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PK 10139 and quinidine: interactions with digoxin concentrations in rats and dogs

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Quinidine induced an increase in digoxin plasma concentrations in rats and dogs. PK 10139, an antiarrhythmic agent 10 times more potent than quinidine, did not change digoxin plasma concentrations in these species. The results indicate that PK 10139 could be associated with digoxin without risk of side-effects.

Concomitant administration of digoxin and quinidine is regarded as a suitable therapy for the control of atrial fibrillation, ventricular ectopic beats and supraventricular arrhythmias. However, quinidine may interact with digoxin to produce elevated digoxin levels associated with gastrointestinal or cardiac side-effects (Woodcock & Rietbrock 1982).

The occurrence in our laboratory of a new class I antiarrhythmic agent, PK 10139 (1-[4-(2-t-butyl-quinolyl]-3-(4-piperidyl) propanol) (Mestre et al 1983), which, like quinidine, possesses a quinoline ring but is 5 to 10 times more potent in animals, prompted us to investigate the possible interaction of this compound with digoxin, in comparison with quinidine.

This investigation was carried out in anaesthetized rats and conscious dogs using either tritiated digoxin or unlabelled digoxin.

Materials and methods

Male Sprague Dawley rats (Charles River, France), 200 g, were anaesthetized with sodium pentobarbitone (50 mg kg^{-1} i.p.). A tracheotomy was performed and a short plastic tube was inserted into the trachea to secure the airway. The penis vein and the right carotid artery were cannulated with a polyethylene tubing for drug administration and blood sample collection, respectively. An i.v. infusion of 0·9% NaCl (saline) solution with either quinidine sulphate (7·6 mg kg^{-1} h^{-1}) or PK 10139 (7·6 and 1·5 mg kg^{-1} h^{-1}) was started at a rate of 5 ml h^{-1}. Control animals were infused with saline alone. After a 60 min infusion, digoxin (0·4 mg kg^{-1} h^{-1}) containing tracer amounts of tritiated digoxin ([12α-^{3}H]digoxin, specific activity 19 Ci $mmol^{-1}$, NEN) was infused for an additional 250 min.

At appropriate times, blood (500 μl) was collected in heparinized tubes. After centrifugation plasma was assayed for radioactivity by using a liquid scintillation spectrometer (Packard). Counting efficiency (approximately 3070) was monitored by the external standard channel method.

After the last blood sampling, the rats were decapitated and the organs removed for measurements of tissue radioactivity after solubilization in Soluene (Packard).

Experiments in dogs were on 7 male Beagles (9–14 kg) to which unlabelled digoxin (Nativelle) was administered as an initial intravenous loading dose (0·5 mg) followed by an oral maintenance dose (0·25 mg) every 24 h throughout the study. Quinidine sulphate (300 mg base, twice daily) and PK 10139 (50 mg base, twice daily) treatments were started on day 8 and continued until day 19. Digoxin was administered at 5 pm and blood samples were obtained for digoxin determination at 9 am daily except on weekends.

Plasma digoxin concentrations were measured by radioimmunoassay using [^{125}I]digoxin (kits from ORIS/CEA, France).

Results

The i.v. infusion of digoxin to anaesthetized rats at a constant rate of 0·4 mg kg^{-1} h^{-1} caused a gradual increase in plasma digoxin concentration over the 250 min infusion (Fig. 1). When quinidine infusion was started 1 h before the glycoside infusion and continued throughout the experimental period (7·6 mg kg^{-1} h^{-1}), the plasma digoxin concentration increased more rapidly and attained higher levels. At the end of the 250 min infusion, the digoxin concentration in the quinidine-treated rats was more than 60% higher than that in control animals. Animals treated with an equiactive dose of PK 10139 (1·5 mg kg^{-1} h^{-1}) yielded results that were similar to those from controls. To rule out any difference due to the lower dosage of PK 10139, a second series of experiments was performed with PK 10139 being given at the same dose as quinidine (7·6 mg kg^{-1} h^{-1}). As in the previous series, the plasma concentrations of digoxin remained similar to controls values (Fig. 1).

The same results were obtained when unchanged digoxin plasma concentrations were measured by RIA (data not shown).

Tissue concentration of digoxin (^{3}H equivalents in ng g^{-1} wet tissue) increased in lungs, spleen and pancreas ($P < 0·05$), brain and diaphragm ($P < 0·10$) from quinidine-treated rats, whereas radioactivity levels

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Table 1. Effect of quinidine (7·6 mg kg^{-1} h^{-1}) and PK 10139 (1·5 and 7·6 mg kg^{-1} h^{-1}) on the tissue concentrations of tritiated digoxin (ng g^{-1}) after 250 min infusion of 0·4 mg kg^{-1} h^{-1} of [^{3}H]digoxin.

	Control digoxin (n = 5)	Quinidine digoxin (n = 5)	PK 10139 (1·5 mg kg^{-1} h^{-1}) digoxin (n = 6)	PK 10139 (7·6 mg kg^{-1} h^{-1}) digoxin (n = 6)
Adrenal	24 820 ± 2170	29 130 ± 2470	27 440 ± 2250	29 070 ± 320
Brain	46·9 ± 3·7	70·2 ± 11·9	36·9 ± 2·5	47·4 ± 3·5
Diaphragm	595·4 ± 71·1	778·7 ± 63·2	591·5 ± 39·6	614·7 ± 42·5
Heart	704·0 ± 54·8	752·3 ± 45·7	659·7 ± 74·8	718·0 ± 53·9
Kidney	1700 ± 200	1590 ± 200	1830 ± 240	1760 ± 90
Liver	3770 ± 380	4000 ± 250	4020 ± 320	4180 ± 190
Lung	547·6 ± 62·7	717·1 ± 34·4*	526·5 ± 49·6	496·4 ± 13·9
Muscle	726·5 ± 39·0	760·8 ± 50·6	691·8 ± 38·3	705·1 ± 65·5
Pancreas	290·8 ± 53·1	520·3 ± 58·3*	175·7 ± 21·9	341·0 ± 43·2
Spleen	404·1 ± 40·8	644·3 ± 58·8*	442·1 ± 35·8	445·9 ± 34·1

* Significantly different from control values $P < 0·05$ by Student's t-test.

remained unchanged in PK 10139-treated animals whatever the administered dose (Table 1).

The chronic administration of unlabelled digoxin to dogs (0·25 mg daily) produced steady-state plasma levels (0·79 ± 0·09 ng ml^{-1}) within approximately 4 days after the loading dose. In all experiments administration of digoxin was continued for 7 days before initiating treatment with any other drug. Administration of quinidine sulphate resulted in a significant increase in plasma digoxin concentration to 1·22 ± 0·21 ng ml^{-1} ($P < 0·05$) within 48 h of beginning quinidine treatment. With continued administration of quinidine, the plasma digoxin level increased further to 1·42 ± 0·22 ng ml^{-1} ($P < 0·05$) on day 12 (i.e. after 5 days of quinidine treatment). On day 13, two dogs had died and a third one on day 14. As the toxicity was evident, the experiment was stopped (Fig. 2).

Over 5 days of orally administered PK 10139 in dogs with an average steady-state plasma digoxin level of 0·85 ± 0·14 ng ml^{-1}, no change was seen; the PK 10139 treatment was continued for one week until day 19 and the plasma digoxin concentration remained constant (1·10 ± 0·11 ng ml^{-1}). All animals remained apparently healthy after co-administration of PK 10139 and digoxin.

Discussion

Our results confirm that quinidine increases digoxin

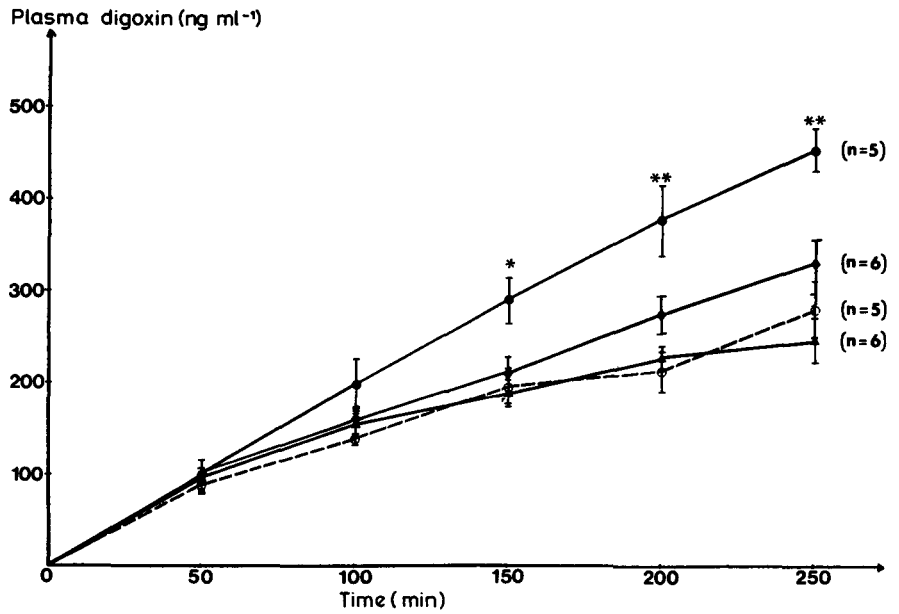

FIG. 1. Effects of quinidine (7·6 mg kg^{-1} h^{-1}) (○) and PK 10139 (1·5 and 7·6 mg kg^{-1} h^{-1}, ▲ and ◆ respectively) infusion on [^{3}H]digoxin levels induced in plasma by 250 min infusion of tritiated digoxin (0·4 mg kg^{-1} h^{-1}) in different groups (n = 5 or 6) of anaesthetized rats. —○— is control. Significantly different from control values for corresponding time points *$P < 0·05$, **$P < 0·01$ by Student's t-test.

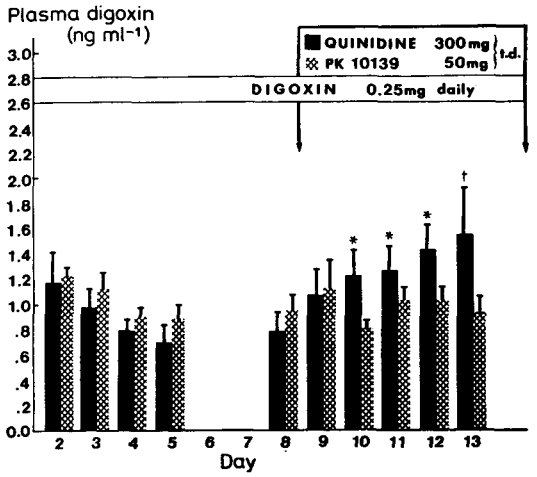

FIG. 2. Effect of repeated oral doses of quinidine (300 mg kg^{-1} twice daily, solid columns) and PK 10139 (50 mg kg^{-1} twice daily, hatched columns) on plasma digoxin concentration determined each day by radioimmunoassay in 7 dogs 16 h after oral digoxin administration (0·25 mg). *$P < 0·05$ when compared with values on day 8 by Student's t-test for paired data. †n = 5 dogs because two animals died of digitalis toxicity ($P < 0·10$).

plasma levels in rats as previously described by Kim et al (1981). But no alteration was seen with PK 10139. The higher plama levels induced by quinidine might not be related to a decreased tissue uptake of digoxin since some tissue concentrations were higher in the quinidine-treated group compared with controls.

Some conflicting results have been found by other authors regarding digoxin tissue distribution following co-administration of quinidine. Doherty et al (1980) found that in dogs with a serum steady-state level of digoxin, quinidine increased brain digoxin concentration but decreased myocardial digoxin levels. In another study (Warner et al 1982), digoxin concentrations were higher in several tissues from digoxin- and quinidine-treated animals. However, no difference was found by the same authors in another experiment comparing dogs that received digoxin alone or digoxin plus quinidine (Warner et al 1983). Finally there is no evidence of a decrease in digoxin volume of distribution in the case of quinidine-digoxin interaction.

In our experimental protocol, which is close to clinical conditions (Wilkerson et al 1980), the plasma digoxin concentrations doubled in dogs when quinidine was associated with digoxin ($P < 0·05$). Side-effects such as vomiting, diarrhoea and convulsions were observed in quinidine-treated animals. Three of seven dogs died after 7 days quinidine treatment. But no toxicity occurred in the PK 10139-treated groups. Moreover, in previous experiments (Mestre et al 1983) a good cardiovascular tolerance was observed when PK 10139 was administered during digitalis intoxication in anaesthetized dogs.

The absence of interaction observed with PK 10139 in animals suggests that this new antiarrhythmic compound might be associated in man with digoxin without risk of side-effects.

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