Effects of indomethacin in rabbit renovascular hypertension

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Summary

1. Indomethacin inhibits prostaglandin synthesis and interferes with renin release; these effects were studied in rabbit renovascular hypertension.

2. Ten intravenous injections (3 mg day$^{-1}$ kg$^{-1}$ after two initial doses of 9 mg/kg) of indomethacin were given daily to ten normal rabbits, ten rabbits with two-kidney Goldblatt hypertension (2KH), and ten rabbits with one-kidney Goldblatt hypertension (1KH). Twelve appropriate control rabbits received diluent phosphate buffer without indomethacin. Plasma renin activity and plasma prostaglandin E$_2$ were measured by radioimmunoassay.

3. In the normal group, indomethacin significantly decreased plasma prostaglandin E$_2$ (1.15 to 0.2 ng/ml, SEM 0.2; $P < 0.01$) and plasma renin activity (20 to 3 ng h$^{-1}$ ml$^{-1}$, SEM 1, $P < 0.01$). Plasma creatinine increased slightly but the mean blood pressure was not significantly changed by indomethacin.

4. Six of ten rabbits with 2KH showed results similar to those in the normal rabbits. In four of ten rabbits in which development of 2KH was accompanied by increments in plasma renin activity (18 to 31.5 ng h$^{-1}$ ml$^{-1}$, SEM 3 and 4 respectively; $P < 0.01$) and plasma prostaglandin E$_2$ (1.2 to 3.4 ng/ml, SEM 0.2 and 0.4 respectively; $P < 0.05$), treatment with indomethacin produced renal failure (plasma creatinine increasing to 7.6 mg/100 ml), oliguria, malignant hypertension (mean blood pressure, 168 mmHg, SEM 7-7) and death within 5 days.

5. In 1KH, indomethacin decreased plasma renin activity and plasma prostaglandin E$_2$, but caused increased mean blood pressure (102 to 121 mmHg, SEM 4 and 6 respectively; $P < 0.01$) and decreased renal function (plasma creatinine 0.9 ± 0.04 to 3.5 ± 1 mg/100 ml, SEM 0.04 and 1 respectively; $P < 0.01$).

6. Aggravation of hypertension was conditioned by pre-existing levels of renal function and, to a lesser extent, by plasma renin activities.

7. These results suggest that prostaglandins exert a protective effect on renal function in renovascular hypertension.

Key words: hypertension, indomethacin, plasma renin activity, prostaglandin E$_2$, renal function.

Introduction

Inhibition of prostaglandin synthesis with indomethacin has been shown to induce hypertension in normal rabbits (Colina-Chourio, McGiff & Nasjelett, 1975) and to produce further elevation of blood pressure in renovascular hypertensive rats (Pugsley, Beilin & Peto, 1975). These observations were of interest because previous studies in our laboratory had shown that when indomethacin inhibits prostaglandin synthesis it also blocks release of renin (Romero, Strong, Torres, Ott & Knox, 1973). The present study was designed to test the effects of indomethacin on normal rabbits and rabbits with two-kidney and one-kidney renal artery-clip hypertension and to monitor plasma renin activity, prostaglandins, creatinine, mean blood pressure and, at appropriate times, effective renal blood flow and glomerular filtration rate.

Methods

Animal protocol

The study was conducted on forty-two New Zealand rabbits weighing 2.5–3 kg. After a control period of 6 days, the left renal artery of twenty-eight of these rabbits was partially constricted with a silver clip.
The remaining fourteen rabbits served as a control group. At the end of the second week the right kidney was removed from fourteen of the twenty-eight rabbits with a clipped renal artery.

After 35 days, indomethacin in phosphate buffer was given intravenously (9 mg/kg for two doses followed by ten daily doses of 3 mg/kg) to ten of each of the three groups of rabbits. The remaining twelve rabbits (four in each group) were treated with the phosphate buffer not containing indomethacin.

**Measurements**

Blood samples were obtained from the central artery of the ear for determination of plasma renin activity (Haber, Koerner, Page, Kliman & Purnode, 1969), plasma prostaglandin E₂ (Zusman, Caldwell, Speroff & Behrman, 1972) and plasma creatinine during the 6 days control period and every week to the end of the pre-indomethacin-treatment period of 35 days. Similar measurements were made 9 h after the first injection of the indomethacin or diluent buffer and then every other day during the indomethacin-treatment period.

Indirect systolic blood pressure measurements were made daily by application of a Grant-Rothschild capsule to the central artery of the ear (Wilson, Romero, Strong, Lee & Schryver, 1975). Blood pressure was measured directly by Grass polygraph and DB Statham 23 pressure transducer via a 21 gauge needle in the central artery of the ear during the 9 h after the first injections of indomethacin or diluent buffer.

Renal clearances of p-aminohippurate and inulin were performed on the sixth day of the control period, on day 35 of the experiment, and on day 5 of indomethacin treatment and remained depressed thereafter.

Statistics

The significance of changes occurring between the groups or within one group at different times was analysed with the unpaired and paired t-tests (Dixon & Massey, 1969). In cases with unequal variance between two groups, treatment differences were analysed by the rank sum test (Dixon & Massey, 1969). All values are reported in the text as mean ± SEM.

**Results**

**Normal rabbits**

Before treatment with indomethacin there were no significant changes in any of the measured variables. Indomethacin decreased plasma prostaglandin E₂ from 1.15 ± 0.2 to 0.2 ± 0.2 ng/ml \((P < 0.01)\) within 9 h and it remained low for 8 days, recovering to 50\% of the control value on day 10. Simultaneously, plasma renin activity fell from 20 ± 1 to 3 ± 1 ng h⁻¹ ml⁻¹ \((P < 0.01)\) within 9 h after indomethacin treatment and remained depressed thereafter.

The renal blood flow decreased from 40.4 ± 3 ml/min (control) to 36.7 ± 2.4 ml/min on day 5 of indomethacin treatment and 33.9 ± 3.3 ml/min on day 10. Glomerular filtration rate decreased in parallel, with values of 8.2 ± 0.3, 8.1 ± 0.5, and 5.1 ± 0.5 ml/min respectively. Plasma creatinine increased from 1.0 ± 0.1 mg/100 ml (control) to 1.3 ± 0.1 mg/100 ml (day 10 of indomethacin treatment).

The mean blood pressure was not changed by indomethacin.

**2KH⁺ Rabbits**

Responses to indomethacin depended on the level of renal function and, to a lesser extent, on the plasma renin activity.

In six rabbits in which the development of 2KH (mean blood pressure increasing from 74 ± 1 to 110 ± 2 mmHg; \(P < 0.05\)) occurred without significant changes in plasma renin activity \((20 ± 3 to 23 ± 4 ng h⁻¹ ml⁻¹)\), plasma prostaglandin E₂ \((from 1.0 ± 0.3 to 2.2 ± 0.6 ng/ml)\), plasma creatinine \((from 1.0 ± 0.1 to 0.9 ± 0.1 mg/100 ml)\), renal blood flow \((39.6 ± 2.4 to 40.0 ± 1.8 ml/min)\), and glomerular filtration rate \((7.8 ± 0.7 to 8.5 ± 0.5 ml/min)\), treatment with indomethacin was followed by a series of changes resembling those seen in normal rabbits: prostaglandin E₂ decreased to 0.1 ± 0.6 ng/ml \((P < 0.01)\) and plasma renin activity decreased \(2.0 ± 0.5 ng h⁻¹ ml⁻¹ (P < 0.01)\), whereas other measured variables were not changed significantly.

On the other hand, in four rabbits in which development of 2KH was accompanied by increased plasma renin activity \((18 ± 3 to 31.5 ± 4 ng h⁻¹ ml⁻¹; \(P < 0.01)\), increased plasma prostaglandin E₂ \((1.2 ± 0.2 to 3.4 ± 0.4 ng/ml; P < 0.05)\), decreased renal blood flow \((40.4 ± 1.4 to 26.8 ± 1.8 ml/min; P < 0.01)\),

\(^{(1)}\) Abbreviations: 2KH, 1KH, two-kidney and one-kidney Goldblatt hypertension respectively.
and decreased glomerular filtration rate (8.5 ± 0.4 to 5.4 ± 1.0; \( P < 0.05 \)), treatment with indomethacin produced renal failure (plasma creatinine increasing to a mean value of 7.6 mg/100 ml), oliguria and malignant hypertension (mean blood pressure increasing to 168 ± 7.7 mmHg). None of these four rabbits survived longer than 5 days after treatment with indomethacin.

**1KH rabbits**

In ten rabbits the development of 1KH (mean blood pressure increasing from 74 ± 2 to 102 ± 4 mmHg; \( P < 0.01 \)) was not accompanied by any significant change in plasma renin activity, prostaglandin E\(_2\) or creatinine. However, renal blood flow (38.5 ± 2.5 to 27.3 ± 1.4 ml/min; \( P < 0.01 \)) and glomerular filtration rate (7.4 ± 0.4 to 5.4 ± 0.2 ml/min; \( P < 0.01 \)) decreased as compared with pre-surgical control values. Indomethacin further decreased renal blood flow (to 17.6 ± 3.7 ml/min; \( P < 0.01 \)) and glomerular filtration rate (to 3.1 ± 0.7 ml/min; \( P < 0.01 \)). As in other animals, indomethacin induced a decrease in plasma renin activity (from 20 ± 1 to 3 ± 1 ng h\(^{-1}\) ml\(^{-1}\); \( P < 0.01 \)) and plasma prostaglandin E\(_2\) (from 2.1 ± 1.3 to 0.1 ± 0.04 ng/ml; \( P < 0.01 \)) with increases in mean blood pressure (from 102 ± 4 to 121 ± 6 mmHg; \( P < 0.05 \)) and plasma creatinine (from 0.9 ± 0.04 to 3.5 ± 0.8 mg/100 ml; \( P < 0.01 \)).

**All control groups**

Administration of phosphate buffer without indomethacin did not induce significant change in any of the variables measured.

**Discussion**

Indomethacin reduced plasma renin activity and prostaglandin E\(_2\) in normal rabbits, 2KH rabbits and 1KH rabbits. It did not induce or aggravate hypertension unless renal function decreased simultaneously. Renal failure and malignant hypertension occurred only in those rabbits with reduced renal blood flow on initiation of treatment with indomethacin.

Failure of indomethacin to induce hypertension in normal rabbits contrasts with results cited earlier (Colina-Chourio et al., 1975). Heterogeneity of responses to indomethacin, dependent on levels of renal function and, to a lesser extent, plasma renin activity (measurements not undertaken in previous studies), may partially account for these discrepancies.

We conclude that prostaglandins exert a protective effect on renal function in renovascular hypertension and that the effect of indomethacin on blood pressure is determined by the relative importance of the divergent influences of simultaneous blockage of prostaglandin synthesis and inhibition of renin release.

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**References**

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