# Sustained Blood Concentration of Salicylic Acid Following Rectal Administration of Salicyluric Acid in Dogs

Junzo NAKAMURA,* Hideo SHIOTA, Hitoshi SASAKI and Juichiro SHIBASAKI

*Faculty of Pharmaceutical Sciences, Nagasaki University, Bunkyo-machi, Nagasaki 852, Japan.* *Received November 28, 1988*

**The blood concentrations of salicyluric acid and salicylic acid following rectal, intravenous and oral administrations of salicyluric acid (5, 10 and 60 mg/kg, respectively: salicylic acid equivalent) were determined in dogs. After rectal administration, a small amount of salicyluric acid was absorbed in intact form. The rest was hydrolyzed to salicylic acid, which was subsequently absorbed. The blood concentration of salicylic acid was maintained at 0.4—0.7 μg/ml from 2 to 12 h. Following intravenous administration of salicyluric acid, salicyluric acid was detected in the blood but was rapidly eliminated. A trace amount of salicylic acid was detected, suggesting that systemic de-conjugation of glycine was involved. After oral administration of salicyluric acid, salicyluric acid was well absorbed. Salicylic acid was detected at low concentration for 12 h. Species difference in the metabolic fate of salicyluric acid in dogs, rabbits, rats and humans reported previously is discussed.**

**Keywords** salicyluric acid; salicylic acid; gut flora; microorganism; presystemic de-conjugation; systemic de-conjugation; glycine conjugate; dog; sustained blood concentration; rectal administration

Drugs will often come into contact with the microorganisms which comprise the normal gastrointestinal flora. It is becoming widely recognized that the intestinal microorganisms may be of great significance in determining the metabolic fate of drugs.[1-5] Despite the well-documented importance of the ability of the intestinal microorganisms to metabolize drugs, little work has been done on the prolongation of the period for which an effective blood concentration of a drug is maintained by utilizing the intestinal microorgahisms to metabolize a prodrug.

In previous reports, we examined the blood concentrations of salicyluric acid and salicylic acid following rectal administration of salicyluric acid in rabbits[6] and rats.[7] A small amount of salicyluric acid was absorbed in intact form. The rest was hydrolyzed to salicylic acid, which was subsequently absorbed. The blood concentration of salicylic acid was maintained at 1.3—1.8 μg/ml from 2 to 12 h in rabbits (5 mg/kg: salicylic acid equivalent) and at 2.6—4.0 μg/ml from 4 to 12 h in rats (10 mg/kg: salicylic acid equivalent). These results suggest the importance of rectal administration of the prodrug, which is converted to the parent drug by intestinal microorganisms, to obtain a sustained blood concentration of the parent drug.

In order to investigate the species difference in the metabolic fate of salicyluric acid, we examined the rectal, intravenous and oral administrations of salicyluric acid in dogs.

## Experimental

**Materials** Salicyluric acid was obtained from Sigma Chemical Co. (St. Louis, U.S.A.). Acetonitrile and *o*-methoxybenzoic acid were purchased from Nakalai Tesque, Inc. (Kyoto, Japan). All other chemicals used in these experiments were of reagent grade.

**Animal Experiments** Male and female mongrel dogs weighing 6—12 kg were used throughout the study. In the case of oral administration of the drug, the animals were starved for about 20 h prior to use for experiments but had free access to water. Salicyluric acid was dissolved in NaOH (equivalent to salicyluric acid). Appropriate amounts of drug solution were administered rectally, intravenously or orally. Animals were anesthetized with sodium pentobarbital (25 mg/kg), given intravenously, *via* a limb vein. Additional sodium pentobarbital was administered as necessary during the experiment to maintain anesthesia.

Rectal Administration of Drug: The drug solution (2 ml/kg) was administered rectally, and the anus was closed with a glass stopper to prevent leakage of the rectal contents during the experiments.

Intravenous Administration of Drug: The drug solution (0.5 ml/kg) was administered intravenously, *via* a limb vein.

Oral Administration of Drug: The drug solution (4 ml/kg) was administered orally by gastric intubation.

Following rectal, intravenous or oral administration of the drug, blood was collected with a heparinized syringe at appropriate time intervals from a limb vein.

**Analytical Method** Salicyluric acid and salicylic acid in blood were analyzed by a high-performance liquid chromatographic method[6] modified from that described by Cham *et al.*[8]

## Results and Discussion

The blood concentrations of salicyluric acid and salicylic acid following rectal administration of salicyluric acid were determined in dogs. As shown in Fig. 1, salicyluric acid reached a peak blood concentration (0.39 μg/ml) at 15 min after the dose and then decreased to below 0.01 μg/ml at 5 h. The blood concentration of salicylic acid was maintained at 0.4—0.7 μg/ml from 2 to 12 h. We demonstrated that the feces of dogs could hydrolyze salicyluric acid (5—37%). Also we reported that the intestinal microorganisms in rabbits[6,9] and rats[7] could biotransform salicyluric acid to salicylic acid *in vivo*. Furthermore, *in vitro* incubation of salicyluric acid with gut contents of rabbits[9] and rats[7] showed that the major location of the hydrolysis was the hind gut. From these results, it is suggested that microbial metabolism of salicyluric acid may be responsible for the prolonged retention of salicylic acid in the blood (Fig. 1).

In order to examine the systemic de-conjugation of glycine, salicyluric acid was administered intravenously.

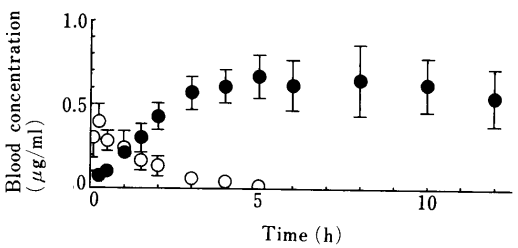


Fig. 1. Blood Concentrations of Salicyluric Acid and Salicylic Acid Following Rectal Administration of Salicyluric Acid

○, salicyluric acid; ●, salicylic acid. Blood concentration and dose (5 mg/kg) of salicyluric acid: salicylic acid equivalent. Each point represents the mean ± S.E. of five experiments.

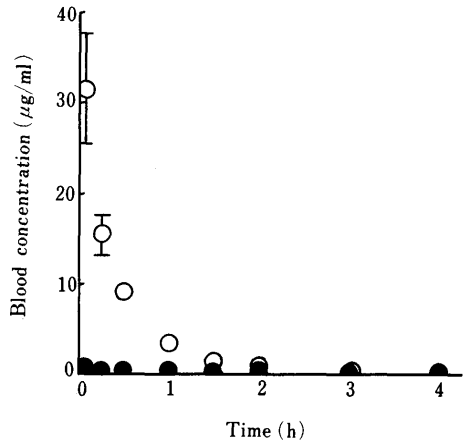


Fig. 2. Blood Concentrations of Salicyluric Acid and Salicylic Acid Following Intravenous Administration of Salicyluric Acid

○, salicyluric acid; ●, salicylic acid. Blood concentration and dose (10 mg/kg) of salicyluric acid: salicylic acid equivalent. Each point represents the mean ± S.E. of three experiments.

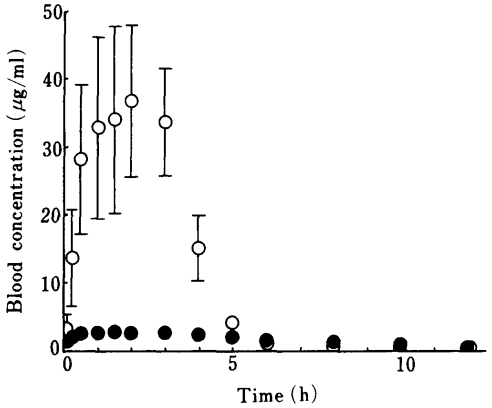


Fig. 3. Blood Concentrations of Salicyluric Acid and Salicylic Acid Following Oral Administration of Salicyluric Acid

○, salicyluric acid; ●, salicylic acid. Blood concentration and dose (60 mg/kg) of salicyluric acid: salicylic acid equivalent. Each point represents the mean ± S.E. of five experiments.

The results are shown in Fig. 2. Salicyluric acid was detected in the blood, but was rapidly eliminated from the blood. A trace amount (<0.67 μg/ml) of salicylic acid was detected up to 4 h, suggesting that systemic de-conjugation of glycine was involved. In a previous report,[9] we examined the fate of salicyluric acid after intravenous administration in rabbits. Only unchanged salicyluric acid was detected in the blood. Boxenbaum *et al.* reported that only salicyluric acid is observed in plasma following intravenous administration of salicyluric acid in healthy subjects.[4] In contrast to the findings in rabbits and humans, a trace amount of salicylic acid was detected for 2 h following intravenous administration of salicyluric acid in rats.[7] Species difference therefore exists in the metabolic fate of salicyluric acid.

Boxenbaum *et al.* demonstrated that salicyluric acid undergoes intestinal microbial metabolism to salicylic acid prior to absorption in healthy subjects.[4] Following the oral administration of salicyluric acid at 3 mg/kg, approximately 80% of the salicyluric acid dose was absorbed intact from the upper gastrointestinal tract; the remaining salicyluric acid apparently passed down to the large intestine and was subjected to microbial hydrolysis to salicylic acid. Results on the blood concentrations of salicyluric acid and salicylic acid following oral administration of salicyluric acid in rabbits[9] and rats[7] were reported previously. In rabbits, salicyluric acid reached a peak blood concentration about 1 h after the dose and then decreased. Salicylic acid was detected at 2 h after the dose and reached the maximum level at 5 h. The concentration of salicylic acid was sustained for several hours, after which it slowly declined. In rats, salicyluric acid was rapidly absorbed after the dose. Salicylic acid was detected at low concentration for 12 h.

In Fig. 3, the blood concentrations of salicyluric acid and salicylic acid following oral administration of salicyluric acid in dogs are shown. Salicyluric acid was well absorbed. In contrast to the findings in humans[4] and rabbits,[9] salicylic acid was detected at low concentration (<2.67 μg/ml) for 12 h. Probably, salicyluric acid was absorbed intact from the upper gastrointestinal tract, and therefore, did not pass down to the large intestine.

In conclusion, a sustained blood concentration of salicylic acid following rectal administration of salicyluric acid was observed in rabbits, rats and dogs. However, species difference in the metabolic fate of salicyluric acid following oral and intravenous administrations of salicyluric acid was recognized.

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