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Interaction between digoxin and indomethacin or ibuprofen

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To study a potential interaction between digoxin and two non-steroid anti-inflammatory drugs, indomethacin (50 mg three times daily) and ibuprofen (600 mg three times daily) were given for 10 days to 10 and 8 patients, respectively, on chronic digoxin treatment. Serum digoxin measured by fluorescencepolarisation immunoassay increased significantly ($P < 0.05$) during treatment with indomethacin from pre-treatment values of 0.73 ± 0.34 nmol l^{-1} (mean ± s.d.) to a mean value of 1.02 ± 0.43 nmol l^{-1}, while administration of ibuprofen did not change the steady state serum concentration of digoxin. The result demonstrates that some non-steroidal anti-inflammatory drugs such as indomethacin increase serum digoxin to levels high in the therapeutic range. This should be taken into consideration when co-administrating other drugs known to increase the serum concentration of digoxin such as several antiarrhythmics.

Keywords digoxin indomethacin ibuprofen interaction

Introduction

Several papers have described a possible interaction between digoxin and non-steroidal anti-inflammatory drugs. Indomethacin was found to increase serum digoxin in preterm infants (Koren *et al.*, 1984; Schimmel *et al.*, 1980), and ibuprofen increased serum digoxin in patients with ischaemic heart disease (Quattrocchi *et al.*, 1983), while long-term treatment with either isoxicam (Zöller *et al.*, 1984), benoxaprofen (Zöller *et al.*, 1982), or tiaprofenic acid (Doering & Isbary, 1983) and single dose studies in healthy volunteers with indomethacin (Finch *et al.*, 1984) or acetylsalicylic acid (Fenster *et al.*, 1982) did not change the serum concentration of digoxin.

It is the aim of the present study to investigate in adult patients the potentially important interaction between digoxin and indomethacin or ibuprofen.

Methods

Eighteen patients (10 males and 8 females) aged 51 to 81 years were studied. All the patients had congestive heart failure in NYHA Class 2 to 3 with normal renal and hepatic function. The patients were prior to the study in long-term therapy with oral digoxin in daily doses varying from 125 to 250 μg. No patient received any drugs known to interact with digoxin and the medication was unchanged during the study.

The patients were randomised to 10 days oral treatment with either indomethacin 50 mg (10 patients) or ibuprofen 600 mg (8 patients) three times daily. Blood samples for measurement of digoxin, creatinine, aspartateaminotransferase, and lactate dehydrogenase were obtained twice with 2 days interval before start of the NSAID treatment, at the eighth and tenth day of the treatment, and again twice with 2 days interval following a washout period of 1 week. Blood samples were taken in the morning (08.30 h) after at least an 0.5 h rest with a fixed interval of 12 h after the last digoxin intake. Serum digoxin was measured with a TD_x-method by a fluorescencepolarisation immunoassay with a lower limit of detection of 0.30 nmol l^{-1} (s.d. 0.10 nmol l^{-1}) (Clark *et al.*, 1986). No analytical interference was found between indomethacin or ibuprofen and digoxin.

Data were statistically evaluated by analysis of variance and *t*-test for paired data.

The study was approved by the Ethics Committee of Copenhagen. Informed consent was obtained from all the subjects after written and oral information.

Results

Figure 1 shows serum-digoxin concentrations in 10 patients before, during and after treatment with indomethacin. As no significant differences were found between the two measurements of serum digoxin before, during and after NSAID-treatment, all serum digoxin values are expressed as a mean of these two values. After indomethacin serum digoxin increased

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significantly ($P < 0.05$) from a value of 0.73 ± 0.34 nmol l^{-1} (mean ± s.d.) before indomethacin to a mean value of 1.02 ± 0.43 nmol l^{-1} after 8 days of treatment. After cessation of indomethacin treatment, the serum digoxin values decreased to values not significantly different from the pretreatment values.

Treatment with ibuprofen did not significantly ($P > 0.1$) change the steady-state serum concentration of digoxin (Figure 2).

Renal and hepatic function was unchanged during the study period.

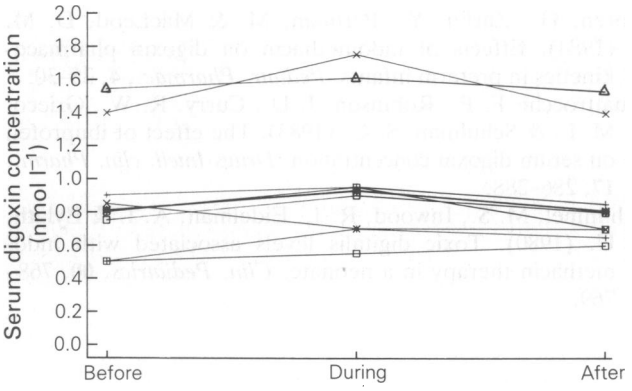

Figure 2 Digoxin serum concentrations in eight patients before, during and after treatment with ibuprofen. The mean value is marked with a full-drawn line.

Discussion

In the present study we have demonstrated a significant increase of about 40% in the serum concentration of digoxin during 8 to 10 days of treatment with therapeutic doses of indomethacin.

After discontinuation of indomethacin, digoxin concentration decreased to levels comparable with pretreatment values consistent with a specific inhibitory effect of indomethacin on the elimination of digoxin. Serum creatinine remained unchanged making a general inhibitory effect on the renal function as a basis for the interaction unlikely.

The exact mechanism of the inhibition of indomethacin on the elimination of digoxin is unknown. A competitive renal inhibition is unlikely as indomethacin and digoxin are secreted by different tubular sites (Koren, 1987). Inhibition of the prostaglandin synthesis by indomethacin might change the renal microcirculation influencing the elimination of digoxin, but no experimental studies, however, support this hypothesis.

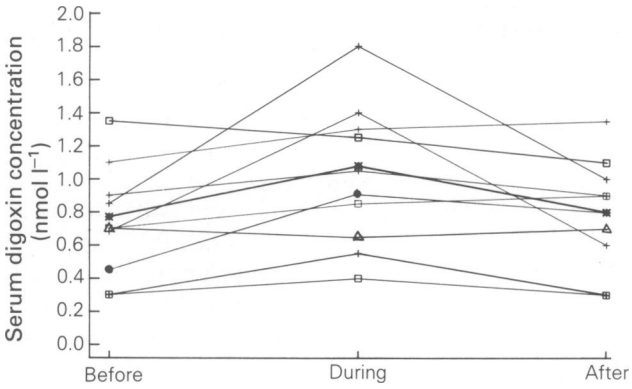

Figure 1 Digoxin serum concentrations in 10 patients before, during and after treatment with indomethacin. The mean value is marked with a full-drawn line.

An effect of indomethacin on hepatic drug metabolism, which accounts for 20–40% of the elimination of digoxin, has never been described in contrast to the inhibition by pyrazolone derivatives such as azapropazone and phenylbutazone.

In the present study therapeutic doses of ibuprofen did not change the serum concentration of digoxin. This is in contrast to the study of Quattrocchi *et al.* (1983) who in 12 patients found a significant increase in the serum concentration of digoxin after 7 days of treatment with at least 1600 mg ibuprofen daily. The concentration of digoxin decreased to pre-treatment levels after 28 days of treatment with digoxin. Doubtful compliance, sampling of digoxin before the termination of distribution, and digoxin measured in non-standardized conditions might have influenced the results. It is well known that the serum concentration of digoxin varies with physical activity (Edner, 1990).

The increase in serum digoxin after treatment with indomethacin varied from zero to more than 100%. The increase was independent of pretreatment levels of digoxin, renal function and cardiac conditions.

The serum digoxin concentrations in our patients were relatively low, and no patient showed any clinical sign of digoxin intoxication, but a 100% increase of serum digoxin after treatment with indomethacin may represent a hazard to patients with digoxin concentration values high in the therapeutic range, in particular added to a regimen including calcium antagonists or other antiarrhythmics.

References

Clark, R. D., Inloes, R. L., Kalman, S. M. & Sussman, H. H. (1986). Abott TDx, Dade Stratus, and Du Pont aca automated digoxin immunoassay compared with a reference radioimmunoassay method. *Clin. Chem.*, **32**, 381–385.

Doering, W. & Isbary, J. (1983). Der einfluss von tiaprofensäure auf die digoxin-konzentration im serum. *Arzneim.-Forsch/Drug Res.*, **33**, 167–168.

Edner, M. (1990). Serum digoxin concentration: Increase after rest in different body positions. *J. cardiovasc. Pharmac.*, **15**, 508–509.

Fenster, P. E., Comess, K. A., Hanson, C. D. & Finley, P. R. (1982). Kinetics of the digoxin-aspirin combination. *Clin. Pharmac. Ther.*, **32**, 428–430.

Finch, M. B., Johnston, G. D., Kelly, J. G. & McDevitt, D. G. (1984). Pharmacokinetics of digoxin alone and in the presence of indomethacin therapy. *Br. J. clin. Pharmac.*, **17**, 353–355.

Koren, G. (1987). Clinical pharmacokinetic significance of the renal tubular secretion of digoxin. *Clin. Pharmacokin.*, **13**, 334–343.

Koren, G., Zarfin, Y., Perlman, M. & MacLeod, D. M. (1984). Effects of indomethacin on digoxin pharmacokinetics in preterm infants. *Pediatr. Pharmac.*, **4**, 25–30.

Quattrocchi, F. P., Robinson, J. D., Curry, R. W., Grieco, M. L. & Schulman, S. G. (1983). The effect of ibuprofen on serum digoxin concentration. *Drugs Intell. clin. Pharm.*, **17**, 286–288.

Schimmel, M. S., Inwood, R. J., Eidelman, A. I. & Eylath, U. (1980). Toxic digitalis levels associated with indomethacin therapy in a neonate. *Clin. Pediatrics*, **00**, 768–769.

Zöller, B., Engel, H. J., Faust-Tinnefeldt, G., Geisller, H. E., Gilfrich, H. J. & Zimmer, M. (1982). An interaction study between benaxoprofen and digoxin. *Eur. J. Rheumatol. Inflamm.*, **5**, 82–86.

Zöller, B., Engel, H. J., Faust-Tinnefeldt, G., Gilfrich, H. J. & Zimmer, M. (1984). Untersuchungen zur wechselwirkung von isoxicam und digoxin. *Z. Rheumatol.*, **43**, 182–184.

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