

Changes in trimethoprim pharmacokinetics after the newborn period

K HOPPU

Children's Hospital and Department of Clinical Pharmacology, University of Helsinki, Helsinki, Finland

SUMMARY The pharmacokinetics of trimethoprim administered orally or intravenously were investigated in six infants aged 1.7 months to 1.1 years. In these infants trimethoprim had a mean half life of 4.6 hours; this was comparable with the values found in young and school age children (3.8 and 5.4 hours respectively) and about a quarter of the half life in newborns. The volume of distribution (1.5 l/kg) was smaller than in newborns but larger than in young or school age children (0.9 and 1.1 l/kg respectively). The plasma clearance in these infants (3.3 ml/min/kg) was slightly larger than in newborns or in either group of older children (2.9 and 2.4 ml/min/kg respectively). Thus the most dramatic changes in trimethoprim pharmacokinetics seem to occur during the first two months of life. A reduced daily dose of trimethoprim is necessary during the first two months only. An increased daily dose, by addition of a third dose each day, is recommended from two months.

Trimethoprim, mostly in combination with a sulphonamide, may be used in infants to treat severe infections.¹ The age related changes in trimethoprim

pharmacokinetics indicate that, as compared with adults, newborn babies need smaller² and children larger doses.³ The pharmacokinetics of trimethoprim

Table 1 Trimethoprim pharmacokinetic results in six infants

Case No	Age	Weight (kg)	Dose (mg/kg)	Half life (hours)	Volume of distribution (l/kg)	Plasma clearance (ml/min/kg)	Drug
1	1.7 months	1.59	3.52	5.6	1.7	3.5	Trimethoprim sulphamethoxazole (oral)
2	2.5 months	2.93	1.63	6.1	2.8	5.3	Trimethoprim sulphamethoxazole (intravenous)
3	2.5 months	4.12	0.61	6.0	1.1	2.2	Trimethoprim (oral)
4	3.0 months	4.83	3.66	3.7	1.0	3.0	Trimethoprim sulphamethoxazole (intravenous)
5	1.05 years	8.38	2.98*	3.3	—	—	Trimethoprim (oral)
6	1.08 years	8.55	2.92	3.2	0.7	2.6	Trimethoprim (oral)
Mean	0.49	5.07	2.77	4.6	1.5	3.3	

*Dose swallowed not exactly known.

Table 2 Mean trimethoprim pharmacokinetic values in newborn babies, children, and adults

Age group	Half life (hours)	Volume of distribution (l/kg)	Plasma clearance (ml/min/kg)	Drug
Newborn babies (n=12)*	19.0	2.7	1.8	Trimethoprim sulphamethoxazole (intravenous)
1.5-3 years (n=7)†	3.8	0.9	2.9	Trimethoprim (oral)
8-10 years (n=9)†	5.4	1.1	2.4	Trimethoprim (oral)
Adults (n=12)†	11.2	1.3	1.4	Trimethoprim (oral)

*Data from Springer *et al*.²; †data from Hoppu.³

rim were investigated in infants falling between these two age groups to serve as a basis for dosage recommendations.

Patients and methods

Six infants were studied during treatment for various infections with either trimethoprim or trimethoprim plus sulphamethoxazole. The drug was administered orally (Trimopan, Farnos Ltd) or intravenously (Bactrim, Hoffman-La Roche). Blood samples were drawn at 0, 1, 3, 6, 9, and 12 hours in cases 2 to 4. The 1 hour sample was omitted for case 1. In cases 5 and 6 blood samples were drawn additionally at 24 hours. In one boy (case 4), who was treated for an infection of his cerebrospinal fluid shunt, samples of cerebrospinal fluid were collected from a ventriculostoma simultaneously with the blood samples.

Concentrations of trimethoprim in serum and cerebrospinal fluid were analysed with high performance liquid chromatography.⁴ The method has a wide range of linearity (0.11–690 $\mu\text{mol/l}$). The accuracy was 99.2% with a coefficient of variation of 6.8%. Pharmacokinetic calculations were made assuming complete absorption and first order kinetics, as described elsewhere.³ Volume of distribution and plasma clearance were not calculated for case 5, as the dose actually swallowed was not known. Results were compared with data from previous studies on newborn babies² and children.³ The difference from children of 1.5 to 3 years was tested with the Mann-Whitney rank sum statistic because of the non-normal distributions. The study protocol was approved by the ethical committee of the hospital.

Results

The tables show data for the patients and individual pharmacokinetic values. The figure shows the half life, volume of distribution/kg, and the plasma clearance/kg in relation to the values found previously for newborn babies, children, and adults.

The mean half life for the infants was 4.6 hours ($p=0.39$ compared with the control children aged 1.5 to 3 years). The mean volume of distribution for the infants was 1.5 l/kg ($p=0.2$ compared with children aged 1.5 to 3 years). The plasma clearance of 3.3 ml/min/kg, was faster than has been observed in any other age group ($p=0.58$ compared with the children aged 1.5 to 3 years).

In case 4 (the infant with a cerebrospinal fluid shunt) the mean ratio of cerebrospinal fluid to serum trimethoprim was 0.43, with a minimum of 0.29 at six hours and a maximum of 0.60 at 12 hours. The ratio of the area under the curves for cerebrospinal fluid to serum concentration was 0.36.

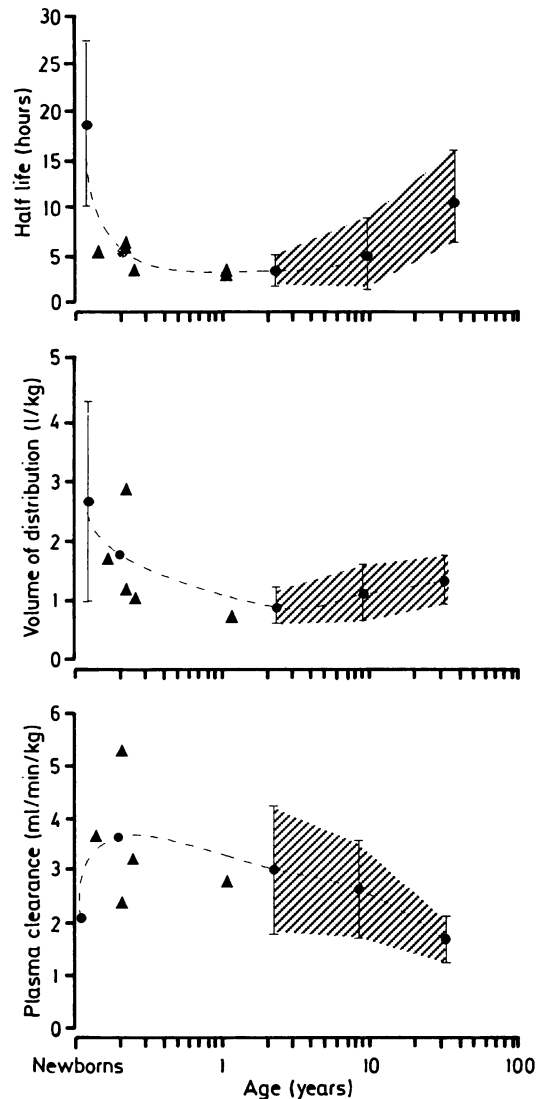


Figure Age related changes in trimethoprim pharmacokinetics. Half life, volume of distribution, and plasma clearance are plotted as a function of age with ● representing the group mean and ▲ representing the individual infants in the study group. The shaded area and bars are the mean (2 SD). Data for the newborn babies is from Springer *et al*² and for children and adults from Hoppu.³

Discussion

The long half life of trimethoprim in neonates (mean 19.0 hours)² shortens during the first two to three months to values comparable with that of school age children.³ This change is due to both an increase in

elimination and a reduction in the volume of distribution. The rapid plasma clearance found in the younger infants was within the 2 SD range for the children 1 to 3 years old, except for patient 2. The half life of trimethoprim seems to be shortest (3.7 hours), the volume of distribution/kg smallest (0.86 l/kg), and the plasma clearance/kg most rapid (2.8 to 3.5 ml/min/kg) during the first three years of life. Thereafter the plasma clearance/kg slowly decreases and the volume of distribution/kg and half life slowly increase to reach adult values around puberty.³

There was no evidence of a systematic difference between volume of distribution and plasma clearance values obtained after oral and after intravenous administration, supporting the assumption of complete absorption. The reduction in volume of distribution/kg observed may be due, at least partly, to age related changes in the protein binding of trimethoprim, indicated by Vree *et al.*⁵ Neither the renal elimination nor the metabolism of trimethoprim have been studied in newborn babies or infants. In children about 50% of a dose is excreted into the urine unchanged.³ The change in plasma clearance after the newborn period probably results from more rapid rates of both metabolism and renal elimination. The cerebrospinal fluid:plasma ratio of the trimethoprim concentration and area under the curve were comparable with previous results in children.^{1,6}

Similar patterns of age associated changes in pharmacokinetics have been found for various other drugs, for instance gentamycin,⁷ theophylline,⁸ and ceftriaxone.⁹

A dose of 1 mg/kg of trimethoprim every 12 hours, after a loading dose of 3 mg/kg, is recommended for newborn babies.² During the first one to two months of life such a reduced dose seems prudent. Thereafter three daily doses, as recom-

mended for children,³ seem more appropriate in the light of the plasma clearance and half life values found. The size of the individual dose depends on the infection treated, being usually 2 to 6 mg/kg. These recommendations are based on pharmacokinetic studies; their safety and efficacy must be subjected to further trial.

This study was supported by a grant from the Foundation of Finnish Medical Sciences, Helsinki, Finland.

References

- 1 Sabel K-G, Brandberg Å. Treatment of meningitis and septicemia in infancy with a sulphamethoxazole/trimethoprim combination. *Acta Paediatr Scand* 1975;**64**:25-32.
- 2 Springer C, Eyal F, Michel J. Pharmacology of trimethoprim-sulfamethoxazole in newborn infants. *J Pediatr* 1982;**100**:647-50.
- 3 Hoppu K. Age differences in trimethoprim pharmacokinetics—need for revised dosing in children? *Clin Pharmacol Ther* 1987;**41**:336-43.
- 4 Hoppu K, Arjomaa P. Determination of trimethoprim in pediatric samples by high-performance liquid chromatography. *Clin Chim Acta* 1987;**163**:81-6.
- 5 Vree TB, Hekster YA, Lippens RJJ. Clinical pharmacokinetics of sulfonamides in children: relationship between maturing kidney function and renal clearance of sulfonamides. *Ther Drug Monit* 1985;**7**:130-47.
- 6 Fries N, Keuth U, Braun JS. Untersuchungen zur Liquorgängigkeit von Trimethoprim im Kindesalter. *Fortschr Med* 1975;**93**:1178-83.
- 7 Rohwedder HJ, Goll U. Untersuchungen über die Pharmakokinetik von Gentamycin bei Kindern. *Dtsch Med Wochenschr* 1970;**95**:1171-4.
- 8 Aranda JV. Maturational changes in theophylline and caffeine metabolism and disposition: clinical implications. In: Lemberger L, Reidenberg MM, eds. *Proceedings of the second world conference on clinical pharmacology and therapeutics*. Rockville Pike: American Society of Pharmacology and Experimental Therapeutics, 1984:868-77.
- 9 Hayton WL, Stoeckel K. Age-associated changes in ceftriaxone pharmacokinetics. *Clin Pharmacokinet* 1986;**11**:76-86.

Correspondence to Dr K Hoppu, Children's Hospital, University of Helsinki, Stenbäckinkatu 11, 00290 Helsinki, Finland.

Accepted 13 September 1988