INVESTIGATION OF ACETYLSALICYLIC ACID BIOAVAILABILITY AND ITS EFFECT ON PROSTAGLANDIN-$F_{2\alpha}$ IN DOGS

by

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INTRODUCTION

Salicylic acid was first obtained from leaves and barks of the willow tree as the glycoside, salicin. Its acetic acid ester, acetyl salicylic acid (aspirin), was first synthesized by Von Gerhardt in 1853. The name, aspirin, was derived from the terms "acetyl" and "spirsaure", the latter referring to the genus Spiraea, one of the botanical sources of salicylic acid[1].

Aspirin is prepared by direct acetylation of salicylic acid with acetic anhydride using a small amount of sulfuric acid as catalyst[2]. Aspirin is generally available as a powder and was introduced into medicinal practice in Germany before the turn of the century. The tablet form was introduced into the United States in 1915. It has since become the most widely used analgesic, antipyretic, and anti-inflammatory drug in the world[3]. Recent experimental and clinical studies[1] suggest aspirin may have antithrombotic properties, preventing cerebro vascular thromboembolism and myocardial infarction, and therefore reducing the incidence of stroke and heart attack. The therapeutic effects of aspirin are apparently due to its inhibitory effect on the synthesis of prostaglandins which act as mediators of pains and fevers[4].

Because aspirin is so readily available, it is also easily abused. Aspirin is the most common cause of drug poisoning in young children[5]. Aspirin is more toxic to the gastric mucosa of man and animals than its parent compound, salicylic acid[6,7]. Aspirin ingestion causes peptic ulcer[8]; doses of 1-3 g/day induces occult gastro intestinal bleeding in about 70% of normal subjects[1]. Aspirin intoxication results in respiratory alkalosis and metabolic

acidosis[9], hyperglycemia or hypoglycemia[5,9], and not infrequent death.

The objective of this study was to investigate: (a) the in vitro and in vivo bioavailability of several popular commercial sources of aspirin; and (b) the effect of aspirin on endofeneous prostaglandin-$F_{2\alpha}$ of dogs.

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THE IN VITRO AND IN VIVO AVAILABILITY OF COMMERCIAL ASPIRIN IN DOGS

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SUMMARY

Bioavailability of eleven commercial brands of aspirin was assessed in vitro using simulated gastric juice and also in vivo in dogs. Gastric juice and salicylate concentrations were measured by fluorescence spectrophotometer. Excedrin was dissolved fastest of all the brands of aspirin, followed by Ascriptin; the slowest was Excedrin PM. In dogs dosed orally with Excedrin or Ascriptin, total plasma salicylate peaked about 2.5 hrs after dosing with Excedrin and 3 hrs post dosing with Ascriptin. About 96% of the salicylate was bound to plasma proteins. The rate at which Excedrin leaves the plasma is different from that of Ascriptin. Plasma salicylate concentration from Excedrin droped to an average of 12 mg/ml in 6 hrs while Ascriptin peaked and remained virtually at that level for more than 12 hrs.

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The salicylates, which include salicylic acid, its esters, and other derivatives, have been used for many years to treat fevers and rheumatism. They were first obtained from willow trees which contain salicin -- a glycoside of salicylic acid. One of the most widely used derivatives of salicylic acid is acetyl salicylic acid (aspirin). Aspirin is prepared directly by the acetylation of salicylic acid with acetic anhydride using a small amount of sulfuric acid as catalyst[1].

Aspirin is used as an analgesic, anti-rheumatic, antipyretic and anti-inflammatory. Recent experimental and clinical studies[2] suggest aspirin may have antithrombotic properties, preventing cerebrovascular thromboembolism and myocardial infarction, and therefore reducing the incidence of stroke and heart attack.

Aspirin is given mainly by oral administration. It is rapidly absorbed for the most part from the stomach and upper small intestine; only a small amount is absorbed in the lower intestinal tract[1]. Aspirin is a moderately strong acid (with a pKa of 3.5), so its gastric absorption is pH dependent[3]. Aspirin is absorbed in the unionised form and is lipid soluble. Its rate of fecal excretion is therefore lowered in the acidic environment of the stomach[4,5]. The rate of absorption of aspirin depends on the rate of dissolution. The dissolution rate of aspirin was found to be independent of the crystal growth rate, salicylic acid content (up to 3.9% w/w), habit anf particle size[6].

Aspirin circulates in the blood mostly bound to plasma protein with a little bound to erythrocytes. Aspirin is bound more

strongly to human serum albumin (HSA) than is salicylic acid[7]. The peak level of aspirin is reached within two hours, but varies with the dose of aspirin given, and species of animal[8].

The purpose of this study was to examine the dissolution rate of 11 commercial sources of aspirin in artificial gastric juice and then to determine the bioavailability in dogs of the two most soluble brands. No previous study of commercial aspirin bioavailability in dogs has been published.

MATERIALS AND METHODS

We placed intact tablets of eleven different commercial aspirin preparations in artificial gastric juice. The commercial brands of aspirin used were Arthritis Pain Formula 7.5 grs; Arthritis Strength Bufferin 7.5 grs; Ascriptin 5 grs; Bayer Aspirin 5 grs; Bufferin 5 grs; Emperin 3.5 grs; Excedrin 3 grs; Excedrin P.M. 3 grs; Parke Davis Aspirin 5 grs; Purity Aspirin 5 grs; and Squibb Aspirin 5 grs. The equivalent of 5 grs (325 mg) of each brand was used for the in vitro study. The gastric juice were incubated in a shaker water bath at 37 C. Six samples of the gastric juice were drawn at 0 time and at 30 minutes intervals until the concentrations stabilized, and the salicylate content was measured in a fluorescence spectrophotometer[a,5,6]. The fluorescence emission and excitation spectra were measured at wavelengths of 468 and 390 nm, respectively.

The two most soluble brands of aspirin (Ascriptin and Excedrin) were used for the in vivo tests with two female shepherd dogs. One weighed 7.3 kg, and the other 20.5 kg. The dogs were off feed for 24 hrs before dosing and throughout the duration of each experiment. The dogs were given a single oral dose of 30 mg of salicylate/kg body weight. This dose was based on the recommendation of 25-35 mg salicylate/kg[8], and was repeated two weeks later with the other brand. Heparinized blood was collected at 0 time and at 30 minutes intervals for 12 hrs after each administration. Blood samples were centrifuged immediately at 27,000g for 20 minutes and the plasma was separated and

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[a]Perkin-Elmer Fluorescence Spectrophotometer model MPF 44A

frozen for analysis[9,10].

Salicylate binding to plasma proteins was determined in all the plasma samples collected[11,12]. Stirred ultrafiltration cells with a volume capacity of 3 ml[b] and pellican membranes with a nominal molecular weight limit of 25,000[b] were used to separate free and bound salicylate. Two and a half milliliters (2.5 ml) of plasma was filtered at 37 C by the pressure of 40 psi of medical grade nitrogen; 0.1 ml of the filtrate was collected. The salicylate concentration of the filtrate and the parent solution before and after filtration was determined. The percentage of bound salicylate was calculated after correcting for non-specific losses by dividing the salicylate concentrates after filtering by the total salicylate concentration in the plasma before filtration. The measured fluorescences were converted to units of ug/ml by a standard curve. The standard curve was linear up to a concentration of 2.0 ug/ml.

Preparation of gastric juice

The artificial gastric juice was prepared by dissolving 2 g sodium chloride (NaCl) and 3.2 g of pepsin powder[c] separately in glass distilled water and then mixing the resulting solution together in a 1 l volumetric flask. Concentrated hydrochloric acid (7.0 ml) was added before bringing the final mixture to 1 l final volume with glass distilled water[13].

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[b]Cat #PSED 01310, Millipore Corp, Bedford, Mass.

[c]Sigma Chemical Company, St. Louis, Mo.

RESULTS

The dissolution and hydrolysis of the various brands of aspirin to salicylic and acetic acids in artificial gastric juice is shown in Figures 1 and 2. The concentration of salicylate increased gradually with time in all samples until a constant level was reached. Excedrin produced the highest concentration of salicylic acid in the solution at the fastest rate. It reached a peak concentration of 16.4 mg/250ml of solution in 2 hrs. Excedrin was followed by Ascriptin and Arthritis Strength Bufferin, which each produced 12.3 mg salicylate/250 ml. Excedrin P.M. gave the least concentration (5.8 mg/250 ml) with a peak concentration about 7 hrs. The remaining seven brands reached their peaks in 6-10 hrs and their concentrations in solution varied from 7.8 to 9.8 mg salicylate/250 ml solution.

Excedrin and Ascriptin were used for the in vivo study in dogs. The Excedrin gave the same pattern of bioavailability as observed in the in vitro study. It peaked in the blood in an average of 2.5 hrs, only 30 minutes later than the artificial gastric juice (Figure 3). Ascriptin peaked between 2 and 4 hrs in the two dogs, and much earlier than in the in vitro study (Figure 4).

The percentages of salicylate found protein bound to each dog's plasma at each sampling time are summarised in Tables 1 and 2. Ascriptin was bound more to dog plasma protein (92.3% in dog A and 97.5% in dog B) than Excedrin during peak concentration of salicylate in the blood. Excedrin-dosed dogs A and B bound just 89.3 and 56.3% to their plasma protein, respectively, during peak blood salicylate concentration.

DISCUSSION

The rate of availability of salicylic acidin vitro and in vivo depends on the rates of disintegration, dissolution and hydrolysis of acetyl salicylic acid (aspirin) to salicylic and acetic acids. Acetyl salicylic acid is hydrolysed by aspirin esterase in blood plasma within 20 to 30 minutes, but the disintegration rate of an uncoated tablet depends on the compression pressure, binders, lubricants, and the amount of disintegrators added[14]. Rates of dissolution of commercial aspirin depend on thermodynamic activity rather than on crystal growth rate, salicylic acid content (up to 3.9% w/w), habit or particle size[6]. Differences in the concentration of salicylic acid released from each of the 11 brands of aspirin could be due to thermodynamic differences (affecting the rates of dissolution and disintegration) among the formulations[15]. Other causes of variation in salicylic acid concentration among the formulations could relate to the relative content of an immunogenic impurity, acetyl salicylic anhydride, in the tablets[16]. Acetyl salicylic anhydride which forms N-salicylol in solution, might reduce the amount of salicylate in solution.

In the in vivo study, Excedrin, which peaked between 2-3 hrs, was biologically available faster than Ascriptin (Figures 3 and 4). The rate at which the salicylate from Excedrin leaves the plasma of dog A was faster than in dog B (see Figure 3). Ascriptin which peaked between 2-4 hrs, maintained relatively high salicylic acid concentration in the plasma of both dogs for 24 hrs.

Our results agree with earlier findings that peak plasma concentration of salicylic acid occur between 2-4 hrs; after which the concentration gradually drops until it is almost zero at 24 hrs[8,17,18].

The data on the percentages of salicylic acid bound to protein suggest that as the plasma salicylate concentration increased, the percent bound to protein also increased until all sites for salicylic acid on the protein are occupied or have reached equilibrium. Then the percent bound remained virtually the same until the plasma concentration of the free salicylic acid started decreasing due to metabolism and excretion. The salicylate bound to plasma protein is gradually released to replace that portion being metabolised. At low concentration of plasma salicylate (dog A, Table 1 and 2), the percent salicylic acid bound to plasma protein was low and may have been subject to sampling error. On the average, about 96% of the salicylates was bound to the plasma protein of the two dogs. This agrees with earlier findings that salicylates are tightly bound to plasma protein, particularly to albumin[7,19].

Slight variations in the time of peak salicylate blood levels in the two dogs may have been due to variation in particle size of the tablets used and to individual animal variation. This may have resulted from different pH environment of gastric absorbing sites[3] and different body mass[1]. The varying plasma salicylate concentrations 4 hrs after dosing also showed that the rates of metabolism and kidney excretion of the two brands varied between the two dogs.

Figure 1.

Concentrations of salicylate from six different commercial preparations of aspirin in simulated gastric juice.

THIS BOOK CONTAINS NUMEROUS PAGES WITH DIAGRAMS THAT ARE CROOKED COMPARED TO THE REST OF THE INFORMATION ON THE PAGE.

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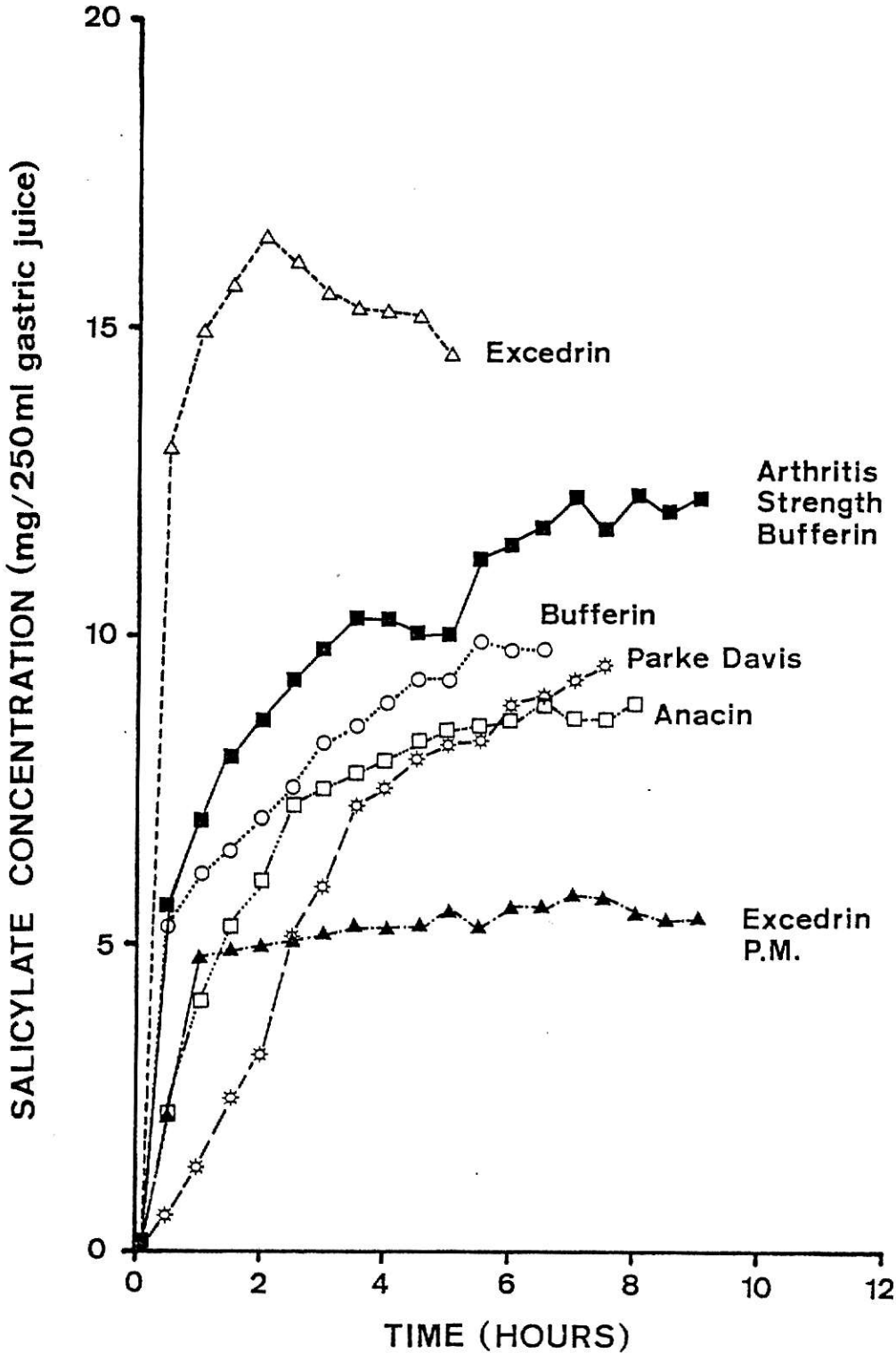
SALICYLATE CONCENTRATION (mg/250ml gastric juice)
20
15
10
5
0
0
2
4
6
8
10
12
TIME (HOURS)
Excedrin
Arthritis Strength Bufferin
Bufferin
Parke Davis
Anacin
Excedrin P.M.

Figure 2.

Concentrations of salicylate from five different commercial preparations of aspirin in simulated gastric juice.

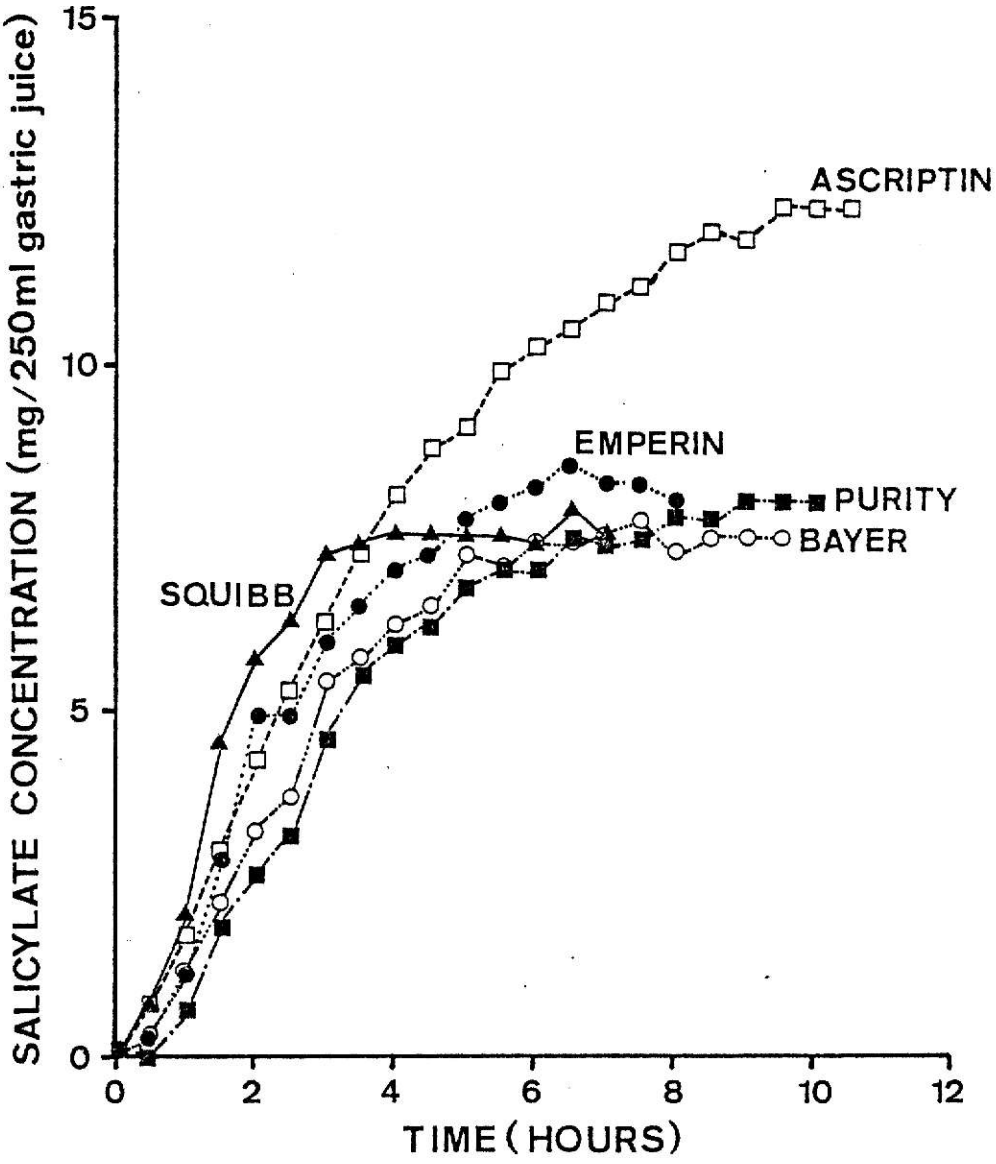
SALICYLATE CONCENTRATION (mg/250ml gastric juice)
15
10
5
0
0
2
4
6
8
10
12
TIME (HOURS)
ASCRIPTIN
EMPERIN
PURITY
BAYER
SQUIBB

Figure 3.

Salicylate concentrations in blood plasma of dog A (- - -) and dog B (———) after single doses of 30 mg/kg of Excedrin.

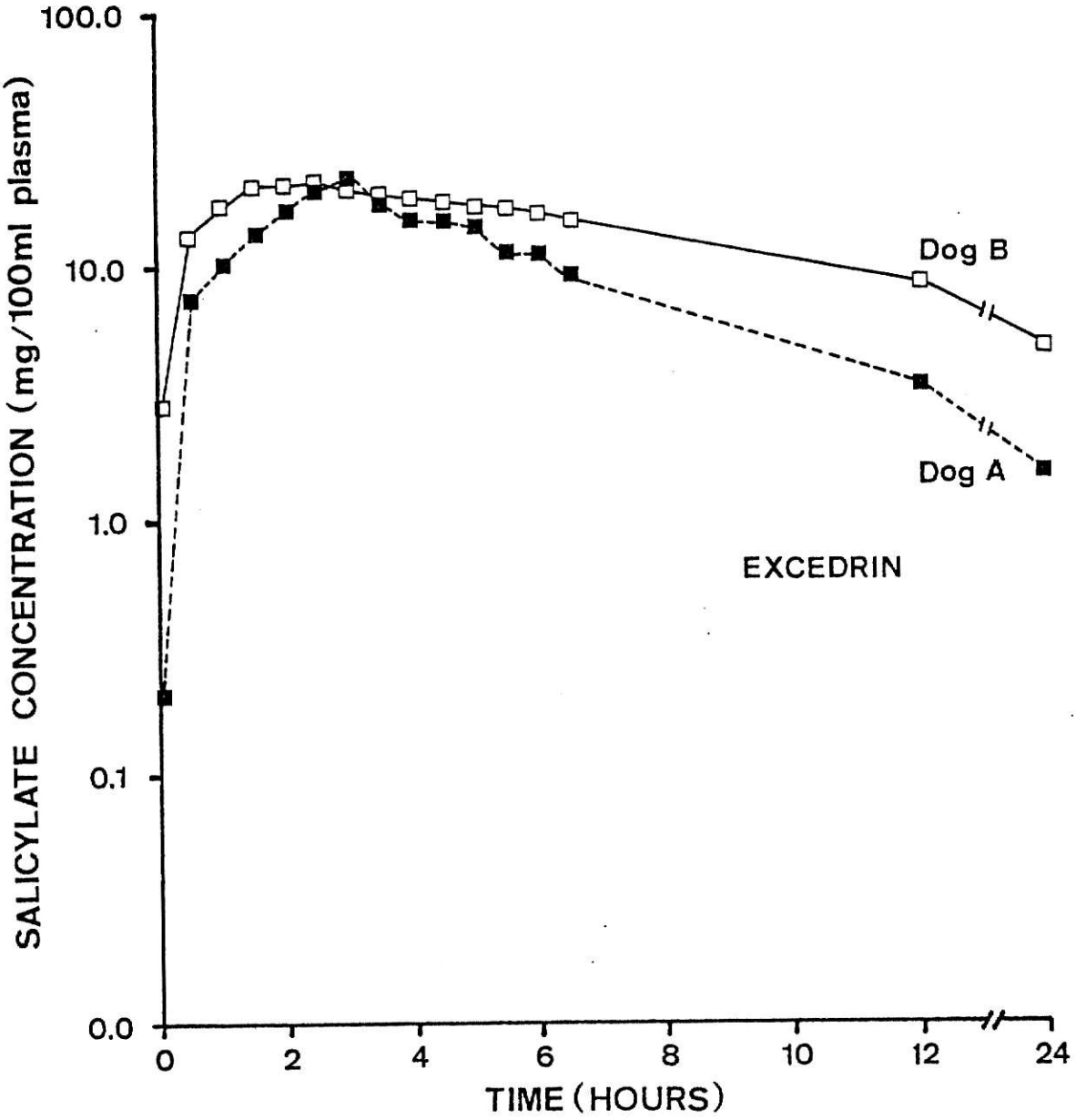
100.0
10.0
1.0
0.1
0.0
SALICYLATE CONCENTRATION (mg/100ml plasma)
0
2
4
6
8
10
12
24
TIME (HOURS)
Dog B
Dog A
EXCEDRIN

Figure 4.

Salicylate concentrations in blood plasma of dog A (- - -) and dog B (———) after single doses of 30 mg/kg of Ascriptin.

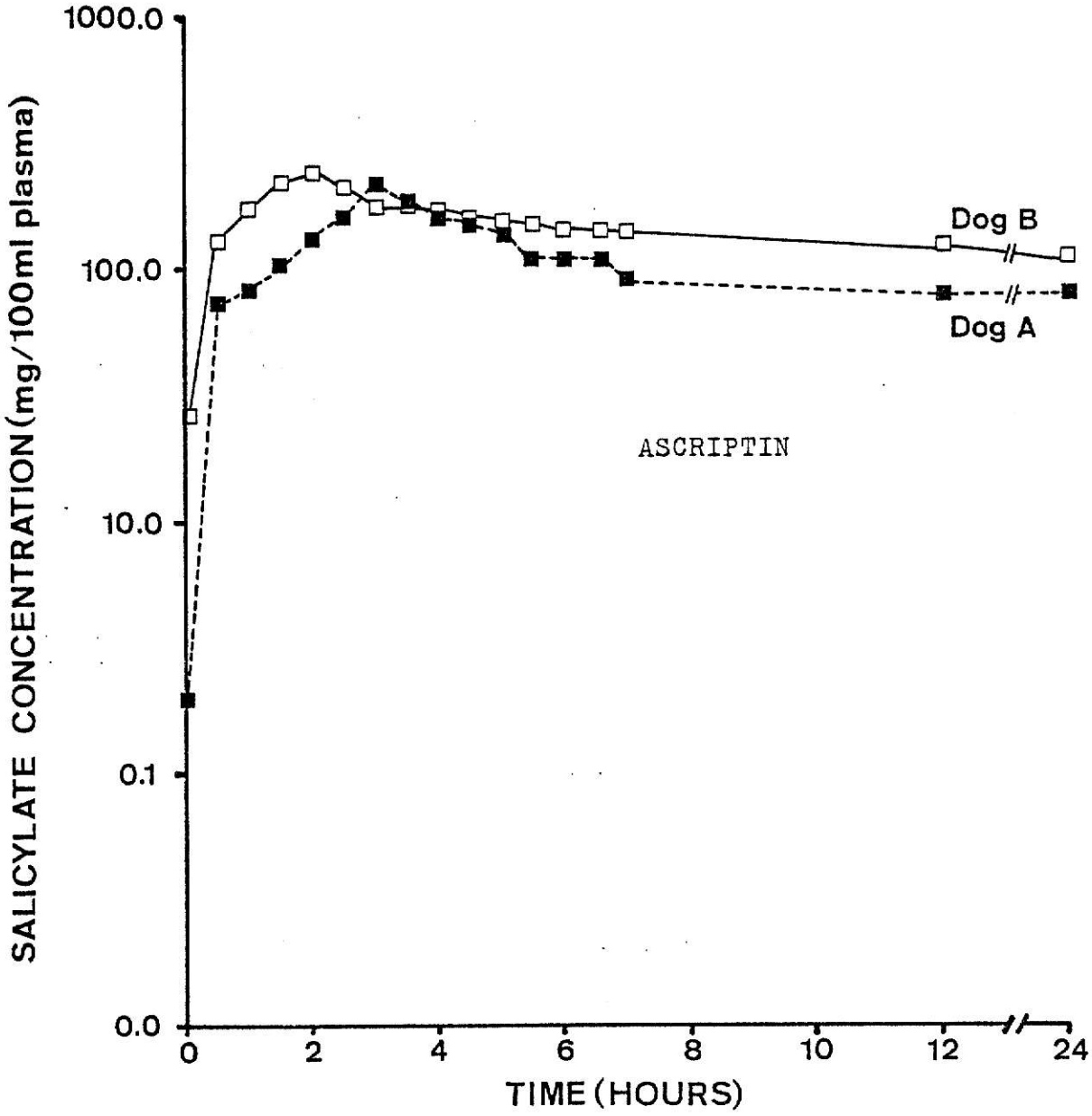
1000.0
100.0
10.0
0.1
0.0
SALICYLATE CONCENTRATION (mg/100ml plasma)
Dog B
Dog A
ASCRIPTIN
0
2
4
6
8
10
12
24
TIME (HOURS)

Table 1. Total salicylate concentration and percent protein bound in blood plasma of two dogs after a single 30 mg salicylic acid /kg of body weight dose of Ascriptin

Time (hrs)	Dog A		Dog B	
	Total conc. (mg/100ml)	Protein bound (%)	Total conc. (mg/100ml)	Protein bound (%)
0.0	7.5	93.3	2.1	91.6
0.5	9.4	93.6	6.9	91.6
1.0	9.5	93.0	12.3	78.3
1.5	12.5	92.0	12.8	74.8
2.0	10.7	93.5	19.2	97.5
2.5	11.3	88.5	17.1	62.6
3.0	9.4	85.1	15.5	77.9
3.5	16.8	92.3	12.9	76.8
4.0	13.6	95.6	11.0	67.3
4.5	10.7	95.3	9.2	70.8
5.0	11.7	94.0	7.7	76.0
5.5	11.3	92.9	11.6	68.2
6.0	10.0	90.0	11.3	77.6
6.5	11.5	91.3	15.8	74.6
7.0	9.5	94.7	8.3	75.7
7.5	10.8	92.6	19.2	84.1
8.0	9.6	93.8	8.0	79.6
8.5	8.1	92.6	8.0	71.7
9.0	10.7	93.5	5.0	77.6
9.5	9.1	93.4	6.9	81.3
10.0	10.9	96.3	3.5	75.0

Table 1 cont'd. Total salicylate concentration and percent protein bound in plasma of two dogs after a single 30 mg salicylic acid/kg body weight dose of Ascriptin

	Dog A		Dog B	
Time (hrs)	Total conc. (mg/100ml)	Protein bound (%)	Total conc. (mg/100ml)	Protein bound (%)
10.5	11.6	94.8	10.5	74.1
11.0	7.9	94.9	9.8	76.4
11.5	9.8	96.9	4.0	75.6
12.0	8.5	94.1	8.6	83.5
24.0	7.0	94.3	6.0	78.3

Table 2. Total salicylate concentration and percent protein bound in blood plasma of two dogs after a single 30 mg salicylic acid/kg of body weight dose of Excedrin

Time	Dog A		Dog B	
	Total conc.	Protein bound	Total conc.	Protein bound
(hrs)	(mg/100ml)	(%)	(mg/100ml)	(%)
0.0	0.2	50.0	2.8	92.9
0.5	7.2	83.3	13.2	98.5
1.0	10.4	83.9	17.5	88.6
1.5	13.6	91.9	20.6	86.5
2.0	16.6	86.0	20.8	86.5
2.5	20.0	90.1	21.4	88.8
3.0	22.4	89.3	18.8	85.3
3.5	18.0	95.8	18.5	89.2
4.0	15.8	88.5	18.1	85.6
4.5	15.4	93.8	17.4	89.3
5.0	14.4	94.9	16.9	86.4
5.5	11.2	92.3	16.4	91.7
6.0	11.2	91.2	15.1	89.4
6.5	9.0	93.8	15.1	89.4
12.0	3.4	64.7	8.0	95.8
24.0	1.5	60.0	4.7	95.3

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THE EFFECT OF ASPIRIN ON ENDOGENEOUS PROSTAGLANDIN-$F_{2\alpha}$ IN DOG PLASMA

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SUMMARY

Aspirin relieves pains and fevers by influencing the level of endogeneous prostaglandin-$F_{2\alpha}$ ($PGF_{2\alpha}$). We determined the effect of two brands of aspirin on the concentration of plasma $PGF_{2\alpha}$ in two dogs over a 24-hr period using radio-immunoassay. Both brands of aspirin, in single doses of 30 mg/kg, reduced $PGF_{2\alpha}$ in the plasma. Lowest concentration of $PGF_{2\alpha}$ occurred 2 and 3 hrs after oral administration of Excedrin and Ascriptin, respectively. The percent free $PGF_{2\alpha}$ increased linearly up to a maximum of 85% free $PGF_{2\alpha}$. The percent free $PGF_{2\alpha}$ decreased as total $PGF_{2\alpha}$ concentrations decreased.

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The therapeutic properties of aspirin are due to its inhibitory effects on prostaglandin synthetase. The precursor of prostaglandin, arachidonic acid, is produced when tissue lipases or cell membrane phospholipases are activated. Aspirin inhibits the activity of prostaglandin synthetase in vitro and reduces biosynthesis of prostaglandin in a variety of systems[1]. Prostaglandins act as mediators of pain, fever, anaphylaxis, platelet aggregation and inflammation in the body. The activation of tissue lipases and cell membrane phospholipases results from cellular injury or cell toxins released from lysosomes[2]. A correlation has been reported between the potencies of anti-inflammatory drugs as inhibitors of prostaglandin synthetase in vitro and their peak concentrations in plasma after therapeutic dosage[3]. Prostaglandins are produced by many organs and are released spontaneously from numerous sites[4]. Aspirin significantly reduced potentiation of paw edema after concurrent administration of carrageenan and arachidonic acid[5].

There are different types of prostaglandins, including PGE, PGA and $PGF_{2\alpha}$. PGE and $PGF_{2\alpha}$ receptors represent two different macromolecular entities with a relatively small size difference between them[6]. Administration of $PGF_{2\alpha}$ raised blood levels of luteinizing hormone and testosterone[7], and increased secretion of estradiol[8], but it also inhibited milk ejection by a central block on oxytocin release[9]. There is individual age variation among sheep in the metabolism of $PGF_{2\alpha}$: maternal cotyledons are more active than fetal cotyledons[10]. Inhibition of prostaglandin synthesis by aspirin is due to acetylation of an active site of

prostaglandin synthetase. That site is the seryl residue at the $-NH_2$ terminus of the enzyme[11].

The purpose of this study was to determine the effect of two popular brands of aspirin on the $PGF_{2\alpha}$ content of dog plasma.