Single dose pharmacokinetics of trimethoprim

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SUMMARY Single oral dose trimethoprim pharmacokinetics were determined in 18 children aged 3 months to 13 years. Trimethoprim suspension was rapidly absorbed and quickly and widely distributed. The mean clearance was considerably faster and the elimination half life considerably shorter than values reported in adults. Only one third of the administered drug dose was recovered from the urine within 24 hours which is considerably less than in adults, suggesting that children may metabolise a greater proportion of the dose given. Urine trimethoprim concentrations greatly in excess of minimum inhibitory concentrations for common pathogens were rapidly achieved and sustained for at least 16 hours.

The combination of trimethoprim and sulphamethoxazole (co-trimoxazole) has been widely used for the treatment of urinary tract infection for many years: more recently, trimethoprim alone has been used. From published reports, there seems to be an increasing use of short courses of antibiotics for the treatment and prophylaxis of certain infections,¹ and trimethoprim has been used successfully as a single drug, single dose treatment of urinary tract infection.²

In adults, the pharmacokinetics of the two individual components of co-trimoxazole are reported to be the same, whether given separately or in combination.³ Although limited pharmacokinetic data exists for trimethoprim in combination with sulphamethoxazole in children,^{4,6} there is no available information on its kinetics when given alone. We report a study to determine the kinetics of a commonly used dosage of trimethoprim.

Methods

Patients and protocol. Eighteen otherwise healthy children with urinary tract infections were included in the study: ethical approval had been obtained from the local research ethical committee. All children were subsequently studied and none were shown to have evidence of renal insufficiency. Their ages ranged from 3 months to 13 years, and their age, sex, and weight are shown in Table 1.

Each child received a 10 mg/kg oral dose of trimethoprim suspension (Ipral - Squibb 50 mg per 5 ml) accurately measured by syringe. The children were in varying states of fasting and no attempt was made to standardise for meal times or meal content,

although none had received a meal within two hours of drug administration. A variable volume of water or juice was given after the dose.

Capillary blood samples for plasma were collected before dosage and at one, two, three, six, 12, 18, and 24 hours afterwards. All urine passed was collected at four hourly intervals for 24 hours as 0-4, 4-8, 8-12, 12-16, 16-20, and 20-24 hour collections.

Assay preparation and technique. Aliquots of urine were diluted 10 fold and 1000 fold in 0.02 M phosphate buffer pH 7.0, and stored at 4°C until assay. After separation, plasma samples were stored at -20°C. Before assay, sera were diluted in antibiotic free horse serum. Plasma collected in the six hours after dosing was diluted 1/30 and later samples were diluted 1/5. Assays were performed within 48 hours of sampling.

Trimethoprim concentrations were determined by a bioassay method using *Bacillus pumilis* as the assay organism. A suspension of *B. pumilis* spores was prepared in advance of the study and contained between 10⁶ and 10⁷ spores per ml. Aliquots of 0.5 ml were stored at -20°C. The medium used was Isosensitest agar (Oxoid) which was steamed to prevent production of inhibitory substances. An 'overlay' method was used to prepare the assay plates. Isosensitest agar (3.2 g in 100 ml of distilled water) was cooled to 56°C after steaming. An aliquot of spores was added and the temperature maintained for 30 minutes to 'heat shock' the spores. Five ml lysed horse blood and 1 ml of 1% para aminobenzoic acid were added, the medium mixed and poured into pre-levelled 25 cm square plates. After the base layer had solidified, an

Table 1 Age, sex, weight, and pharmacokinetic parameters after a single 10 mg/kg dose of trimethoprim

Patient	Sex	Age (years)	Weight (kg)	k_a (/hour)	C_{max} (mg/l)	t_{max} (hours)	k_{el} (/hour)	$t_{1/2}$ (hours)	AUC (mg/l/hour)	Cl_B (l/kg/hour)	V_d (l/kg)
1	M	0.3	5.1	0.80	6.9	2.9	0.125	5.5	47.2	0.212	1.69
2	F	0.4	5.1	1.15	5.4	1.8	0.126	5.5	27.4	0.365	2.90
3	M	0.6	7.3	0.19	4.2	5.9	0.090	7.7	40.9	0.244	2.72
4	F	0.7	8.0	4.79	6.0	1.1	0.110	6.3	33.7	0.297	2.70
5	M	2.7	10.5	0.94	5.4	1.8	0.132	5.3	31.9	0.313	2.37
6	F	3.7	15.7	0.63	5.4	3.1	0.129	5.4	47.1	0.210	1.63
7	F	3.7	21.1	1.70	9.3	1.6	0.086	8.1	83.9	0.119	1.39
8	F	4.4	17.5	2.81	4.8	0.9	0.086	8.1	48.8	0.205	2.38
9	F	6.3	21.8	0.84	4.0	3.1	0.077	9.0	40.5	0.247	3.21
10	F	6.5	25.1	1.04	5.0	2.0	0.118	5.9	34.8	0.287	2.44
11	F	7.1	20.3	0.44	6.0	2.1	0.149	4.7	28.8	0.347	2.33
12	M	7.6	20.3	3.44	4.6	1.7	0.155	4.5	27.9	0.358	2.31
13	F	7.6	24.1	6.09	4.8	0.8	0.071	9.8	46.5	0.215	3.03
14	F	7.9	31.7	0.48	4.8	2.4	0.123	5.6	34.2	0.292	2.38
15	F	9.3	28.4	0.81	6.0	3.1	0.079	8.8	66.9	0.149	1.89
16	F	9.3	33.9	3.33	10.5	1.2	0.090	7.7	83.7	0.119	1.33
17	F	9.7	24.2	1.39	5.2	1.9	0.108	6.4	44.6	0.224	2.08
18	F	13.1	55.0	1.53	9.9	2.1	0.096	7.2	77.0	0.141	1.47
Mean		5.8	20.8	1.80	6.0	2.2	0.108	6.8	46.7	0.241	2.24
(SD)		3.6	12.2	1.64	1.9	1.2	0.025	1.6	18.1	0.079	0.57

k_a =absorption rate constant; C_{max} =peak plasma concentration; t_{max} =time to reach peak; k_{el} =elimination rate constant; $t_{1/2}$ =elimination half life; AUC=area under concentration time curve; Cl_B =total body clearance; V_d =apparent volume of distribution.

Conversion—traditional units to SI: trimethoprim 1 mg/l=3.44 µmol/l.

overlay of 100 ml isosensitest agar without additions, was poured.

Trimethoprim standards, ranging from 0.025 mg/l to 0.8 mg/l at doubling concentrations, were prepared in horse serum for plasma assays and in 0.02 M phosphate buffer pH 7.0 for urine assay. Wells were cut in the assay plate and filled with 120 µl of sample or standard. There were three replicates of each. Plates were incubated at 30°C for 18 hours and zone sizes measured on a zone reader (Leebrook Scientific Engineering). Concentrations were determined from the standard curves produced for each separate plate.

Data analysis. A modified non-linear least squares regression programme (MULTI)⁷ was used to calculate the absorption rate constant (k_a), peak plasma concentration (C_{max}), and the time to reach this peak (t_{max}).

The elimination rate constant (k_{el}) was derived from the slope of the least squares regression line of best fit to the log concentration-time data. The elimination half life ($t_{1/2}$) was calculated from:

$$t_{1/2} = \frac{0.693}{k_{el}} \quad (1)$$

The area under the concentration-time curve (AUC $0-\infty$) was calculated by summation of the AUC from zero time to the last concentration-time point, C_{tx} (AUC_{0-tx}) and the AUC from time tx to infinity derived from the equation:

$$AUC_{tx-\infty} = \frac{C_{tx}}{k_{el}} \quad (2)$$

Thus:

$$AUC_{0-\infty} = AUC_{0-tx} + \frac{C_{tx}}{k_{el}} \quad (3)$$

Total body clearance (Cl_B) of trimethoprim was calculated from the equation:

$$Cl_B = \frac{FD}{AUC_{0-\infty}} \quad (4)$$

Where D is the dose given (mg/kg) and F the fraction of dose which reaches the systemic circulation assumed from previous reports to be 100% of 1.⁸

The apparent volume of distribution (V_d) was then calculated from the relation:

$$V_d = \frac{Cl_B}{k_{el}} \quad (5)$$

The amount of trimethoprim in each four hour urine sample was the product of concentration and volume.

The trimethoprim elimination rate constant (k_{el}) was also derived from the slope of the least squares regression line of best fit to the plot of the logarithm of urine excretion rate against time, using combined

data of all children studied. From this plot, the intercept at time zero was used to determine the renal excretion rate constant (k_e) from the equation:

$$k_e = \frac{\text{Intercept}}{D} \quad (6)$$

where D is the mean dose given to all children.

The fraction of trimethoprim excreted unchanged (fe) is equal to the ratio of the rate of renal excretion to the rate of plasma elimination and can therefore be calculated from:

$$fe = \frac{k_e}{k_{el}} \quad (7)$$

Results

The individual and mean (SD) values for the absorption and elimination rate constants, peak concentration and time to reach it, elimination half life, area under the curve, apparent volume of distribution, and total body clearance are given in Table 1.

Table 2 shows the individual mean and range values of the urine trimethoprim concentration in each four hour period of the first 24 hours after dosage. Seven children on one or two occasions were unable to pass urine to complete the four hour

Table 2 Urine trimethoprim concentrations in the 24 hours after dose administration

Patient	Four hour collection period concentrations of trimethoprim (mg/l)					
	0-4	4-8	8-12	12-16	16-20	20-24
1	—	54	66	80	120	44
2	74	68	84	80	84	30
3	130	110	180	230	110	120
4	—	300	66	27	1.2	<0.25
5	7	350	310	44	—	44
6	96	23	210	—	110	20
7	14	10	15	10	5.0	2.9
8	20	105	48	200	100	98
9	44	64	—	—	100	20
10	86	110	28	240	66	5.2
11	42	27	20	88	125	—
12	56	29	—	33	—	30
13	160	52	240	330	170	49
14	81	145	160	300	140	25
15	80	450	320	530	180	260
16	35	14	18	13.5	wet bed	11
17	155	90	33	31	40	36
18	530	720	530	640	420	360
Mean	101	151	146	180	119	68
Range	(7-530)	(10-450)	(15-530)	(10-640)	(1.2-420)	(0.2-360)

—=no sample obtained.

Conversion—traditional units to SI: trimethoprim 1 mg/l=3.44 µmol/l.

Table 3 Cumulative urine trimethoprim excretion as percentage of 10 mg/kg dose administered

Patient	Collection time periods (hours)					
	0-4	4-8	8-12	12-16	16-20	20-24
1	—	5	7	11	16	22
2	5	19	21	26	31	35
3	2	10	20	24	33	40
4	—	25	—	40	43	44
5	2	—	29	46	—	48
6	8	15	25	—	37	42
7	7	12	19	23	26	28
8	2	5	11	14	17	22
9	7	16	—	—	24	26
10	6	10	15	17	20	22
11	10	22	32	41	44	—
12	13	33	—	45	—	54
13	2	7	11	17	20	22
14	6	14	23	28	31	32
15	5	24	33	38	41	47
16	10	15	20	23	—	27
17	—	19	21	—	24	30
18	5	12	15	18	23	25
Mean	6	16	20	27	29	34
(SD)	3	8	8	12	9	11

—=no sample obtained.

collection period and their running total was added to their next four hour collection. The mean and range values were calculated from all available samples.

One child wet the bed and his sample was therefore lost. Of the 16 children for whom the first four hour urine sample was available, 14 (88%) had a urine concentration of 20 mg/l or more over this period. Fifteen of 18 children (83%) had urine concentrations above 20 mg/l for all but one of the four hour collection periods in the first 24 hours for which samples were available. Eleven of the children (61%) had urine concentrations greater than 50 mg/l for at least 12 of the first 24 hours.

The cumulative urine trimethoprim excretion over the first 24 hours after dosing is shown in Table 3 expressed as a percentage of the 10 mg/kg dose administered. The 24 hour excretion of the child who wet the bed was not included in the mean (SD) data, although up to the point of her collection loss, the cumulative data have been included in the mean (SD) results.

The amount of unchanged trimethoprim excreted into urine in the first 24 hours after dosing was mean (SD), 34 (11)% of the dose administered.

From the plot of the logarithm of urine trimethoprim excretion rate against time of combined data points from all children ($n=60$), the correlation coefficient (r) of the line having the best fit by least squares regression analysis was 0.551 ($t=5.026$; $P<0.001$). The elimination rate constant from the slope of the line was 0.088 giving a mean elimination

half life of 7.9 hours. The intercept on the log urine drug excretion rate axis was 7.24 mg/hour and from equation (6), the renal excretion rate constant (k_e) was 0.035/hour. The mean fraction of dose excreted unchanged as calculated from equation (7) was 0.035/0.108 or 0.33.

Discussion

The results show that trimethoprim is rapidly absorbed from suspension (Ipral). The mean time to peak concentration (t_{max}), 2.2 hours, is similar to values reported in adults for suspension and tablets,⁹ although, as might be expected, some workers have found faster rates of absorption of drug from suspension than tablets.¹⁰ There was wide variation in t_{max} between individuals in this study and similar wide variability was found for absorption rate constant. Almost complete absorption has been reported in adults⁹ and this has been assumed in this study for kinetic calculations.

The mean apparent volume of distribution in these children is slightly larger than values reported in newborn babies and children taking cotrimoxazole^{6 11} and considerably greater than values in adults taking trimethoprim alone.⁹ It greatly exceeds the volume of total body water and shows that the drug is widely distributed and bound in tissues.

Trimethoprim was rapidly cleared from the body in this group of children with a mean total clearance rate of 0.241/kg/hour; approximately three times faster than rates reported in adults.^{9 12} As renal clearance by glomerular filtration and tubular secretion in children is not generally more efficient for other drugs that are mainly dependent upon the kidney for elimination, the results suggest that trimethoprim is eliminated by extrarenal mechanisms to a greater extent in children, presumably as a result of enhanced hepatic metabolism. Although it is commonly accepted that trimethoprim is almost completely excreted by the kidney, unchanged or as metabolites,¹³ and less than 4% of a dose is present in faeces,⁸ the amounts of unchanged drug excreted in urine have varied in reports from 50 to 75%.⁹ The lower mean fraction of drug excreted in our children, 0.33, and that recovered in the urine in the first 24 hours, 0.34, supports the explanation of enhanced extrarenal elimination in children. As many drugs dependent upon these hepatic microsomal enzymes for biotransformation are eliminated at appreciably greater rates in children after the first few months of life than in adults,¹⁴ a greater proportion of trimethoprim metabolism of the dose given to children might be expected.

This metabolism preference may prevent

trimethoprim accumulation in children with renal insufficiency. Although 'usual' doses are reported to be safe in adults with a renal clearance of 10 ml/minute, most published reports suggest that the rate of trimethoprim elimination is significantly affected at or below this figure.^{9 11} It may be that dose modification is unnecessary in children with lower surface area-corrected values than this.

The total body trimethoprim clearance rate is so much greater in children that the mean elimination half life for plasma, 6.8 hours, is considerably shorter than values of 7 to 17 hours in adults,⁹ even though the mean volume of distribution is twice as large in children. The relatively short half life and rapid absorption rate suggests that during multiple dosing at usually employed 12 hour dose intervals, the fluctuation of plasma concentration may result in values below the minimum inhibitory concentration for common pathogens at sites other than the urinary tract. We know that the free concentration of antibiotics in tissues is in equilibrium with the free plasma value and the effect of such subminimum inhibitory concentrations on treatment outcome is uncertain. The high persistent concentrations achieved in urine in this single dose study suggests, however, that 12 hourly dosing is appropriate when multiple dose treatment for urinary tract infection is indicated.

Interestingly, and perhaps reassuringly, the mean elimination half life calculated from the combined urine data in this study, 7.9 hours, was similar to that derived from the individual plasma data, 6.8 hours.

Minimum inhibitory concentration for trimethoprim against *Escherichia coli*, klebsiella, enterobacter, and proteus range from below 1.0 mg/l to 4 mg/l. Urine trimethoprim concentrations considerably in excess of these values were rapidly achieved and maintained in all but two of the children (patients 4 and 7).

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