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Inhibiton of Furosemide Induced Increase in Renal Blood Flow by Indomethacin[1] (38497)

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In addition to its potent saluretic action furosemide also increases renal blood flow (1). This response is dose related and varies directly with initial renal vascular resistance (2). Thus, the higher the resistance the greater the increase in flow will be. Another facet of the response is a slight delay before onset. Also, the dilation is usually preceded by a small transient constriction. The mechanism by which dilation is induced has not been reported. In view of the delayed onset of action of the response it seemed possible that the response could be mediated via a release mechanism. Inasmuch as the kidney is a source of several prostaglandins (3, 4), which have been shown to increase renal blood flow (5, 6), it was of interest to determine if indomethacin, an inhibitor of prostaglandin systhesis (7), could modify the furosemide induced increase in renal blood flow.

Methods. Mongrel dogs of either sex, weighing between 16 and 22 kg, were anesthetized with pentobarbital sodium (30 mg/kg iv) and the trachea was intubated. Mean arterial blood pressure (MAP) was monitored with a pressure transducer (Statham P23AA) via a carotid artery catheter. A jugular vein was catheterized for administration of solutions. An infusion of 0.9% NaCl was administered at a rate of 4 ml/min. A kidney was exposed via a retroperitoneal flank incision. A flow probe was placed around the renal artery and connected to a square wave electromagnetic flow meter (Carolina Medical Electronics) in order to measure total renal blood flow (RBF). If more than one renal artery was encountered, the contralateral kidney was used. The ipsilateral ureter was cannulated in order to monitor urinary volume. MAP and RBF were recorded continuously on a Beckman Type R Dynograph. A 23 gauge scalp needle was passed retrograde into the renal artery for drug administration. A solution of 0.9% NaCl was infused continuously at a rate of 0.8 ml/min. For drug administration, this solution was replaced with one containing furosemide. This route of administration was employed to limit the duration of action of the drug and allow a second dose to be given within a hour.

The protocols employed are as follows: In the first series of experiments furosemide was administered, 0.2 mg/kg, via the renal artery over a 2-min period. Thirty minutes later, indomethacin, 5 mg/kg, was administered iv via the jugular infusion. Thirty minutes later, the same dose of furosemide was repeated. In a second series of experiments, the indomethacin was omitted but furosemide was given as previously, i.e. 2 doses, one hr apart.

Data were analysed by Students' t test (paired comparisons) (8). A P value of less than 0.05 was used as the criterion of significance.

Results and Discussion. The tracing in the upper part of Fig. 1 shows the effect of furosemide on RBF. There is a slight decrease in flow which occurs about 50 sec after beginning administration of furosemide and this is followed by prolonged increase which occurs about 2 min after beginning the infusion. The tracing in the lower part of Fig. 1 shows the response to a second dose of furosemide which was administered 30 min after indomethacin. The small constriction is still present but the dilation is antagonized. In six dogs, furosemide produced a significant peak increase in RBF of 51 ± 6 ml/min (from 210 to 261 ml/min)

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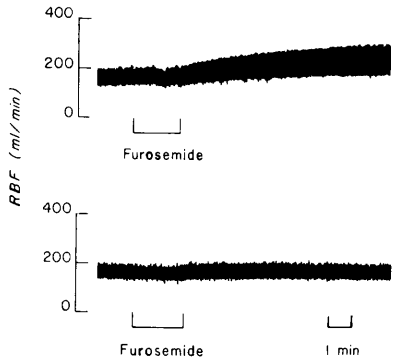

FIG. 1. Effect of furosemide on RBF before (upper tracing) and after (lower tracing) administration of indomethacin.

before indomethacin while RBF was non-significantly increased only 4 ± 6 ml/min (from 197 to 201 ml/min) after indomethacin. In contrast to the inhibition of renal blood flow, indomethacin did not affect furosemide induced increases in urinary volume or sodium excretion. Since no inhibition was noted it would appear that the diuresis and natriuresis induced by furosemide is mediated primarily by a mechanism which does not involve prostaglandins. It is possible that prostaglandins might be responsible for a small amount of diuresis and natriuresis, but an amount too small to be detected readily when added to the massive diuresis and natriuresis induced by furosemide which is unrelated to release of prostaglandins. MAP was not altered significantly throughout the experiments.

The effect of indomethacin on RBF was variable. In three animals there was a definite decrease in RBF while in the other three no effect was seen. This difference in effect is probably related to different basal outputs, a decrease in flow occurring with higher outputs and no change occurring when outputs are low. The possibility that responsiveness in the renal bed might differ under these circumstances was determined by administration of nitroglycerin (20 or 40 μg) before and after indomethacin. No significant changes in the response were noted.

As a control for the first series of experiments, furosemide was administered to another series of three dogs in which indomethacin was not administered. The first dose significantly increased RBF by 50 ± 13 ml/min (from 213 to 263 ml/min). The second dose significantly increased RBF by 47 ± 12 ml/min (from 200 to 247 ml/min). Thus, no evidence of a decreased response was seen with the time interval employed in this study.

Summary. The ability of furosemide to increase RBF was found to be significantly inhibited by indomethacin. The implication of this observation is that the dilation of the renal vasculature produced by furosemide is mediated by prostaglandins. Inhibition of the synthesis of these agents by indomethacin inhibits the increase in RBF produced by furosemide.

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