Acta vet. scand. 1960, *1*, 188—200.

From the Department of Pharmacology and Toxicology,
The Royal Veterinary and Agricultural College, Copenhagen.

RENAL CLEARANCE STUDIES ON THE HORSE. II.*)

PENICILLIN, SULFATHIAZOLE AND SULFADIMIDINE**)

By
Emil Knudsen.

In the treatment of infectious diseases in veterinary medicine, penicillin and the sulfonamides are still absolutely dominating. It is well known that the blood concentration of penicillin and certain sulfonamides will decline very fast while that of other sulfonamides will drop slowly. Similarly it is observed that the concentration curves of the various sulfonamides differ from one animal species to another (*Welsh et al.* 1946, *Francis* 1947, 1949). The connection between these phenomena and the excretion rate of these drugs is demonstrated in man and a series of animal species (e.g. see *Jensen et al.* 1945, *Reinhold et al.* 1945, *Lundquist* 1945, *Becker-Christensen & Schou* 1945, *Poulsen et al.* 1955, *Dalgaard-Mikkelsen & Poulsen* 1956, *Poulsen* 1956, 1959).

However, experimental data obtained on one animal species cannot be transferred directly to another. In order to elucidate whether a connection might be demonstrated, in the horse, between the decline of the blood concentration of these compounds and their renal excretion, a series of clearance experiments were carried out. The investigation includes the excretion of penicillin and sulfathiazole, the blood concentration of which substances declines rapidly in the horse and of sulfadimidine as representative of those sulfonamides which produce a gradually dropping bloodconcentration (*Zeller & Kayser* 1958).

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*) Aided by a grant from *Statens almindelige Videnskabsfond.*

**) Sulfamethazine.

MATERIAL AND TECHNIQUE

The test animals for the penicillin experiments were five mares. These mares are the same as those identified by the numbers 2, 3, 4, 7 and 8 in the previously published paper (*Knudsen* 1959) and are herein indicated with the same numbers. The sulfonamide investigation was carried out with four other mares, similiarly clinically healthy and non-pregnant. Their weight and age is presented in Table 2. The animals were sacrificed after the experiments and their kidneys and urinary tracts submitted to macro- and microscopic examination and found to be normal.

The experimental technique, establishment of drop-infusion and the sampling of blood and urine, was carried out as described by *Knudsen* (1959) with the addition that in the sulfathiazole blocking experiments and all penicillin experiments, two infusion containers were used simultaneously, each connected with a separate plastic catheter in the right V. jugularis. Additionally, both blood and urine sampling in the penicillin experiments were carried out aseptically. As a penicillin test-solution 1 million i.u. sodium benzylpenicillin per liter isotonic sodium chloride solution (625 μg penic./ml) was used, given as a continuous intravenous drop-infusion in amounts from 3000 to 5000 i.u. per kgm of body weight (1.9—3.1 mg/kgm) in each experiment. In this manner, a practically constant plasma concentration was obtained in each experiment.

The sulfonamides were applied in a 0.5—1.0 per cent aqueous solution by continuous intravenous drop-infusion, resulting in an approximately constant plasma concentration. Both sulfathiazole and sulfadimidine were investigated partly at low (17—49 μg/ml), partly at high (138—312 μg/ml) sulfonamide concentrations in the plasma, and as a rule the clearance experiments at the two levels were carried out on the same day for each animal. In these experiments, the simultaneously measured creatinine clearance was used as a measure of the filtration clearance. In the diodrast blocking experiments, however, filtration clearance was measured by inulin clearance in order to avoid the effect of a tubular block against sulfathiazole being masked by an eventual contemporaneous reduction of creatinine clearance.

The ultrafiltration experiments were carried out according to *Poulsen*'s modification (1956) of *Lausen*'s method (1955),

with a cellophane quality corresponding with that described by *Dalgaard-Mikkelsen & Kvorning* (1949). Sulfathiazole ultrafiltrate clearance is designated as "Uf.St"; sulfadimidine ultrafiltrate clearance as "Uf.Sd". Plasma was ultrafiltrated from each blood sample and the percentage of diffusible sulfonamide measured in this way was used for computing the ultrafiltrate clearance, viz. $\frac{\text{plasma clearance} \times 100}{\%\ \text{ultrafiltrable}}$. In the current experiments the plasmaprotein binding proved to vary considerably from one animal to another, and in a few cases even from one experiment to another on the same animal. It was, however, always greater at low than at high plasma concentrations.

Analytical Methods.

Inulin: *Brun's* method (1946). Clearance is designated as "I".

Endogenous creatinine: *Folin's* method as modified by *Thomsen* (1938) and *Poulsen* (1956). Clearance is designated as "Cr".

Penicillin: The agar-cup method of *Jensen, Møller & Overgaard* (1945) using Staphylococcus aureus, strain 209 P*) as test bacteria. Sodium benzylpenicillin was used both for standards and for experiments. Clearance is designated as "Pe".

Diodrast (3,5-diiodo-4-pyridine-N-acetic acid): Diodrast iodine according to *Bak, Brun & Raaschou's* method (1943). Recovery experiments, using the plasma from the animals concerned, were carried out in order to calculate the plasma concentration. The recovery was ca. 90 % (*Brun* 1946, *Poulsen* 1956).

Sulfonamides: *Bratton & Marshall's* method (1939). Sulfathiazole plasma clearance is designated as "St", sulfadimidine plasma clearance is designated as "Sd".

PENICILLIN CLEARANCE

In 9 experiments with a total of fortyfive observations, penicillin clearance was measured simultaneously with inulin clearance. In the entire material the penicillin plasma level varied from 0.35 to 1.47 i.u. per milliliter (0.2—0.9 μg/ml), which is considerably below the selfdepression limit as stated by *Eagle & Newman* (1947) and *Pers* (1954).

*) Supplied by courtesy of A/S Novo Terapeutisk Laboratorium, Copenhagen.

Table 1.
Penicillin clearance.

Mare no.	Penicillin clearance ml/min.		Ratio Pe/I	Number of observations
	per 100 kgm body weight	per 100 gm kidney weight		
2	756 ± 191	241 ± 65	5.04 ± 1.16	13
3	829 ± 121	318 ± 46	4.21 ± 0.66	12
4	973 ± 133	402 ± 58	5.43 ± 0.60	13
7	570 ± 114	244 ± 49	3.31 ± 0.55	4
8	958 ± 137	325 ± 41	5.29 ± 0.71	3
Average	829 ± 187	314 ± 103	4.79 ± 1.04	45

The clearance values for each experimental animal are presented in table 1. The average clearance computed per 100 kgm body weight was found to be 829 ± 187 ml/min., and per 100 gm kidney weight to be 314 ± 103. A few experiments, especially at small diureses, showed extremely high and fluctuating penicillin clearances (from 9 to 15 times filtration clearance), which seemed to be due to unavoidable dilution errors, since diuresis errors would be of no importance in the computation of ratios. These experiments are omitted here.

The ratio of penicillin clearance/inulin clearance was found to be 4.79 ± 1.04 (2.78—6.77). *Jensen, Møller & Overgaard* (1945) found the ratio of penicillin clearance/filtration clearance in man was from 4.5—8.1, and the penicillin/creatinine clearance ratio in the rabbit to be the same. In the dog however it was 1.4—3.8. *Pers* (1954) found the ratio penicillin clearance/creatinine clearance in man to be 4.0 and *Poulsen, Simesen & Skude* (1955) found this ratio in the dog to be 3.6. In the cow *Poulsen* (1956) found the penicillin/creatinine clearance ratio to be 5.8 ± 1.62. If the above mentioned ratio in the horse is converted by means of the value: creatinine clearance = inulin clearance × 0.9 (*Knudsen* 1959), the resulting value for penicillin clearance/creatinine clearance is 5.30, i.e. in close accordance to the ratio in the cow.

For comparison of the penicillin and diodrast clearance values, diodrast clearance was investigated in mare no. 4 in seven observations, resulting in a clearance value of 691 ± 81 ml/min. computed per 100 kgm of body weight and 302 ± 36 per 100 gm of kidney weight. The ratio of diodrast clearance/inulin clearance was 4.15 ± 0.30. It is apparent from Table 1 that these values

are all lower than the corresponding penicillin values in mare no. 4. This is contrary to what might be expected from the protein binding of the two compounds, but the material hardly permits further inferences.

The results demonstrate that the horse also excretes penicillin by filtration as well as by tubular secretion, and that the extent of this tubular secretion explains the rapid drop in the blood concentration of penicillin (*Doll and co-workers* 1946, 1949, 1950). The extent of the tubular secretion is in accordance with the basic observation of *Jensen, Møller & Overgaard* (1945) that about 80 % of the penicillin quantity excreted in the urine originates in tubular secretion.

SULFATHIAZOLE CLEARANCE

From the analytical method applied in the sulfonamide experiments a quantity of acetylated sulfonamide corresponding to approximately 15 % of total sulfonamide was found in the urine, whereas acetylated sulfonamide in these acute experiments could not be demonstrated in the plasma (*Welsh et al.* 1946). Clearance was consequently calculated for non-acetylated sulfonamide only.

Sulfathiazole clearance was determined in 7 experiments with a total of 39 observations. From 17 observations at low plasma concentrations the average plasma clearance was calculated per 100 kgm of body weight as 184 ± 48 ml/min, and 67 ± 15 per 100 gm of kidney weight. The corresponding values for ultrafiltrable sulfathiazole were 537 ± 242 and 192 ± 72. The values for each experimental animal are presented in Table 2, which demonstrates the self-depression of this compound at high plasma concentrations. Further, as the ratio of sulfathiazole plasma clearance/creatinine clearance was 1.25 ± 0.22 and that of ultrafiltrable sulfathiazole 3.57 ± 1.28, the excretion seems to infer an extensive tubular secretion, such as is demonstrated in man (*Lundquist* 1945), rabbit (*Becker-Christensen & Schou* 1945), pig (*Dalgaard-Mikkelsen et al.* 1953, *Dalgaard-Mikkelsen & Poulsen* 1956) and cow (*Poulsen* 1956, 1959).

In conformity with several of the above mentioned authors it was consequently attempted to block this tubular secretion. Diodrast was applied as permanent drop-infusion in two experiments, comprising 17 observations, in which filtration clearance was measured as inulin clearance. In the first experiment (mare

Table 2.

Sulfathiazole clearance.

Mare no.	Age in years	Weight kgm	Kidney weight kgm	Kidn. wt. in % of body wt.	Plasma level μg/ml	Clearance ml/min. Plasma per 100 kgm body weight	Plasma per 100 gm Kidney wt.	Ultrafiltrate per 100 kgm body weight	Ultrafiltrate per 100 gm Kidney wt.	Ratios St/Cr	Ratios Uf. St/Cr	Numbers of observations
1 S	12	748	1.629	0.22	190—262	124±37	57±17	273± 81	126±37	1.08±0.15	2.39±0.33	6
2 S	18	225	0.580	0.26	42— 49	138±18	54± 7	340± 51	132±20	1.12±0.10	2.63±0.45	7
					226—312	108±17	42± 7	194± 35	75±13	1.03±0.11	1.84±0.24	10
3 S	7	845	1.790	0.21	25— 29	187±15	89± 9	535± 56	252±26	1.04±0.09	2.98±0.24	3
					204—210	133±18	63± 9	310± 43	147±20	1.11±0.04	2.59±0.09	3
4 S	16	313	1.015	0.32	17— 30	229±31	71±10	736±248	227±77	1.46±0.16	4.65±1.26	7
					149—182	221± 4	68± 1	622± 11	192± 4	1.41±0.10	3.98±0.30	3
				Average	low	184±48	67±15	537±242	192±72	1.25±0.22	3.57±1.28	17
					high	131±44	51±14	290±168	115±47	1.11±0.11	2.38±0.75	22

no. 2 S) the ratio of sulfathiazole plasma clearance/inulin clearance in three control observations was 0.80, 0.94 and 1.00 respectively. At a plasma level of diodrast iodine from 83 to 86 μg/ml this ratio declined to 0.71 and 0.59 in two periods, and in four subsequent observations at a diodrast iodine level from 408 to 575 μg/ml was 0.24, 0.23, 0.24 and 0.26. The ratio of ultrafiltrate clearance/inulin clearance in the 3 control observations was 1.91, 2.23 and 2.37. In the two first blocking observations it declined to 1.69 and 1.40 and, at the higt diodrast level, it became 0.58, 0.55, 0.57 and 0.62 respectively. The ratio of creatinine clearance/inulin clearance in the first five observations was 0.88 dropping to 0.80 at the high diodrast iodine level.

Experiment no. 2 (mare no. 4 S) tallied well with the above results, as is represented graphically in Figure 1. The figure shows the ratio between inulin clearance and sulfathiazole plasma clearance (St/I), ultrafiltrate clearance (Uf.St./I) and creatinine clearance (Cr/I) together with the plasma concentrations of diodrast iodine. The points of the graph are plotted in the middle of the corresponding observation periods. It is manifest that the sulfathiazole plasma clearance, which in 3 control observations exceeds inulin clearance by 30—50 per cent, upon diodrast loading drops to values less than half the filtration clearance. Ultrafiltrate clearance is in the control periods approximately 3 times higher than inulin clearance, but declines during diodrast loading to values identical with creatinine clearance. In mare no. 4 S, total depression of the tubular secretion thus seems to have already occurred at low diodrast iodine plasmaconcentrations (112—122 μg/ml). Whereas the ratio of creatinine clearance/inulin clearance dropped approximately 10 % at heavy diodrast loading in the first experiment, the figure shows that the ratio, in this case, declines approximately 10 % at low and approximately 20 % at a high diodrast iodine level. This indicates that a certain tubular secretion of creatinine probably occurs in the horse also. (*Taggart* 1950, *Smith* 1951, *Poulsen* 1956, 1957, *Knudsen* 1959).

It is further manifest from Figure 1 that ultrafiltrate clearance during diodrast loading is less than filtration clearance. This is in agreement with observations in pigs (*Dalgaard-Mikkelsen & Poulsen* 1956) and cows (*Poulsen* 1956, 1959), therefore it appears that also in the horse a tubular back diffusion is involved in the excretion mechanism of sulfathiazole. This, too, would

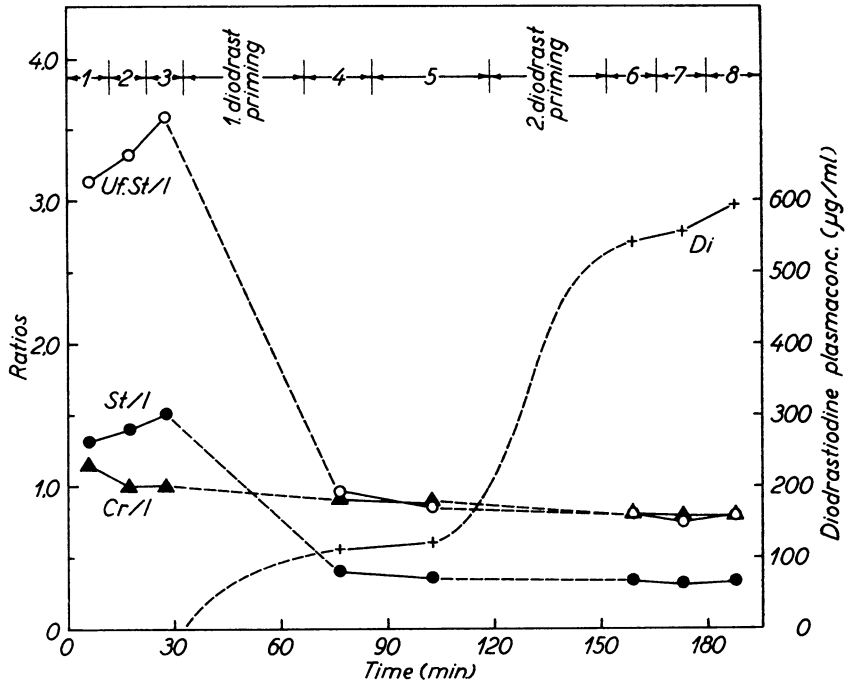

Fig. 1. Sulfathiazole clearance at tubular diodrast blockade (1 mare).
Period 1, 2 and 3: Control periods.
Period 4 and 5: Low diodrast iodine plasma level.
Period 6, 7 and 8: High diodrast iodine plasma level.
Uf.St/I (○): Ratio sulfathiazole ultrafiltrate clearance/inulin clearance.
St/I (●): Ratio sulfathiazole plasma clearance/inulin clearance.
Cr/I (▲): Ratio creatinine clearance/inulin clearance.
Di (+): Diodrast iodine plasma level in µg/ml.

Period no.	St/I	Uf.St/I	Cr/I	Di
1	1.32	3.13	1.15	—
2	1.40	3.32	1.00	—
3	1.51	3.58	1.01	—
4	0.40	0.96	0.91	112
5	0.36	0.85	0.89	122
6	0.34	0.80	0.80	542
7	0.32	0.75	0.79	556
8	0.33	0.79	0.79	593

explain why ultrafiltrate clearance of sulfathiazole in the horse is always lower than the penicillin clearance.

SULFADIMIDINE CLEARANCE

Clearance was calculated for non-acetylated sulfadimidine only. Sulfadimidine clearance was determined in 5 experiments, with a total of 35 observations. Average plasma clearance was found to be 35 ± 16 ml/min. per 100 kgm of body weight and 14 ± 7 per 100 gm of kidney weight, whereas the corresponding values for ultrafiltrate clearance were 66 ± 23 and 27 ± 12, respectively. The values for each experimental animal are presented in Table 3. No decline of plasma clearance at high sulfadimidine plasma concentrations was demonstrated, as is seen by 34 ± 13 ml/min (17 obs.) per 100 kgm body weight at low plasma concentrations and 35 ± 19 (18 obs.) at high plasma concentrations. Neither was there in the ultrafiltrate any significant difference between clearances at low and high sulfadimidine levels. At low concentrations it was 75 ± 15 ml/min. (17 obs.) per 100 kgm of body weight and at high concentrations 58 ± 25 (18 obs.), which, at the most, may be interpreted as a possible tendency towards lower clearance values at high sulfadimidine levels, but is not proof of self-depression.

Table 3.
Sulfadimidine clearance.

Mare no.	Plasma level µg/ml	Clearance ml/min. plasma per 100 kgm body weight	plasma per 100 gm kidney wt.	ultrafiltrate per 100 kgm body weight	ultrafiltrate per 100 gm kidney wt.	Ratios Sd/Cr.	Ratios Uf. Sd/Cr	Number of observations
2 S	29— 35	16± 3	6±1	58±10	22± 4	0.13±0.02	0.48±0.06	5
	173—185	12± 3	4±2	27± 6	10± 2	0.10±0.02	0.25±0.03	6
3 S	22— 35	43± 4	20±2	87± 7	41± 3	0.31±0.04	0.63±0.07	8
	138—164	41± 4	19±2	73±16	34± 6	0.31±0.03	0.53±0.08	8
4 S	32— 33	41± 6	13±2	76±13	23± 4	0.27±0.03	0.50±0.06	4
	152—175	58± 6	18±2	74± 8	23± 2	0.38±0.04	0.49±0.06	4
Average	low	34±13	14±6	76±15	31±10	0.25±0.08	0.55±0.09	17
	high	35±19	14±7	58±25	24±12	0.25±0.11	0.43±0.14	18
Total average		35±16	14±7	66±23	27±12	0.25±0.10	0.49±0.14	35

From Table 3 it is further manifest that clearance, even after correction for plasma protein binding, does not reach the value

of filtration clearance, as the ratio of ultrafiltrate clearance/creatinin clearance was found to be 0.49 ± 0.14. Because of these constantly low values, no attempt was made to block the excretion of sulfadimidine. The low clearance of this compound in the horse must be ascribed to an extensive back diffusion in the tubules after the glomerular filtration, in accordance with conditions in man, dog and pig (*Reinhold et al.* 1945, *Beyer et al.* 1944, *Dalgaard-Mikkelsen & Poulsen* 1956), whereas no parallel was found in the horse to the complex excretory mechanism of sulfadimidine in the cow (*Poulsen* 1956, 1959).

CONCLUSION

The experiments performed demonstrate that it is possible in the horse also to explain, on the basis of excretion studies, the differing slope of the blood concentration/time curves of penicillin, sulfathiazole and sulfadimidine by means of the renal excretion of these compounds. As for penicillin and sulfathiazole, the extensive tubular secretion results in a rapid elimination with the urine, and consequently a rapidly declining blood concentration, whereas the tubular back diffusion of sulfadimidine causes a retarded excretion and a significantly more stable blood concentration of this compound.

The experiments demonstrate further the fundamental difference in the treatment by the equine kidney of these two sulfonamides. Sulfathiazole is excreted by a three component system (*Barcley et al.* 1947) including glomerular filtration, extensive tubular secretion and a slight tubular back diffusion, whereas the sulfadimidine excretion bears strong resemblance to the excretion of urea, since the filtration is followed by so comprehensive a backdiffusion that the ratio of sulfadimidine ultrafiltrate clearance/creatinine clearance becomes ca. 0.5, analogous with the ratio of urea clearance/creatinine clearance at diureses above the augmentation limit.

REFERENCES

Bak, B., C. Brun & F. Raaschou: Acta med. scandinav. 1943, *114*, 271.

Barcley, J. A., W. T. Cooke & R. A. Kennedy: Acta med. scandinav. 1947, *128*, 500.

Becker-Christensen, P. & P. Schou: Acta pharmacol. et toxicol. 1945, *1*, 357.

Beyer, K. H., L. Peters, E. A. Patch & H. F. Russo: J. Pharmacol. Exper. Therap. 1944, *82*, 239.

Bratton, A. C. & E. K. Marshall: J. Biol. Chem. 1939, *125*, 537.
Brun, C. in: *Iversen, P., T. Bjering & J. Bing:* De medicinske Nyrelidelser, Copenhagen 1946.
Dalgaard-Mikkelsen, S. & S. A. Kvorning: Acta pharmacol. et toxicol. 1949, *5*, 173.
Dalgaard-Mikkelsen, S. & E. Poulsen: Acta pharmacol. et toxicol. 1956, *12*, 233.
Doll, E. R. & W. W. Dimock: J. Amer. vet. med. Ass. 1946, *108*, 209 and 310.
Doll, E. R. & M. E. Wallace: Vet. Med. 1949, *44*, 34.
Doll, E. R., M. E. Wallace & F. E. Hull: Kentucky Agricult. Exper. St. Bull. 549, 1950.
Doll, E. R., M. E. Wallace & W. H. McCollum: Vet. Med. 1950, *45*, 309.
Eagle, H. & E. Newman: J. Clin. Invest. 1947, *26*, 903.
Folin, O.: Ztschr. physiol. Chem. 1904, *41*, 223.
Francis, J.: Vet. J. 1947, *103*, 193.
Francis, J.: J. comp. Path. 1949, *59*, 245.
Jensen, K. A., K. O. Møller & K. Overgaard: Acta pharmacol. et toxicol. 1945, *1*, 184.
Knudsen, E.: Acta vet. scandinav. 1959, *1*, 52.
Lausen, H. H.: Acta pharmacol. et toxicol. 1955, *11*, 353.
Lundquist, F.: Acta pharmacol. et toxicol. 1945, *1*, 307.
Pers, M.: Scandinav. J. Clin. & Lab. Invest. 1954, *6*, 341.
Poulsen, E.: Renale clearanceundersøgelser hos køer, Dissert. Copenhagen 1956.
Poulsen, E.: Royal Veterinary and Agricultural College. Yearbook, 1957, p. 97.
Poulsen, E.: Zbl. f. Vet. med. 1959, *6*, 127.
Poulsen, E., M. Simesen & I. M. Skude: Nord. Vet. med 1955, *7*, 1.
Reinhold, J. G., H. F. Flippin, A. H. Domm, J. J. Zimmermann & L. Schwartz: J. Pharmacol. Exper. Therap. 1945, *83*, 279.
Smith, H. W.: The Kidney Structure and Function in Health and Disease, New York 1951.
Taggart, J. V.: Amer. J. Med. 1950, *9*, 678.
Thomsen, A.: Kreatinuri. Dissert. Copenhagen 1938.
Welsh, M., C. R. Schroeder, D. F. Vroman, L. Reddin, R. Burkhart & P. Langer: Proc. 50th Ann. Meet. U. S. Livestock Sanitary Ass. 1946.
Zeller, R. & G. Kayser: Tierärztl. Umsch. 1958, *13*, 188.

SUMMARY

In 45 observations on 5 mares, penicillin clearance was found to be 829 ± 187 ml/min. per 100 kgm of body weight and 314 ± 103 per 100 gm of kidney weight. The ratio of penicillin clearance/inulin clearance was 4.79 ± 1.04. Corresponding values for diodrast clearance in one mare (7 obs.) was 691 ± 81 and 302 ± 36. The ratio of diodrast clearance/inulin clearance was 4.15 ± 0.30.

Sulfathiazole clearance was studied in 39 observations on 4 mares.

At sulfathiazole plasma concentrations below 50 μg/ml, plasma clearance was found to be 184 ± 48 ml/min. per 100 kgm of body weight and 67 ± 15 per 100 gm of kidney weight, while ultrafiltrate clearance was 537 ± 242 ml/min. per 100 kgm of body weight and 192 ± 72 per 100 gm of kidney weight (17 obs.). The ratio of plasma clearance/creatinine clearance was 1.25 ± 0.22 and the ratio of ultrafiltrate clearance/creatinine clearance 3.57 ± 1.28. Self-depression was manifest at higher plasma concentrations. Blocking of the tubular secretion of sulfathiazole by diodrast resulted in plasma clearance identical with creatinine clearance, whereas ultrafiltrate clearance dropped to values essentially lower than inulin clearance.

In 35 observations on 3 mares sulfadimidine plasma clearance was found to be 35 ± 16 ml/min. per 100 kgm of body weight and 14 ± 7 per 100 gm of kidney weight. Ultrafiltrate clearance was 66 ± 23 ml/min. per 100 kgm of body weight and 27 ± 12 per 100 gm of kidney weight. The ratio of plasma clearance/creatinine clearance was 0.25 ± 0.10 and the ratio of ultrafiltrate clearance/creatinine clearance was 0.49 ± 0.14. Selfdepression was not demonstrated.

It is concluded that the tubular secretion of penicillin and sulfathiazole as well as the tubular back-diffusion of sulfadimidine offer an adequate explanation of the slope of the blood concentration/time curves of these compounds.

ZUSAMMENFASSUNG

Renale Clearance-Studien beim Pferde. II. Penicillin, Sulfathiazol und Sulfadimidin.

In 45 Beobachtungen bei 5 Stuten betrug die Penicillin-Clearance 829 ± 187 ml/Min. pro 100 kg Körpergewicht und 314 ± 103 pro 100 g Nierengewicht. Das Verhältnis der Penicillin-Clearance/Inulin-Clearance war 4.79 ± 1.04. Die entsprechenden Werte für Diodrast-Clearance bei einer Stute (7 Beobachtungen) waren 691 ± 81 und 302 ± 36. Das Verhältnis von Diodrast-Clearance/Inulin-Clearance war 4.15 ± 0.30.

Die Sulfathiazol-Clearance wurde in 39 Beobachtungen bei 4 Stuten studiert. Bei Sulfathiazol-Plasma-Konzentrationen unter 50 μg/ml betrug die Plasma-Clearance 184 ± 48 ml/Min. pro 100 kg Körpergewicht und 67 ± 15 pro 100 g Nierengewicht, während sich die Ultrafiltrat-Clearance auf 537 ± 242 ml/Min. pro 100 kg Körpergewicht und 192 ± 72 pro 100 g Nierengewicht belief (17 Beobachtungen). Das Verhältnis der Plasma-Clearance/Kreatinin-Clearance war 1.25 ± 0.22 und das Verhältnis der Ultrafiltrat-Clearance/Kreatinin-Clearance 3.57 ± 1.28. Die Selbstdepression war bei höheren Plasma-Konzentrationen manifest. Eine Blockierung der tubulären Sekretion von Sulfathiazol durch Diodrast ergab im Plasma Clearancen, die mit der Kreatinin-Clearance identisch waren, während die Ultrafiltrat-Clearance zu Werten abfiel, welche wesentlich niedriger als die Inulin-Clearance lagen.

In 35 Beobachtungen bei 3 Stuten betrug die Sulfadimidin-Plasma-

Clearance 35 ± 16 ml/Min. pro 100 kg Körpergewicht und 14 ± 7 pro 100 g Nierengewicht. Die Ultrafiltrat-Clearance war 66 ± 23 ml/Min. pro 100 kg Körpergewicht und 27 ± 12 pro 100 g Nierengewicht. Das Verhältnis der Plasma-Clearance/Kreatinin-Clearance belief sich auf 0.25 ± 0.10 und das Verhältnis der Ultrafiltrat-Clearance/Kreatinin-Clearance auf 0.49 ± 0.14. Eine Selbstdepression wurde nicht festgestellt.

Es wird die Schlussfolgerung gezogen, dass dis tubuläre Sekretion von Penicillin und Sulfathiazol ebenso wie die tubuläre Rückdiffusion von Sulfadimidin eine hinreichende Erklärung für die Neigung der Blutkonzentration/Zeitkurven dieser Verbindungen bieten.

RESUMÉ

Renale clearanceundersøgelser på hest.
Penicillin, Sulfathiazol og Sulfadimidin.

I 45 observationer på 5 hopper fandtes penicillinclearance til 829 ± 187 ml/min. per 100 kg legemsvægt og 314 ± 103 per 100 g nyrevægt. Ratio penicillincl./inulincl. var 4.79 ± 1.04. Tilsvarende værdier for diodrastclearance hos een hoppe (7 obs.) var 691 ± 81 og 302 ± 36. Ratio diodrastcl./inulincl. fandtes til 4.15 ± 0.30.

Sulfatiazolclearance er undersøgt i 39 observationer på 4 hopper. Ved sulfatiazol-plasmakoncentrationer under 50 μg/ml fandtes plasmaclearance til 184 ± 48 ml/min. per 100 kg legemsvægt og 67 ± 15 per 100 g nyrevægt, mens ultrafiltratclearance var 537 ± 242 ml/min. per 100 kg legemsvægt og 192 ± 72 per 100 g nyrevægt (17 obs.). Ratio plasmacl./kreatininincl. var 1.25 ± 0.22 og ratio ultrafiltratcl./kreatininincl. 3.57 ± 1.28. Der påvistes selvdepression ved højere plasmakoncentrationer. Ved diodrastblokade af sulfatiazolets tubulære sekretion blev plasmaclearance identisk med kreatininclearance, mens ultrafiltratclearance faldt til værdier lavere end inulinclearance.

I 35 observationer på 3 hopper fandtes sulfadimidin-plasmaclearance til 35 ± 16 ml/min. per 100 kg legemsvægt og 14 ± 7 per 100 g nyrevægt. Ultrafiltratclearance var 66 ± 23 ml/min. per 100 kg legemsvægt og 27 ± 12 per 100 g nyrevægt. Ratio plasmacl./kreatininincl. fandtes til 0.25 ± 0.10 og ratio ultrafiltratcl./kreatininincl. til 0.49 ± 0.14. Selvdepression kunne ikke påvises.

Det konkluderes, at den tubulære ekskretion af penicillin og sulfathiazol ligesom den tubulære tilbagediffusion af sulfadimidin giver en rimelig forklaring på hældningen af blodkoncentrationen/tidkurverne for disse stoffer.

(Received March 9. 1959).