Pharmacokinetics of digoxin alone and in the presence of indomethacin therapy

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The effects of maintenance indomethacin therapy on single dose digoxin pharmacokinetics and dynamics were studied in six healthy volunteers with normal renal function. Indomethacin did not alter the elimination half-life, systemic clearance or distribution of digoxin. No pharmacodynamic interaction as assessed by changes in the systolic time intervals QA_2 and LVET was found. This study does not lend support for a significant digoxin-indomethacin interaction in man.

Keywords digoxin indomethacin pharmacokinetics interaction

Introduction

A variety of drugs, quinidine, verapamil, nifedipine and amiodarone, have recently been shown to increase plasma digoxin concentrations at steady-state (George, 1982). Significant elevations of serum digoxin levels have also been observed in anaesthetised dogs following the administration of indomethacin (Wilkerson *et al.*, 1980). In humans, there have been case reports of a digoxin-indomethacin interaction in premature infants, a situation where renal function is reduced (Mayes *et al.*, 1980; Schimmel *et al.*, 1980). We therefore investigated this potentially important clinical interaction in adult healthy volunteers with normal renal function. In view of the high incidence of fatal digoxin levels in anaesthetised dogs given repeated doses of digoxin (Wilkerson *et al.*, 1980), we felt it prudent in the first instance to observe the effect of maintenance indomethacin therapy on single dose digoxin pharmacokinetics and dynamics, rather than at steady-state.

Methods

The study was approved by The University Ethical Committee. Six healthy volunteers (three male, three female) with a mean $\pm$ s.e. mean age of 20 ± 2.5 years were studied. In an

open study, each subject received on Day 1, a 20 min infusion of $750 \mu\text{g}$ of digoxin. Venous blood samples for digoxin estimation were obtained at 10 and 20 min during infusion, at 10, 20, 30, 45, 60 min during the first hour after infusion and at 2, 3, 4, 5, 12, 24, 48, 72 and 96 h thereafter. Following a 7-day drug-free washout period, each subject received indomethacin 50 mg orally three times per day for 2 days before and on each study day. The digoxin infusion with blood sampling was then repeated. During the second phase of the study, daily blood samples were obtained for indomethacin levels. Plasma digoxin levels were measured using the Dac-Cel digoxin radioimmunoassay kit, incorporating a double antibody suspension and [^{125}I]-labelled digoxin, and indomethacin levels by a high performance liquid chromatographic method (Soldin & Gero, 1979). Digoxin pharmacodynamics were assessed using measurements of the systolic time intervals. Following a 15 min rest period, systolic time intervals were recorded in mid-inspiration with the subject in the supine position: recordings were made before, 0.5, 2, 4 and 6 h post-infusion and mid-morning on days 2–5. The systolic time intervals were corrected for heart rate using the linear regression equations of Weissler *et al.* (1972). Pharmacokinetic parameters were compared using the paired Student's *t*-test and pharmacodynamic values by analysis of variance and Duncan's multiple range test. Results are shown as the mean $\pm$ s.d.

Table 1 Pharmacokinetic parameters for digoxin in the absence and presence of indomethacin

	$t_{1/2}(h)$	AUC_x ($ng\ ml^{-1}\ h$)	$V_d(l)$	CL (ml/min)
Digoxin	37.2 ± 12.0	147.7 ± 78.6	311.4 ± 94.0	108.6 ± 59.1
Digoxin-indomethacin	34.9 ± 11.9	140.6 ± 49.0	276.6 ± 99.0	96.6 ± 27.3

Results

No significant differences were found in the pharmacokinetic parameters for digoxin in the absence and presence of indomethacin (Table 1). Pre-digoxin values of QA_2 (396 ms: 406 ms) and LVET (290 ms; 300 ms) were not significantly different between the two groups. Digoxin reduced the mean QA_2 (-32.3 ms) and mean LVET (-20.1 ms) at 4 h and the mean QA_2 (-27.2 ms) and mean LVET (-19.5 ms) at 6 h. In the presence of indomethacin the reductions of the means were smaller (QA_2 -25.5 and -24.4 ms; LVET -11.0 and -12.8 ms at 4 and 6 h respectively) (Table 2) but not statistically different from the values with digoxin alone. Indomethacin levels were within a therapeutically acceptable range (0.3 – $3.0\ \mu g/ml$).

Discussion

In contrast to several studies in animals (Mayes *et al.*, 1980; Wilkerson *et al.*, 1980) this single dose study does not lend support for a pharmacokinetic interaction between digoxin and indomethacin, at least in healthy subjects with normal renal function. The reasons are unclear, but one possibility is that the adequacy of renal function may be important. A possibility exists that because of the small number of subjects and the variability of the pharmacodynamic measurements (QA_2 LVET) that we failed to detect a real difference at a statistically significant level (Type 1 error).

Studies in anaesthetised animals have shown

reductions in renal blood flow after blockade of prostaglandin synthesis (Feigen *et al.*, 1976; Lonigro *et al.*, 1973). However, no reduction was observed in conscious dogs following indomethacin administration (Swain *et al.*, 1975). It has been shown that renal prostaglandin release is enhanced by noradrenaline (Gagnon *et al.*, 1976) and angiotensin II (McGiff *et al.*, 1970), both of which produce renal vasoconstriction. In animal studies, invasive procedures may result in the release of renal vasoconstrictors resulting in a reduction in renal blood flow. Inhibition of prostaglandin synthesis further potentiates the vasoconstrictor effect of angiotensin II (Negus *et al.*, 1976) resulting in an even greater fall in renal blood flow. This may explain the reports of a digoxin-indomethacin interaction occurring in anaesthetised dogs (Wilkerson *et al.*, 1980).

Although in normal human subjects indomethacin does not appear to reduce renal blood flow (Donker *et al.*, 1976), a lowering of effective renal plasma flow has been observed in patients with renal function following indomethacin administration (Donker *et al.*, 1976). Stimulation of the renin-angiotensin system induced by sodium restriction or occurring in patients with congestive heart failure, results in an increased formation of angiotensin II and renal prostaglandin synthesis. The vasoconstrictor effect of angiotensin II is therefore potentiated by inhibition of prostaglandin synthesis with a net reduction in renal blood flow (Negus *et al.*, 1976). As digoxin is principally eliminated by glomerular filtration which is dependent on renal blood flow, the potential for a digoxin-indomethacin interaction might be greater in subjects with abnormalities of renal function. This possibility has yet to be excluded.

Table 2 Reductions in systolic*time intervals QA_2 and LVET for digoxin in the absence and presence of indomethacin (mean $\pm$ s.d., $n = 6$)

		Time (h)					
		0	0.5 h	2 h	4 h	6 h	24 h
QA_2 (ms)	Digoxin	396.2 ± 17.5	381.2 ± 6.9	372.2 ± 11.4	$364.0 \pm 9.9^*$	$369.0 \pm 17.7^*$	384.2 ± 10.0
	Digoxin-indomethacin	406.7 ± 10.1	392.2 ± 4.3	390.2 ± 10.0	$381.2 \pm 11.9^*$	$382.3 \pm 10.4^*$	396.2 ± 15.8
LVET (ms)	Digoxin	290.0 ± 12.4	276.7 ± 14.4	$271.4 \pm 15.3^*$	$269.9 \pm 12.9^*$	$270.5 \pm 11.8^*$	277.7 ± 10.8
	Digoxin-indomethacin	300.0 ± 9.2	289.7 ± 11.3	$287.5 \pm 5.5^*$	$289.0 \pm 8.0^*$	$287.2 \pm 11.1^*$	296.7 ± 14.4

* $P < 0.05$ (compared to zero time)

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