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Cardiovascular Responses to 6-Keto-prostaglandin E_1 in the Dog (41027)[1]

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Abstract. Prostacyclin (PGI_2) is readily converted to 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) which is both a stable and biologically less potent compound. Recently, another stable metabolite of PGI_2 namely 6-keto-prostaglandin E_1 (6-keto-PGE_1) was found to be equipotent to PGI_2 in inhibiting platelet aggregation and reducing renal vascular resistance. In this study, cardiac, pulmonary, and systemic vascular responses to exogenously administered 6-keto-PGE_1 were characterized and compared with responses to PGI_2. Systemic arterial diastolic pressure (DP), pulmonary arterial pressure (PAP), and myocardial contractile force (MCF) were measured in intact dogs following intravenous (iv) and intraarterial (ia) administration of PGI_2 (0.1, 0.3, 1.0 μg/kg), 6-keto-PGE_1 (0.1, 0.3, 1.0 μg/kg), prostaglandin E_2 (0.3, 1.0, 3.0 μg/kg), and 6-keto-$PGF_{1\alpha}$ (1.0, 3.0, 10.0, 30.0 μg/kg). 6-Keto-PGE_1 was found to be equipotent to PGI_2 in reducing DP following either iv or ia administration. 6-Keto-PGE_1 mimics the response to PGI_2 in reducing PAP and MCF when both are administered intravenously. All responses to PGI_2 and 6-keto-PGE_1 are dose dependent. 6-Keto-PGE_1, like PGI_2, is unaffected by pulmonary transit. These results suggest that vascular responses previously attributed to PGI_2 may be due in part to 6-keto-PGE_1.

Prostacyclin (PGI_2), the principal product of arachidonic acid metabolism in vascular endothelial tissue (1–3), is a potent inhibitor of platelet aggregation (1–3), a smooth muscle relaxing agent (2, 3) and a systemic hypotensive agent in rats, rabbits (4), dogs (5–7), baboons (8), and man (9–11). At physiological pH, PGI_2 is readily converted to 6-keto-prostaglandin $F_{1\alpha}$ (6-keto-$PGF_{1\alpha}$) via a nonenzymatic, acid catalyzed hydrolysis reaction (12–14). 6-Keto-$PGF_{1\alpha}$ is ineffective as an inhibitor of platelet aggregation (12) or as a systemic hypotensive agent (4, 5). In the liver, 6-keto-$PGF_{1\alpha}$ may be converted to 6-keto-prostaglandin E_1 (6-keto-PGE_1) via the 9-hydroxyprostaglandin dehydrogenase pathway (15). In contrast to 6-keto-$PGF_{1\alpha}$, 6-keto-PGE_1 is a potent inhibitor of platelet aggregation (15–18) and a systemic vasodilator in the anesthetized rat (19).

The objectives of this study were to characterize the cardiac, pulmonary, and systemic vascular responses to exogenously administered 6-keto-PGE_1 in the intact dog; to study the effect of pulmonary transit on 6-keto-PGE_1 metabolism; and to compare all responses with those of PGI_2.

Materials and Methods. Mongrel dogs (n = 14) of either sex weighing 9–22 kg were anesthetized with intravenous (iv) sodium pentobarbital (30 mg/kg) and intubated with a cuffed endotracheal tube. Ventilation was maintained with a positive-pressure respirator. The right femoral artery and vein were catheterized to record systemic arterial pressure (SAP) and to administer test compounds, respectively. Intraarterial (ia) drugs were administered into the left ventricle via a catheter (Elecath, 100 cm) advanced from the left femoral artery. Following a thoracotomy at the fourth left intercostal space, a catheter was placed in a branch of the left pulmonary artery to measure pulmonary arterial pressure (PAP). A Walton–Brodie strain gauge arch was sutured onto the left ventricle for the measurement of myocardial contractile force (MCF).

Stock solutions of PGI_2 and 6-keto-$PGF_{1\alpha}$ were prepared in 0.1 M Tris buffer (pH 9.0) (1 mg/ml). Prostaglandin E_2 (PGE_2) and 6-keto-PGE_1 were prepared in ethanol (1 mg/ml). All solutions were stored at −20°. On the day of each experiment, stock solutions of PGI_2 and 6-keto-$PGF_{1\alpha}$ were diluted

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to 20 and 100 μg/ml, respectively, with Tris buffer. PGE$_2$ and 6-keto-PGE$_1$ were evaporated under nitrogen and resuspended in 0.9% saline to 100 and 20 μg/ml, respectively. 6-Keto-PGE$_1$ is stable for at least 24 hr when prepared in ethanol as a stock solution or in a saline vehicle (20). Indomethacin (Sigma) was prepared daily as a 2 mg/ml solution (pH 9.0) in 100 m*M* sodium carbonate.

To inhibit endogenous prostaglandin synthesis, each dog was pretreated with indomethacin (2 mg/kg iv) 30 min before drugs were administered (21). Bolus injections of ia and iv PGI$_2$ (0.1, 0.3, 1.0 μg/kg), 6-keto-PGE$_1$ (0.1, 0.3, 1.0 μg/kg), PGE$_2$ (0.3, 1.0, 3.0 μg/kg), and 6-keto-PGF$_{1\alpha}$ (1.0, 3.0, 10.0, 30.0 μg/kg) were administered in a random order. Changes in SAP, PAP, and MCF were recorded by a direct writing physiograph (Gould Brush 480) and allowed to return to control values before subsequent doses were administered.

Data are expressed as arithmetic mean ± SEM and were analyzed using Student's *t* test for either paired or unpaired observations where appropriate. Significance was judged at the $P < 0.05$ level. Linear regression lines were calculated by method of least squares.

Results. The cardiovascular responses to iv administration of 6-keto-PGE$_1$ (1.0 μg/kg) are characterized by a significant decrease in SAP, MCF, and a slight decrease in PAP (Fig. 1A). Similar changes are produced by iv administration of PGI$_2$ (1.0 μg/kg) as shown in Fig. 1B.

When administered intravenously, PGI$_2$ and 6-keto-PGE$_1$ produced dose-dependent decreases in arterial diastolic pressure (DP) that were not significantly different from one another (Fig. 2A). Following intraarterial administration, PGI$_2$ and 6-keto-PGE$_1$ produced a similar dose-dependent decrease in arterial DP (Fig. 2B). In addition, the systemic vascular response produced by PGI$_2$ and 6-keto-PGE$_1$ was unaffected by the route of administration.

When administered intravenously, PGI$_2$ and 6-keto-PGE$_1$ produced dose-dependent decreases in pulmonary arterial pressure that were not significantly different from one another (Fig. 3). In contrast, ia administration of both 6-keto-PGE$_1$ and PGI$_2$ did not significantly alter PAP in the doses employed.

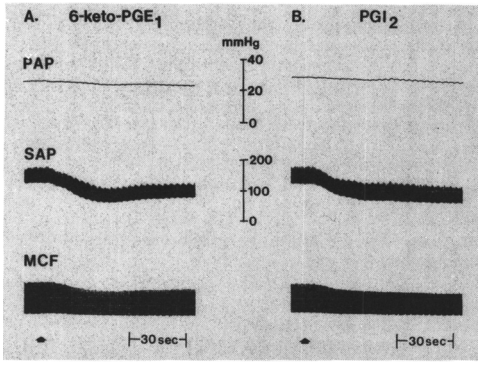

FIG. 1. (A) Effects of 6-keto-PGE$_1$ (1.0 μg/kg) on pulmonary arterial pressure (PAP), systemic arterial pressure (SAP), and myocardial contractile force (MCF). (B) Effects of PGI$_2$ (1.0 μg/kg) on PAP, SAP, and MCF. Arrows indicate point of intravenous (iv) injection. Panels (A) and (B) represent response from the same intact dog 30 min following iv administration of indomethacin (2 mg/kg).

Intravenously administered 6-keto-PGE$_1$ elicited a dose-dependent decrease in MCF from 3.8 ± 1.4 to 11.7 ± 4.2% in the dose range studied. PGI$_2$ iv caused a significantly similar decrease in MCF from 5.4 ± 2.3 to 12.1 ± 5.5%. In contrast, ia administration of PGI$_2$ and 6-keto-PGE$_1$ produced inconsistent decreases in MCF.

PGE$_2$ elicited a dose-dependent decrease in arterial DP from 5.1 ± 2.3 to 36.4 ± 2.9% when administered intravenously. In-

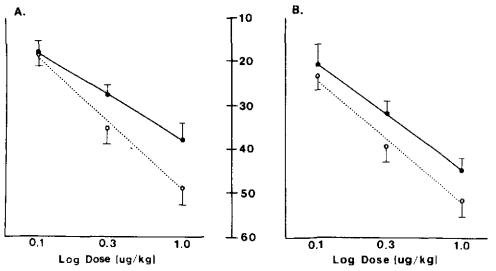

FIG. 2. Percentage decrease in arterial diastolic pressure produced by 6-keto-PGE$_1$ ($N \geq 11$) (●——●) and PGI$_2$ ($N \geq 8$) (○– – –○) following (A) intravenous and (B) intraarterial administration.

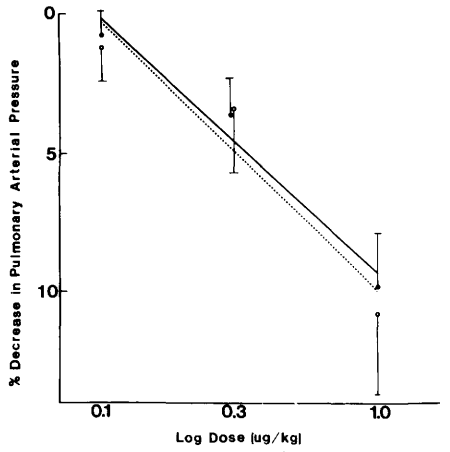

FIG. 3. Percentage decrease in pulmonary arterial pressure in response to intravenous administration of 6-keto-PGE$_1$ (N = 11) (●——●) and PGI$_2$ (N = 8) (○- - -○).

traarterial administration of PGE$_2$ produced a dose-dependent decrease in DP from 29.9 ± 4.9 to 46.4 ± 1.9%, which was significantly greater than the response to iv PGE$_2$. PGE$_2$ caused a dose-dependent increase in PAP from 0.4 ± 0.4 to 11.8 ± 2.8% when administered intravenously. When administered intraarterially, PGE$_2$ increased PAP from 1.1 ± 0.8 to 7.4 ± 1.8% in the dose range studied.

6-Keto-PGF$_{1\alpha}$ had no significant effect on DP, PAP, and MCF by either route of administration in the dose range studied.

Discussion. Administration of 6-keto-PGE$_1$ to intact dogs demonstrates this prostanoic compound to be active in the cardiovascular system. Responses to 6-keto-PGE$_1$ are both qualitatively and quantitively similar to those of PGI$_2$.

The decrease in systemic arterial pressure produced by PGI$_2$ is most likely due to a dilation of peripheral resistance vessels. PGI$_2$ relaxes arterial muscle strips (2, 3) and reduces renal vascular resistance (22). Similarly, 6-keto-PGE$_1$ decreases systemic arterial pressure and reduces renal vascular resistance (19). The similarity between dose–response curves of PGI$_2$ and 6-keto-PGE$_1$ on SAP suggests a comparable mechanism of action.

The only known metabolites of arachidonic acid that act directly as pulmonary vasodilators are prostacyclin (23) and 6-keto-PGE$_1$. The classical prostaglandins of the bisenoic series, PGE$_2$, PGF$_{2\alpha}$, and PGD$_2$, are all pulmonary vasopressors (23, 24). Because the pulmonary vascular bed is a low pressure system, it is relatively difficult to cause large reductions in PAP. When prostacyclin and 6-keto-PGE$_1$ are administered intraarterially, they have a much reduced effect on pulmonary arterial pressure. This suggests that 6-keto-PGE$_1$ may be inactivated in the systemic circulation in a manner similar to that of PGI$_2$ (25, 26).

The dose-dependent decrease in myocardial contractile force observed following intravenous administration of PGI$_2$ and 6-keto-PGE$_1$ could be related to alterations in preload or afterload, or to a negative inotropic effect. In the left ventricular bypass preparation, PGI$_2$ produced only a slight decrease in MCF that was not dose dependent (6). Therefore, reductions in MCF in the intact dog in response to PGI$_2$ and 6-keto-PGE$_1$ must be due at least in part to variations in preload or afterload.

15-Hydroxyl prostaglandin dehydrogenase (15-OH PGDH), an enzyme responsible for the inactivation of circulating prostaglandins, is located intracellularly in the lung (27, 28). PGI$_2$ and PGE$_2$ are good substrates for 15-OH PGDH (13). Unlike PGE$_2$, both PGI$_2$ and 6-keto-PGE$_1$ are unaffected by pulmonary transit. Pulmonary-prostaglandin metabolism requires an initial step of transmembrane transport (27–29). PGI$_2$ and 6-keto-PGE$_1$ may be poor substrates for the transmembrane carrier system and thereby escape inactivation by the degradative enzymes of the lung. In the liver, however, the transmembrane carrier system appears to be less important as PGI$_2$ is readily metabolized following liver perfusion (15, 25, 26).

6-Keto-PGF$_{1\alpha}$, which is biologically less active than PGI$_2$, was previously believed to be the predominant stable breakdown product of PGI$_2$ (3–5, 17). 6-Keto-PGE$_1$, the more recently discovered stable metabolite of PGI$_2$ (15), is equipotent to PGI$_2$ (17, 18). We therefore suggest that the response to PGI$_2$ may be partly due to 6-keto-PGE$_1$

activity. 6-Keto-PGE$_1$ is thought to be a product of 6-keto-PGF$_{1\alpha}$ metabolism (15, 17, 18); however, the lack of biological activity of 6-keto-PGF$_{1\alpha}$ in this and other studies (3–5, 17) suggests a more direct metabolic pathway.

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