Studies on the Transport Mechanism of Sulfonamide Compounds in Renal Tubules

Stopflow Analysis Applied to the Excretion of Sulfonamide Compounds

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It has been accepted that unconjugated sulfonamide compounds are reabsorbed by renal tubules and acetylated compounds are secreted from the tubules. In the previous study the present authors have indicated that both unconjugated and acetylated compounds is possibly secreted and reabsorbed by renal tubules from the standpoint of clearance ratios of sulfonamide compounds to thiosulfate or inulin in man and the dog.

To study this possibility further, the stopflow method was tried in normal dogs. Then the results obtained were discussed quantitatively starting from a qualitative approach. Problems of energy required in the transport of sulfonamide compounds were also pursued.

METHODS

(1) Stopflow Localization of Sulfadimethoxine and Sulfathiazole

Normal adult dogs weighing about 10 kg were anesthetized with Na-pentobarbital, 30 mg/kg, intravenously. The ureter was unilaterally exposed by a flank incision and catheterized with a polyethylene tube. A catheter was passed into the renal pelvis to collect urine samples. The ureter and catheter were firmly fixed. A perfusion solution consisting 10% mannitol, 0.2% inulin and 0.1% sulfonamide compound was infused through the femoral artery at a rate of about 6 to 10 ml/min. In some instances 0.005% PSP was added to the perfusion solution. When the urine flow had stabilized at a rate of 8-10 ml, two control clearance periods were begun, each exactly 3 minutes in duration. Then the catheter was clamped. At the end of 4 minutes of occlusion, 0.5 mg of creatinine was injected intravenously requiring 20 seconds. At the end of 5 minutes the catheter was released and small (0.5 ml) serial urine samples were collected during 2 minutes and again, two additional 3-minute control clearance periods were obtained. Blood was drawn from the femoral artery at the exact mid-point of each clearance period.

(2) Analysis of Proximal Secretion Pattern of Sulfadimethoxine in Stopflow Method

The method employed was similar to that in the experiment (1). Steady intravenous loads of NaCl, mannitol, inulin were maintained by intravenous infusion supplied at constant rates. The infusions contained 10% mannitol and 0.2% inulin dissolved in 0.9% NaCl. The catheter was clamped when urine flow had stabilized. At the end of 4 minutes of occlusion, 0.5 gm of sulfadimethoxine and creatinine each were intravenously injected required 20 seconds. At the end of 5 minutes the catheter was released and small (0.5 ml) serial urine samples were collected during 2 minutes. Patterns were plotted against urinary concentrations of sulfadimethoxine and creatinine.

(3) Stopflow Localization of PAH and PSP

Perfusion was done by a solution containing 0.9% NaCl, 10% mannitol, 0.2% inulin, 0.05% PAH and 0.005% PSP. Experimental procedures were similar to those in the experiment (1).

(4) Stopflow Localization of Acetylated Sulfadimethoxine

The perfusion solution employed contained 0.9% NaCl, 10% mannitol, 0.05% unconjugated and acetylated sulfadimethoxine and 0.2% inulin. Procedures were based on the experiment (1). Acetylated sulfadimethoxine was synthetized as follows: sulfadimethoxine and acetic acid anhydride were mixed in a 2.7 to 3.0 gm ratio, heated 15 minutes at 100°C in a water bath, then cooled. The mixture was filtrated after being added with distilled water; recrystallization was made in methanol. The melting point of synthetic acetyl sulfadimethoxine was

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219–226°C.
(5) Effect of Acetate Loading on Stopflow Patterns of Sulfadimethoxine and Sulfathiazole

The perfusion solution employed contained 0.9% NaCl, 10% mannitol, 0.1% sulfonamide compound and 0.2% inulin. After a control stopflow experiment animals were subjected to an injection of 0.1% Na-acetate and a continuous infusion. Approximately 30 minutes later, the 2nd experiment was performed.

(6) Effect of NaHCO₃ Loading on Stopflow Pattern of Sulfadimethoxine

Following a control stopflow experiment, the same animals were alkalinized by addition of 3% NaHCO₃ to the perfusion solution. About 30 minutes later, the 2nd experiment was repeated. pH of the arterial blood and urine was determined within 2 to 3 minutes after collection of the samples in the experiment (5) and (6).

(7) Effect of 2,4-DNP Loading on Stopflow Patterns of Sulfadimethoxine and Sulfathiazole

The control stopflow experiment was followed by administration of 2,4-DNP initially at a dosage of 10⁻⁴M 5ml and then a maintenance dosage of 2×10⁻³M. About 30 minutes later, the 2nd experiment was repeated.

Sulfonamide compounds and PAH were determined with Bratton-Marshall, inulin with resorcinothiores, PSP with alkaline coloration, Na and K with Beckman's flame spectrometry, creatinine with Jaffe method and pH with Beckman's meter (Model 76).

Determination of serum PSP was made with alkalinalimetry after protein precipitation by the use of the method of Hagedorn-Jensen. Effects of PSP on the colorimetry of inulin, PAH and sulfonamide compounds were corrected in the following ways: for inulin estimation, a part of each sample similarly treated but not hydrolyzed was employed for blind check; and for PAH and sulfonamide compounds, samples treated similarly except coloration by N-(1-Naphthyl) ethylenediamine dihydrochloride were used for blind check.

RESULTS

(1) Stopflow Localization of Sulfadimethoxine and Sulfathiazole

The stopflow pattern of sulfadimethoxine had a convex curve in the proximal segment and a concave curve in the distal segment as seen in Fig. 1. The proximal peak was reached at the same point on the volume scale as the site of PSP secretion and the latter lay between the site of Na reabsorption and K secretion.

A ratio, \( \frac{U_{SN}}{P_{SN}} \) divided by \( \frac{U_{IN}}{P_{IN}} \) was definitely smaller than unity in all samples, suggesting a net reabsorption in tubules. However, the significance of the proximal convex curve should be carefully interpreted. It was evident in Fig. 2 that the stopflow pattern of sulfathiazole also had a convex curve in the proximal segment and a concave curve in the distal segment. The former was roughly identical with the secretion site of PSP, the latter being between the sites of Na reabsorption and K secretion. A ratio, \( \frac{U_{NT}}{P_{NT}} \) divided by \( \frac{U_{IN}}{P_{IN}} \) was greater than unity in the proximal segment and smaller than unity in the distal segment. This result indicated that sulfathiazole was secreted in the proximal segment and reabsorbed in the distal segment.

(2) Analysis of Proximal Secretion Pattern of Sulfadimethoxine in Stopflow Method

In Fig. 3 the points on the volume scale where urinary concentration of sulfadimethoxine and creatinine reached 50 per cent of peak concentration were illustrated. This point of

![Fig. 1. Stopflow localization of sulfadimethoxine secretion and reabsorption in the nephron of the dog. 5 min. clamp time. Mongrel Dog 9.5 kg 9. Urine flow 10.6~6.8 ml/min./kidney.](attachment:image.png)

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sulfadimethoxine lay distal to that of creatinine and proximal to the site of Na reabsorption. It was suggested that sulfadimethoxine was secreted in this site, although a ratio, \( \frac{U_{\text{STI}}}{P_{\text{STI}}} \)

divided by \( \frac{U_{\text{IN}}}{P_{\text{IN}}} \) was smaller than unity.

(3) Stopflow Localization of PAH and PSP

It was evident from Fig. 4 that the sites of PAH and PSP secretion were almost the same. When PSP was loaded, the color of urine samples was pink from the beginning of the glomerulus to the site of PAH secretion, becoming yellowish in the distal segment and orange in the site of Na reabsorption or K secretion.

(4) Stopflow Pattern of Acetylated Sulfadimethoxine

As indicated in Fig. 5 the stopflow pattern of acetylated sulfadimethoxine was similar to that of the unconjugated compound, namely a convex curve in the proximal segment and a concave curve in the distal segment. However,

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Fig. 2. Stopflow localization of sulfathiazole secretion and reabsorption in the nephron of the dog. 5 min. clamp time.
Mongrel Dog 7.0 kg ♀. Urine flow 5.9−6.1 ml/min/kidney.

Fig. 3. Localization of sulfadimethoxine secretion. Sulfadimethoxine appears at a more distal point than creatinine given simultaneously by stopflow technique.
Mongrel Dog 8.0 kg ♀. Urine flow 6.4−6.8 ml/min/kidney.

Fig. 4. Stopflow localization of PAH and PSP secretion and the reabsorption of sodium in the nephron of the dog. 5 min. clamp time.
Mongrel Dog 8.0 kg ♀. Urine flow 6.5−5.9 ml/min./kidney.
Fig. 5. Stopflow localization of the secretion and re-absorption of unconjugated and acetylated sulfadimethoxine in the nephron of the dog. 5 min. clamp time.
Mongrel Dog 10kg 5. Urine flow 7.4~7.9ml/min/kidney.

Fig. 6. Stopflow analysis of the effect of Na-acetate on urinary excretion of sulfadimethoxine. After the 1st experiment, 0.1% Na-acetate was infused. Approximately 1/2 hr. later, the 2nd experiment was performed.
Mongrel Dog 10kg 9.
pHr  pHr  Urine flow ml/min/kidney
Exp. I......7.40  7.01  7.5~8.0
II......7.40  7.02  9.3~15.3

Fig. 7. Stopflow analysis of the effect of Na-acetate on urinary excretion of sulfathiazole. After the 1st experiment, 0.1% Na-acetate was infused. Approximately 1/2 hr. later, the 2nd experiment was performed.
Mongrel Dog 9.5kg 9.
pHr  pHr  Urine flow ml/min/kidney
Exp. I......7.41  7.10  8.6~10.6
II......7.40  7.11  7.3~8.6

Fig. 8. Stopflow analysis of the effect of Na-bicarbonate on urinary excretion of sulfadimethoxine. After the 1st experiment, 3% Na-bicarbonate was infused. Approximately 1/2 hr. later, the 2nd experiment was performed.
Mongrel Dog 12kg 9.
pHr  pHr  Urine flow ml/min/kidney
Exp. I......7.38  7.00  9.0~9.7
II......7.42  7.04  8.3~9.0

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in all samples and in some cases this value was greater than unity in the proximal segment.

(5) Effect of Acetate Loading on Stopflow Patterns of Sulfadimethoxine and Sulfathiazole

As indicated in Fig. 6 and 7, the stopflow patterns of both sulfadimethoxine and sulfathiazole tended to be elevated by acetate loading along the whole length of the nephron as compared with the control pattern, although pH in the blood and the urine showed no changes.

(6) Effect of NaHCO₃ Loading on Stopflow Pattern of Sulfadimethoxine

Urinary pH was increased from 7.00 to 7.64 by addition of NaHCO₃, and blood pH from 7.28 to 7.42. As indicated in Fig. 8 the stopflow pattern of sulfadimethoxine was markedly elevated along the whole length of the nephron.

(7) Effect of 2, 4-DNP Loading on Stopflow Patterns of Sulfadimethoxine and Sulfathiazole

As indicated in Fig. 9 the stopflow pattern of sulfadimethoxine was slightly elevated by 2, 4-DNP loading in the distal segment but it remained on a similar level in the proximal segment. But in sulfathiazole it was elevated in the distal segment and lowered in the proximal segment by 2, 4-DNP loading, resulting in a flat curve. (Fig. 10)

DISCUSSION

The stopflow method is useful in analyzing the transport mechanism of substances in renal tubules. As inulin is neither reabsorbed nor secreted, its concentration results from water movement. \( U_{IN}/P_{IN} \) must be estimated to correct changes of concentration gradient between the tubular and peritubular fluid as induced by water movement across tubule cells. The concentration gradient produced by the transport of a given substance (x) independently of water movement, is determined by a ratio, \( \frac{U_X}{P_X} \) divided by \( \frac{U_{IN}}{P_{IN}} \), where \( U_X \) is the

![Graph](image)

Fig. 9. Stopflow analysis of the effect of 2, 4-DNP on urinary excretion of sulfadimethoxine. After the 1st experiment, 2, 4-DNP was infused. Approximately 1/2 hr. later, the 2nd experiment was performed.

Mongrel Dog 8.6 kg 9.
Exp. I......Urine flow 8.2~5.0 ml/min./kidney
Exp. II......8.0~7.3 ml/min./kidney

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urinary concentration of x and Px is the serum concentration of the same substance. However, a ratio, \( \frac{U_X}{P_X} \) divided by \( \frac{U_{IN}}{P_{IN}} \) in the stopflow analysis may be somewhat different from true values. Therefore factors involved in the stopflow analysis, which affect the ratio, must be carefully interpreted.

The present study showed that both unconjugated and acetylated sulfonamide compounds were secreted in the proximal segment of nephrons and reabsorbed in the distal segment. The site of proximal sulfonamide compound secretion was almost the same as that of PSP and PAH. The site of distal sulfonamide compound reabsorption is between the sites of K secretion and Na reabsorption. An average volume difference between the peaks of sulfathiazole and PSP was about 0.5 ml. The peaks of PAH and PSP also differ by about 0.5 ml on a volume scale. However, the proximal peak of sulfadimethoxine was reached at the same point on a volume scale as the site of PSP secretion. In the stopflow experiment the first samples come from a more distal segment of nephrons and later samples from a more proximal segment. The width of peaks in the proximal segment becomes larger than that in the distal segment because of nephron population. Therefore it is doubtful whether such small difference on a volume scale in the proximal segment is really significant. A mutual inhibition between PAH and PSP in reports \(^9,10\) suggests two substances transported in the same site.

Judging from the color of samples during PSP loading, urinary acidification already may occur in the proximal segment and the maximum concentration of hydrogen is localized at the site of Na reabsorption or K secretion.

Theoretically the stopflow pattern of sulfonamide compound may be analyzed by the following formulation:

\[
S_{IN} = U_{IN}^0 \quad ..........(1)
\]

\[
\alpha \cdot S_N = U_{IN}^0 \quad ..........(2)
\]

from (1) and (2)

\[
\frac{U_{IN}^0}{S_N} = \frac{U_{IN}^0}{S_{IN}} \quad ..........(3)
\]

in which: \( S_N \) is the serum concentration of sulfonamide compound; \( \alpha (<<1) \) is the ratio of free form (non-protein bound) of sulfonamide compound; \( S_{IN} \) is the serum concentration of inulin;

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**Figure 10.** Stopflow analysis of the effect of 2,4-DNP on urinary excretion of sulfathiazole. After the 1st experiment, 2,4-DNP was infused. Approximately 1/2 hr. later, the 2nd experiment was performed. Mongrel Dog 9.0 kg △.

Exp. I......Urine flow 9.9→6.5 ml/min./kidney

Exp. II......6.9→5.1 ml/min./kidney

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$U^*_S$ is the concentration of sulfonamide compound in glomerular filtrate; $U^*_IN$ is the concentration of inulin in glomerular filtrate; $U^X_S$ is the concentration of sulfonamide compound in a given site $x$ of the nephron and $U^*_IN$ is the concentration of inulin in the site $x$ of the nephron.

On an assumption that in the site 1 sulfonamide compound is not secreted, and that the urinary concentration of inulin is concentrated $k_1$-fold by water reabsorption, the concentration gradient of sulfonamide compound independently of water movement may be expressed as follows:

$$\frac{(U^I_S)}{(S^*_R)} \underset{\text{non-secrete}}{\rightarrow} \frac{(k_1U^0_S)}{(S^*_R)} = \alpha \leq 1 \quad \text{(4)}$$

Fig. 11. Stopflow analysis of renal tubular excretion of sulfonamide compounds

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If sulfonamide compound is not transported in renal tubules, its stopflow pattern is always represented by a line parallel to the base line (1,0) with a distance \(\alpha (<1)\) independently of water reabsorption (Fig. 11 (i)).

On an assumption that under the same condition the urinary concentration of sulfonamide compound is increased \(\beta_1\)-fold \((\beta_1 > 1)\) by secretion of sulfonamide compound in the site 1, the concentration gradient of sulfonamide compound independently of water movement is expressed by the following equation:

\[
\frac{\langle U^1_{IN} \rangle}{\langle S^1 \rangle_{secret}} = \frac{k_1 \beta_1 \langle U^0_{IN} \rangle}{\langle S^1 \rangle_{secret}}
\]

\[
= \alpha \beta_1 \geq 1 \quad (5)
\]

Therefore the maximum value of sulfonamide compound in the site 1 lies either above or below the base line depending on whether the value, \(\alpha \beta_1\), is larger or smaller than unity. It follows that when the influence of plasma protein binding is greater than that of sulfonamide compound secretion, maximum value is smaller than unity as seen in Fig. 11 (ii).

On an assumption that in the site 2 the urinary concentration of inulin is increased \(k_2\)-fold by water reabsorption, and that at the same time the urinary concentration of sulfonamide compound is decreased \(\beta_2\)-fold \((\beta_2 < 1)\) by reabsorption of sulfonamide compound, the concentration gradient of sulfonamide compound independently of water movement is expressed by the following equation:

\[
\frac{\langle U^2_{IN} \rangle}{\langle S^2 \rangle_{reab}} = \frac{k_2 \beta_2 \langle U^0_{IN} \rangle}{\langle S^2 \rangle_{reab}}
\]

\[
= \alpha \beta_2 < 1 \quad (6)
\]

The urinary compositions in the site 1 is modified by an influence, \(E_0\) (E: effect, D: distal) of the tubular function of the site 2 when passing the site 2 after a release of the catheter and the urinary compositions in the site 2 likewise receive an influence \(E_p\) (p: proximal) at the site 1 before the catheter is clamped. Finally, as indicated Fig. 11 (iii) the concentration gradient of sulfonamide compound independently of water movement in the proximal segment may be expressed by the following equation:

\[
\frac{\langle U^1_{IN} \rangle}{\langle S^1 \rangle_{secret}} = \frac{\alpha \beta_1 \langle U^0_{IN} \rangle}{\langle S^1 \rangle_{secret}}
\]

\[
= \alpha \beta_1 E_0 \geq 1 \quad (7)
\]

Similarly, as indicated in Fig. 11 (iii), the concentration gradient of sulfonamide compound independently of water movement in distal segment may be expressed by the following equation:

\[
\frac{\langle U^2_{IN} \rangle}{\langle S^2 \rangle_{reab}} = \frac{\alpha \beta_2 E_p \geq 1 \quad (8)
\]

It is evident from the equations (7) and (8) that in the stopflow pattern a convex indicates a tubular secretion and a concave curve a reabsorption, independently of whether a ratio, \(\langle U^X_{IN} \rangle / \langle S^X_{IN} \rangle\) divided by \(\langle U^0_{IN} \rangle / \langle S^0_{IN} \rangle\) is larger or smaller than unity. An assumption in the experiment (1) and (2) that the proximal peak in the stopflow pattern of sulfadimethoxine indicates tubular secretion although the maximum value is smaller than unity, is theoretically evidenced.

It has been shown that both unconjugated and acetylated sulfonamide compounds are excreted in the urine by routes of glomerular filtration, and tubular secretion and reabsorption. The ability of the kidneys to excrete sulfonamide compounds may be calculated on the basis of clearance concept as follows:

\[
C_S = \frac{U_S V}{\alpha S_S} = \frac{\alpha S_S GFR (T^p_S - T^D_S)}{\alpha S_S} \quad (9)
\]

\[
= \frac{1}{\alpha S_S GFR (T^p_S - T^p_D)} \quad (10)
\]

in which: \(C_S\) is the clearance of sulfonamide compound; \(GFR\) is a glomerular filtration rate; \(T^p_S\) is the amount (mg/min) of secreted sulfonamide compound in the proximal segment and \(T^D_S\) is the amount of reabsorbed sulfonamide compound in the distal segment. The equation (10) shows that clearance of sulfonamide compound depends on various factors such as a glomerular filtration rate, tubular secretion and reabsorption, as well as on the serum.

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concentration and the plasma protein binding of sulfonamide compounds. It is obvious from the above equation that \( \frac{GFR}{C_R} \) may be larger or smaller than unity, depending on whether \( T_R^p \) is larger or smaller than \( T_R^p \).

In studying the energy required in the renal transport of sulfonamide compound, a ratio, \( \frac{U_S}{S_R} \) divided by \( \frac{U_{IN}}{S_{IN}} \) is an important factor for secretion and \( U_S/S_R \) for reabsorption. As water is reabsorbed from the tubular lumen, urinary concentration of the substance is elevated. Therefore in a secretion process \( U_S/S_R \) must be corrected by \( U_{IN}/S_{IN} \). When a ratio, \( \frac{U_S}{S_R} \) divided by \( \frac{U_{IN}}{S_{IN}} \) is larger than unity, it seems reasonable to conclude that sulfonamide compounds may be secreted against the concentration gradient. If \( \frac{U_S}{S_R} \) is still smaller than unity in a reabsorption process, it probably followed that sulfonamide compounds are reabsorbed against the concentration gradient. In the foregoing discussion it has been suggested that, in the stopflow patterns of sulfonamide compounds the maximum value may be smaller than the true concentration gradient across tubule cells and the minimum value may be larger than the true concentration gradient because the tubular fluid is modified by passage through the nephron. It is strongly suggested that other factors which include a diffusion of the solute, a mixing of the tubular contents and an intratubular fluid movement during stopped flow, have influence the maximum and minimum values.

As indicated in Table I, the maximum values for \( \frac{U_S}{S_R} \) divided by \( \frac{U_{IN}}{S_{IN}} \) of sulfathiazole and acetylsulfadimethoxine are larger than unity without correction for plasma protein binding.

As a result it is suggested these sulfonamide compounds may actively be secreted in the proximal segment. The maximum value of sulfadimethoxine, corrected for plasma protein binding, is calculated 0.375. Such calculation may be reflected in the influence of sulfadimethoxine reabsorption in the distal segment.

The minimum value for \( \frac{U_S}{P_S} \) of sulfadimethoxine in the distal segment is still smaller than unity, corrected for plasma protein binding, suggesting an active reabsorption of sulfadimethoxine in this site. The minimum value for \( \frac{U_S}{P_S} \) of sulfathiazole in the distal segment is larger than unity. However, the tubular maximal reabsorption rate of sulfathiazole was demonstrated in the dog as described in the previous paper\(^5\), suggesting an active reabsorption.

It is suggested that sulfonamide compounds are actively transported in renal tubules. To confirm this suggestion further, dual experiments were carried out. During acetate infusion the stopflow pattern was slightly elevated along the whole length of the nephrons although pH of the blood and urine remained unchanged. Such elevation of the pattern after acetate is difficult to interpret as to whether it is caused by the enhancement of the proximal secretion or the abolishment of distal reabsorption. However, from a finding that acetate increases the secretion of PAH\(^5\) or para-aminosalicylic acid\(^5\), it may follow that the secretion of sulfonamide compound was enhanced in the proximal segment.

### Table I  (U/P) Ratio of Sulfonamide Compounds

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<thead>
<tr>
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<th>Plasma Protein Binding Ratio (%)</th>
<th>Proximal Segment</th>
<th>Distal Segment</th>
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<tr>
<td></td>
<td>Uncorrected Corrected</td>
<td>( (U/P)<em>R ) ()/(U/P)</em>{IN} )</td>
<td>( (U/P)<em>R ) ()/(U/P)</em>{IN} )</td>
</tr>
<tr>
<td>Sulfadimethoxine</td>
<td></td>
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<tr>
<td>(10 dogs)</td>
<td>( 60%^{10} )</td>
<td>( 0.15 )</td>
<td>( 0.046 )</td>
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<tr>
<td></td>
<td>(20 mg/dl)</td>
<td>( \pm 0.037 )</td>
<td>( \pm 0.010 )</td>
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<tr>
<td>Sulfathiazole</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>(7 dogs)</td>
<td>( 53.2%^{10} )</td>
<td>( 1.29 )</td>
<td>( 0.63 )</td>
</tr>
<tr>
<td></td>
<td>(5 mg/dl)</td>
<td>( \pm 0.10 )</td>
<td>( \pm 0.19 )</td>
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<tr>
<td>Acetylsulfadimethoxine</td>
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<tr>
<td>(2 dogs)</td>
<td></td>
<td>( 1.12 )</td>
<td>( 0.26 )</td>
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<td></td>
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<td>( 3.08 )</td>
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During NaHCO₃ infusion the stopflow pattern was markedly elevated throughout the tubule both proximal and distal. Urinary pH was higher than that of plasma after bicarbonate. Sulfadimethoxine with a pKa value of 6.4₃ and sulfathiazole (pKa 7.2)⁴₀ are dissociated more in an alkaline than in an acid solution and negatively ionized molecules may be significantly increased. The cell membrane allows non-ionized molecules to pass more readily than ionized molecules because the cell membrane has an electrical charge. The permeability is also known to be related with a partition ratio of oil/water or ether/water. As indicated in Fig. 12, the ether/water partition ratio of sulfadimethoxine rapidly decreases as pH increases. Reabsorption would be reduced during production of alkaline urine because of a decreased partition ratio and electrical repulsion between ionized molecules of sulfonamide compounds and cell membrane. This suggests that the reabsorption of sulfonamide compounds involves more or less a passive process.

During 2, 4-DNP infusion the stopflow pattern of sulfadimethoxine was slightly elevated in the distal segment in the absence of remarkable change in the proximal segment. The pattern of sulfathiazole tended to be flat throughout the tubule both proximal and distal. But the changes after 2, 4-DNP were too small to evaluate its significance. As based on changes of sulfonamide compound clearance during 2,4-DNP infusions in the dog, Yamamoto et al.¹⁰ assumed that for transport of sulfonamide compound which is actively secreted from the tubule cells, energy is supplied by oxidative phosphorylation, while for transport of sulfonamide compound which is reabsorbed, some other energy system seems to be involved. It is generally accepted that the renal metabolic system is varying depending upon the locality. The medulla has a metabolic system different from that in the cortex e.g. the paucity of mitochondria in Henle's loop⁵⁰, low oxygen pressure in the medulla especially in the papillae⁶⁰ and marked glycolysis in the papillae⁶⁰.

It is difficult to indicate where sulfonamide compounds are reabsorbed in the stopflow study. However, from the present data it is suggested that the site of sulfonamide compound reabsorption is in the cortex or in the boundary portion between the cortex and medulla. This suggestion needs further study before it is fully substantiated theoretically as well experimentally.

**SUMMARY**

1) Tubular transport of sulfonamide compound occurs in a bidirectional manner; that is, both unconjugated and acetylated sulfonamide compound are secreted in the proximal segment and reabsorbed in the distal segment of the kidneys. The site of sulfonamide compound secretion is approximately identical with that of PSP or PAH secretion and the site of reabsorption lies between the sites of Na reabsorption and K secretion.

2) It is suggested that sulfonamide compounds are actively secreted in the proximal segment, and that for distal reabsorption an active transport and a partly diffusion mechanism are involved.

**REFERENCES**

siologist. 1: 58, 1957.