Effects of deracoxib and aspirin on serum concentrations of thyroxine, 3,5,3′-triiodothyronine, free thyroxine, and thyroid-stimulating hormone in healthy dogs

David L. Panciera, DVM, MS; Kent R. Refsal, DVM, PhD; Kathleen A. Sennello, DVM, MS; Daniel L. Ward, PhD

Objective—To evaluate the effects of deracoxib and aspirin on serum concentrations of thyroxine (T_4), 3,5,3′-triiodothyronine (T_3), free thyroxine (fT_4), and thyroid-stimulating hormone (TSH) in healthy dogs.

Animals—24 dogs.

Procedure—Dogs were allocated to 1 of 3 groups of 8 dogs each. Dogs received the vehicle used for deracoxib tablets (PO, q 8 h; placebo), aspirin (23 to 25 mg/kg, PO, q 8 h), or deracoxib (1.25 to 1.8 mg/kg, PO, q 24 h) and placebo (PO, q 8 h) for 28 days. Measurement of serum concentrations of T_4, T_3, fT_4, and TSH were performed 7 days before treatment (day –7), on days 14 and 28 of treatment, and 14 days after treatment was discontinued. Plasma total protein, albumin, and globulin concentrations were measured on days –7 and 28.

Results—Mean serum T_4, fT_4, and T_3 concentrations decreased significantly from baseline on days 14 and 28 of treatment in dogs receiving aspirin, compared with those receiving placebo. Mean plasma total protein, albumin, and globulin concentrations on day 28 decreased significantly in dogs receiving aspirin, compared with those receiving placebo. Fourteen days after administration of aspirin was stopped, differences in hormone concentrations were no longer significant. Differences in serum TSH or the free fraction of T_4 were not detected at any time. No significant difference in any of the analytes was detected at any time in dogs treated with deracoxib.

Conclusions and Clinical Relevance—Aspirin had substantial suppressive effects on thyroid hormone concentrations in dogs. Treatment with high dosages of aspirin, but not deracoxib, should be discontinued prior to evaluation of thyroid function. (*Am J Vet Res* 2006;67:599–603)

Nonsteroidal anti-inflammatory drugs have been found to influence results of thyroid function tests in dogs and other species.[1–8,a] As in humans, results of studies[3–5,8,a] in dogs indicate that some NSAIDs affect thyroid function test results, whereas others do not.

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From the Department of Small Animal Clinical Sciences (Panciera, Sennello) and Office of Graduate Studies and Research (Ward), Virginia-Maryland Regional College of Veterinary Medicine, Blacksburg, VA 24061-0442; and the Endocrine Section Diagnostic Center for Population and Animal Health, College of Veterinary Medicine, Michigan State University, East Lansing, MI 48824-1314 (Refsal).
Address correspondence to Dr. Panciera.

Abbreviations

NSAID	Nonsteroidal anti-inflammatory drug
T_4	Thyroxine
T_3	3,5,3′ -Triiodothyronine
TSH	Thyroid-stimulating hormone
fT_4	Free T_4

Salicylate and salsalate consistently decrease serum T_4, T_3, and TSH concentrations, whereas fT_4 is unchanged.[4,9,10] Inhibition of protein binding, cellular transport, and deiodination of thyroid hormones are likely mechanisms responsible for altered thyroid function test results.[11–14]

Deracoxib is an NSAID that preferentially inhibits cyclooxygenase-2, compared with cyclooxygenase-1. As a member of the coxib class of anti-inflammatory drugs, deracoxib is expected to be highly bound to plasma proteins, although the extent of protein binding is not known.[15] Competition for binding sites on plasma proteins between the highly protein-bound thyroid hormones and deracoxib could result in a decrease in serum T_4 and T_3 concentrations.

The purpose of the study reported here was to evaluate the effects of deracoxib and aspirin on serum concentrations of T_4, T_3, fT_4, and TSH in healthy dogs. We hypothesized that administration of aspirin or deracoxib would decrease serum T_4 and T_3 concentrations without affecting results of other thyroid function tests.

Materials and Methods

Dogs—Twenty-four random source adult dogs (14 sexually intact females and 10 sexually intact males) were included in the study. Mean ± SD body weight of dogs was 19.5 ± 4.1 kg. Dogs were healthy as determined by physical examination findings and results of CBC, serum biochemical analyses, and fecal examination. Dogs were housed in indoor runs with a 12-hour light-dark cycle and were acclimated to their environment for 4 weeks prior to the study. All dogs were euthyroid as determined by serum T_4, fT_4, and TSH concentrations; all values were within reference ranges. The study was approved by the Virginia Tech Animal Care and Use Committee.

Experimental protocol—Dogs were randomly allocated to 1 of 3 treatment groups consisting of 8 dogs each. The vehicle used for deracoxib tablets was administered (PO, q 8 h) to 1 group of dogs (placebo group). Dogs in the aspirin group received aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h). Dogs in the deracoxib group received deracoxib[b] (1.25 to 1.81 mg/kg [mean, 1.60 mg/kg], PO, q 24 h) and placebo (PO, twice daily at 8 h intervals). All treatments were administered for 28 days.

Table 1—Mean (95% confidence intervals) values for results of thyroid function tests in healthy dogs 7 days before treatment (-7) and after receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 12 h), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h) and placebo (PO, q 12 h) for 28 days and 14 days (day 42) after treatment.

	T_3 (nmol/L)			
Group	**–7**	**14**	**28**	**42**
Placebo	1.49 (1.28–1.7)	1.43 (1.23–1.65)	1.68 (1.34–2.01)	1.61 (1.45–1.78)
Aspirin	1.50 (1.29–1.71)	1.06* (0.85–1.27)	1.18* (0.54–1.51)	1.81 (1.65–1.98)
Deracoxib	1.43 (1.21–1.64)	1.51 (1.3–1.72)	1.61 (1.28–1.95)	1.69 (1.52–1.85)
	T_4 (nmol/L)			
	–7	**14**	**28**	**42**
Placebo	29 (22–36)	29 (24–34)	28 (21–35)	31 (23–39)
Aspirin	30 (23–37)	14* (9–19)	13* (5–20)	36 (28–44)
Deracoxib	25 (18–32)	24 (19–29)	24 (16–31)	25 (17–32)
	fT_4 (pmol/L)			
	–7	**14**	**28**	**42**
Placebo	17 (12–21)	16 (13–19)	15 (11–19)	15 (11–18)
Aspirin	18 (13–23)	9* (7–12)	7* (3–11)	14 (11–18)
Deracoxib	14 (10–19)	14 (11–17)	12 (8–16)	11 (8–15)
	TSH (ng/mL)			
	–7	**14**	**28**	**42**
Placebo	0.16 (0.06–0.25)	0.17 (0.08–0.25)	0.20 (0.13–0.27)	0.18 (0.08–0.28)
Aspirin	0.27 (0.17–0.36)	0.15 (0.06–0.23)	0.26 (0.19–0.33)	0.3 (0.2–0.4)
Deracoxib	0.17 (0.07–0.26)	0.14 (0.05–0.22)	0.22 (0.16–0.29)	0.2 (0.10–0.29)
	fT_4/T_4 (%)			
	–7	**14**	**28**	**42**
Placebo	0.056 (0.047–0.066)	0.054 (0.046–0.063)	0.053 (0.047–0.059)	0.047 (0.042–0.051)
Aspirin	0.062 (0.053–0.072)	0.069 (0.061–0.078)	0.057 (0.051–0.063)	0.040 (0.036–0.045)
Deracoxib	0.056 (0.047–0.066)	0.056 (0.048–0.065)	0.049 (0.043–0.055)	0.045 (0.041–0.049)

*Significantly ($P < 0.05$) different from placebo group.

Blood samples for measurement of serum concentrations of T_4, T_3, fT_4, and TSH were obtained 7 days before treatment (day –7), on days 14 and 28 of treatment, and 14 days after treatment was discontinued (day 42). In addition, plasma total protein, globulin, and albumin concentrations were measured on days –7 and 28 of treatment. For dogs in the aspirin group, serum salicylate concentrations were measured on day 14, 6 to 8 hours after administration of treatment. Food was withheld from dogs for 12 hours prior to each sampling time. Because the study was performed in conjunction with another study evaluating the gastric effects of deracoxib, dogs were anesthetized for endoscopy on days –7, 6, 14, and 28. All blood samples were obtained between 7 and 8 AM prior to administration of anesthetic or sedative drugs. Dogs were observed 3 times daily for vomiting and diarrhea. Dogs were fed once daily, food intake was assessed daily, and body weight was recorded weekly.

Serum T_4 and TSH concentrations were measured by use of a commercially available radioimmunoassay[c] and a immunoradiometric assay,[d] respectively, which had been validated for use with canine serum.[3] Serum concentrations of T_3 were measured with an in-house charcoal-separation radioimmunoassay; procedures and performance in canine serum have been reported.[16] Serum concentrations of fT_4 were measured by use of a commercial equilibrium dialysis radioimmunoassay[e] previously validated for use in canine serum. The free fraction of T_4 was calculated by dividing the serum fT_4 concentration by the serum T_4 concentration. Plasma proteins were measured by the Virginia-Maryland Regional College of Veterinary Medicine Veterinary Teaching Hospital's clinical pathology laboratory by use of standard techniques.[f] Serum concentrations of

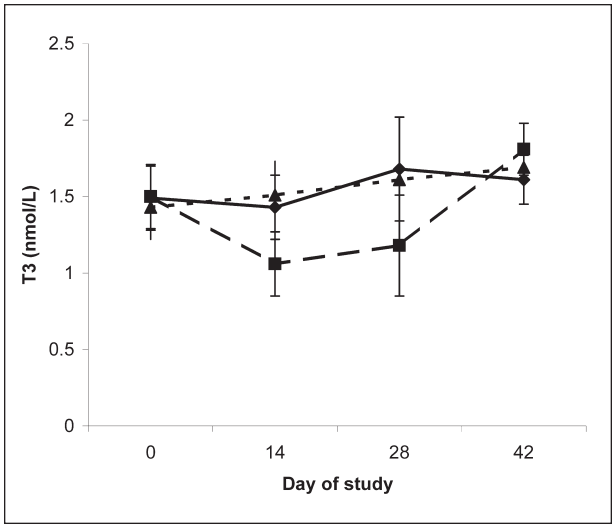

Figure 1—Serum T_3 concentrations in healthy dogs receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo; diamonds), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h; squares), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h and placebo [PO, q 12 h]; triangles) for 28 days. Day 42 represents results obtained 14 days after treatment was discontinued.

salicylate were measured by use of a modification of the Trinder colorimetric assay.[g]

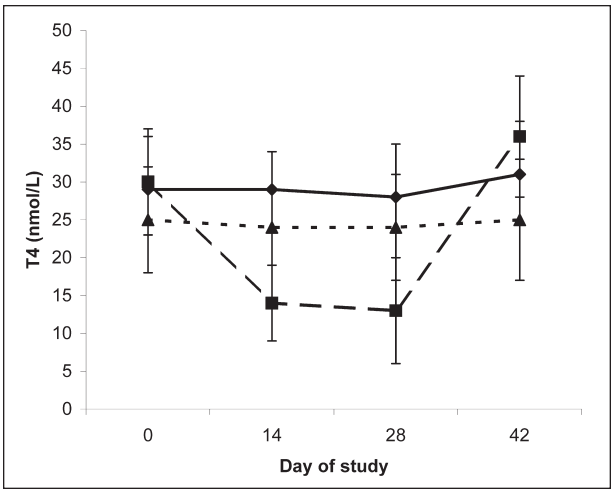

Figure 2—Serum T_4 concentrations in healthy dogs receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo; diamonds), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h; squares), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h) and placebo (PO, q 12 h); triangles) for 28 days. Day 42 represents results obtained 14 days after treatment was discontinued.

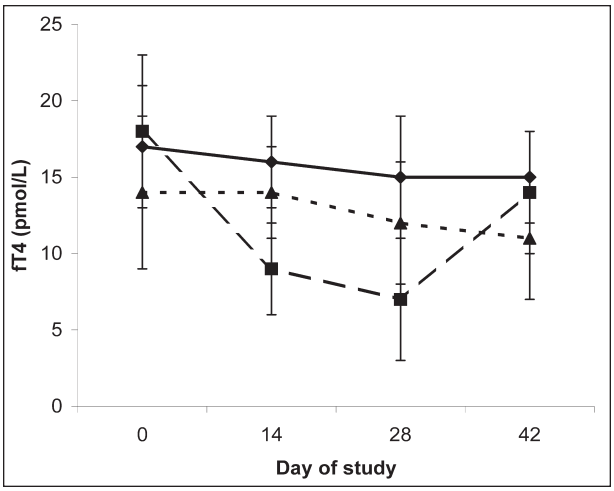

Figure 3—Serum fT_4 concentrations in healthy dogs 7 days before treatment and (–7) after receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo; diamonds), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h; squares), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h and placebo [PO, q 12 h]; triangles) for 28 days. Day 42 represents results obtained 14 days after treatment was discontinued.

Statistical analysis—Data are expressed as mean and 95% confidence intervals. Repeated-measures ANOVA was performed for each analyte by use of a computer software program.[h] Effects of each treatment were further evaluated using the Bonferroni correction to compare results during treatment with those before and after treatment; a value of $P < 0.05$ was considered significant.

Results

Mean serum concentrations of T_4, fT_4, and T_3 decreased significantly from baseline on days 14 and 28 of treatment in dogs receiving aspirin, compared with those receiving placebo (**Table 1**; **Figures 1–3**). Serum T_4 concentration was less than the reference range (15 to 67 nmol/L) in 4 and 5 dogs treated with aspirin at 14 and 28 days, respectively, whereas no dogs in the placebo or deracoxib group had low serum T_4 concentrations. In the aspirin group, 2 and 5 dogs on days 14 and 28, respectively, had serum fT_4 concentrations less than reference range (6 to 42 pmol/L), whereas all values in dogs in the placebo and deracoxib groups were within reference range. Serum T_3 concentrations were below the reference range (1.0 to 2.5 nmol/L) in 1 dog in the placebo group on day –7 and in 1 dog each in the aspirin group on day 14 and 28 of treatment. There was no significant difference in the free fraction of T_4 (fT_4/T_4) during treatment with aspirin or deracoxib, compared with placebo (**Figure 4**). Fourteen days after treatment was discontinued, serum T_4, T_3, and fT_4 concentrations returned to baseline values in dogs receiving aspirin. Plasma total protein, albumin, and globulin concentrations decreased significantly on day 28 of treatment in dogs receiving aspirin (**Table 2**). Significant changes in serum TSH concentration were not detected at any time during the study (**Figure 5**). Serum TSH concentration was within the reference range (0 to 0.68 ng/mL) in all dogs at all sample times. There were no significant changes in any hormone or protein concentration in dogs treated with deracoxib, compared with placebo. The mean ± SD serum salicylate concentration was 16.3 ± 3.4 mg/dL. During treatment, vomiting occurred on at least 1 day in 1 and 6 dogs in the control and aspirin groups, respectively. Vomiting occurred on more than 2 days during aspirin treatment in only 2 dogs, both vomiting on 13 of the 28 days of treatment. Anorexia was not detected in any dog in any treatment group, and body weights did not change significantly among groups.

Table 2—Mean (95% confidence intervals) plasma concentrations of total protein, albumin, and globulins in healthy dogs receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h) and placebo (PO, q 12 h) for 28 days.

	Total protein (g/dL)		Albumin (g/dL)		Globulins (g/dL)	
Group	–7	28	–7	28	–7	28
Placebo	6.6 (6.0–7.3)	6.7 (6.1–7.4)	3.4 (3.2–3.6)	3.5 (3.3–3.7)	3.2 (2.7–3.8)	3.3 (2.8–3.8)
Aspirin	6.8 (6.2–7.5)	6.2* (5.6–6.9)	3.2 (3.0–3.4)	3.1* (3.0–3.3)	3.6 (3.1–4.1)	3.1* (2.6–3.6)
Deracoxib	6.8 (6.1–7.5)	6.6 (6.0–7.2)	3.3 (3.1–3.5)	3.4 (3.2–3.6)	3.5 (3.0–4.0)	3.2 (2.7–3.7)

*Significantly ($P < 0.05$) different from placebo group.

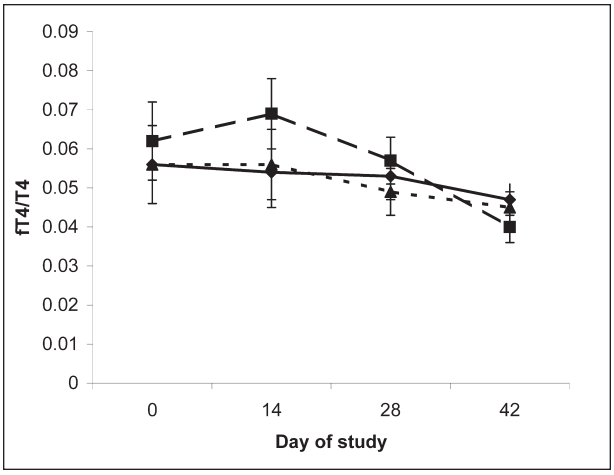

Figure 4—Percentage free fraction of T_4 (fT_4/T_4) in healthy dogs receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo; diamonds), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h; squares), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h) and placebo (PO, q 12 h; triangles) for 28 days. Day 42 represents results obtained 14 days after treatment was discontinued.

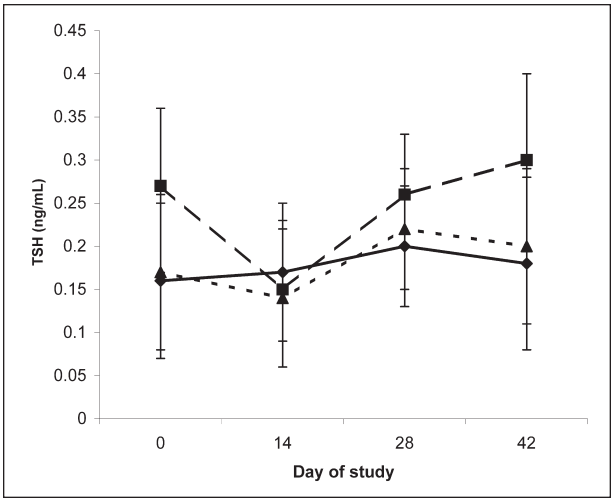

Figure 5—Serum TSH concentrations in healthy dogs receiving vehicle used for deracoxib tablets (PO, q 8 h; placebo; diamonds), aspirin (23 to 25 mg/kg [mean, 24 mg/kg], PO, q 8 h; squares), or deracoxib (1.25 to 1.81 mg/kg [mean, 1.6 mg/kg], PO, q 24 h) and placebo (PO, q 12 h; triangles) for 28 days. Day 42 represents results obtained 14 days after treatment was discontinued.

Discussion

On the basis of results of our study, aspirin decreases serum concentrations of T_4, T_3, and fT_4 without affecting serum TSH concentrations. These results differ from those of another study[4] on the effect of aspirin on results of thyroid function tests in dogs in which T_4 and T_3 decreased, but fT_4 was not affected. The difference between results of these studies may have been attributable to the high dosage (75 mg/kg per day vs 50 mg/kg per day) and long duration (28 vs 7 days) of treatment used in our study. Although the dosage of aspirin used in our study was higher than that often used clinically, it was within the range stated for clinical use for its analgesic and anti-inflammatory effects.[17] The proposed mechanism by which aspirin affects serum thyroid hormone concentrations is primarily by displacing them from binding sites on plasma proteins.[9–11] The expected result of impaired protein binding is an increase in the fraction of T_4 that is free, measured in our study and other studies as percentage fT_4/T_4. The effect of aspirin on protein binding was reported by Daminet et al.[4] In that study, the increase in the free fraction of T_4 increased 1 and 7 days after initiating aspirin treatment. Because we did not evaluate results of thyroid function tests until day 14 of treatment, any displacement of thyroid hormones during the early treatment period would not have been detected in our study. However, if this were the sole mechanism for hormonal changes detected in the study reported here, serum fT_4 concentrations should not have been affected and the free fraction of T_4 should have increased. Therefore, it appears that other mechanisms play some role in aspirin-induced reductions in plasma thyroid hormones.

Phenylbutazone administration to horses results in altered thyroid function[6,7] similar to that detected after administration of aspirin in our study.[6,7] In addition to the effect of competition for binding sites on plasma proteins, salicylates and other NSAIDs may impair 5′-deiodination and inhibit binding of thyroid hormones to receptors in the plasma membrane, cytosol, or nucleus.[9,12–14,18] Decreased thyroid responsiveness to TSH, decreased bioactivity of TSH, impaired thyroid hormone synthesis, and increased clearance of thyroid hormones from the circulation are possible reasons for the decrease in fT_4 detected in dogs treated with high dosages of aspirin. Biliary excretion of T_4 is increased acutely in rats administered salicylate, but whether this is merely a reflection of increased fT_4 secondary to displacement from plasma proteins is not known.[14] Because no alteration in TSH was detected despite considerable decreases in serum T_4 and fT_4 concentrations, reduced sensitivity of pituitary gland thyrotropes or impaired secretion of TSH may have occurred. Alternatively, the low sensitivity of the assay used for detection of TSH could have accounted for the lack of change in serum TSH concentration in response to decreases in serum T_4 and fT_4 concentrations.[19]

A significant decrease in all plasma proteins measured was detected in dogs in the aspirin group, possibly secondary to gastrointestinal tract loss. Although decreased concentration of plasma transport proteins could account for some of the decrease in serum T_4 and T_3 concentrations, the reduction was minor, compared with the decrease in thyroid hormones. In addition, the serum concentration of fT_4 would not be affected by the decrease in proteins. In a previous study[8] in which etodolac administration decreased plasma proteins, serum concentrations of T_4, fT_4, and T_3 were not affected. Therefore, mechanisms other than a mild decrease in plasma proteins are likely to be responsible for decreases in thyroid hormones detected in our study.

Decreases in serum thyroid hormone concentrations in dogs receiving aspirin may have resulted from gastrointestinal tract effects of the drug, which may

have induced nonthyroidal illness. However, moderate to severe illness is necessary to cause consistent decreases in serum concentrations of both T_4 and fT_4.[20,21] Because dogs treated with aspirin in our study did not have anorexia or weight loss, it is unlikely that decreases in thyroid hormones resulted from nonthyroidal illness.

The effects of aspirin administration on thyroid function tests are transient, with concentrations returning to pretreatment values within 14 days of stopping treatment. Results of a study[4] evaluating a lower dose of aspirin (50 mg/kg per day) found that serum T_4 concentrations returned to pretreatment values within 7 days of discontinuing treatment. Therefore, treatment with aspirin should be discontinued 7 to 14 days prior to evaluating thyroid function.

Deracoxib administered at a mean dosage of 1.6 mg/kg, PO, every 24 hours did not affect results of thyroid function tests. A similar lack of effect of NSAID administration on thyroid function in dogs has been reported with etodolac, ketoprofen, meloxicam, and carprofen.[3,4,8] However, results of other studies[5,a] indicate a slight decrease in serum T_4 and TSH concentrations in dogs treated with carprofen for 5 weeks or a slight decrease in serum T_4 concentration and an increase in serum TSH concentration after treatment with etodolac for 14 to 19 days. In humans, administration of NSAIDs results in a similar variable effect, depending on the specific drug administered.[1,2,22] Salicylates consistently decrease serum concentrations of T_4 and T_3, whereas other NSAIDs have less marked and consistent effects.

Results indicated that aspirin, but not deracoxib, altered results of thyroid function tests in dogs. Serum T_4 and fT_4 concentrations were frequently less than the reference ranges in dogs treated with high dosages of aspirin. Hypothyroidism could be misdiagnosed in these dogs

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