Lack of effect of tenoxicam on glibornuride kinetics and response

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1 The pharmacokinetics of glibornuride (25 mg i.v.) and the accompanying insulin and glucose responses were characterized in eight human subjects in the presence and absence of steady-state tenoxicam (20 mg p.o./day for 2 weeks).

2 Tenoxicam affected neither the pharmacokinetic parameters of glibornuride (systemic clearance, volume of distribution and biological half-life) nor the responses of plasma insulin and blood glucose to glibornuride.

3 The single i.v. dose of glibornuride had no detectable effect on the kinetics of tenoxicam.

Keywords glibornuride tenoxicam pharmacokinetics glucose insulin response

Introduction

Tenoxicam (Figure 1) belongs to a new chemical class (thieno-thiazine) of non-steroidal anti-inflammatory drugs (NSAID). Similar to other NSAIDs it is an inhibitor of both platelet aggregation and prostaglandin synthesis (Tanaka *et al.*, 1981). Clinically it shows a marked anti-inflammatory effect on acute and chronic inflammation and a pronounced analgesic effect on inflammatory or traumatic pain (Valdés *et al.*, 1982). Preclinical and clinical trials indicate that tenoxicam is well tolerated (Heintz *et al.*, 1984; Valdés *et al.*, 1982).

The NSAIDs interact with many drugs including the hypoglycaemic sulphonylureas (Verbeeck *et al.*, 1983). For example the hypoglycaemic effects of tolbutamide and glibenclamide were enhanced when phenylbutazone was administered concurrently (Hansen & Christensen, 1977). However, not all NSAIDs interact with sulphonylureas. Pirofen affected neither glibenclamide kinetics nor the response of insulin and glucose to

Figure 1 The structural formula of tenoxicam.

glibenclamide (Morrison *et al.*, 1982). Furthermore, neither tolmetin nor naproxen altered the pharmacological response to tolbutamide (Verbeeck *et al.*, 1983). Thus, the capacity of each new NSAID to interact with other drugs should be assessed individually. The purpose of the present study was to determine the effect of tenoxicam on the pharmacokinetics of intravenously administered glibornuride and on the response of plasma insulin and blood glucose to glibornuride.

Methods

Subject and study design

Our subjects were eight (four male, four female), healthy, volunteer medical students (ages 20–24 years; body weights 50–85 kg), from whom written informed consent was obtained before the study (Table 1). The study protocol conformed with the guidelines of the Institutional Committee on Human Investigations, Cantonal Hospital, Basel. A series of biochemical parameters (SMAC-profile) was measured for each subject on two occasions: immediately before the first dose and at the end of the sampling schedule of the second dose of glibornuride.

All subjects had a glucose tolerance test 2–3 weeks before the study. On the first study day, each subject after an overnight fast received 25 mg glibornuride intravenously over 1 min. Venous blood samples were taken before and at 5, 15, 20, 30, 45 min, 1, 2, 4, 6, 8, 12, 24 and 28 h for estimation of plasma glibornuride concentrations. Blood samples for glucose and insulin determination were taken before and at 3, 6, 9, 12, 15, 20, 30, 45 min, 1, 1.5, 2 and 3 h after the glibornuride injection. After 1 week (seventh day of study) the subjects began a daily oral regimen of 20 mg tenoxicam for the remaining 2 weeks. On study days 17, 18, 19 and 20, venous blood samples were taken immediately before the tenoxicam dose for the estimation of plasma

tenoxicam concentrations. On the 20th day, 2 h after the last dose of tenoxicam, each subject received 25 mg of glibornuride intravenously. Venous blood samples were removed for the estimation of the plasma concentrations of glibornuride and tenoxicam as well as the blood glucose and plasma insulin concentrations. These samples were taken at the same times as on day one of the study. Subjects were not allowed caffeine-containing beverages, ethanol and smoking on the study days. A standard meal (60 g carbohydrate, 30 g protein, 30 g fat) was served at 4 h after glibornuride administration.

Assays

Both tenoxicam and glibornuride concentrations in plasma were determined by high pressure liquid chromatography. The extraction procedure for both compounds was a slight modification (0.5 N HCl and 7 ml methylene chloride) of the method described by Pickup *et al.* (1981). The analytical column used was μ -Bondapak C18 or Supelcosil LC 18, 30 cm $\times$ 3.9 mm. For the eluent mixture (0.025 M KH_2PO_4 instead of 0.05 M $\text{NH}_4\text{H}_2\text{PO}_4$) and other chromatographic details see Adams & Krueger (1979). Piroxicam was used as an internal standard and the u.v. absorbance of the column eluate was monitored at 377 nm for tenoxicam and at 228 nm for glibornuride. The detection limit was 20 ng/ml

Table 1 Kinetic parameters derived from plasma concentrations of glibornuride after intravenous doses of 25 mg in the absence (Group A) and presence (Group B) of steady-state tenoxicam concentrations (20 mg/day).

	Subject	Age (years)	Weight (kg)	AUC ($\mu\text{g ml}^{-1} \text{ h}$)	CL (l/h)	V (l)	V _{ss} (l)	t _{1/2} (h)
Group A	1	21	58	19.0	1.32	18.4	18.4	9.7
	2	20	73	18.3	1.36	19.6	19.6	10.0
	3	23	82	17.3	1.44	26.4	26.2	12.7
	4	24	85	16.1	1.55	22.6	22.5	10.1
	5	24	73	11.4	2.20	20.5	20.3	6.5
	6	20	64	18.7	1.34	13.6	13.5	7.1
	7	23	70	21.6	1.16	17.1	16.9	10.2
	8	22	50	25.4	0.99	11.1	11.0	7.8
	Average $\pm$ s.d.			18.5 4.1	1.42 0.36	18.7 4.9	18.5 4.8	9.2 2.0
Group B	1	21	58	18.7	1.34	17.4	17.4	9.0
	2	20	73	20.1	1.25	19.7	19.6	10.9
	3	23	82	12.8	1.95	30.8	30.6	10.9
	4	24	85	18.7	1.34	20.5	20.3	10.6
	5	24	73	13.7	1.82	21.8	21.3	8.3
	6	20	64	23.0	1.09	15.9	15.7	10.1
	7	23	70	17.6	1.42	16.7	16.6	8.1
	8	22	50	25.3	0.99	13.8	13.6	9.7
	Average $\pm$ s.d.			18.7 4.2	1.40 0.33	19.6 5.2	19.4 5.2	9.7 1.1

for both compounds. The coefficient of variation was (i) for glibornuride 8% at 0.05 µg/ml and 0.3% at 1.5 µg/ml, and (ii) for tenoxicam, 0.5% at 2 µg/ml and 0.3% at 8 µg/ml. Blood glucose was determined with an autoanalyzer method, using glucose dehydrogenase as an oxidizing agent (Scholer *et al.*, 1980; Scholer & Piazzesi, 1976). Plasma insulin was estimated by a commercial radioimmunoassay kit (Sorin Biomedica, Saluggia, Italy).

Kinetic analysis

The plasma glibornuride concentration, time (C, t) data could be described by the biexponential equation $C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t}$, where C_1 and C_2 are the coefficients of the biexponential equation and λ_1 and λ_2 are the disposition rate constants. C_1, C_2 and λ_1 and λ_2 were estimated by fitting the equation to the data using the nonlinear least squares techniques; a weighting factor of $1/(\text{observed concentration})$ was used. The area under the C, t , curve (AUC) was calculated from the coefficients and the exponents of the biexponential equation (see above) by

$$\text{AUC} = \frac{C_1}{\lambda_1} + \frac{C_2}{\lambda_2}$$

The AUC values were used to calculate the total systemic clearance (CL):

$$\text{CL} = \frac{D_{i.v.}}{\text{AUC}}$$

The volume of distribution after pseudo-equilibrium (V) was calculated by

$$V = \frac{D_{i.v.}}{\lambda_z \times \text{AUC}}$$

where $D_{i.v.}$ was the intravenous dose and λ_z was the terminal elimination rate constant that was obtained from the biexponential equation (see above). The $t_{1/2,z}$ was calculated by $t_{1/2,z} = 0.693/\lambda_z$. The volume of distribution at steady state was calculated by a model-independent method (Benet & Galeazzi, 1979):

$$V_{ss} = \frac{D_{i.v.} \times \text{AUMC}}{(\text{AUC})^2}$$

where AUMC was the area under the first moment curve from time zero to infinity.

For tenoxicam the area under the plasma C, t curve for the last dosing interval (AUC) was calculated by the linear trapezoidal rule. The average plasma concentration at steady state (C_{av}) was calculated by

$$C_{av} = \frac{\text{AUC}(0, \tau)}{\tau}$$

where τ was the dosing interval and AUC(0, τ) was the area under the C, t curve at steady state during this 24 h dosing interval.

Statistical analysis

The Wilcoxon rank test (Snedecor & Cochran, 1978) was used to test the effect of tenoxicam on fasting glucose and insulin levels as well as on the kinetic (CL, $V, V_{ss}, t_{1/2,z}$) and dynamic (maximum response levels, time to maximum response, AUC under the response curve of insulin and glucose) parameters after glibornuride administration. In view of the non-normal distribution of the parameters used for quantification of the insulin and glucose response, the median rather than the mean values are reported.

Results and discussion

Subject identifications are listed in Table 1. All biochemical parameters (SMAC profile) including those characterizing liver (ALT, AST, γ -GT, albumin, bilirubin) and kidney function (creatinine, urea) were within the normal range for all subjects before and after the study. In addition, all subjects had a normal glucose tolerance test.

The plasma C, t data of glibornuride both in the presence and absence of tenoxicam were adequately described in all subjects by a biexponential equation. Individual as well as mean pharmacokinetic parameters (AUC, CL, $V_{ss}, t_{1/2,z}, V$) of glibornuride after both treatments are summarized in Table 1. A comparison of the parameter values of both treatments showed no statistically significant difference ($P > 0.05$) for any of them. Thus, the presence of tenoxicam at C_{av} values between 3.5 and 14.3 µg/ml, achieved in our subjects after 2 weeks treatment with 20 mg tenoxicam/day (Table 3), produced no significant influence on the pharmacokinetics of the sulphonylurea, glibornuride. The pharmacokinetic parameters of glibornuride, estimated in this study were also in good agreement with literature data (Rentsch *et al.*, 1972). Moreover, there was no detectable influence of the single intravenous dose of glibornuride on the pharmacokinetics of tenoxicam since neither the trough steady-state plasma concentrations (Table 2) nor the AUCs of tenoxicam (Table 3) were altered significantly (both $P > 0.05$) in the presence of glibornuride. Because no plasma C, t course of tenoxicam was followed in the absence of glibornuride in this study, AUC values (Table 3) were compared to literature data (Heintz *et al.*, 1984).

Figure 2 Plasma insulin (a) and blood glucose (b) concentrations in a representative subject (number 1) following intravenous administration of 25 mg glibornuride in the absence (-O-) and presence (-●-) of steady-state tenoxicam concentrations (20 mg/day).

Both glibornuride and tenoxicam belong to the class of drugs with low extraction ratios. Their clearance and steady-state concentration should therefore be affected by binding changes (Tozer, 1981). The fact that neither the clearance of glibornuride nor the trough steady-state plasma concentration of tenoxicam was altered in the presence of the other respective compound indicates that at therapeutic dosage levels no significant binding interactions occurred between the two substances.

The lack of effect of tenoxicam on glibor-

nuride kinetics was also substantiated by the insulin and glucose response to glibornuride, measured in the presence and absence of tenoxicam. Both responses were quantified by the maximum (insulin) or minimum (glucose) levels, the time of occurrence of the maximum or minimum level and the area under the corresponding response time curves (Table 4). Due to the different maximum response times of insulin (3–6 min) and glucose (30–60 min) and the different time spans for the return of the altered plasma concentrations to their base

Table 2 Trough steady-state plasma concentrations ($\mu\text{g/ml}$) of tenoxicam after a dosage of 20 mg/day.

Subject	Before glibornuride dosing				Mean ($\pm$ s.d.)	After glibornuride dosing Study day 21
	17	18	19	20		
1	6.72	6.83	5.56	4.03	5.79 ($\pm$ 1.3)	1.71 ¹
2	6.22	4.94	4.76	4.94	5.21 ($\pm$ 0.68)	4.20
3	8.97	9.63	9.37	8.62	9.15 ($\pm$ 0.44)	9.16
4	8.31	8.09	8.69	10.47	8.89 ($\pm$ 1.08)	9.46
5	5.96	6.14	5.31	6.53	5.99 ($\pm$ 0.51)	5.37
6	10.19	9.18	11.68	14.15	11.30 ($\pm$ 2.16)	12.01
7	4.84	3.96	4.77	5.06	4.66 ($\pm$ 0.48)	4.84
8	n.d.	10.06	11.03	11.86	11.0 ($\pm$ 0.9)	11.65

¹Extrapolated from 12 h value by $C(24) = C(12)e^{-\lambda_z \times 12}$

n.d. = not determined

levels (Figure 1) the areas under the response-time curves were estimated over different periods (insulin 0–90 min, glucose 0–180 min, Table 4). In addition, fasting plasma insulin and blood glucose levels were measured in the presence and absence of tenoxicam (Table 4). Comparison of the parameter values in Table 4 for both treatments revealed that tenoxicam did not change the fasting plasma insulin and blood glucose levels ($P > 0.05$) nor did it affect any of the parameters employed for quantification of the insulin and glucose response to glibornuride ($P > 0.05$ for all three parameters: maximum response level, time to maximum response, area under the plasma response curve).

In summary, it may be concluded that tenoxicam neither interfered with the kinetics of glibornuride nor disturbed the diabetic control with this substance in eight young healthy volunteers of both sexes. Moreover, there was

Table 3 Areas under the plasma concentration-time curves and average plasma concentrations of tenoxicam for a steady-state dosing interval in the presence of glibornuride.

Subject	$AUC_{(0,24)}$ ($\mu\text{g ml}^{-1} \text{h}$)	C_{av} ($\mu\text{g/ml}$)
1	84	3.5
2	116	4.8
3	236	9.8
4	256	10.7
5	167	7.0
6	314	13.1
7	142	5.9
8	344	14.3
Mean ($\pm$ s.d.)	207 ($\pm$ 95)	8.6 ($\pm$ 3.9)

no indication that the single dose of glibornuride affected the kinetics of tenoxicam.

Table 4 Effect of steady-state tenoxicam on insulin and glucose response (median values for eight subjects, range in parentheses) to 25 mg glibornuride administered intravenously

	Glibornuride	Glibornuride and tenoxicam
<i>Insulin</i>		
Fasting concentration ($\mu\text{U/ml}$)	10.8 (7.6–28.2)	12.7 (8.7–17.8)
Maximum response, ($\mu\text{U/ml}$)	62.0 (42.1–100)	61.7 (31.2–97.2)
Time to maximum (h)	3 (3–6)	3 (3–20)
$\text{AUC}_{(0, 1.5)}$ response, ($\mu\text{U ml}^{-1} \text{ min}$)	1836 (1548–3254)	1810 (1130–2424)
<i>Glucose</i>		
Fasting concentration (mmol/l)	4.35 (4.0–4.7)	4.50 (4.0–5.6)
Maximum response (mmol/l)	2.45 (1.9–2.8)	2.75 (2.0–3.1)
Time to maximum, (min)	37.5 (30–45)	37.5 (30–60)
$\text{AUC}_{(0, 3)}$ response, (mmol $\text{l}^{-1} \text{ min}$)	638 (548–713)	616 (565–673)

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