Myocardial Imaging in Dogs Treated with Grisorixin: Relationship Between Thallium-201 Uptake and Coronary Blood Flow

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Thallium-201 myocardial imaging was performed in dogs after pretreatment with grisorixin, which appeared to increase the myocardial uptake of Tl-201. This effect of grisorixin was found to be dose dependent, with an optimal dose of 60 μg/kg. The myocardial-to-background ratio, which was 1.92 in the control dogs, rose to 4.45. The increase in the absolute myocardial uptake was demonstrated in guinea pigs that received Tl-201 after similar pretreatment with grisorixin. In the animals treated with 500 μg/kg, the uptake of Tl-201 by the heart was 35% over the control value. With 60 μg/kg grisorixin, the coronary blood flow increased from 40 to 176 ml/min 5 min after the injection. This dose, optimal for imaging, induced the maximum vasodilator effect with only a very slight concomitant increase in the left-ventricular pressure and myocardial contractility. Above 60 μg/kg, grisorixin appeared to be a potent inotropic agent, whereas below this dose it showed only coronary vasodilator properties. Some evidence for an ionophore effect of this compound was found in dogs pretreated with 60 μg/kg. In these the radionuclide was injected when the coronary vasodilatation had become insignificant, but a significant improvement of the M/B ratio was still evident.

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Because of its metabolic similarity to potassium and its affinity for the myocardium (*1–3*) thallium-201 (Tl-201) is to date the preferred radionuclide for detecting and evaluating coronary artery disease (*4–12*). However, analysis of the scintigrams remains difficult, owing to non-negligible circulating activity and to high uptake by liver, spleen, and sometimes lungs. Because of its heterogeneity, this background activity cannot be fully corrected for, even after data processing (*13,14*).

Grisorixin is an ionophore antibiotic of the nigericin group (*15*). These compounds have the ability to complex and transport monovalent cations across biological membranes (*16*). Grisorixin has been described as a preferential potassium carrier rather than sodium, but it also presents a high affinity for thallium (*17*). Moreover, it is a potent positive inotropic agent (*18*). In a preliminary paper (*19*), we demonstrated its ability to increase the myocardial-to-background activity ratio (M/B ratio) in thallium-201 scintigrams in dogs.

The present study was undertaken in an attempt to explain the mechanism of action of grisorixin upon scintigraphic imaging. The effects of the ionophore on the biodistribution of Tl-201 were studied in guinea pigs, and the modifications of some hemodynamic parameters in dogs were correlated with the observed scintigraphic effects at different doses.

METHODS

Scintigraphic imaging in anesthetized dogs. Mongrel dogs of either sex weighing from 9 to 22 kg were starved for 12 hr, then anesthetized with sodium pentobarbital (30 mg/kg i.v.). All injections were made intravenously through a cephalic vein. Each dog received 0.5 to 1.5 mCi of thallium-201. Grisorixin was administered in a

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water-ethanol mixture (70/30, v/v). The dilutions were made in such a way that all the dogs received 0.3 ml/kg of solvent. The dogs were split into three groups:

Group I: the animals were treated with grisorixin or the solvent alone as control (n = 5). Seven doses of grisorixin were used: 7 (n = 2), 15 (n = 4), 30 (n = 5), 60 (n = 4), 125 (n = 4), 500 (n = 4), or 1000 μg/kg (n = 4). Then, 10 min later, all dogs received thallium-201,

Group II: the dogs received 60 μg/kg of grisorixin, and thallium-201 was injected: 5 (n = 4), 10 (n = 4), or 15 min (n = 4) later. The control animals received the solvent alone and Tl-201 10 min later (n = 10),

Group III: the dogs were given grisorixin: 60 (n = 3) and 500 μg/kg (n = 3), 10 min after Tl-201.

Starting at the beginning of the Tl-201 injection, sequential images of 30 sec each were stored over at least 20 min as 64 × 64 matrices in an on-line computer. Regions of interest were manually drawn on the myocardium, liver, and postero-superior region surrounding the myocardium for background estimation (Fig. 1). Changing detected activity was plotted against time by the computer. From these data, the mean myocardium-to-background (M/B) and liver-to-background (L/B) activity ratios were calculated for a 90-sec time interval by dividing the mean activity counted inside the myocardial or liver ROI by the mean activity counted inside the background region. The M/B and L/B values were calculated 5 min after injection of Tl-201.

Thallium biodistribution in the guinea pig. Guinea pigs of either sex, weighing between 450 and 700 g, were anesthetized with urethan (1500 mg/kg i.p.) after a 12-hr fast. Grisorixin was administered intravenously in an aqueous ethanol (70/30, v/v) solvent mixture, with 1 ml solvent/kg. Four doses of grisorixin were used 100, 250, 500, and 1000 μg/kg. The control animals were treated under the same conditions with the solvent alone (1 ml/kg). The injections were completed within 30 sec and Tl-201 (1 μCi/kg) was injected as thallous chloride 10 min later. The guinea pigs were decapitated 5 min after the injection of Tl-201, and the heart, kidneys, liver, and lungs were rapidly excised, washed in saline solution at 4°C, dried, and weighed. Samples of blood (2 ml) were also collected and weighed. Radioactivity was measured in a gamma well counter using the 63–85 keV peak, and results were expressed as a percentage of the injected dose per gram of fresh tissue or blood.

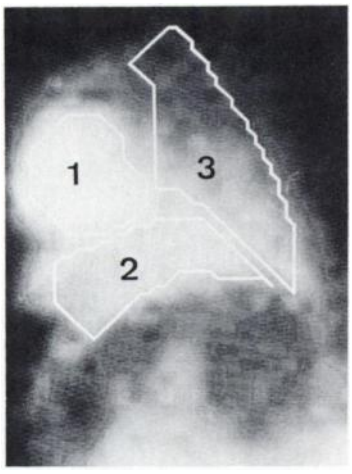

FIG. 1. Chest scintigram of dog in left lateral projection, 10 min after thallium-201 injection. Regions of interest delimiting the myocardium 1, the liver 2, and the lungs 3 are shown. Regions 1 and 2 were drawn directly on this picture, whereas region 3, which is used for background, was obtained from the picture corresponding to first pass in the lungs.

Hemodynamic studies. Mongrel dogs of either sex weighing from 13 to 28 kg were fasted overnight, then anesthetized with chloralose (0.08 g/kg i.v.) and ventilated artificially with room air so that arterial blood pH and gases were maintained in the normal range. Through left thoracotomy the anterior descending coronary artery was dissected free and a blood-flow transducer was placed around it approximately 1 cm from its origin. The blood-flow transducer was precalibrated and provided with an automatic nonocclusive zero; its signal was monitored on a flow meter.* Left-ventricular pressure (LVP) was measured with a transducer† connected to a polyethylene catheter inserted into the left-ventricular cavity through the right carotid artery. Left-ventricular dP/dt was obtained by electronic differentiation‡ of the left-ventricular pressure. The maximum LV dP/dt was used as an indicator of myocardial contractility. All parameters were recorded simultaneously on a multichannel polygraph.

The dogs were divided into four groups, which received respective doses of 30, 60, 125, and 500 μg/kg of grisorixin, administered intravenously over 30 sec. in a water-ethanol solvent (70/30, v/v). All the dogs received 0.3 ml/kg of solvent. Two control animals received the solvent alone.

Statistical analysis. Statistical significances were determined using either a two-way analysis of variance followed by Student's t-test or, when inappropriate, nonparametric statistical tests such as Kruskal-Wallis one-way analysis of variance by ranks (*20*) followed by a Dunn test (*21*), or a Friedman two-way analysis of variance by ranks followed by a multiple comparison test (*20*). Results were considered significant when $p < 0.05$.

RESULTS

Scintigraphy. The results obtained with the dogs treated with different doses of grisorixin first and Tl-201 10 min later (Group I) are shown in Fig. 2 and Table 1. A significant improvement in the M/B ratio was obtained from 60 μg/kg up to 500 μg/kg grisorixin, but the optimal dose appeared to be 60 μg/kg (232% increase compared with the control value). The M/B ratios for 30, 60, and 500 μg/kg are plotted against time in Fig. 3. With all three doses of grisorixin, M/B decreased

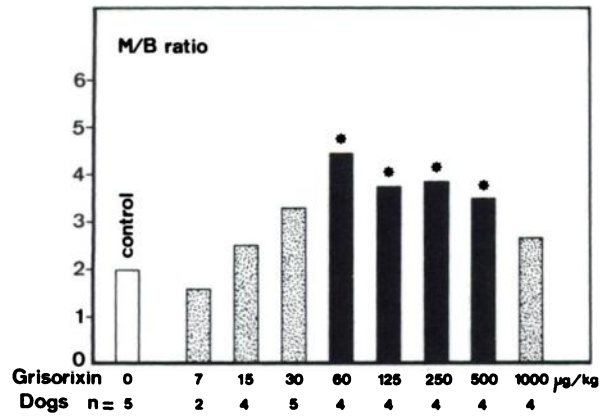

FIG. 2. Dose-dependent effect of grisorixin on myocardial-to-background ratio (M/B) in anesthetized dogs. Thallium-201 was injected 10 min after grisorixin, or solvent alone in control dogs. M/B ratio was calculated 5 min after injection of Tl-201. Asterisks denote $p < 0.05$, treated against control dogs [Kruskal-Wallis nonparametric test (*20*)].

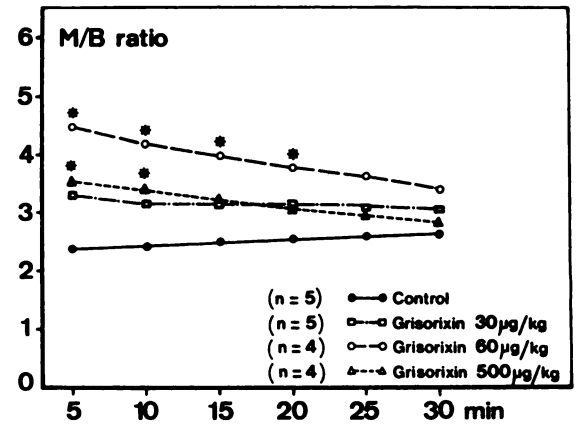

FIG. 3. Effect of grisorixin on evolution of myocardial-to-background ratio (average from 3 images). Dogs were treated as in Fig. 2. Asterisks denote $p < 0.05$, treated against control dogs at different times [Kruskal-Wallis nonparametric test (*20*)].

regularly from the fifth minute after injection of Tl-201 whereas in the controls it increased slightly. A much slighter decrease in the M/B ratio was induced by 30 μg/kg of grisorixin than by 60 or 500 μg/kg. With the optimal dose of 60 μg/kg, there was still a significant difference between the control values and those obtained 20 min after injection, whereas with 500 μg/kg this difference was not significant from the fifteenth minute on.

The increase of the M/B ratio with the 60 μg/kg dose of grisorixin was clearly apparent in the scintigrams (Figs. 4a and 4b). The values of the L/B ratio (Table 1) remained steady.

When dogs were injected with 60 μg/kg grisorixin and then with Tl-201 at different times—i.e., 5, 10, and 15 min later (Group II)—a significant improvement of the M/B ratio was observed with the 5- or 10-min delay (Fig. 5).

The effect of grisorixin on the evolution of the activities of the myocardial, liver, and lung areas is illustrated in Fig. 6. In these dogs (Group III), 60 and 500 μg/kg grisorixin was injected a long enough time after Tl-201 i.e., at least 10 min to ensure that the myocardial activity had become stable. Myocardial, lung, and liver activities remained unchanged in control dogs for at least 30 min. The regions of interest are the same as in Fig. 1. With both doses grisorixin induced slight but continuous release of Tl-201 from myocardium (Fig. 6). However, whereas the lung activity decreased immediately after the injection of 500 μg/kg of the ionophore, the release of Tl-201 by the myocardium occurred 5 min. later. In no case did the ionophore affect liver activity.

Thallium biodistribution in guinea pigs. The values of Tl-201 uptake by myocardium, liver, kidneys, and blood in guinea pigs are given in Table 2. In myocardium, the four doses of grisorixin induced a significant increase of Tl-201 fixation. The best result was obtained with 500 μg/kg: an increase of 35% over the control. There was no significant difference among the four doses used. There was a parallel increase in the concentration of Tl-201 in kidneys. In contrast, with 500 μg/kg of grisorixin, liver fixation was significantly lowered. The

TABLE 1. EFFECT OF GRISORIXIN ON THE MYOCARDIUM-TO-BACKGROUND RATIO (M/B) AND LIVER-TO-BACKGROUND RATIO (L/B)

Grisorixin dose (μg/kg)	Dogs (n)	M/B*	L/B*
0 (control)	5	1.92(1.90–2.14)	2.05(1.73–2.45)
7	2	1.56(1.28–1.83)	1.27(1.04–1.49)
15	4	2.48(1.43–3.21)	1.86(1.22–2.63)
30	5	3.28(2.22–4.26)	1.96(0.96–2.60)
60	4	4.45(3.59–4.97)	1.93(1.68–2.27)
125	4	3.76(2.95–4.45)	1.91(1.31–2.47)
250	4	3.84(3.44–4.42)	1.99(1.63–2.43)
500	4	3.49(3.22–3.73)	2.10(1.91–2.25)
1000	4	2.65(2.29–3.12)	1.76(1.34–2.21)

* Values are means, with ranges in parentheses.

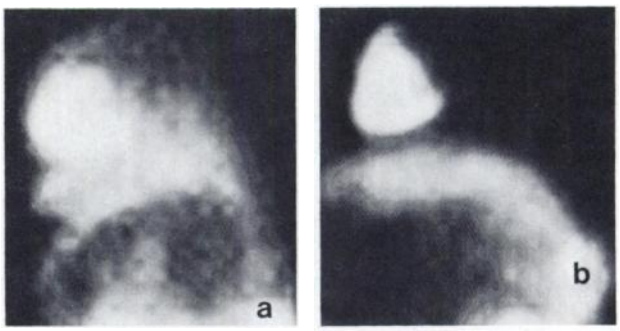

FIG. 4. Left lateral scintigrams of myocardium at 10 min after Tl-201 injection in control dog (a) and in dog having received 60 μg/kg grisorixin 10 min before Tl-201 (b).

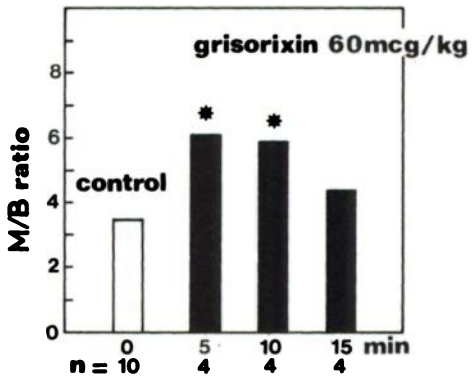

FIG. 5. Variations of myocardial-to-background ratio as related to time of injection of Tl-201 after grisorixin pretreatment. Dogs received grisorixin 60 μg/kg first and then Tl-201, 5, 10, or 15 min later. Control dogs received solvent alone and Tl-201 10 min later. M/B values were calculated 5 min after injection of radionuclide. Asterisks denote $p < 0.05$, treated against control dogs [Kruskal-Wallis nonparametric test (*20*)].

blood and lung activities appeared very slightly but not significantly increased.

Hemodynamic study. The dose-response relationship for grisorixin was studied in 20 anesthetized dogs. Grisorixin induced strong coronary dilatation even at the lowest dose, as shown in Fig. 7. Maximum effect (+363%) was obtained with 60 μg/kg, the maximum occurring 5 min after injection. Coronary blood flow then decreased rapidly, returning to a level similar to the control value by 15 min. With the largest doses, and especially with 500 μg/kg, coronary dilatation was less intense but more persistent, still being significant at 15 min.

Table 3 shows the effects of grisorixin on coronary blood flow (CBF), LVP, and myocardial contractility. The lowest dose of grisorixin (30 μg/kg) affected neither the LVP nor the myocardial contractility as indicated by LV dP/dt. Sixty micrograms per kilogram appeared to be a critical dose since it induced the highest coronary dilatation and a very slight (nonsignificant) increase in LVP and LV dP/dt. In contrast, doses of 125 and 500 μg/kg induced a very prominent positive inotropic effect.

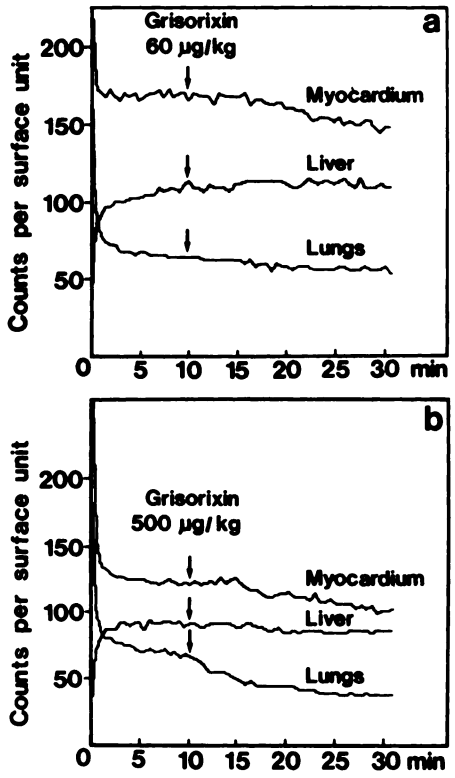

FIG. 6. Changes in activities of different regions of interest after grisorixin injection. Dogs received Tl-201 first, then grisorixin 10 min later, as indicated by arrows, with doses as in *a* and *b*. Regions of interest were drawn as in Fig. 1, so lung area represents background activity.

The LVP reached the maximum value of 215 mm Hg 10 min after the injection of 500 μg/kg grisorixin, against 118 mm Hg at time zero. At the same time, the LV dP/dt value was increased by 200%.

DISCUSSION

Over the past few years, many attempts have been made to improve myocardial imaging (*9–12,22–25*). In particular, Semenoff et al. (*26*) showed that when Tl-201 was injected as a complex with certain ionophores rather than in its ionic form, its biodistribution was modified

TABLE 2. EFFECT OF GRISORIXIN ON Tl-201 UPTAKE IN GUINEA PIGS, EXPRESSED AS THE PERCENTAGE OF INJECTED DOSE OF Tl-201 PER GRAM OF FRESH TISSUE OR BLOOD

		Grisorixin dose (μg/kg)			
Tissue	Control n = 22	100 n = 6	250 n = 6	500 n = 18	1000 n = 6
Heart	1.68 ± 0.06	2.01 ± 0.19*	2.09 ± 0.13†	2.26 ± 0.12‡	2.17 ± 0.11‡
Liver	0.37 ± 0.03	0.57 ± 0.04†	0.32 ± 0.03	0.24 ± 0.02†	0.30 ± 0.05
Kidney	2.70 ± 0.16	3.11 ± 0.20	3.54 ± 0.11†	3.45 ± 0.19‡	3.41 ± 0.27*
Lungs	0.94 ± 0.08	1.33 ± 0.23*	1.15 ± 0.17	1.10 ± 0.12	1.10 ± 0.25
Blood	0.061 ± 0.004	0.082 ± 0.007	0.074 ± 0.003	0.069 ± 0.008	0.067 ± 0.003

Values are expressed as mean ± standard error of mean.
* $p < 0.05$, † $p < 0.02$, ‡ $p < 0.01$ versus control values (two-way analysis of variance followed by Student's t-test).

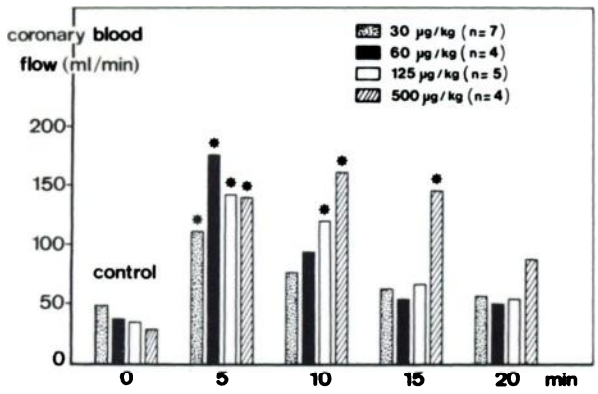

FIG. 7. Dose-dependent effect of grisorixin on coronary blood flow in anesthetized dog. Asterisks denote $p < 0.05$, against time zero values [Friedman nonparametric test (*20*)].

in favor of the myocardium. Even better results were obtained with various sizes of crown polyethers, which are cation complexors rather than real carriers. The only monocarboxylic ionophore tested was X-537 A, which did not give very good results with Tl-201 (*26*), presumably due to its known low affinity for monovalent cations.

In the present study we thought that the carrier properties of the monocarboxylic ionophores might make the myocardium more permeable to subsequently administered thallium. Grisorixin appeared to be an appropriate compound, given its high affinity for thallium (*17*) and its ability to transport it through biological membranes. Thus, ionophore and radionuclide were injected consecutively; first grisorixin and then Tl-201 in a separate injection at least 5 min later.

Our scintigraphic study in dogs shows that a considerable increase in M/B is obtained when grisorixin is injected before Tl-201. This effect appears to be dose dependent. The results obtained with the guinea pigs suggest that the improvement in M/B observed in dogs is due to an increase in the absolute heart uptake, concomitant with a very much smaller increase in the concentration of Tl-201 in the lungs, which contribute part of the background activity. These results are similar to those of Gould et al. (*23*) with dipyridamole, and thus suggest that grisorixin behaves mainly as a coronary dilator.

Coronary dilator effect of grisorixin. The hemodynamic study shows that its effects on the cardiovascular system are dose dependent. Below 60 µg/kg it induces a strong coronary dilatation with no, or only slight, modifications of other cardiac parameters such as myocardial contractility. In contrast, above this dose of 60 µg/kg, grisorixin is still a strong coronary dilator but also exhibits a potent inotropic effect, as shown by the considerable increase in the left-ventricular pressure and myocardial contractility observed. This critical dose of 60 µg/kg corresponds to the highest coronary-dilator effect of grisorixin and also to the optimal dose observed in the Tl-201 imaging. However, in our scintigraphic study, the injections of Tl-201 were performed 10 min

TABLE 3. EFFECTS OF GRISORIXIN ON CORONARY BLOOD FLOW, LEFT-VENTRICULAR PRESSURE, AND MYOCARDIAL CONTRACTILITY

Grisorixin dose	Dogs (n)	Control	Time after grisorixin (min) 5	10	15	20
30 µg/kg:CBF		49(25–75)	111(39–170)*	77(52–110)	63(40–115)	57(35–105)
LVP	7	131(105–155)	129(100–150)	132(102–155)	133(105–160)	134(105–160)
LV dP/dt max		2957(2000–4500)	3114(2200–4500)	3100(2200–4500)	3192(2250–4500)	3071(2300–4000)
60 µg/kg: CBF		40(31–50)	176(140–220)*	94(50–175)	55(41–60)	50(42–59)
LVP	4	120(110–125)	114(105–120)	125(115–140)	133(120–145)	136(120–150)
LV dP/dt max		2400(2100–2700)	2825(2400–3100)	2975(2100–3600)	2850(2100–3300)	3075(2200–3700)
125 µg/kg: CBF		35(19–45)	142(118–200)*	121(100–150)*	67(52–100)	54(45–65)
LVP	5	144(110–155)	149(115–165)	177(150–200)*	176(152–200)*	179(155–200)*
LV dP/dt max		3120(2700–4000)	4110(3200–5000)	5125(4000–6750)*	4190(3400–5250)	4260(3500–5250)
500 µg/kg:CBF		29(23–35)	139(89–240)*	162(95–265)*	145(60–230)*	88(48–115)
LVP	4	118(105–132)	161(130–190)	215(150–280)*	209(165–260)*	203(175–250)*
LV dP/dt max		2550(2000–3700)	5140(3300–7000)	7663(4900–11500)*	7190(5250–10000)*	6375(4500–9500)

CBF = coronary blood flow (ml/min); LVP = left-ventricular systolic pressure (mm Hg); LV dP/dt max = maximum rate of rise of LVP (mm Hg/sec). Values are means, with ranges in brackets.

* $p < 0.05$ versus control values [Friedman two-way analysis of variance by ranks, followed by a multiple comparison test (*20*)].

after injection of the ionophore. At this time, the coronary dilatation induced by 60 μg/kg grisorixin has already decreased considerably and is less than that observed with 500 μg/kg (Fig. 7). If the M/B ratio were solely dependent on the variations of coronary blood flow, the M/B obtained should be higher for the 500 μg/kg dose than for 60 μg/kg, even though the effects of 500 μg/kg are much more general and diversified. This observation suggests that the beneficial effect of grisorixin upon myocardial images may be due mainly to the induced coronary dilatation, although a specific ionophorous effect may also be involved.

The experiments performed in dogs treated with 60 μg/kg grisorixin at different times before Tl-201 do suggest a specific ionophore effect of this compound. No difference in M/B ratio is visible between dogs given Tl-201 5 and 10 min after grisorixin (Fig. 5) although the coronary dilatation induced is much greater at the former time (Fig. 7). This lends support to the hypothesis that grisorixin modifies the myocardial Tl-201 uptake both by a coronary dilatation and by an ionophore action that increases the permeability of the membranes of the myocardial cells to thallium, thus favoring its fixation. Any such ionophore effect would be positive. However, grisorixin induces a permanent exchange of monovalent cations across the cell membranes and so also permits a release of thallium from the cells into the circulating blood. This is shown by the slow but continuous decrease in the M/B observed in dogs (Fig. 3). This is also demonstrated by the experiments performed in the dogs given grisorixin after Tl-201. As shown in Fig. 6, grisorixin induces a release of thallium from the myocardium with both 60 and 500 μg/kg.

Clinical implications and limitations. Like all the monocarboxylic ionophores (*27–30*) grisorixin is a potent positive inotropic agent (*18*). Such a property could be an obstacle in diagnostic applications. However, the optimal scintigraphic effect is observed with a dose low enough so that no great modification in the myocardial contractility is observed; in fact, no significant difference at all is observed with 30 and 60 μg/kg.

We have shown that grisorixin acts mainly as a coronary dilator but also increases permeability of myocardial cells to thallium. These properties suggest that grisorixin at low doses may be clinically useful. As Gould has already pointed out (*23*), a coronary dilator can be used for diagnosis of subcritical stenosis by external detection. It might be expected that the greater the coronary dilator effect, the more visible such anomalies would become. In that sense, grisorixin should be a better drug than dipyridamole, since the coronary dilator effects of low doses seem to be greater than those of dipyridamole (*31*). However, the principle of such a technique to diagnose stenosis is based on the induction or accentuation of a discrepancy between the blood flow in the healthy area and the tissue irrigated by poststenotic arteries. This imbalance may lead to a coronary steal, which may have dangerous consequences (*32*). This may impose a restriction on the use of such a coronary dilator unless an antagonist with an immediate effect can be used, such as aminophylline with dipyridamole (*33*). To date, no such antagonist is available for grisorixin, thus limiting its use in man as a scintigraphic adjuvant.

Numerous ionophore antibiotics of the monocarboxylic polyether family have been described (*28,30*) and several derivatives of grisorixin that exhibit a variety of ionophore properties are available. We hope some of these compounds may prove to have high ionophore activities without strong coronary dilation, while others may be found to exhibit powerful coronary vasodilator properties in conjunction with very low ionophore activity. Further research with a view to finding suitable coronary-dilator antagonists is also required in order that such drugs may be useful in clinical practice.

FOOTNOTES

* Statham Model SP 2202.
† P23 Gb Statham.
‡ Beckman "9840" differentiator.

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