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Lack of effect of tenoxicam on dynamic responses to concurrent oral doses of glucose and glibenclamide

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1 In a single-blind, placebo controlled study the influence of tenoxicam on responses of glucose, insulin and C-peptide to oral doses of glucose and glibenclamide was examined in 16 healthy male volunteers.

2 The subjects received once daily doses of 2.5 mg glibenclamide for 12 days. From day 5 through 12 eight subjects received concomitantly 20 mg tenoxicam once daily and the remaining eight subjects received placebo.

3 On days 1, 4, 5 and 12 glibenclamide was taken with 75 g glucose and blood glucose, serum insulin and C-peptide were measured over 5 h. Plasma levels of glibenclamide and tenoxicam (where appropriate) were followed over 10 h.

4 Characteristic parameters of blood glucose and insulin and C-peptide responses did not change significantly with time (day) and there was no difference between both treatment groups.

5 Baseline insulin increased from 11.7 mu l^{-1} on day 1 to 15.6 mu l^{-1} on day 4 ($P = 0.009$), likewise baseline C-peptide increased from 478 pmol l^{-1} to 530 pmol l^{-1} ($P = 0.05$), but there was no further change in the subsequent treatment period.

6 The AUC of the glibenclamide plasma concentration-time curve did not show changes with time or differences between treatment groups. The mean (s.d.) oral clearance of tenoxicam was 2.5 (1.5) ml min^{-1} and appeared slightly higher than in previous studies.

7 It was concluded that tenoxicam did not affect overall glycoregulation in healthy subjects under glibenclamide steady state conditions.

Keywords tenoxicam glibenclamide interaction glucose tolerance

Introduction

Tenoxicam (Tilcotil®) is a new non-steroidal anti-inflammatory drug (NSAID) belonging chemically to the oxicam group (Wiseman & Lombardino, 1981). The drug is effective in the symptomatic treatment of rheumatic and inflammatory diseases and shows a favourable tolerability (Gonzalez & Todd, 1987). The pharmacokinetics of tenoxicam are characterized by a long half-life of 70 h allowing once daily dosing. Binding of tenoxicam to plasma protein is 99% and oral bioavailability amounts to 100%. The compound is exclusively metabolized with a plasma clearance of 2 ml min^{-1} (Gonzalez & Todd, 1987).

The anti-inflammatory activity of tenoxicam is predominantly mediated by inhibition of prosta-

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glandin (PG) synthesis. PGs may play a role in the homeostasis of glucose and in insulin secretion but the findings with various PG synthesis inhibitors are rather contradictory (Micossi *et al.*, 1978; Newman & Brodows, 1983; Robertson, 1983; Robertson & Metz, 1979). Acetylsalicylic acid (ASA) was reported to enhance glucagon and insulin secretion and to increase glucose tolerance (Micossi *et al.*, 1978), and clinically relevant hypoglycaemic events were found with this drug during co-administration with sulphonylurea compounds (Hansten, 1985). In contrast, indomethacin decreased or failed to affect insulin secretion (Bratusch-Marrain *et al.*, 1985; Micossi *et al.*, 1978). Clinically important pharmacokinetic interactions were observed with sulphonylureas and phenylbutazone (Hansten, 1985). Although other NSAIDs (Morrison *et al.*, 1982; Todd & Sorkin, 1988; Verbeeck *et al.*, 1983; Whiting *et al.*, 1981) did not interfere to a clinically relevant extent with the kinetics and/or the hypoglycaemic action of sulphonylureas and also no influence of tenoxicam on glibornuride kinetics and response was found (Stoeckel *et al.*, 1985), the potential to interact with diabetic control requires the investigation of each new NSAID individually.

The purpose of the present study was to determine the effect of tenoxicam on responses of glucose, insulin and C-peptide to concomitant oral doses of glucose and glibenclamide. Plasma levels of the test drugs were furthermore to be assessed.

Methods

Subjects

Sixteen healthy male volunteers, between 20 and 41 years of age (median 26 years) and having a body weight of ±10% of ideal weight (Geigy Tables), participated. The subjects were in good health as assessed by physical examination, 12-lead ECG and clinical laboratory tests. Fasting blood glucose was in all cases within the normal range (4.2–6.1 mmol l^{-1}) and at 1 and 2 h after an oral glucose load of 75 g blood glucose concentrations were between 3.4 and 9.4 mmol l^{-1} and between 3.5 and 6.2 mmol l^{-1} respectively thus proving normal glucose tolerance. All subjects were non-smokers and none was taking any other medication the 7 days before and during the study period. Subjects gave their written informed consent and the study protocol was approved by an Ethics Committee.

Procedure

The study was conducted with two parallel treatment groups (A,B) comprising eight subjects each. Allocation to the groups was random and single-blind. Subjects of both groups received once daily oral doses of 2.5 mg glibenclamide (Semi-Euglucon®) on days 1 through 12. In group A oral doses of 20 mg tenoxicam (Tilcotil®) were administered twice daily on days 5 and 6 and once daily on days 7 through 12, while placebo matching tenoxicam was administered in group B.

On days 1, 4, 5 and 12 tablets with glibenclamide (and where appropriate with tenoxicam or placebo) were ingested together with 300 ml of a 25% aqueous glucose solution (OGTT) after an overnight fast. On all other days drugs were taken with 100 ml tap water immediately before breakfast. Intake of tablets was under the supervision of the clinical investigator on all days.

Subjects were requested to consume a diet rich on carbohydrates the 3 days before the first OGTT (day 1) and during the whole study period. During the OGTTs subjects were in a sitting position over 5 h. Blood pressure and heart rate were measured hourly for 6 h. To detect a possible glycosuria urine was quantitatively collected for 2 h after the glucose load. Before the OGTT on day 4 further laboratory tests on blood biochemistry, haematology and a urinalysis were performed for safety reasons.

Venous blood samples of 4 ml for the determination of blood glucose, serum insulin and C-peptide were collected at −10 and −5 min before and 20, 40, 60, 80, 100, 120, 150, 180, 210, 240, 270, 300 min after intake of glucose. On days 1 and 4 blood samples of 5 ml for the assessment of plasma glibenclamide and on days 5 and 12 samples of 10 ml for the assessment of glibenclamide and tenoxicam were drawn immediately before and at 0.5, 1, 2, 3, 5, 7, 10 h after drug intake. Additional blood samples of 5 ml for the determination of pre-dose plasma concentrations of tenoxicam were collected on days 6, 8, 10 and 11. Handling of samples for drug assay was under light protection (instability in light of tenoxicam) and plasma samples were stored at −20° C until analysis.

Analytical methods

Glucose in blood and urine was measured by the glucose hexokinase method. Serum insulin and C-peptide were determined by radioimmunoassays (Waldhäusl *et al.*, 1979). Tenoxicam in plasma was measured by h.p.l.c. (Heizmann *et*

al., 1986). Plasma glibenclamide was analysed using an h.p.l.c. method (Emilsson *et al.*, 1986).

Data evaluation

Blood glucose on days 1, 4, 5 and 12 was characterized by the following parameters: Fasting blood glucose was calculated as mean of the two pre-dose concentrations and served as baseline (G_b). The time of intersection with baseline (T_0) was estimated by linear interpolation between the last data point (when moving along the time axis) above baseline and the first one below baseline. The incremental area formed by blood glucose and baseline from zero to T_0 (AUC^+) and the decremental area from T_0 to 300 min (AUC^-) were assessed by the linear trapezoidal rule.

Serum insulin and C-peptide respectively on days 1, 4, 5 and 12 were characterized by baseline levels (I_b and P_b), maximum responses corrected for baseline (I_{max} and P_{max}) and area under the curves above baseline (AUC_I and AUC_P). The arithmetic means of the two pre-dose concentrations of insulin and C-peptide respectively were taken as baselines (I_b and P_b). AUC_I and AUC_P were estimated by the linear trapezoidal rule.

The pharmacokinetics of glibenclamide were characterized by the area under the concentration-time curve from time 0 to 10 h (AUC_g) which was estimated by the linear trapezoidal rule. The oral clearance of tenoxicam at steady state was calculated by CL_t = dose/AUC_t. The area AUC_t during a dosing interval of 24 h was estimated by the linear trapezoidal rule using the average pre-dose concentration of days 8–12 as 24 h value ($C_{min,ss}$).

The parameters on glucose, insulin, C-peptide and glibenclamide were evaluated by two-way analysis of variance with repeated measures in one factor (day) using a general linear model procedure (programme GLM, SAS$^{(R)}$-statistics package). The sphericity of the error covariance matrix was tested by Mauchly's criterion (Huynh & Feldt, 1970). In cases of a significant time effect (within subject effect) parameters on days 1, 5 and 12 were contrasted to the respective parameters on day 4. The level of significance was set to 0.05.

Results

Clinical report

All subjects completed the study according to the protocol. About 180 min after dosing of glibenclamide mild hypoglycaemic effects (sweating, restlessness) were observed with subject 13 (group A) on days 4, 5, 12 and with subject 16 (group B) on days 5 and 12. Medical action was not needed. Otherwise there were no reports on subjective adverse feelings during the whole study period and vital signs (BP, HR) did not show clinically relevant changes on any test day. Routine laboratory tests of haematology and blood biochemistry were without clinically important findings. Subject 6 on day 4 and subject 10 on days 4 and 5 excreted measurable amounts of glucose (< 0.45 g) into the 2 h urine after the glucose load.

Dynamic parameters

The responses (mean ± s.e. mean) of blood glucose, serum insulin and C-peptide are plotted in Figures 1, 2 and 3 respectively. Characteristic parameters of the blood glucose profile are given in Table 1 and those of insulin and C-peptide are summarized in Table 2.

The pattern with time of parameters on blood glucose did not differ significantly between both groups in any case (Day × Group, Table 1). There was no significant change with time (Day). Group differences were also not significant, but subjects in group A happened to have in general (i.e. already on day 1) a lower glucose response leading independently of time to trendwise smaller G_{max} ($P = 0.066$) and AUC^+ ($P = 0.107$).

Baseline insulin (I_b) showed a time-effect ($P = 0.021$). Further evaluation revealed a significant ($P = 0.009$) increase from 11.7 mu l^{-1} on day 1 to 15.6 mu l^{-1} on day 4, whereas no further changes occurred from day 4 onwards. Both the baseline corrected maximal insulin response (I_{max}) and the area under the insulin time-curve (AUC_I) did not change significantly with time and there were no differences between the groups (Table 2).

Baseline C-peptide (P_b) showed also a significant effect of time ($P = 0.012$). There was an increase ($P = 0.050$) from 478 pmol l^{-1} on day 1 to 530 pmol l^{-1} on day 4 and a trendwise further increase ($P = 0.095$) to 590 pmol l^{-1} on day 5 (Table 2). The overall pattern with time did not differ between groups (Day × Group) and also no differences between the groups could be detected. The parameters P_{max} and AUC_P did not change with time and there were no significant differences between the groups.

Pharmacokinetics

The limit of detection of plasma glibenclamide was 8 ng ml^{-1}. From quality control samples and

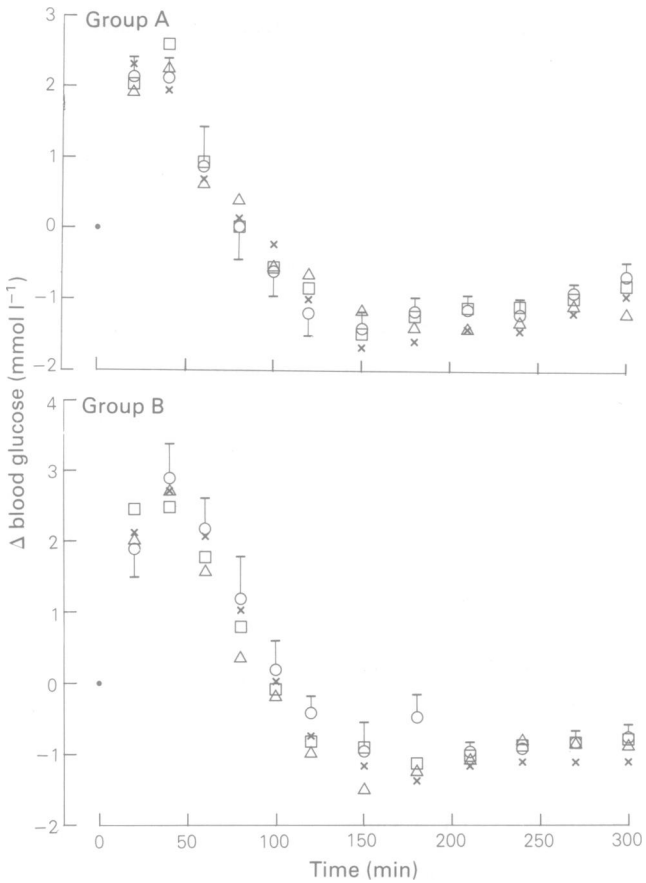

Figure 1 Blood glucose corrected for baseline (mean ± s.e. mean) in the tenoxicam group (A) and in the placebo group (B) on day 1 (○), day 4 (△), day 5 (□) and day 12 (×) respectively. The s.e. means on day 1 are representative for the other days.

Table 1 Mean (s.d.) of characteristic parameters of blood glucose corrected for baseline (G_b) in the tenoxicam group (A) and in the placebo group (B) on different days

Parameter	*Group*	*Day* 1	4	5	12	*Anova (P values)* Day × Group	Group	Day
G_b (mmol l^{-1})	A	4.2 (0.31)	4.2 (0.44)	4.2 (0.25)	4.4 (0.62)	0.925	0.685	0.117
	B	4.1 (0.44)	4.1 (0.27)	4.1 (0.38)	4.5 (0.23)			
G_{max} (mmol l^{-1})	A	2.5 (0.81)	2.5 (1.02)	2.7 (0.76)	2.5 (0.70)	0.945	0.066	0.971
	B	3.3 (1.22)	3.2 (0.68)	3.2 (0.97)	3.2 (0.97)			
G_{min} (mmol l^{-1})	A	−1.9 (0.66)	−1.9 (0.52)	−1.8 (0.75)	−2.0 (0.51)	0.946	0.453	0.803
	B	−1.6 (0.63)	−1.8 (0.84)	−1.6 (0.83)	−1.8 (0.47)			
T_o (min)	A	81 (21)	84 (29)	88 (29)	94 (19)	0.651	0.179	0.891
	B	108 (39)	106 (67)	90 (24)	100 (13)			
AUC^+ (mmol l^{-1} min)	A	115 (60)	113 (82)	125 (45)	106 (40)	0.869	0.107	0.838
	B	181 (93)	152 (74)	165 (108)	165 (83)			
AUC^- (mmol l^{-1} min)	A	236 (87)	246 (59)	235 (96)	265 (120)	0.728	0.226	0.259
	B	159 (86)	225 (103)	195 (94)	220 (95)			

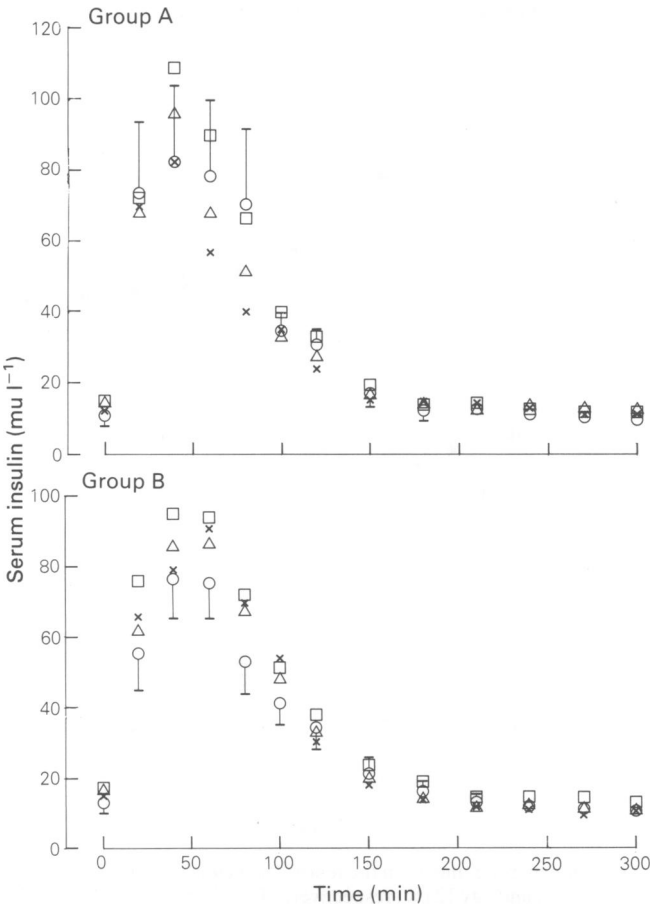

Figure 2 Serum insulin (mean ± s.e. mean) in the tenoxicam group (A) and in the placebo group (B) on day 1 (○), day 4 (△), day 5 (□) and day 12 (×) respectively. The s.e. means on day 1 are representative for the other days.

Table 2 Mean (s.d.) of characteristic parameters of serum insulin (I) and C-peptide (P) in the tenoxicam group (A) and in the placebo group (B) on different days

		Day				*Anova (P values)*		
Parameter	*Group*	*1*	*4*	*5*	*12*	*Day × Group*	*Group*	*Day*
I_b (mu l^{-1})	A	11.0 (4.0)	15.4 (4.8)	14.1 (2.9)	12.2 (3.5)	0.844	0.439	0.021
	B	12.4 (3.0)	15.8 (7.3)	16.4 (8.2)	14.7 (5.8)			
I_{max} (mu l^{-1})	A	90 (46)	82 (40)	96 (34)	80 (37)	0.529	0.747	0.241
	B	71 (28)	79 (27)	94 (28)	84 (39)			
AUC_I (mu l^{-1} min)	A	6.4 (3.9)	5.3 (2.8)	6.6 (2.6)	5.1 (2.6)	0.562	0.732	0.259
	B	5.8 (2.3)	5.9 (2.1)	7.0 (2.1)	6.3 (3.2)			
P_b (pmol l^{-1})	A	459 (164)	538 (114)	559 (80)	472 (88)	0.402	0.417	0.012
	B	497 (132)	521 (116)	621 (164)	563 (156)			
P_{max} (pmol l^{-1})	A	1660 (585)	1630 (430)	1730 (350)	1500 (370)	0.727	0.290	0.868
	B	1750 (455)	1880 (545)	1870 (575)	1900 (800)			
AUC_P (nmol l^{-1} min)	A	163 (53)	153 (49)	168 (43)	150 (37)	0.786	0.195	0.579
	B	207 (70)	180 (51)	183 (60)	185 (80)			

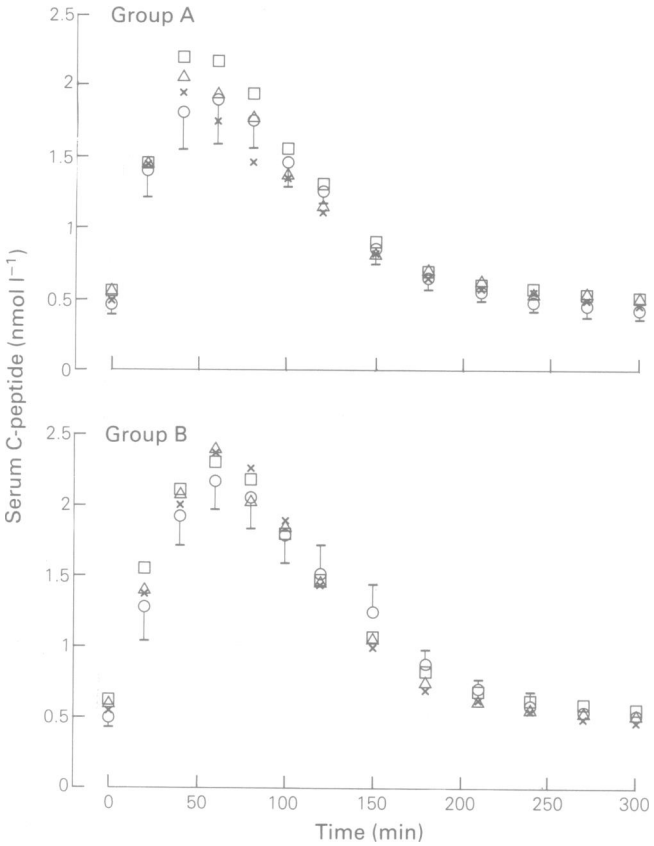

Figure 3 Serum C-peptide (mean ± s.e. mean) in the tenoxicam group (A) and in the placebo group (B) on day 1 (○), day 4 (△), day 5 (□) and day 12 (×) respectively. The s.e. means on day 1 are representative for the other days.

some replicate measurements the interassay coefficients of variation were estimated to be 17% for concentrations below 20 ng ml^{-1} and 6% above 20 ng ml^{-1}. The areas under the concentration-time curves from time 0 to 10 h (AUC_g) are depicted in Table 3. There was no change of AUC_g with time ($P = 0.803$) and also no difference between the group on tenoxicam and the placebo group ($P = 0.903$). The mean (s.d.) oral clearance of tenoxicam at steady state (CL_t) was 2.5 (1.5) ml min^{-1} and the median (range) was 2.2 (1.4–6.0) ml min^{-1}. The mean (s.d.) pre-dose concentration at steady state ($C_{min,ss}$) was 5.7 (2.5) μg ml^{-1} with an intra-subject coefficient of variation of 13% on average.

Table 3 Mean (s.d.) of the area under the concentration-time curve (AUC_g) of glibenclamide in the tenoxicam group (A) and in the placebo group (B) on different days

Parameter	*Group*	*Day* 1	4	5	12	*Anova (P values)* Day × Group	Group	Day
AUC_g	A	347 (149)	385 (126)	362 (130)	366 (129)	0.849	0.903	0.803
(ng l^{-1} min)	B	377 (133)	381 (96)	346 (79)	336 (107)			

Discussion

The present study was conducted at a steady state with respect to plasma levels of both glibenclamide and tenoxicam (pharmacokinetic steady state). Those conditions are clearly more suited to yield relevant information than do single dose interaction studies. Administration of glibenclamide together with an oral glucose load basically does not allow discrimination between an influence on glucose tolerance *per se* and/or a modulation of the hypoglycaemic (pancreatic and/or extra-pancreatic) action of glibenclamide, but this dosing scheme was nevertheless applied, because it simulates most closely the situation in therapy.

Upon initiation of the glibenclamide treatment regimen the baseline (fasting) serum levels of both insulin and C-peptide increased significantly until day 4 and day 5 respectively and remained essentially unchanged thereafter. In contrast to these findings there were no changes, whatsoever, of baseline blood glucose. The time courses of baseline insulin, C-peptide and blood glucose levels were the same in the placebo group and in the group on tenoxicam thus indicating that tenoxicam did not affect these parameters. The parallel rise of baseline insulin and C-peptide reflected most likely the effect of glibenclamide on beta-cell sensitivity to glucose as a stimulus for insulin release (Asmal & Marble, 1987). Since basal glucose utilization is only to a minor part mediated by insulin (Kolterman *et al.*, 1980), baseline blood glucose consequently did not change in spite of higher insulin levels. It is interesting to note that the pharmacodynamic response to glibenclamide, also in these healthy subjects, reached stable levels only after some days. Single dose cross-over studies without a stabilization period may therefore lead to erroneous results.

Characteristic parameters of blood glucose after the oral glucose load did not show any evidence of an effect of tenoxicam. Also glucose and glibenclamide stimulated insulin and C-peptide responses were without relevant changes. These parameters represent the results of a complicated regulatory process. One could well imagine several scenarios where an NSAID may interfere with components of this process although at the end no relevant overall effect may result. The present study design does not allow differentiation of the various components, but it appears to be warranted to conclude that tenoxicam did not affect glycoregulation under glibenclamide steady state conditions.

Several studies in humans revealed that exogenous PGs inhibit insulin secretion and impair glucose tolerance (Robertson, 1983). The lack of effect of tenoxicam and other PG-synthesis inhibitors, e.g. such as naproxen (Whiting *et al.*, 1981) and diclofenac (Todd & Sorkin, 1988), on diabetic control is therefore to a certain extent unexpected. One possible explanation for these findings could be that endogenous PG levels affect insulin secretion only to a minor extent and modification of these levels consequently then do not lead to clinically important effects. Whether glibenclamide has a counterregulatory influence on PG balance is not known. The ASA induced hypoglycaemic episodes (Micossi *et al.*, 1978) are very likely not related to the inhibition of PG-synthesis but rather represent direct effects of this drug on insulin clearance and insulin sensitivity (Bratusch-Marrain *et al.*, 1985; Newman & Brodows, 1983; Ratzmann *et al.*, 1982).

The plasma level profiles of glibenclamide showed in several cases double-peaks which did not allow us to derive pharmacokinetic parameters other than the area under the concentration-time curve up to 10 h (AUC_g). The area AUC_g essentially represented the total area to time infinity (Karttunen *et al.*, 1985; Neugebauer *et al.*, 1985) and the means ± s.d. of AUC_g in both treatment groups on different days (Table 3) compared well with the mean area of 364 ± 178 $\mu g\,ml^{-1}\,h$ ($n = 10$) found previously by using the same preparation (Neugebauer *et al.*, 1985). The lack of cumulation, as reflected by the constant AUC_g over time, is consistent with the short half-life of glibenclamide of 1–3 h (Karttunen *et al.*, 1985; Neugebauer *et al.*, 1985; Rogers *et al.*, 1982; Sartor *et al.*, 1980).

AUC_g is a measure for the oral clearance of the drug which determines its mean plasma level after repeated dosing. The present results did not indicate any influence of tenoxicam on this pharmacokinetic determinant.

The oral clearance of tenoxicam ($CL_t = 2.5 \pm 1.5$ ml min^{-1}) appeared to be slightly higher than reported by others (Gonzalez & Todd, 1987). The mean pre-dose plasma concentration in steady state ($C_{min,ss} = 5.7 \pm 2.5\ \mu g\,ml^{-1}$) likewise was rather at the lower end of the range found previously (Heintz *et al.*, 1984) and an influence of glibenclamide cannot be excluded. With regard to the undefined relationship between plasma concentrations and therapeutic efficacy of NSAIDs these findings are considered to be not of clinical relevance.

The present results do not indicate an influence of tenoxicam on diabetic control in glibenclamide treated healthy volunteers. With regard to the risk to extrapolate to arthritic

patients with type-II diabetes and to the special care which is required in any drug combination with an oral hypoglycaemic agent, a close supervision of patients on this combined treatment is warranted.

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