Acta vet. scand. 1975, *16*, 405—410.

From the Department of Pharmacology and Toxicology, Royal Veterinary and Agricultural University, Copenhagen, Denmark.

CONCENTRATIONS OF TRIMETHOPRIM AND SULPHADOXINE IN TISSUES FROM GOATS AND A COW*

By

Poul Nielsen and *Folke Rasmussen*

NIELSEN, POUL and FOLKE RASMUSSEN: *Concentrations of trimethoprim and sulphadoxine in tissues from goats and a cow.* Acta vet. scand. 1975, *16*, 405—410. — The concentration of trimethoprim and sulphadoxine in plasma and tissue from goats and a cow have been determined after a single intravenous injection. Furthermore, the concentration of the two drugs and their metabolites in plasma and tissues have been determined after continuous intravenous infusion for 2½—3 hrs. Trimethoprim was present in all tissues but brain at higher concentrations than in plasma while the concentration of sulphadoxine in the different tissues were lower than in plasma. The highest concentration of the 2 drugs and their metabolites was found in the kidney. The distribution pattern of trimethoprim and sulphadoxine was similar in cow and goats.

trimethoprim; sulphadoxine; tissue concentrations.

Previously it has been shown that trimethoprim is eliminated at a fast rate from plasma in cows and goats and that the apparent volume of distribution is higher than one which means that the drug is present in certain tissues in a higher concentration than in plasma (*Davitiyananda & Rasmussen* 1974, *Nielsen & Rasmussen* 1975c). Contrary the apparent volume of distribution for sulphadoxine is 0.3—0.4 in cows and goats (*Davitiyananda &*

* Supported by the Danish Agricultural and Veterinary Research Council.

Rasmussen, Nielsen & Rasmussen 1975c) indicating that this drug is not accumulated in the tissues.

To support these assumptions the actual tissue concentrations of trimethoprim and sulphadoxine have been determined after a single intravenous injection in a cow and in goats and after continuous infusion in goats.

MATERIALS AND METHODS

The experiments were performed on 9 clinically healthy goats and 1 cow.

After a single intravenous injection the concentrations of trimethoprim and sulphadoxine were measured in plasma and different tissues from 3 male and 2 female goats and 1 cow. The animals were killed by shooting 3 hrs. after the injection of Trivetrin®* (0.33 ml/kg b.wt. i.e. 13 mg trimethoprim and 67 mg sulphadoxine/kg b.wt. in goats and 0.2 ml/kg b.wt. in the cow).

Four halothane-anaesthetized male goats were administered an initial dose of 10 mg ^{14}C-trimethoprim** + 5 mg sulphadoxine/kg b.wt./hr. which was followed by a continuous intravenous infusion of 4 mg ^{14}C-trimethoprim + 15 mg sulphadoxine/kg b.wt./hr. The continuous infusion was stopped after 2½—3 hrs. and the goats killed by bleeding. The concentrations of trimethoprim, sulphadoxine and their metabolites in plasma and different tissues were determined.

The concentration of trimethoprim was determined spectrofluorimetrically as described by *Schwartz et al.* (1969) after pretreatment of the samples as described by *Nielsen & Rasmussen* (1975b). The concentration of trimethoprim and its metabolites was determined by liquid scintillation counting in the experiments where ^{14}C-trimethoprim was used (*Nielsen & Rasmussen* 1975b).

The concentration of sulphadoxine was determined according to the method of *Bratton & Marshall* (1939). The concentration of N^4-acetyl sulphadoxine was determined by the same method after hydrolysis.

---

* Trivetrin® was generously supplied from the Wellcome Research Laboratories, Beckenham, Kent, England.

** ^{14}C-labelled trimethoprim was a gift from dr. J. Rieder, Hoffmann-La Roche & Co. Ltd., Basel, Switzerland.

RESULTS

Tissue concentrations of trimethoprim and sulphadoxine after a single intravenous injection

With brain tissue as the only exception the concentration of trimethoprim was found higher in all tissue samples than in the corresponding plasma samples (Table 1). The highest concentration of trimethoprim was found in the kidney, but the concentration in muscle, liver and lung was also considerably higher

Table 1. Concentrations (μg/ml or μg/g) of trimethoprim and sulphadoxine in plasma and tissue from goats and a cow 3 hrs. after a single intravenous injection. Dose: Goats, 0.33 ml Trivetrin®/kg b.wt.; cow, 0.2 ml Trivetrin®/kg b.wt.. The results are the averages ± s.e.m.

	Trimethoprim		Sulphadoxine	
	goats	cow	goats	cow
Plasma	0.21±0.05	2.8	154±6	117
Brain	0.13±0.03	0.7	39±4	31
Heart	0.44±0.07	2.9	64±5	41
Muscle	1.1 ±0.2	3.5	43±2	32
Lung	0.7 ±0.2	8	76±6	58
Liver	0.8 ±0.1	14	72±4	61
Kidney	2.1 ±0.4	16	96±4	88
Testicle	0.9 ±0.2		56±1	
Uterus	1.3		91	

than in plasma. It should be noticed that the concentrations in tissue samples from the cow were much higher than in the corresponding samples from goats although the cow was administered a relatively smaller dose than the goats.

The concentration of sulphadoxine was smaller in all tissue samples than in the plasma (Table 1). The highest concentration was found in the kidney while the brain had the lowest one. The distribution of sulphadoxine was similar in cow and goats.

Tissue concentrations of trimethoprim and sulphadoxine after continuous infusion

The concentration of trimethoprim and sulphadoxine in plasma was kept nearly constant during the experimental period which lasted 2½—3 hrs. Table 2 shows the distribution of tri-

methoprim, sulphadoxine and their metabolites in plasma and tissue samples.

The concentration of trimethoprim was in all tissues but brain higher than or equal to that in plasma. The concentration of trimethoprim metabolites was higher in liver and kidney tissue than in plasma, but lower in all other tissue samples.

The concentration of sulphadoxine in tissue samples was in all cases lower than in plasma (Table 2). The concentration of N^4-acetyl sulphadoxine was low in both plasma and tissue samples with the highest concentration found in the kidney.

Table 2. Concentrations (μg/ml or μg/g) of trimethoprim, sulphadoxine and their metabolites in plasma and tissue from goats after continuous intravenous infusion of the 2 drugs for 2½—3 hrs. The table gives the averages ± s.e.m.

	Trimethoprim	Trimethoprim metabolites	Sulphadoxine	N^4-acetyl sulphadoxine
Plasma	3.2±0.6	9 ±1	86±7	3±1
Brain	1.1±0.3	0.3±0.2	23±2	1±1
Heart	4.7±0.6	1.2±0.2	40±5	1±1
Muscle	4.7±0.3	0.6±0.5	26±3	trace
Lung	9 ±1	3.6±0.3	41±5	6±2
Liver	7 ±2	39 ±7	62±8	6±2
Kidney	22 ±3	65 ±27	52±6	11±2
Testicle	3.4±0.3	2.4±0.5	34±4	4±1
Spleen	6 ±1	0.8±0.5	39±5	3±1
Salivary gland	5 ±1	3.5±0.5	48±12	3±1

DISCUSSION

The low concentration of trimethoprim in plasma from goats 3 hrs. after a single intravenous injection is in agreement with the short half-life of trimethoprim in this species (*Nielsen & Rasmussen* 1975c). The concentration of trimethoprim in all tissue samples but brain was higher than in plasma as it has been found in man (*Nielsen & Hansen* 1972, *Hansen et al.* 1973) and in swine (*Nielsen & Rasmussen* 1975d). These findings are in agreement with the fact that the apparent volume of distribution is found to be greater than one in goats, cows, swine, humans and rats (*Nielsen & Rasmussen* 1975c, vide *Nielsen & Rasmussen* 1975a).

During the continuous intravenous infusion of trimethoprim a tissue distribution of the parent compound takes place similar to that after a single intravenous injection. The distribution of the trimethoprim metabolites corresponds to that of acidic compounds and is thus completely different from that of the parent compound. In plasma the metabolites constituted about 75 % of the total amount, and it has been demonstrated that in goats these metabolites were glucuronide conjugates or other water soluble conjugates (*Nielsen & Rasmussen* 1975e). The metabolites were mainly formed in the liver and excreted into bile and urine. Consequently, the concentrations of the metabolites were high in liver and kidney while they were present in other tissues in concentrations well below that in plasma.

The lower concentrations of sulphadoxine in tissue than in plasma from goats and cow are in agreement with the results from cows (*Hübl* 1973) and from swine (*Nielsen & Rasmussen* 1975d) and also in accordance with the apparent volume of distribution lower than one (0.4 in cow, *Davitiyananda & Rasmussen* 1974; 0.3 in goat, *Nielsen & Rasmussen* 1975c; 0.3 in swine, *Nielsen & Rasmussen* 1975d). In the experiments with continuous intravenous infusion of sulphadoxine the N^4-acetyl sulphadoxine was present in the tissues but in much lower concentrations than the parent compound as earlier described by *Nielsen* (1973). Compared to swine (*Nielsen & Rasmussen* 1975d) sulphadoxine is N^4-acetylated to a very small degree in goats.

REFERENCES

Bratton, A. C. & E. K. Marshall: A new coupling component for sulphanilamide determination. J. biol. Chem. 1939, *128*, 537—550.

Davitiyananda, D. & Folke Rasmussen: Half-lives of sulphadoxine and trimethoprim after a single intravenous infusion in cows. Acta vet. scand. 1974, *15*, 356—365.

Hansen, I., M. Lykkegaard Nielsen & S. Bertelsen: Trimethoprim in human saliva, bronchial secretion and lung tissue. Acta pharmacol. (Kbh.) 1973, *32*, 337—344.

Hübl, H.: Untersuchung der Wirkstoffspiegel im Blutplasma und Lungengewebe nach intratrachealer Injektion von Borgal-Hoechst beim Rind. (Investigation of drug concentration in blood plasma and lung tissue after intratracheal injection of Borgal-Hoechst in cattle). Berl. Münch. tierärztl. Wschr. 1973, *86*, 141—144.

Nielsen, P.: The metabolism of four sulphonamides in cows. Biochem. J. 1973, *136*, 1039—1045.

Nielsen, M. Lykkegaard & I. Hansen: Trimethoprim in human prostatic tissue and prostatic fluid. Scand. J. Urol. Nephrol. 1972, *6*, 244—248.

Nielsen, P. & Folke Rasmussen: Half-life and renal excretion of trimethoprim in swine. Acta pharmacol. (Kbh.) 1975a, *36*, 123—131.

Nielsen, P. & Folke Rasmussen: Elimination of trimethoprim in swine. Comparison of results obtained by three analytical methods. Acta pharmacol. (Kbh.) 1975b, *37*. In press.

Nielsen, P. & Folke Rasmussen: Influence of age on half-life of trimethoprim and sulphadoxine in goats. Acta pharmacol. (Kbh.) 1975c. In press.

Nielsen, P. & Folke Rasmussen: Trimethoprim and sulphadoxine in swine. Half-lives, volume of distribution and tissue concentrations. Zbl. Vet.-Med. A 1975d. In press.

Nielsen, P. & Folke Rasmussen: Elimination of trimethoprim, sulphadoxine and their metabolites from goats. Acta pharmacol. (Kbh.) 1975e. In press.

Schwartz, D. E., B. A. Koechlin & R. E. Weinfeld: Spectrofluorimetric method for determination of trimethoprim in body fluids. Chemotherapy (Basel) 1969, *14*, Suppl., 22—29.

SAMMENDRAG

Koncentrationen af trimethoprim og sulfadoxin i væv fra geder og en ko.

Koncentrationen af trimethoprim og sulfadoxin blev bestemt i plasma og væv fra 5 geder og 1 ko efter en enkelt intravenøs injektion. Endvidere blev koncentrationen af de to lægemidler og deres metabolitter bestemt i plasma og væv fra 4 geder efter permanent intravenøs infusion i 2½—3 timer. Koncentrationen af trimethoprim var i de undersøgte væv med undtagelse af hjernen (tabel 1 og 2) højere end i plasma, mens koncentrationen af sulfadoxin i samtlige væv var lavere end i plasma. Den højeste koncentration af de to lægemidler og deres metabolitter blev påvist i nyrerne. Fordelingen af trimethoprim og sulfadoxin i vævene hos gederne svarede til fordelingen hos koen.

(Received June 9, 1975).

Reprints may be requested from: Poul Nielsen, Department of Pharmacology and Toxicology, Royal Veterinary and Agricultural University, Bülowsvej 13, DK-1870 Copenhagen V, Denmark.