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Renal Actions of Oxyphenbutazone

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Abstract □ Oxyphenbutazone decreased the renal excretion of sodium and water in anesthetized dogs. As these excretions decreased, the drug also produced a decrease in renal blood flow and in the glomerular filtration rate. Blood pressure increased slightly. These changes are consistent with an inhibition of renal prostaglandin synthesis and could explain why oxyphenbutazone is reported to produce weight gain and edema when used clinically.

Keyphrases □ Oxyphenbutazone—effect on renal sodium and water excretion, renal blood flow, glomerular filtration rate, blood pressure, prostaglandin synthesis ■ Anti-inflammatory agents—oxyphenbutazone, renal effects ■ Kidney—effect of oxyphenbutazone

Oxyphenbutazone[1] is an analog of phenylbutazone[2] and, like the latter compound, is employed as an anti-inflammatory agent. Both agents produce edema and weight gain as side effects (1). A possible renal mechanism has been suggested for phenylbutazone since this agent markedly reduced renal blood flow and decreased the glomerular filtration rate at the time that urinary volume and sodium excretion were reduced (2). In this study, the effect of oxyphenbutazone on several renal functions was determined.

EXPERIMENTAL

Mongrel dogs of either sex, 13–16 kg, were anesthetized with pentobarbital sodium (30 mg/kg iv), and the trachea was intubated to maintain an open airway. Mean arterial blood pressure was monitored with a pressure transducer[3] *via* a femoral artery catheter. A femoral vein was catheterized for administration of a 0.9% NaCl infusion (4 ml/min) during preparation of the animals and throughout the experiments. Inulin was added to the infusion to estimate the glomerular filtration rate.

The left kidney was exposed *via* a retroperitoneal flank incision, and a flow probe was placed around the renal artery and connected to a square wave electromagnetic flowmeter[4] to monitor renal blood flow. Blood pressure and renal blood flow were recorded[5] continuously. Urine was collected at timed intervals by a cannula placed in the left ureter. Arterial blood samples were obtained from the femoral artery catheter. After stabilization of the preparation, control urine collections (10-min periods) and blood samples at the midpoint of alternate urine collection periods were obtained. Oxyphenbutazone was administered intravenously over 3 min, and urine collections were continued for several periods.

[1] Tanderil, Ciba-Geigy Corp., Summit, N.J.
[2] Butazolidin, Ciba-Geigy Corp., Summit, N.J.
[3] Model P23AA, Statham, Hato Rey, Puerto Rico.
[4] Carolina Medical Electronics, King, N.C.
[5] Dynograph (type R), Beckman Instruments, Fullerton, Calif.

Table I—Effect of Oxyphenbutazone (5 mg/kg iv) on Renal Function

Parameter	Control Period[a]	Oxyphenbutazone Period[b]	Difference
Blood pressure, mm Hg	115	128	+13 ± 5[c]
Renal blood flow, ml/min	262	220	−42 ± 5[c]
Urine volume, ml/min	1.1	0.4	−0.7 ± 0.2[c]
Glomerular filtration rate, ml/min	33	23	−10 ± 4[c]
Sodium excretion, μEq/min	136	77	−59 ± 1.9[c]

[a] Values are from the clearance period preceding oxyphenbutazone administration. [b] Values are from the clearance period 10–20 min after oxyphenbutazone administration. [c] Significant difference ($p < 0.05$); Student paired t test; $n = 7$.

Urinary and plasma inulin levels were determined by a reported method (3). Urinary sodium concentrations were measured with a flame photometer[6]. Data were analyzed using the Student paired t test (4); a $p < 0.05$ was the significance criterion.

RESULTS AND DISCUSSION

The effect of oxyphenbutazone on renal blood flow and blood pressure is shown in Fig. 1. Following oxyphenbutazone administration, 5 mg/kg iv, blood pressure increased slightly while renal blood flow decreased gradually. These effects, as well as effects on other renal functions, are summarized in Table I. At 20 min after oxyphenbutazone administration, blood pressure was increased while renal blood flow, the glomerular filtration rate, urinary volume, and sodium excretion were decreased. All changes were statistically significant. These changes also were present at 60 min.

Since similar changes were reported with phenylbutazone (2) and since both agents are similar structurally, it seems reasonable that these two agents act by the same mechanism. Both oxyphenbutazone and phenylbutazone have been reported to be inhibitors of prostaglandin syn-

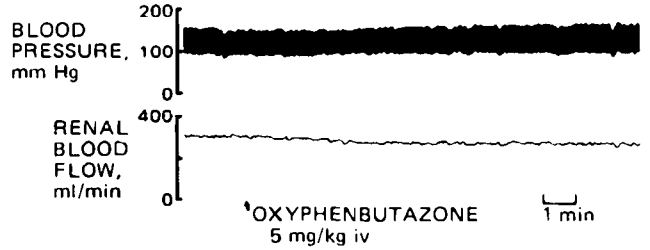

Figure 1—*Effect of oxyphenbutazone, 5 mg/kg iv, on blood pressure and renal blood flow.*

[6] Instrumentation Laboratories, Lexington, Mass.

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thesis (5). The latter compound also has been shown to decrease prostaglandin E synthesis at the time that it decreases renal blood flow and the glomerular filtration rate (2). Since a prostaglandin synthesis reduction can reduce renal blood flow by removing prostaglandin E, an endogenous vasodilator (6), the reduction in renal blood flow by oxyphenbutazone could be due to such a mechanism.

A reduction in sodium and water excretion can occur as a result of such a hemodynamic change. Early and Schrier (7) showed that a decrease in renal blood flow can alter the distribution of blood flow or physical factors to enhance sodium and water reabsorption.

A decrease in the glomerular filtration rate would also be expected to reduce sodium and water excretion. Whether the decrease in the glomerular filtration rate is a consequence of the inhibition of prostaglandin synthesis, as is the decrease in renal blood flow and the increase in blood pressure (8), or a separate action is not clear. Previous studies with prostaglandin synthesis inhibitors showed variable effects on the glomerular filtration rate (2, 8).

Thus, these experiments demonstrate that oxyphenbutazone reduces renal blood flow and the glomerular filtration rate during the time that it decreases sodium and water excretion. A decrease in renal blood flow and the glomerular filtration rate could cause or contribute to the decrease in water and sodium excretion produced by oxyphenbutazone.

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Effects of Pyridoxine Hydrochloride (Vitamin B_6) on Chlorpromazine-Induced Serum Prolactin Rise in Male Rats

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Abstract □ To investigate if vitamin B_6 inhibits prolactin release and to compare this effect to that of bromocriptine, a known suppressor of prolactin release, a study was conducted in male rats. Animals were pretreated with pyridoxine hydrochloride, pyridoxal hydrochloride, saline, or bromocriptine 30 min prior to receiving varying doses of chlorpromazine hydrochloride. Blood samples were obtained 90 min later and analyzed for serum prolactin by a double-antibody radioimmunoassay. Another study involved pyridoxal hydrochloride and saline pretreatments 30 min prior to doses of chlorpromazine hydrochloride. Blood samples collected 60 min later were also analyzed for serum prolactin. Pyridoxine hydrochloride significantly suppressed the chlorpromazine-induced prolactin rise ($p < 0.01$). However, the suppression was significantly less than that produced by bromocriptine ($p < 0.01$). Pyridoxal hydrochloride, another natural form of vitamin B_6, failed to suppress prolactin under the conditions of both studies. This investigation may lend support to the concept that pyridoxine hydrochloride partially inhibits prolactin by a mechanism not involving dopamine.

Keyphrases □ Pyridoxine—effect on chlorpromazine-induced serum prolactin rise, rats □ Chlorpromazine—induction of serum prolactin rise, effect of pyridoxine, rats □ Prolactin—chlorpromazine-induced rise, effect of pyridoxine, rats

In 1973, Foukas (1) suggested that oral pyridoxine suppressed lactation within 7 days in 95% of postpartum women. This finding was supported by Marcus (2) but not by other investigators (3–6). Pyridoxine reduction of serum prolactin levels in the galactorrhea–amenorrhea syndrome has been reported (7, 8). Other studies showed that pyridoxine has no effect on elevated plasma prolactin levels due to various causes, including two subjects with chlorpromazine-induced hyperprolactinemia and galactorrhea (9, 10). However, Reiter and Root (11) observed a significant decrease in plasma prolactin in children following intravenous pyridoxine.

An *in vitro* investigation indicated that pyridoxine possessed some inhibitory effect on prolactin release from whole rat pituitary culture (12). Harris *et al.* (13) demonstrated that pyridoxine suppressed the plasma prolactin rise associated with proestrus and thyrotropin-releasing hormone stimulation in the rat. More recently, Husami *et al.* (14) presented evidence that high pyridoxine doses affected neither prolactin secretion nor lactation in humans, monkeys, and rats, including animals stimulated with thyrotropin-releasing hormone.

The present study was undertaken to determine the effects of pyridoxine and pyridoxal, two natural forms of vitamin B_6, on chlorpromazine-induced prolactin secretion in rats (15) and to compare the inhibition by these vitamins with the effects of bromocriptine, a known potent inhibitor of prolactin release (16).

EXPERIMENTAL

Two hundred and forty male Sprague–Dawley adult rats[1], 245–280 g, were divided into four equal groups. The rats were housed for 21 days prior to the study in a temperature-controlled (23 ± 3°) artificially illuminated (lights on from 7:00 am to 7:00 pm daily) room. The animals were given food[2] and water *ad libitum*. Each group was intraperitoneally in-

[1] Taconic Farms, Germantown, N.Y.
[2] Purina Lab Chow, Ralston Purina Co., St. Louis, Mo.

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