dependent on cytochrome activity, the utilization of the aminopyrine breath test in children affords a unique method to examine the time course of the postnatal development of demethylase function. The aims of this study, therefore, were to determine age-related changes in N-demethylase activity as demonstrated by the aminopyrine breath test and to ascertain the time course for development of such changes.

## METHODS

*Subjects.* Sixteen hospitalized infants less than 1 yr of age were studied (Table 1). The subjects had neither a history of liver disease nor evidence of liver disease on clinical examination. Serum alanine transaminase, aspartate transaminase, alkaline phosphatase, total and direct bilirubin were normal in all infants. None of the infants had lung disease or were on drugs known to affect hepatic function. Because a hospitalized population was studied and nutritional status could potentially affect the results of the breath test, nutritional assessments were performed, using the clinical examination and weight to height and arm to head circumference ratios (Table I (8, 9).

*Materials.* The N,N- 4,4,-dimethyl-[$^{13}C$]-aminoantipyrine (Merck, Sharpe & Dome Ltd., Point Claire, Canada) had an isotopic content of 90 atom% $^{13}C$ in the exocyclic methyl positions. The drug was dissolved in normal saline and passed through a 0.22 $\mu$ filter (Millipore Corp., Bedford, MA). The solution was cultured to assure sterility and tested for pyrogens before use.

*Protocol.* The protocol was approved by the Institutional Review Boards for Human Research of Baylor College of Medicine, Texas Children's Hospital, and the Harris County Hospital District. Informed consent was obtained from parents of the infants.

The infants were fasted for a minimum of 2 h before the oral administration of 2 mg/kg of aminopyrine. Although aminopyrine is rapidly and completely absorbed (10), selected infants were given the drug both orally and intravenously in random order on sequential days to rule out the effects of gastrointestinal function, as a variable, on the results. Additionally, sequential studies were obtained in some of the infants. Breath samples were collected 30, 15, and 0 min before and at 30-min intervals up to 4 h, then hourly for a total of 6 h after the oral administration of the aminopyrine. When the drug was given intravenously, breath samples were collected at -30, -15, 0, 1, 2, 3, 5, 7, 10, 15, 20, 30, 45, and 60 min, after which the collection times were the same as those for the oral studies.

Breath samples were obtained using a face mask fitted with one-way valves with the expiration valve attached to a collection bag (11). Samples were transferred to 50-ml Vacutainers (Becton, Dickinson & Co., Rutherford, NJ) for storage (12). Total $CO_2$ production was determined hourly during the test by sweeping the mask with a known rate of air flow and analyzing the sample for $CO_2$ concentration (11).

Although there has been no documentation of a case of neutropenia resulting from the use of aminopyrine for a breath test, rare cases have occurred after continuous use of the drug. Thus, as a precaution, a complete blood count was obtained before and 24 h after each breath test.

Table 1. *Clinical summary of patients*

| Patient | Age (wk) | Nutritional status | Feeding route | Aminopyrine route |
|---|---|---|---|---|
| 1 | 1 | N* | TPN† | PO‡, IV§ |
| 2 | 1 | N | TPN | PO |
| | 2 | N | TPN | PO, IV |
| | 3 | N | Oral | PO, IV |
| 3 | 1 | N | Oral | PO |
| | 2 | N | TPN | PO |
| | 3 | N | TPN | PO |
| 4 | 4 | M‖ | Oral | PO, IV |
| | 5 | M | Oral | PO, IV |
| 5 | 4 | N | Oral | PO, IV |
| 6 | 5 | M | Oral | PO, IV |
| 7 | 5 | M | TPN | PO, IV |
| 8 | 5 | M | TPN | PO |
| | 6 | N | TPN | PO, IV |
| 9 | 6 | N | Oral | PO, IV |
| 10 | 6 | N | Oral | PO, IV |
| 11 | 7 | N | Oral | PO |
| 12 | 14 | M | TPN | PO |
| | 18 | N | TPN | PO |
| | 19 | N | TPN | PO |
| 13 | 16 | N | TPN | PO |
| | 17 | N | TPN | PO |
| 14 | 27 | M | TPN | PO |
| 15 | 33 | M | TPN | PO |
| | 34 | M | Oral | PO |
| 16 | 34 | M | Oral | PO |
| | 36 | M | TPN | PO |
| | 38 | M | TPN | PO |

* Normal.
† Total parenteral nutrition.
‡ Oral.
§ Intravenous.
‖ Malnourished (wt/ht < 5%, arm/head circumference ratio < 0.31) (8, 9).

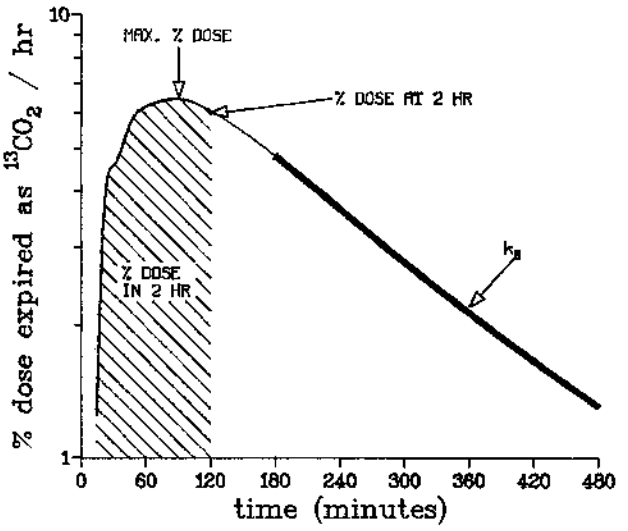


Fig. 1. Aminopyrine breath test scoring techniques. Cum% 2h is represented by the *hatched area.* Max% exp and the %Dose 2h are determined by inspection of the curve. Not shown is total percentage dose recovered which is derived from the area under the curve during the test period. Note the log scale of the y-axis.

*Analytical procedures.* Isotopic composition ($^{13}CO_2/^{12}CO_2$) in breath was determined using a dual inlet gas isotope ratio mass spectrometer (13). Carbon dioxide concentration was measured using gas chromatography (14).

*Data analysis.* $CO_2$ production values (μmol/kg/min) for each infant were averaged and the mean was used in calculations of percentage dose recovery determined from the $^{13}C$ enrichment of breath $CO_2$ (15). The $^{13}CO_2$ breath test curves were evaluated using scoring techniques which have been described in detail elsewhere (15–17). In brief, the cumulative percentage dose recovered over the first 2 h of the study was calculated from the trapezoidal integration of a plot of percentage dose expired/h *versus* time from zero to 120 min; the maximum percentage dose expired/h and the percentage dose recovered at 2 h were determined by inspection of the breath test curve; the total percentage dose recovery was calculated from the area under the curve of the percentage dose of labeled $CO_2$ expired/h; the disappearance rate constant ($K_b$) was obtained from the slope of the least-squares regression line fitted to a semi-log plot of percentage dose expired/h from 120 min to 6 h. A graphic summary of these methods is depicted in Figure 1.

Differences between age groups for the scored results were compared using Student's *t* test. The mean values of the breath test results for individual infants in whom multiple tests were carried out were used in the comparisons between different age groups. Results of studies in the same infant were compared using a paired *t* test. The relationships between age and breath test scores, nutritional status, and type of diet (enteral or parenteral nutrition) were analyzed using multiple regression analysis.

## RESULTS

The percentage dose expired/h after oral administration of the drug is shown in Figure 2. Except for infant 2 (*vide infra*), there was little or no increase in breath $^{13}CO_2$ in infants between 1 and 4 wk of age following administration of the aminopyrine. At 5 to 7 wk, some infants began to show a small increase in the percent dose eliminated per hour. In the 14- to 19-wk age group, the percentage dose excreted rose sharply over the first 60 min and then decreased gradually over the next 5 h; these results are similar to those seen in aminopyrine breath studies carried out in adults (15). In the infants studied between 27 and 38 wk, interindividual differences in drug elimination were apparent, but overall there was increased elimination when compared to the younger infants.

Table 2 gives the results of the breath tests when parameters

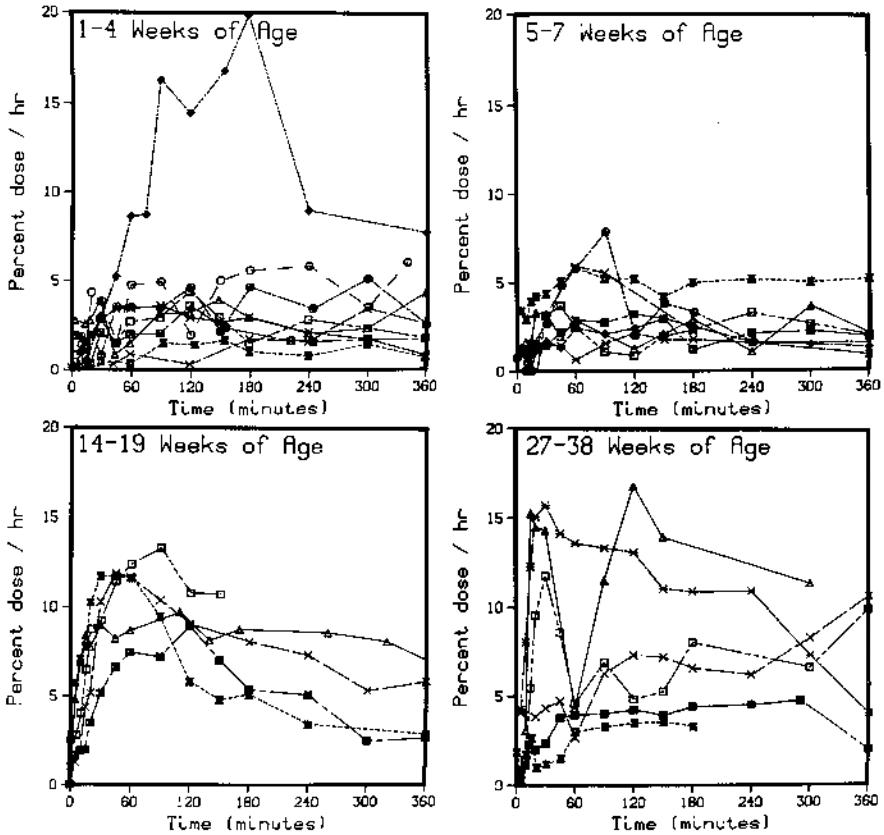


Fig. 2. Aminopyrine breath test results expressed as Cum% 2h over time according to age. Data shown are results obtained after oral administration of the aminopyrine.

Table 2. *Results of scored aminopyrine breath tests (mean ± SD)*

| Age (wk) | *n* | Cum% 2 h | Max% exp | % Dose 2 h | Tot % 6 h | Elimination constant |
|---|---|---|---|---|---|---|
| 1–4 | 5 | 5.9 ± 1.1 | 5.6 ± 1.8 | 4.0 ± 0.9 | 19.3 ± 5.0 | 1.9 ± 10.5 |
| 5–8 | 6 | 5.6 ± 2.8 | 4.5 ± 2.0 | 2.5 ± 1.6 | 16.4 ± 7.0 | 1.4 ± 13.5 |
| 16–36 | 5 | 15.9 ± 4.1 | 11.8 ± 3.3 | 9.6 ± 4.3 | 41.3 ± 11.1 | 6.7 ± 10.9 |
| | | $p < 0.0001$* | $p < 0.006$* | $p < 0.02$* | $p < 0.004$* | NS |
| | | $p < 0.0001$† | $p < 0.0001$† | $p < 0.004$† | $p < 0.0001$† | NS |

* 1–4 *versus* 16–36 wk.

† 5–8 *versus* 16–36 wk.

suggested by various authors (15–17) were used in the analyses. The cumulative percentage dose recovered over 2 h (Cum% 2 h), the maximum percentage dose expired/h (Max% exp), the percentage dose recovered at 2 h (% Dose 2 h), and the total percentage dose (Tot% 6 h) recovered over 6 h were greater in the infants aged 16 to 36 wk compared with those in infants aged 1 to 4 or 5 to 8 wk. No differences were seen in the mean disappearance rate constants ($K_b$) among the groups.

No significant differences were seen between the results of the oral and intravenous studies carried out in the same infants, eliminating gastrointestinal absorption as a variable to account for the findings (per os *versus intravenous* 1 to 4 wk: Cum% 2h, 7.1 ± 5.5 *versus* 5.9 ± 4.3; Max% exp, 7.5 ± 7.2 *versus* 4.6 ± 2.2; % Dose 2 h, to 5.1 ± 5.3 *versus* 2.9 ± 2.6; per os *versus* intravenous 5 to 7 wk: Cum% 2 h, 5.6 ± 2.6 *versus* 5.5 ± 5.5; Max% exp, 4.2 ± 1.3 *versus* 4.5 ± 2.8; % Dose 2 h, 3.0 ± 1.8 *versus* 3.4 ± 3.2). All the breath test scores except mean disappearance rate constants showed a significant correlation with age (Fig. 3).

In order to examine changes in drug elimination with age in an individual, sequential studies were carried out in eight infants. Because the route of feeding or nutritional status changed in some subjects who had more than one study, the results of only one test were included in any given regression. Once again, a significant correlation with age was seen, but no effect of nutritional status or route of feeding was found. Although interindividual differences in aminopyrine elimination were evident, overall within individuals there was an increase in the cumulative percentage dose recovered over 2 h (Fig. 4).

No side effects, including changes in the blood count, were noted after the administration of the aminopyrine (mean neutrophil count pretest: 4800 ± 4000 $mm^3$; posttest 5000 ± 3300 $mm^3$).

## DISCUSSION

The present study is consistent with investigations carried out in rats which have demonstrated age-related changes in aminopyrine demethylase activity (18). The maturation of activity measured *in vitro* correlated with increases in drug elimination found *in vivo* (18).

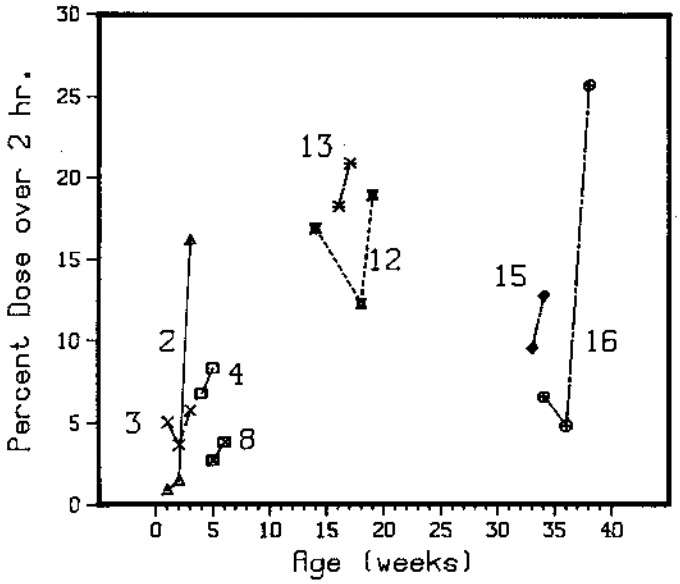


Fig. 4. Cum% 2h *versus* age for infants in whom sequential studies were performed. *Numbers* are patient numbers; see Table 1, column 1.

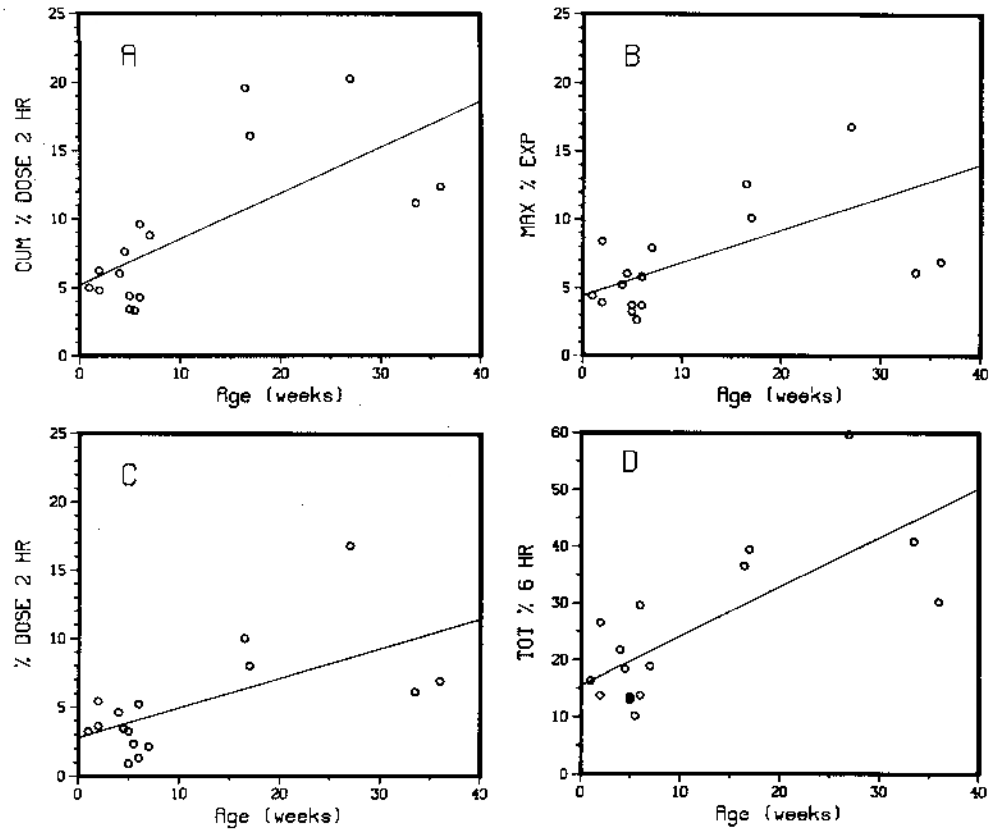


Fig. 3. Correlation between mean breath test scores and age for the orally administered aminopyrine. *A*, cumulative percent dose expired over two hours, y = 5.2 + 0.336x, $r = 0.7$, $p < 0.005$. *B*, Max% exp, y = 4.43 + 0.24x, $r = 0.7$, $p < 0.005$. *C*, %Dose 2h, y = 2.79 + 0.216x, $r = 0.6$, $p < 0.01$. *D*, total percentage dose expired over 6 h, y = 15.4 + 0.868x, $r = 0.7$, $p < 0.002$.

Studies that examine the maturation of drug metabolizing capacity in humans, however, have been limited, for the most part, to *in vitro* work done with human liver obtained from fetuses after abortion or from infants who have died. These investigations have shown the presence of cytochrome P 450, albeit diminished in concentration compared to that in adults (3–5). The amount of P 450 per se, however, does not necessarily reflect drug metabolizing capacity (19). The components of the monooxygenase complex, such as NADPH-cytochrome c reductase or aminopyrine N-demethylase, show a better correlation with *in vivo* drug metabolism (19). Aranda *et al.* (20) found overlap in the amount of aminopyrine demethylase activity between fetal and adult liver tissues; however, some of the infants in their study had received drugs known to stimulate demethylase activity. In addition, the infants and adults who were studied had severe illnesses prior to death, a factor which may have affected the results. The results of the present study suggest that the capacity to eliminate the labeled methyl group increases with age (Fig. 3).

The findings of this investigation are consistent with those of studies in infants in which increases in the serum clearance of aminopyrine with age were demonstrated (21). Jaeger-Roman *et al.* (7) studied a small number of infants with the aminopyrine breath test and found that the amount of labeled $CO_2$ eliminated in breath increased with age. The maximum percentage dose $^{13}CO_2$ eliminated per hour was lower than that found in the present study. Our results, however, are not directly comparable to those of Jaeger-Roman *et al.* (7) because the $CO_2$ production rate was not measured in their study.[1]

In two of the infants who underwent sequential studies, the increases in drug elimination were quite marked (patients 2 and 16). It cannot be determined with certainty whether demethylation in these individuals initially was retarded or subsequently induced. Because their clinical status was little different from that of the other infants, and they, as the others, did not receive drugs that could induce hepatic function, the increases in elimination of the label probably reflected maturation. There are no data to suggest that repeat doses of aminopyrine increase its subsequent rate of metabolism. Repetitive studies carried out in adults give reproducible results.

The large SDs in the elimination constant, which showed no differences among groups, likely were related to the uneveness of the $^{13}CO_2$ elimination curves seen in some of the infants. The lack of smoothness in the curves may have resulted in part from a small increase in $^{13}CO_2$ after drug administration, which occurred against a varying background level of $^{13}C$ found in foodstuffs (22).

It is unclear whether malnutrition impairs (23) or stimulates (24) drug elimination. In the present study, increases in the elimination of the $^{13}C$ label in breath with age were seen regardless of the infant's nutritional status. Indeed, patients 15 and 16 who were malnourished and whose nutritional status did not change over the study period showed an increase in $^{13}CO_2$ elimination when studied at an older age. Animal studies suggest that fasting itself has little effect on aminopyrine kinetics (25).

Certain factors must be borne in mind in the final interpretation of the results. Approximately 50% of the $^{13}C$ label after leaving the aminopyrine molecule is excreted as $^{13}CO_2$ in breath (15, 26); the remainder is shunted into other pathways such as urinary metabolites and bicarbonate (15). Additionally, it has been suggested that pathways other than demethylation exist for the monomethyl moiety (26). Although the results of many studies support the relationships among elimination of label in breath, hepatic function, and demethylating capacity, further investigation is needed to clarify the effect that alternate pathways of elimination and the one carbon pool (27, 28) may have on the results.

[1] In this paper (7), the column designated maximal $^{13}CO_2$/h ($^{13}C$ mmol/h) was mislabeled and should be % dose/h (Helge H, personal communication, 1982).

*Acknowledgments.* The authors thank M. Nelson, and K.Lobb for sample analysis; R. Heathcock, K. Evans, and L. Wise for sample collection; M. Perez for manuscript preparation, E. R. Klein for editorial review, and E. O. Smith, Ph.D. for help in the statistical analysis.

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