A New Uricosuric Diuretic, S-8666, in Rats and Chimpanzees

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Abstract—5-Dimethylsulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (S-8666) was studied as a possible new uricosuric diuretic agent using rats and chimpanzees. Various new compounds belonging to the 5-sulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acids were clearly diuretic with uricosuric activity in intraperitoneally oxonate-treated rats. S-8666 was chosen as a favorable candidate because its uricosuric activity due to the effects of tubular transport of uric acid were apparently more marked than those of known uricosuric agents such as probenecid, benz bromarone, ti enilic acid and indacrinone in oxonate-treated rats. S-8666 was also uricosuric in rats not given urate oxidase inhibitor. The diuretic effect of S-8666 in oxonate-treated rats was as high-ceilinged as that of furosemide, while those of ti enilic acid, indacrinone and a known compound of a 5-carbonyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid were rather low-ceilinged. These uricosuric and diuretic activities of S-8666 were manifested by two enantiomers, of which the (+)-enantiomer displayed predominantly uricosuric activity and the (-)-enantiomer, diuretic activity like furosemide. The new compound was also uricosuric and diuretic in chimpanzees, although the potency of the uricosuric activity was similar to that of probenecid and less than that of indacrinone. Thus, it seems that S-8666 is a different type of uricosuric diuretic from known agents which have already been tried in humans.

Diuretic thiazides and various loop diuretics have been generally utilized as useful antihypertensive agents, but the hyperuricemic effect incident to their major effects has sometimes necessitated their withdrawal (1–3). Uricosuric (generally used to mean ‘hyperuricosuric’) diuretics have been studied over the past decade to improve diuretic antihypertensives.

At first, ti enilic acid (4) was considered to be an excellent uricosuric diuretic, which could lower the blood level of uric acid during medication, but its hepatotoxicity forced it to be banned from clinical use (5). This accelerated further studies on a new generation of diuretic antihypertensives (6–10), but their development as drugs has been delayed because the evaluation of uricosuric activity requires tests on primates, due to species differences in the metabolism and excretion of uric acid. To help alleviate this problem, we recently devised a practical method employing a commonly used experimental animal, the rat, which was treated with an inhibitor of urate oxidase, potassium oxonate (11). Rats are different from primates in how they metabolize uric acid to allantoin in the liver, but the net flux of uric acid in the renal tubules is clearly reabsorptive (12). Therefore, the animals have sometimes been used to support the uricosuric activity of test compounds (13, 14). However, the results do not always demonstrate the effect of test compounds on the renal clearance of uric acid under experimental conditions using animals displaying both hepatic metabolism and renal excretion of uric acid, and hence the animals are not feasible for evaluating the uricosuric activity of new compounds. On the other hand, oxonate-treated rats also had
a reabsorptive net flux of uric acid in the renal tubules and responded well to various known agents which had already been demonstrated to have effects on uric acid excretion in humans, although all responses were not always identical to those in primates. In addition, an experiment using rats is much easier than that using primates. It thus seems that the clearance experiment using oxonate-treated rats is feasible for the first screening of favorable candidates from various new compounds. In the present study, 5-dimethylsulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid (S-8666) was studied as a favorable candidate for a uricosuric diuretic after being chosen from a screening with the animals, and then it was confirmed to also be uricosuric and diuretic in chimpanzees.

Materials and Methods

Chemicals: Probenecid (Sigma), furosemide (Sigma) and furosemide solution for injection (LASIX, Hoechst) were commercial preparations. The other compounds used were prepared in our laboratories.

Experiments in rats: Uricosuric activity in oxonate-treated rats was determined by the method described previously (11); ten-week-old male Slc-Wistar rats which had received 250 mg/kg potassium oxonate i.p. were cannulated in the right femoral artery, left femoral vein and urinary bladder under anesthesia with sodium pentobarbital within 2 hr after dosing with oxonate. The same dose of oxonate, i.p.; 2 ml/kg of 60% urethane, s.c.; and 4 ml/kg of 15% inulin, s.c., were given just 2 hr after the first administration of oxonate, and then the animals were infused with 4% mannitol-1.5% inulin-0.9% sodium chloride solution at a flow rate of 0.03 ml/min after the cannulation. After the equilibration for 60 min, continuous 20-min urine samples were collected four times, and blood was collected at the midpoint of each urine collection period. In these experiments, uric acid was determined by the fluorometric method, basically according to the procedure of Sumi et al. (16), while inulin was estimated according to the method of Vurek and Pegram (17).

Data are given as the mean±standard error, and the significance of the difference from the level before dosing was evaluated by Student's t-test.

The abbreviations used here are UuaV, urine-excreted amounts of uric acid; Fua, glomerular filtered amounts of uric acid; FEua, fractional excretion of uric acid; and Cin, inulin clearance.

Experiments in chimpanzees: Three 10-year-old male laboratory-born chimpanzees (Pan troglodytes) weighing 55 to 65 kg were used. Clearance experiments were performed basically according to the commonly used procedure under anesthesia (18); the animals were anesthetized by the premedication of ketamine hydrochloride, 10 mg/kg, i.m., and atropine sulfate, 0.05 mg/kg, i.m., and then the introductory and maintenance anesthesia with oxygen-nitrous oxide-halothane mixture. The clearance experiments were started with an intravenous infusion of Ringer-lactate solution at a flow rate of 3 ml/min, a bolus administration of inulin, 50 mg/kg, i.v., and then an intravenous infusion of 1 mg/kg/min inulin in saline as a sustaining dose. Blood

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and urine samples were collected every 30 min. After equilibration for 120 min, the test compound dissolved into 1.26% sodium bicarbonate solution was administered orally by a stomach tube; and thereafter, the infusion volume of the Ringer-lactate solution was adjusted to the urine flow to prevent volume loss in the animals after the administration of diuretic agents.

**Determination of S-8666 and the metabolite, 5-monomethylsulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid:**
Part of the plasma and urine samples in the clearance studies using chimpanzees was used to determine the concentrations of S-8666 and the metabolite to confirm the reliability of the clearance experiments. The plasma sample (0.5 ml) was mixed and shaken well with 1.0 ml of 1 N NaOH and 2.0 ml of dichloromethane containing 20 μg of 5-(pyrrolidin-1-yl-sulfonyl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid as an internal standard.

After centrifuging, 1.0 ml of the aqueous phase was mixed and shaken with 1.0 ml of 2 N HCl and 2.0 ml ethyl acetate; then an aliquot of the organic phase was evaporated to dryness at reduced pressure. The urine sample, 2.0 ml, was mixed and shaken with 0.5 ml 1 N NaOH and 2.0 ml dichloromethane. Next, 1.0 ml of the aqueous phase was mixed with 0.5 ml 2 N HCl and 2.0 ml ethyl acetate containing 100 μg of the same internal standard compound. The residue from the organic phase was dissolved in 200 μl of developing solvent [11/9 (V/V) mixture of methanol and a phosphate buffer containing 10 mM of Na₂HPO₄, 30 mM of NaH₂PO₄ and 5 mM of PIC-A reagent (Waters Associates)]; then a portion (1–10 μl) was used for analysis by an HPLC method employing a Nucleosil 5C₁₈ column (Chemco), in which S-8666 and the metabolite were analyzed at 254 nm at the flow rate of 1.0 ml/min.

**Results**

**Uricosuric and diuretic activities of various compounds in oxonate-treated rats:**
As described previously (11), the average value of fractional excretion of uric acid (FÉua) in many experiments using oxonate-treated rats ranged from 0.5 to 0.7, which was apparently higher than those in humans and chimpanzees, and meant that the net flux of uric acid in the renal tubules in the animals was definitely reabsorptive. Therefore, it should be possible to evaluate the increase of the FÉua value in the animals due to inhibition of the tubular transport of uric acid. The uricosuric and diuretic effects of various compounds which have been well known for their effects on uric acid excretion in primates are summarized in Table 1.

Experiments on each drug were performed with 8 to 10 animals, of which part of the experimental results had been reported previously (11). The increases of urine-excreted amounts of uric acid (UuaV), glomerular-filtered amounts of uric acid (Fua), FÉua and urine volume were calculated using the mean values in each experimental period, when the values were significantly different from the level before dosing with the drug at P<0.05, and then the increases were shown as the average value for 80 min after the dosing. The high doses of test drugs except for benz bromarone increased the UuaV value with a rising Fua value in the animals. Such an increase of UuaV was also brought about by furosemide, which is not a uricosuric drug. The typical uricosuric drug probenecid clearly elevated the FÉua value in the animals. Benz bromarone and tienilic acid also increased the FÉua value, but the activities were obviously lower. On the other hand, indacrinone and a known 5-carbonyl dihydrobenzofurancarboxylic acid derivative did not increase the FÉua value in the animals, in spite of being markedly uricosuric in chimpanzees (6, 7). Thus, oxonate-treated rats produced two different types of uricosuric responses: an increase of UuaV due to higher glomerular-filtered amounts of uric acid and elevation of the FÉua value due to inhibition of the tubular reabsorption.

Among the new compounds, those of a series of 5-sulfamoyl-6,7-dichloro-2,3-dihydrobenzofurancarboxylic acids were markedly uricosuric, causing a rise of the FÉua value and acting as a diuretic in the animals as shown in Table 2.

These new compounds were compared
Table 1. Uricosuric and diuretic effects of known compounds in oxonate-treated rats

| Compound          | Dose (mg/kg, i.p.) | Increase of UuaV (mg/kg·min) | Increase of Fua (mg/kg·min) | Increase of FEua | Urine volume (ml/kg·min) |
|-------------------|--------------------|------------------------------|----------------------------|-----------------|--------------------------|
| None              |                    |                              |                            |                 |                          |
| Probenecid        | 20                 | 0.124                        | 0.144                      | 0.031           |                          |
|                   | 50                 | 0.182                        | 0.191                      | 0.070           |                          |
|                   | 100                | 0.083                        | 0.120                      | —               | 0.06                     |
| Benzobromarone    | 50                 |                              |                            |                 | 0.08                     |
| Tienilic acid     | 50                 |                              |                            |                 | 0.20                     |
|                   | 100                | 0.123                        | 0.153                      | 0.055           | 0.18                     |
| Indacrinone       | 50                 | 0.083                        | 0.120                      | —               | 0.10                     |
| 5-(2-Thiethyl)-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acid | 0.5 | — | — | 0.08 | — |
|                  | 10                 |                              |                            |                 | 0.20                     |
|                  | 50                 | 0.041                        | 0.078                      | —               | 0.18                     |
| Furosemide        | 1                  |                              |                            |                 | 0.10                     |
|                   | 10                 | 0.020                        | 0.089                      | —0.101          | 0.42                     |
|                   | 50                 | 0.028                        | 0.149                      | —0.124          | 0.53                     |

Each experiment was done using 8–10 animals; then the increases of UuaV, Fua, FEua and urine volume were calculated as the average values for 80 min after dosing in the clearance experiment. —: Unchanged.

Table 2. Uricosuric and diuretic effects of 5-sulfamoyl-6,7-dichloro-2,3-dihydrobenzofuran-2-carboxylic acids in oxonate-treated rats

| 5-Substituent                  | UuaV (mg/kg·min) | Fua (mg/kg·min) | FEua | Urine volume (ml/kg·min) |
|-------------------------------|-----------------|-----------------|------|-------------------------|
| H₂NSO₂⁻                      | 0.154           | 0.057           | 0.421| 0.18                    |
| CH₃NH₂SO₃⁻                    | 0.100           | 0.063           | 0.302| 0.40                    |
| (CH₃)₂NSO₂⁻                   | 0.107           | 0.092           | 0.212| 0.42                    |
| (CH₃CH₂)₂NSO₂⁻                | 0.047           | 0.050           | 0.092| 0.37                    |
| CH₃CH₂CH₂NH₂SO₃⁻              | 0.090           | 0.033           | 0.339| 0.36                    |
| (CH₃CH₂CH₂)₂NSO₂⁻             | 0.046           | 0.087           | —    | 0.06                    |
| CH₃CH₂CH₂CH₂₃>NSO₂⁻-Ch₃        | 0.085           | 0.087           | 0.065| 0.15                    |
| C₆H₅CH₂>NSO₂⁻-Ch₃             | 0.032           | 0.067           | —    | 0.13                    |
| □NSO₂⁻                        | 0.075           | 0.069           | 0.122| 0.23                    |
| ◯NSO₂⁻                        | 0.110           | 0.097           | 0.202| 0.15                    |

Test compounds were given at the dose of 50 mg/kg, i.p. Data are shown as described in the footnote of Table 1.

as to their utility as diuretic antihypertensives by the tests of their natriuretic and antihypertensive activities and acute toxicity (data not shown). S-8666 was chosen as the most favorable candidate.

Uricosuric and diuretic effects of S-8666 in rats: S-8666 at 1 mg/kg, i.p., had no effect on the urine volume and uric acid excretion in oxonate-treated rats, but doses of more than 10 mg/kg, i.p., were apparently diuretic with uricosuric activity also appearing as shown in Table 3. The uricosuric response at 10 mg/kg was due to enhancement of the FEua value, while
Table 3. Uricosuric and diuretic effects of S-8666 in oxonate-treated rats

| Time (min) | Urine volume (ml/kg·min) | UuaV (mg/kg·min) | Fua (mg/kg·min) | FEua | Cin (ml/kg·min) |
|------------|--------------------------|-------------------|-----------------|------|-----------------|
| -20-0      | 0.31±0.03                | 0.107±0.014       | 0.173±0.020     | 0.616±0.023 | 5.83±0.54       |
| S-8666, 10 mg/kg, i.p. (n=8) |            |                   |                 |      |                 |
| 0-20       | 0.82±0.05**              | 0.167±0.011**     | 0.193±0.020**   | 0.912±0.083** | 6.32±0.44       |
| 20-40      | 0.66±0.02**              | 0.143±0.009*      | 0.170±0.016     | 0.874±0.076** | 5.36±0.35       |
| 40-60      | 0.46±0.02**              | 0.136±0.008*      | 0.186±0.017**   | 0.783±0.067 | 5.71±0.35       |
| 60-80      | 0.33±0.01                | 0.143±0.006*      | 0.188±0.023     | 0.841±0.100* | 5.64±0.58       |
| -20-0      | 0.32±0.03                | 0.137±0.016       | 0.218±0.024     | 0.646±0.044 | 6.30±0.71       |
| S-8666, 50 mg/kg, i.p. (n=9) |            |                   |                 |      |                 |
| 0-20       | 1.04±0.06**              | 0.230±0.018**     | 0.240±0.023     | 0.982±0.052** | 5.72±0.42       |
| 20-40      | 0.79±0.04**              | 0.233±0.019**     | 0.245±0.021     | 0.980±0.073** | 4.15±0.39*      |
| 40-60      | 0.62±0.04**              | 0.262±0.019**     | 0.341±0.030**   | 0.815±0.080 | 4.21±0.42*      |
| 60-80      | 0.49±0.03**              | 0.252±0.017**     | 0.412±0.029**   | 0.643±0.066 | 4.33±0.41*      |

Data represent the mean±standard error, and the number of animals is in parentheses. The average increases of UuaV, Fua, FEua and urine volume are 0.040, 0.016, 0.232 and 0.26 at the dose of 10 mg/kg, and 0.107, 0.092, 0.212 and 0.42 at the dose of 50 mg/kg, respectively. *,**, : Significantly different from the level before dosing at P<0.05 and 0.01, respectively.

Table 4. Uricosuric and diuretic effects of S-8666 enantiomers in oxonate-treated rats

| Time (min) | Urine volume (ml/kg·min) | UuaV (mg/kg·min) | Fua (mg/kg·min) | FEua | Cin (ml/kg·min) |
|------------|--------------------------|-------------------|-----------------|------|-----------------|
| -20-0      | 0.32±0.02                | 0.174±0.012       | 0.260±0.018     | 0.674±0.023 | 7.03±0.29       |
| (+)-Enantiomer, 50 mg/kg, i.p. (n=8) |            |                   |                 |      |                 |
| 0-20       | 0.48±0.03**              | 0.210±0.011*      | 0.264±0.013     | 0.800±0.033** | 7.69±0.26       |
| 20-40      | 0.46±0.03**              | 0.194±0.011       | 0.239±0.012     | 0.811±0.027** | 7.30±0.26       |
| 40-60      | 0.35±0.02                | 0.184±0.012       | 0.240±0.015     | 0.785±0.058 | 7.52±0.26       |
| 60-80      | 0.29±0.02                | 0.179±0.011       | 0.230±0.013     | 0.791±0.061 | 7.23±0.32       |
| -20-0      | 0.37±0.03                | 0.173±0.007       | 0.275±0.018     | 0.638±0.032 | 8.24±0.83       |
| (-)-Enantiomer, 50 mg/kg, i.p. (n=8) |            |                   |                 |      |                 |
| 0-20       | 1.26±0.05**              | 0.198±0.009*      | 0.289±0.023     | 0.710±0.052 | 7.51±0.84       |
| 20-40      | 0.85±0.02**              | 0.173±0.017       | 0.287±0.026     | 0.653±0.032 | 4.55±0.37**     |
| 40-60      | 0.66±0.01**              | 0.203±0.013       | 0.407±0.049*    | 0.538±0.052 | 4.75±0.32**     |
| 60-80      | 0.53±0.02**              | 0.220±0.008**     | 0.459±0.026**   | 0.491±0.028** | 4.54±0.22**     |

Data represent the mean±standard error, and the number of animals is in parentheses. *,**, : Significantly different from the level before dosing at P<0.05 and 0.01, respectively.

the 50 mg/kg dose involved a rise of the Fua value. The diuretic effect of S-8666 was a high-ceiling one as in the case of furosemide. Known uricosuric diuretics such as tienilic acid, indacrinone and a 5-carbonyl dihydrobenzofuran carboxylic acid derivative were also diuretic in the animals, but the activities had lower ceiling levels than furosemide (Table 1).

S-8666 is composed of two enantiomers, with the (+)-enantiomer producing a response with an increase in the FEua value in oxonate-treated rats and the (-)-enantiomer being markedly diuretic like furosemide (Table 4).

Next, the uricosuric effect of S-8666 was evaluated using rats without oxonate. As reported previously (15), a high dose of probenecid by intravenous administration increased the FEua value in the rats without urate oxidase inhibitor. S-8666 also elevated the FEua value in a similar experiment as shown in Table 5, while furosemide decreased the FEua value.

Uricosuric and diuretic effects of S-8666 in chimpanzees: Two chimpanzees which
Table 5. Uricosuric and diuretic effects of S-8666 and furosemide in rats without urate oxidase inhibitor

| Time (min) | Urine volume (ml/kg·min) | FEtA | Cin (ml/kg·min) |
|-----------|--------------------------|------|-----------------|
| -20-0     | 0.053±0.009              | 0.36±0.03 | 10.24±1.20     |
| Saline, 2 ml/kg, i.v. (n=7) | 0.077±0.021              | 0.37±0.03 | 11.35±1.06     |
| 20-40     | 0.054±0.010              | 0.40±0.03 | 9.28±0.90      |
| 40-60     | 0.045±0.005              | 0.42±0.02 | 10.90±1.67     |
| -20-0     | 0.060±0.009              | 0.38±0.03 | 11.41±1.22     |
| S-8666 sodium salt, 50 mg/kg, i.v. (n=8) | 0.366±0.079**            | 0.53±0.03* | 6.29±0.79**    |
| 0-20      | 0.272±0.024**            | 0.53±0.03** | 4.29±0.30**    |
| 20-40     | 0.184±0.010**            | 0.50±0.03* | 4.26±0.28**    |
| -20-0     | 0.055±0.006              | 0.46±0.06  | 9.93±0.99      |
| Furosemide, 20 mg/kg, i.v. (n=7) | 0.303±0.104*             | 0.34±0.03  | 5.70±0.99*     |
| 0-20      | 0.242±0.036**            | 0.30±0.02* | 5.54±0.65**    |
| 20-40     | 0.183±0.020**            | 0.27±0.02** | 5.98±0.35**    |

Furosemide was used as a commercial preparation 'LASIX', and S-8666 was prepared as the sodium salt. Drugs were dissolved in saline; then administered intravenously as a bolus from the tail vein. Data represent the mean±standard error, and the number of animals is in parentheses. *,**: Significantly different from the level before dosing at P<0.05 and 0.01, respectively.

Fig. 1. Diuretic and saluretic effects of S-8666 in chimpanzees. A and B are for chimpanzee identification. S-8666 was administered at the dose of 10 mg/kg, p.o., at zero time.

received S-8666, 10 mg/kg, p.o., showed obviously enhanced diuresis and saluresis (Fig. 1), and also uric acid excretion after the dosing (Fig. 2). Although a generalization cannot be made from the data from two or three animals, the uricosuric potency of S-8666 was similar to that of probenecid and less than that of indacrinone, as seen in Fig. 3. On the other hand, indacrinone and furosemide were markedly diuretic in chim-
Fig. 2. Uricosuric effect of S-8666 in chimpanzees. A and B are for chimpanzee identification. S-8666 was administered at the dose of 10 mg/kg, p.o., at zero time.

Fig. 3. Uricosuric effects of probenecid and indacrinone in chimpanzees. A, B and C are for chimpanzee identification. The normal level of FEua was assessed using the values before dosing in all experiments.

panzees (data not shown). The diuretic and saluretic effects of S-8666, 10 mg/kg, p.o., were less than those of 5 mg/kg indacrinone and 5 mg/kg furosemide, p.o. Thus, S-8666 showed uricosuric activity like probenecid with a milder diuresis than those of indacrinone and furosemide in chimpanzees.

Discussion
Various nonhuman mammalian species have been studied to characterize uricosuric drugs (12), but only a few primates have
been useful for such studies. De Rougemont et al. (19) proved that the net flux of uric acid in the renal tubules of rats is also reabsorptive under constant venous infusion of a urate oxidase inhibitor, potassium oxonate, although no evidence was presented on the effects of uricosuric agents in the animals. We also recognized a similar level of FEua in intraperitoneally oxonate-treated rats, in which various known compounds produce uricosuric responses (11). The FEua value in the oxonate-treated rats was obviously higher than those in humans and chimpanzees, and the animals produced two different types of uricosuric responses, that is, an increase of UuaV with a rise of Fua together with elevation of plasma uric acid level and an increase of UuaV that was dependent upon the elevation of FEua. The rise of plasma uric acid might be due to various causes not connected with uricosuric drugs. If this is true, the former response cannot be used to evaluate uricosuric activity on new compounds, even if known uricosuric drugs such as probenecid and indacrinone had such a response. On the contrary, the increase of FEua in oxonate-treated rats should mean that the test compound inhibits the tubular reabsorption of uric acid. However, the response might be modified by the activity of the test compound on inhibiting tubular secretion of uric acid more than in primates, because of the high FEua value before dosing. We, therefore, presume that the tubular transport function on uric acid in oxonate-treated rats differs from those in primates, and thus the uricosuric responses of various compounds in the animals may not always be identical to those in primates. However, as experiments using primates are not always easy to perform, oxonate-treated rats are useful for screening some candidates for uricosuric agents. Probenecid increased the FEua value in oxonate-treated rats most obviously among the known compounds, but S-8666 elevated the FEua value even more than probenecid. The new compound is composed of two enantiomers, which predominantly display either uricosuric or diuretic activity, as found with indacrinone. However, the diuretic effect of S-8666 in oxonate-treated rats was high-ceilinged like that of furosemide, while indacrinone was less diuretic and low-ceilinged. Thus, S-8666 should be classified as a different type of uricosuric diuretic from indacrinone, and also from tienilic acid which has no enantiomer.

The uricosuric activity of S-8666 was also recognized in oxonate-untreated rats in the intravenous administration of its high dose which markedly decreased the glomerular filtration rate. Furosemide decreased the FEua value under a similar diuretic condition. Such effects of S-8666 and furosemide, however, were not observed at a lesser dose without the decrease of glomerular filtration rate and by intraperitoneal dosing (data not shown). Accordingly, although the rats without urate oxidase inhibitor can be used to characterize uricosuric activity as demonstrated in the studies on tienilic acid (13) and indacrinone (14), oxonate-treated rats are better for evaluating the uricosuric activity of new compounds.

The present study using oxonate-treated rats offered a new candidate for uricosuric diuretics. However, the final conclusion on whether the oxonate-treated rats are useful for studying uricosuric drugs should be decided only confirming that the new candidate is also uricosuric in primates such as chimpanzees and humans. Tests using chimpanzees were done for this purpose in TNO. The experiments were performed as a blind test on compounds; then the reliability of the experimental results was judged first by whether a reasonable glomerular filtration rate (inulin clearance: 70–130 ml/min) was maintained during the experiments. Also, the data of the animals which had received S-8666 were also confirmed by measuring the levels of S-8666 and the metabolite in plasma and urine samples. As indicated in Fig. 4, the two chimpanzees which were uricosuric and diuretic by the administration of S-8666, 10 mg/kg, p.o., showed an appreciable concentration of S-8666 in the plasma and urine, and a slight amount of the monomethylsulfamoyl metabolite in the urine. Thus, the two animals were carefully studied, and S-8666 was found to be uri-
cosuric and diuretic also in chimpanzees. However, the uricosuric and diuretic activities were quantitatively less than those of indacrinone which had been already demonstrated to be highly uricosuric and diuretic in chimpanzees (6), in spite of its not displaying these qualities in oxonate-treated rats. Furosemide was also found to be as potently diuretic as indacrinone in chimpanzees, although the activity in oxonate-treated rats was near that of S-8666. Although the causes for the different responses among the tested animals are not clear, these differences suggest that S-8666 should be classified as a different type of diuretic from indacrinone and furosemide. As reported by Tobert et al. (20), the markedly diuretic effect of indacrinone made its uricosuric activity ineffective for preventing the incidence of hyperuricemia. The utility as a practical uricosuric diuretic should be considered not only from the potency of uricosuric and diuretic activities, but also from the well-balanced activities on hyperuricosuria and diuresis to produce an iso- or hypouricemic effect during the medication. Uricosuric responses in chimpanzees have been well investigated by Fanelli et al. (18), who also demonstrated a qualitative difference in the uricosuric characteristics between probenecid and indacrinone (21). Though the details on uricosuric activity of S-8666 have not been examined in chimpanzees as yet, the experimental results using oxonate-treated rats support the hypothesis that the activity of S-8666 is nearer to that of probenecid, rather than that of indacrinone. Thus, the new agent should be further studied to find its utility as a new drug for humans, independent of its lesser uricosuric effect in chimpanzees than that of indacrinone.

In the present report, the uricosuric and diuretic activities were focused on the character of S-8666. We now have information on its toxicity and antihypertensive activity in experimental animals. The new candidate displayed markedly low toxicity in experimental animals, and the antihypertensive activity in the hypertensive rats established with deoxycorticosterone acetate and sodium chloride was two or three times higher than that of tienilic acid. These data will be reported elsewhere. Thus, S-8666 is a new class of uricosuric diuretic that is effective in rats and chimpanzees. Further studies are needed to evaluate the utility as a useful drug in humans.

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