Antagonism of the Renal Vasodilator Activity of Dopamine by Metoclopramide

Richard A. Hahn and Joe R. Wardell, Jr.

Department of Biological Research, Smith Kline & French Laboratories, Philadelphia, Pennsylvania, USA

Summary. The interaction of metoclopramide with renal dopamine receptors has been characterized in anesthetized dogs surgically prepared with arterial blood pressure catheters and renal artery blood flow probes.

In normal dogs, i.v. dopamine (3 μg/kg) produced consistent and selective decrements in renal vascular resistance (RVR) and increments in renal blood flow over a 220 min test period; mean arterial blood pressure and cardiac rate were minimally affected. Pretreatment with metoclopramide, 1 and 10 mg/kg i.v., resulted in dose-related inhibition (maximum inhibition 44% and 94%, respectively) of the renal vasodilator activity of dopamine without altering baseline parameters. The duration of antagonism produced by 1 mg/kg of metoclopramide was approximately 30 min, while 10 mg/kg resulted in significant attenuation for the entire test period. Decreases in RVR produced by prostaglandin A1 (0.03 and 0.3 μg/kg, i.v.) and bradykinin (3 and 15 μg/kg, i.v.) that were comparable to those of dopamine were unaltered by metoclopramide. Furthermore, metoclopramide did not affect the diastolic blood pressure responses to noradrenaline (0.1–3 μg/kg, i.v.) or isoproterenol (0.03–0.3 μg/kg, i.v.), nor did it alter dopamine-induced vasoconstriction of the iliac vasculature.

In phenoxybenzamine (3 mg/kg, i.v.) treated dogs, dopamine (0.3–30 μg/kg, i.v.) produced dose-related reductions in RVR. Administration of metoclopramide (10 mg/kg, i.v.) resulted in a 10-fold parallel displacement, to the right, of the RVR dose-response curve to dopamine.

These findings demonstrate that metoclopramide is an effective antagonist of renal dopamine receptors following systemic administration in the dog. The results are not consistent with the classification of metoclopramide as a selective antagonist of D-2 receptors.

Key words: Dopamine — Renal vasodilation — Metoclopramide — Competitive antagonism.

Introduction

Metoclopramide has been reported to antagonize emetic responses and stereotypic behavior induced by several centrally-acting drugs including apomorphine, amphetamine and piribedil (Justin-Besancon and Laville 1972; Janssen et al. 1967; Klein et al. 1968; Poignant et al. 1972; Hackman et al. 1973). Metoclopramide also produces catalepsy in association with accelerated turnover of brain dopamine, as judged by increased concentrations of striatal and mesolimbic homovanillic acid (Costall and Naylor 1973a, 1973b; Ahtee and Buncombe 1974; Peringer et al. 1975). Partially on the basis of these observations, metoclopramide has been classified as an antagonist of central dopamine receptors.

In contrast to its effects in the central nervous system, relatively few studies appear in the literature regarding the interaction of metoclopramide with peripheral dopamine receptors of the cardiovascular system. Dopamine inhibits contractile amplitude of isolated spontaneously beating mollusc hearts, and this activity is antagonized in a selective and reversible manner by concentrations of metoclopramide having little intrinsic activity (Dougan et al. 1974). Intravenous injection of dopamine produces arterial hypotension and increased renal blood flow in anesthetized cats with adrenoceptor blockade, and the subsequent administration of metoclopramide selectively attenuates these effects (Day and Blower 1975). Metoclopramide has also been reported to inhibit the renal vasodilator

Send offprint requests to R. A. Hahn, Lilly Research Laboratories, Indianapolis, Indiana 46285, USA
activity of dopamine following intra-arterial injection in anesthetized dogs pretreated with alpha and beta receptor antagonists (Goldberg et al. 1978; Kohli et al. 1978).

The aforementioned studies provide evidence of the ability of metoclopramide to inhibit certain cardiovascular effects of dopamine. However, several contain relatively little quantitative data and intra-arterial administration of metoclopramide to a regional circulation gives limited information as to the systemic effects of effective receptor blocking doses. The purpose of the present study was to obtain more precise information regarding the potency, efficacy and specificity of metoclopramide as an antagonist of renal dopamine receptors following systemic administration, and to ascertain the nature of the antagonism.

Methods

Adult mongrel dogs of either sex were anesthetized with pentobarbital sodium (50 mg/kg, i.p.). The trachea was intubated and the dogs were ventilated with room air delivered from a respiratory pump (tidal volume 10–15 ml/kg, 16 cycles/min). Catheters were placed in a femoral or antecubital vein and a carotid artery for i.v. administration of all drug solutions and measurement of arterial blood pressure, respectively. Phasic arterial blood pressure was recorded using a Statham transducer (P23AA). Mean arterial blood pressure was calculated as diastolic blood pressure plus 1/3 pulse pressure. A cardiatocthemeter (Brush), which was triggered by a lead II electrocardiogram, was used to record cardiac rate.

A short segment of the left renal artery was exposed by a flank incision and cleared of adhering tissue to accommodate positioning of an electromagnetic flowprobe (Carolina Medical Electronics). Mean renal blood flow (RBF) was measured by connecting the flowprobe to a flowmeter (Carolina Medical Electronics) and recorded by relaying the signal to an oscillograph. In some experiments, the mean right iliac arterial blood flow was also measured electromagnetically. Renal and iliac vascular resistances (RVR and IVR) were calculated as the ratio of pressure/flow and expressed as mmHg/ml/min. The directly measured parameters, arterial blood pressure (mm Hg), cardiac rate (beats/min), and renal (iliac) blood flow (ml/min) were recorded on a multichannel oscillograph (Brush). Following surgery, approximately 15 min were allowed to elapse for equilibration.

The efficacy and duration of action of metoclopramide as an antagonist of renal dopamine receptors was determined in an initial series of experiments by infusing dogs with either metoclopramide (1 and 10 mg/kg) or saline, in the case of control experiments. Ten minutes after the completion of drug or saline infusion, dopamine (3 µg/kg) was administered by bolus injection. This dose of dopamine was chosen on the basis of preliminary experiments demonstrating it was selective for the renal vasculature and produced submaximal and short-lived increases in RBF and decreases in RVR.

The specificity of antagonism produced by metoclopramide was evaluated in several types of experiments. In the first, renal vasodilator responses evoked by prostaglandin A1 (0.03 and 0.3 µg/kg) and bradykinin (3 and 15 µg/kg) were determined before and after administration of metoclopramide (10 mg/kg). In other experiments, the effect of dopamine infusion (3 µg/kg/min for 10 min) on RVR and IVR was determined simultaneously prior to and 10 min after metoclopramide (10 mg/kg). Possible alpha and beta adrenoceptor blocking activity of metoclopramide (10 mg/kg) was evaluated by determining its effect on diastolic blood pressure dose-response curves to noradrenaline (0.1–3 µg/kg) and isoproterenol (0.03–0.3 µg/kg).

The nature of the antagonism of renal dopamine receptors by metoclopramide was studied in a series of dogs pretreated with phenoxybenzamine (3 mg/kg). Sixty minutes after administration of the alpha receptor antagonist, dogs were infused with either saline (control experiments) or metoclopramide (10 mg/kg). Ten minutes later, RVR dose-response curves were determined for dopamine by injecting increasing dose levels of the agonist (0.3–30 µg/kg) at approximately 10 min intervals. All drug solutions were prepared fresh daily in 0.9% saline. Bolus doses of dopamine, prostaglandin A1, noradrenaline, and isoproterenol were administered in a constant dose volume of 0.1 ml/kg. With regard to drug infusions, test doses of dopamine (30 µg/kg), metoclopramide (1 and 10 mg/kg), bradykinin (3 and 15 µg/kg), and phenoxybenzamine (3 mg/kg) were dissolved in 10.3 ml of saline and infused (Harvard Infusion Pump, Model 600) at a rate of 1.03 ml/min for 10 min. In control experiments, separate dogs were infused with saline (1.03 ml/min for 10 min) in place of metoclopramide. The drugs used in this study were: dopamine hydrochloride (Calbiochem), metoclopramide hydrochloride (SK & F), prostaglandin A1 (ONO), bradykinin acetate (Scherin), phenoxybenzamine hydrochloride (SK & F), noradrenaline bitartrate (Sigma), and isoproterenol hydrochloride (Aldrich). All doses are expressed as the free base or acid. Statistical analyses were performed using methods described by Snedecor (1956). Each variability term refers to the standard error of the mean. Statistical significance between group mean values was calculated using paired or non-paired Student's t-tests.

Results

Repeated bolus i.v. injection of dopamine (3 µg/kg) produced decreases in RVR and increases in RBF that did not vary significantly over time. For example, the initial administration of dopamine lowered RVR 18.1 ± 1.4% and increased RBF 16.4 ± 1.8%, while responses recorded after an elapsed time of 220 min were 23.7 ± 6.1% and 18.2 ± 5.2%, respectively. The attending alterations in mean arterial blood pressure and cardiac rate were minimal, averaging less than 5% change from the respective control value. Pretreatment with metoclopramide, 1 and 10 mg/kg, resulted in dose-related attenuation of the renal vasodilator activity of dopamine (Fig. 1); the average maximum inhibition produced by 1 and 10 mg/kg was 44% and 94%, respectively. The duration of antagonism at the lowest dose of metoclopramide was short (approximately 30 min), while 10 mg/kg produced significant antagonism for the entire 220 min test period (Fig. 1). Metoclopramide pretreatment did not alter baseline parameters in this series of experiments; baseline RVR 10 min after infusion of saline and 1 and 10 mg/kg of metoclopramide was 1.01 ± 0.14, 1.47 ± 0.36 and 1.21 ± 0.19 mm Hg/ml/min, respectively.

To examine the specificity of the antagonism, renal vascular responses to prostaglandin A1 (0.03 and 0.3 µg/kg) and bradykinin (3 and 15 µg/kg) were recorded before and 10 min after metoclopramide...