ABSENCE OF A PHARMACOKINETIC INTERACTION BETWEEN QUINIDINE AND DIAZEPAM

B. Ramesh Rao and D. Rambhau

University College of Pharmaceutical Sciences, Kakatiya University, Warangal - 506 009, India

SUMMARY

Influence of diazepam on the pharmacokinetics of quinidine was studied in eight healthy human volunteers by administering 250 mg of quinidine sulphate either alone or in combination with 10 mg diazepam in a cross-over study. Quinidine in the biological samples was estimated fluorimetrically. Comparison of various pharmacokinetic parameters of quinidine (C_{max} 2.165 ± 0.457 vs 2.239 ± 0.338 μg/ml, T_{max} 2 ± 0.71 vs 2.13 ± 0.58 h, $T_{½}$ 7.004 ± 1.302 vs 7.82 ± 1.63 h, Cls/f 153.63 ± 45.65 vs 134.87 ± 31 ml/h/kg, $AUC_{0-\alpha}$ 22.131 ± 6.118 vs 24.321 ± 4.924 μg.h/ml) by means of a two tailed t-test revealed no significant ($p > 0.05$) effect of diazepam on quinidine disposition kinetics.

KEY WORDS

quinidine, diazepam, pharmacokinetic interaction

Address for correspondence:
Dr. B. Ramesh Rao
Institute of Clinical Pharmacology
Faculty of Medicine, Technical University
Fiedlerstrasse 27, D-01307, Dresden, Germany

INTRODUCTION

Administration of a tranquiliser along with cardiovascular drugs is a common practice in the treatment of heart ailments. Pharmacokinetic interactions between antiarrhythmic drugs and benzodiazepines have been studied by earlier workers /1-3/. We have undertaken a pharmacokinetic interaction study between the class I antiarrhythmic agent quinidine and diazepam in healthy human volunteers.

MATERIALS AND METHODS

Subjects and protocol

Eight healthy male volunteers (weight range: 48-62 kg, height range: 162.5-180 cms, age range: 18-26 yrs) participated in the study. They were checked by a physician to ensure that they were in good health. They were all non-smokers and neither alcoholic beverages nor any medication was allowed for two weeks before and throughout the study. All the participants were briefed about the study and they gave written consent; the local ethical committee approved the study.

The subjects were divided into two groups at random and were treated with either 250 mg plain quinidine sulphate in the form of a hard gelatin capsule or 250 mg quinidine sulphate and 10 mg diazepam (two 5 mg CALMOD® tablets) in a cross-over design with a wash-out period of 10 days between each treatment. The drug(s) was administered with a glass of water after an overnight fast. No food and drinks were allowed up to 3 h after the drug(s) administration. Blood samples were withdrawn after 0, 0.5, 1, 1.5, 2, 3, 5, 7, 10, 12, 15, 20 and 30 hours. Serum was separated and stored at -20°C until assayed.

Assay

Quinidine in the biological samples was estimated by the spectrofluorimetric method of Crammer and Issakson /4/ modified by Armand and Badinand /5/, using a sequotia Turner fluorimeter. Earlier workers /6,7/ have established the specificity of this assay method in single dose bioavailability studies comparing the fluorimetric data with those of GC-MS and HPLC techniques. Before adapting the technique non-interference of diazepam in the quinidine estimation was established.

To 0.5 ml serum or 1 ml saliva in a stoppered conical flask an equal volume of 0.1 N NaOH was added and mixed. The alkaline sample was extracted with 15 ml benzene by shaking for 30 min. Clear benzene extract was separated and washed twice by shaking for 5 min each time with 5 ml of 0.1 N NaOH. 9 ml of the benzene layer was extracted with 6 ml of 0.1 N H_2SO_4 for 10 min. The acid layer was separated and its fluorescence was measured against the blank at an excitation wave length of 350 nm and emission wave length of 450 nm. Quinidine concentrations in the unknown samples were obtained by referring to the standard graph prepared using drug spiked serum samples. The reproducibility of the assay method was tested by analysing 10 serum samples spiked with 100 ng/ml and 2 μg/ml. The mean concentrations obtained were 97 ng/ml and 2.05 μg/ml with coefficients of variation 8% and 6.5% respectively.

Treatment of the data

The bioavailability data obtained were subjected to non-compartmental computations on a computer to obtain various pharmacokinetic parameters of quinidine in both the presence and absence of diazepam. The means of various parameters thus obtained were compared by means of Student's paired t-test. The differences were tested at a probability level of 95%.

RESULTS

Mean serum levels versus time profiles of quinidine following the oral administration of 250 mg quinidine sulphate either alone or in combination with 10 mg diazepam are shown in Figure 1. The mean values of various pharmacokinetic parameters of quinidine are summarized in Table 1. None of the pharmacokinetic parameters of the drug was significantly altered ($p > 0.05$) when it was administered with diazepam.

DISCUSSION

The influence of benzodiazepines on the disposition of antiarrhythmic drugs has been studied by earlier workers. Castillo-Ferrando *et al.* /2/ observed increased digoxin half-life and reduced urinary excretion of digoxin when administered with diazepam. Guven

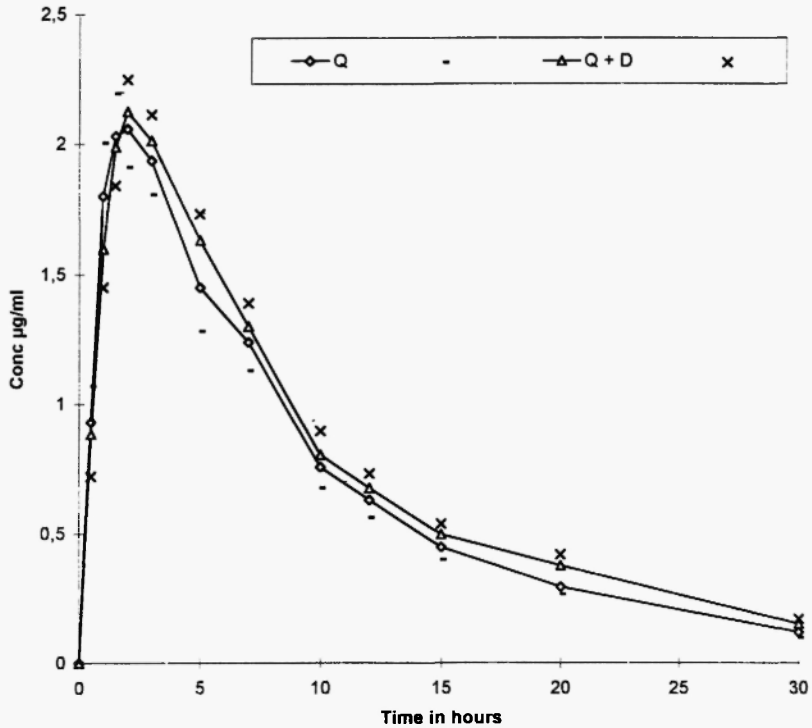

Fig. 1: Mean ± S.E.M. serum levels of quinidine following oral administration of 250 mg of quinidine sulphate either alone or in combination with 10 mg diazepam in healthy volunteers.

et al. /1/ observed a significantly higher area under the serum digoxin concentration-time curve following the addition of alprazolam to digoxin regimen in 12 patients and such an increase was more prominent in elderly patients. In contrast to this Ochs *et al.* /8/ found that therapeutic doses of alprazolam did not significantly alter digoxin clearance in healthy subjects. These reports indicate the need for more investigations involving interactions between benzodiazepines and antiarrhythmic agents.

Benzodiazepines are reported to alter the physiological functioning of the gastrointestinal tract via changes in gastric secretions, gastric emptying time and gastrointestinal motility. Birnbaum *et al.* /9/ observed a marked reduction in human basal gastric acid secretion for 5 h after either oral or parenteral administration of 10 mg diazepam.

TABLE 1

Mean + S.D. pharmacokinetic parameters of quinidine following oral administration of 250 mg quinidine sulphate either alone or with 10 mg diazepam

Parameter	Treatment	
	Quinidine (n=8)	Quinidine + Diazepam (n=8)
C_{max} μg/ml	2.165 ± 0.457	2.239 ± 0.338
T_{max} hrs	2.000 ± 0.710	2.130 ± 0.580
Ka hr^{-1}	2.516 ± 1.111	2.305 ± 0.581
T½ hrs	7.004 ± 1.302	7.820 ± 1.630
V_{ss} ltr/kg	1.480 ± 0.395	1.435 ± 0.338
Cls/f ml/hr/kg	153.630 ± 45.65	134.870 ± 31.00
AUC_{0-30} μg.hr/ml	20.845 ± 5.596	22.549 ± 3.809
$AUC_{0-\alpha}$ μg. hr/ml	22.131 ± 6.118	24.321 ± 4.294
AUMC μg.hr^2 /ml	206.31 ± 52.68	277.04 ± 81.66
MRT hrs	10.25 ± 1.22	11.24 ± 1.94

C_{max} : Peak serum levels, T_{max} : Time to C_{max}, K_a : absorption rate constant, T½ : Elimmation half life, V_{ss} : Steady state volume of distribution, Cls/f : Clearance, AUC: Area under the serum concentration-time curve, AUMC : Area under the first moment curve, MRT: Mean residence time.

Murie and Colin /10/ noted a significant reduction in pentagastrin stimulated gastric secretion after pretreatment with lorazepam in humans. In addition, increase in gastric emptying rate, enhanced amplitude of contraction and motility and increased gastric pH following ingestion of diazepam have been reported /11/. As quinidine is a weakly basic drug, its absorption would be expected to be affected due to one or more of the above changes induced by diazepam. However, the results of the present study reveal no such effect.

Diazepam is extensively bound to plasma proteins (98-99%) especially the albumin fraction /12/. Since quinidine is also primarily

bound to the albumin fraction of plasma proteins /13/, an interaction between the two drugs resulting in the displacement of quinidine from its binding sites could be expected. Displacement of quinidine from its plasma protein binding sites by heparin resulting in 120% increase in the unbound quinidine fraction was observed by Kessler *et al.* /14/. However, the results of this study do not support this view as there was no significant change in the volume of distribution of quinidine.

Although both quinidine and diazepam share some common metabolic pathways and are metabolised in the liver by hydroxylation and desmethylation /15-16/, the present study reveals no effect of diazepam on the metabolism of quinidine when the two drugs are administered together.

CONCLUSION

Since none of the pharmacokinetic parameters of quinidine was altered upon its administration with diazepam, the combination may be safely given in short term treatments.

ACKNOWLEDGEMENTS

We thank the Council of Scientific and Industrial Research, New Delhi for supporting the study financially in the form of a SRF to Dr. B. Ramesh Rao. Our hearty thanks to all the volunteers who enthusiastically participated in the study.

REFERENCES

1. Guven H, Tuncok Y, Guneri S, Covdar C, Fowler J. Age-related digoxin-alprazolam interaction. Clin Pharmacol Ther 1993; 54: 42-44.
2. Castillo-Ferrando JR, Garcia M, Carmona J. Digoxin levels and diazepam. Lancet 1980; 1: 368.
3. Dunbar RW, Boetiner RB, Haley JV, Gatz RN. The effect of diazepam on the antiarrhythmic response to lidocaine. Anesth Analg 1971; 50: 685-692.
4. Cramer G, Isaksson B. Quantitative determination of quinidine in plasma. Scand J Clin Lab Invest 1963; 15: 553-556.
5. Armand J, Badinand A. Dosage de la quinidine (ou de la quinine) dans les milieux biologiques. Ann Biol Clin 1972; 30: 599-604.
6. Huffman OH, Hignite CE. Serum quinidine concentration: Comparison of fluorescence, gas chromatographic and gas chromatographic/mass spectrometric methods. Clin Chem 1976; 22: 810-811.

7. Sved S, McGilveray IJ, Beaudoin N. The estimation of quinidine in human plasma by ion pair extraction and high performance liquid chromatography. J Chromatogr 1978; 145: 437-444.
8. Ochs HR, Greenblatt DJ, Verburg Ochs B. Effect of alprazolam on digoxin kinetics and creatinine clearance. Clin Pharmacol Ther 1985; 38: 595-598.
9. Birnbaum D, Karmell F, Tefera M. The effect of diazepam on human gastric secretion. Gut 1971; 12: 616-618.
10. Murie JA, Colin M. The effect of lorazepam on human gastric secretion. Clin Therapy 1980; 2: 387-389.
11. Schurizek BA, Asmin B, Kragiuno K, Andreasen F, Jensen LV et al. Gastrointestinal motility and gastric pH and emptying following ingestion of diazepam. Br J Anaesthesiol 1988; 61: 712-719.
12. Gilman AG et al., eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th ed; New York: Pergamon Press, 1990.
13. Conn HL Jr, Luchi RJ. Some quantitative aspects of the binding of quinidine and related quinoline compounds by human serum albumin. J Clin Invest 1961; 40: 509-516.
14. Kessler KM, Leech RC, Spann JF. Blood collection techniques, heparin and quinidine protein binding. Clin Pharmacol Ther 1979; 25: 204-210.
15. Palmer KH, Martin B, Baggett B, Wall ME. The metabolic fate of orally administered quinidine gluconate in humans. Biochem Pharmacol 1969; 18: 1845-1860.
16. Moffat AC, Jackson JV, Moss MS, Widdop B, eds. Clarke's Isolation and Identification of Drugs, 2nd Ed. London: Pharmaceutical Press, 1986.