EFFECT OF PIRPROFEN ON GLIBENCLAMIDE KINETICS AND RESPONSE

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Pirprofen (a new non-steroidal anti-inflammatory agent), 200 mg 8 hourly, or placebo was administered orally to eight normal volunteers to investigate its effect on the pharmacokinetics and glucose and insulin responses after 1 mg i.v. glibenclamide. No significant changes were produced in these measures and *in vitro* studies showed no displacement of glibenclamide by pirprofen from plasma protein binding.

Introduction

Pirprofen (2-(3-chloro-4-(3-pyrrolin-1-yl)-phenyl-propionic acid) is a potent inhibitor of the prostaglandin synthetase system which inhibits both monocyte and neutrophil chemotaxis. Pre-clinical and clinical trials (van der Korst, 1981) indicate that it is a well-tolerated non-steroidal anti-inflammatory analgesic (NSAIA). Some NSAIAs may affect glucose tolerance. Thus aspirin enhances insulin and glucagon secretion and increases glucose tolerance in normal and diabetic subjects although ketoprofen and ibuprofen have no effect (Micossi *et al.*, 1978). Furthermore, naproxen has no effect on plasma glucose concentrations or insulin responses during an intravenous glucose tolerance test (Whiting *et al.*, 1981). Therefore, despite the possible regulatory rôle of prostaglandins in glucose metabolism (Robertson & Metz, 1979) the effects of NSAIAs cannot be predicted *a priori*. Kinetic interactions between NSAIAs and oral hypoglycaemic drugs have also been described, e.g. phenylbutazone may potentiate the hypoglycaemic actions of tolbutamide (Hansen & Christensen, 1977). The purpose of the study reported here was therefore to determine the effects of pirprofen on the pharmacokinetics and response of plasma insulin and blood glucose to intravenously administered glibenclamide.

Methods

Eight (four male, four female) normal healthy volunteers (ages 21–32 years; body weights 57–88 kg)

who were known to have normal glucose tolerance gave informed consent to take part in a double-blind study, the protocol of which was approved by the Guy's Hospital Medical School Ethics Committee. For 1 week before and during the whole period of the study the subjects took three regular meals, smoked less than ten cigarettes daily (if applicable: three of the females were smokers) and consumed less than one half pint of beer or equivalent daily. The subjects received pirprofen 200 mg or matching placebo 8 hourly for 10 days in a randomised crossover fashion. On the 11th day of each period subjects took their capsule and reported to the Clinical Pharmacology Unit in a fasting state. Two hours after drug ingestion an intravenous injection of 1 mg glibenclamide (Boehringer Mannheim) was administered over 3 min. Venous blood samples were taken before and at 1, 15, 20, 30, 45 min, 1, 2, 4, 6, 8, 12 and 24 h for estimation of plasma glibenclamide concentrations. Blood samples for insulin and glucose determination were taken before and at 3, 6, 9, 12, 15, 20, 30, 45, 60, 90 and 120 min after the glibenclamide injection. Caffeine-containing beverages were not allowed until the evening meal and alcohol and smoking were forbidden on test days; a standard meal (60 g carbohydrate, 30 g protein, 30 g fat) was served at 4 h.

Plasma glibenclamide concentrations in plasma were estimated by a high pressure liquid chromatographic technique (Rogers *et al.*, 1982) with a minimum level of detection of 2 ng ml⁻¹ and coefficients of variation of 11.6%, 5.3%, 6.8% at 20 ng ml⁻¹, 50 ng ml⁻¹ and 100 ng ml⁻¹ respectively. Blood glucose was

determined by a glucose oxidase method (Trinder, 1969) and plasma immunoreactive insulin was estimated by a commercial radio-immunoassay kit (Lisophase, Lepetit, Milan, Italy).

The plasma glibenclamide concentration, time data was found to be adequately fitted by a two compartment open pharmacokinetic model as represented by the biexponential function $C_t = Ae^{-\alpha t} + Be^{-\beta t}$ where C_t is concentration at time, α and β are apparent first order distribution and disposition rate constants and A and B are coefficients. These parameters were estimated by computer fitting the model to the data using a non-linear regression simplex algorithm (Nelder & Mead, 1965). Initial parameter estimates were provided by the exponential curve stripping program ESTRIP (Brown & Manno, 1978). The elimination phase half-life was found from $t_{1/2\beta} = 0.693/\beta$. Area under the plasma concentration, time curve (AUC) were calculated by the linear trapezoidal rule with appropriate extrapolation for the infinite portion of the curve and the total body clearance (CL) was calculated from Dose/AUC. The apparent volume of distribution in the β phase, V , was found from CL/β and the apparent steady-state volume of distribution from the equations of Benet & Galeazzi (1979): $V_{ss} = \text{Dose (AUMC)}/(\text{AUC})^2$ where AUMC is the area under the first moment of the plasma curve.

Results and Discussion

The estimates of the various pharmacokinetic parameters for glibenclamide after treatment with pirofen or placebo are summarised in Table 1. It was found that no significant changes were produced in the half-life or apparent volumes of distribution by administration of pirofen although the total body clearance of glibenclamide was reduced and the AUC was increased.

The estimates of $t_{1/2}$ of glibenclamide (mean 1.47 ± 0.42 h) are shorter than those published by previous

workers using a radiolabelled glibenclamide. Rupp *et al.* (1972) determined a half-life of 10 ± 2 h following 5 mg glibenclamide orally whilst Balant *et al.* (1975) using a similar dose found that the apparent half-life of total radioactivity in plasma increased with time giving values for $t_{1/2}$ up to 16 h. The present data are consistent with more recent radio-immunoassay data (Sartor *et al.*, 1980) which shows the half-life to be about 2.4 h. The reduced systemic clearance of glibenclamide after chronic pirofen administration suggests that there could be some minor inhibitory effect on glibenclamide metabolism but this is insufficient to increase the $t_{1/2}$ significantly, although this was apparently prolonged. Inhibition of metabolism of the related oral hypoglycaemic agent tolbutamide by NSAIA (phenylbutazone and oxyphenbutazone) has been described and results in 3 to 4 fold prolongation of tolbutamide $t_{1/2}$ (Pond *et al.*, 1977). V_{ss} is virtually independent of elimination rate when extraction is low and reflects drug distribution. However, for drugs like glibenclamide which are extensively bound to plasma proteins and have virtually no intracellular binding changes in the unbound fraction would produce very small changes in the apparent volume of distribution. In addition since clearance is low, and therefore likely to be a function of plasma binding, if pirofen reduces glibenclamide binding the half-life is likely to decrease (Tozer, 1981). The fact that if anything the half-life is increased by pirofen is also evidence of no effect of pirofen on the *in vivo* binding of glibenclamide.

In vitro displacement from protein binding of tolbutamide has been demonstrated with several NSAIA's (phenylbutazone, salicylate, paracetamol). Glibenclamide is relatively unaffected by such agents, perhaps because it is bound by non-ionic forces to serum albumin in contrast to the ionic forces binding tolbutamide and chlorpropamide (Brown & Crooks, 1976). In studies in which 1 ml serum was dialysed at 37°C against 1 ml Sørensen phosphate buffer (pH 7.4, 0.067 M) containing either [^{14}C]-glibenclamide (0.1, 0.3 and 1.0 $\mu\text{g ml}^{-1}$) or pirofen (3, 10 and 30 μg

Table 1 Summary of pharmacokinetic parameters of glibenclamide administered intravenously after 10 days treatment with either pirofen (200 mg, 8 hourly) or placebo to eight normal subjects

	After pirofen		After placebo		Significance of difference of means*
	Mean	s.d.	Mean	s.d.	
β (h^{-1})	0.450	0.150	0.517	0.190	NS
$t_{1/2}$ (h)	1.81	0.98	1.47	0.42	NS
AUC ($\text{ng ml}^{-1} \text{h}$)	275	64	193	61	0.015
CL ($\text{ml h}^{-1} \text{kg}^{-1}$)	52.5	13.9	78.1	28.9	0.02
V (ml kg^{-1})	136.2	86.6	154.8	43.6	NS
V_{ss} (ml kg^{-1})	111.3	60.9	125.1	38.9	NS

*Student's paired *t*-test (NS = not significant at $P = 0.05$)

Table 2 Effect of pirprofen on fasting insulin and glucose concentrations and the responses to intravenous glibenclamide

	After <i>pirprofen</i>		After <i>placebo</i>		Significance of difference*
	Median	MAD	Median	MAD	
<i>Plasma insulin</i>					
Fasting concentration ($\mu\text{U ml}^{-1}$)	9	1	11	3.5	NS
Maximum increment ($\mu\text{U ml}^{-1}$)	15.5	6	17.3	6.5	NS
Time of maximum response (min)	20	0	25	5	NS
AUC of response ($\mu\text{U ml}^{-1} \text{ min}$)	775	324	677	435	NS
<i>Blood glucose</i>					
Fasting concentration (mmol l^{-1})	4.45	0.15	4.25	0.48	NS
Maximum decrease (mmol l^{-1})	2.6	0.4	2.2	0.5	NS
Time of maximum response (min)	45	7.5	53	7.5	NS
AUC of response ($\text{mmol l}^{-1} \text{ min}$)	137	23	147	23	NS

*Wilcoxon test (NS = not significant at $P = 0.05$).

Figure 1 (a) Plasma insulin and (b) glucose concentrations following intravenous administration of 1 mg glibenclamide to eight normal subjects. Points (● after placebo; ○ after pirprofen treatment) represent medians, bars represent median absolute deviations.

ml^{-1}) or both using Dianorm® dialysis cells (Diacema AG, Switzerland) and Visking membrane (type 27/32 Serva GmbH), it was found that at all concentrations of glibenclamide the binding was 96.3%. Even with the highest pirprofen concentration this was not significantly altered, indicating no propensity for a drug-drug displacement.

The lack of effect of pirprofen on glibenclamide kinetics was substantiated by the effects of the insulin and glucose responses to glibenclamide. The overall responses are summarised in Table 2 and shown in Figure 1. Two of the eight subjects had peak insulin responses which were some four times higher than those of the others. In view of this non-normal distribution of the variates, the data is summarised by the median and its dispersion characterised by the median absolute deviation. It is clear that pirprofen administration does not change the fasting plasma insulin and blood glucose levels, nor does it affect their response to glibenclamide. It may therefore be tentatively concluded that pirprofen is unlikely to disturb diabetic control with glibenclamide although, as with any drug combination with an oral hypoglycaemic agent, this treatment requires special care and vigilance.

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