EFFECT OF NAPROXEN ON GLUCOSE METABOLISM AND TOLBUTAMIDE KINETICS AND DYNAMICS IN MATURITY ONSET DIABETICS

***B. WHITING & R.L. WILLIAMS**

The Drug Studies Unit,
University of California, San Francisco,
San Francisco, CA 94143, USA

MARA LORENZI

Metabolic Research Unit,
University of California, San Francisco,
San Francisco, CA 94143, USA

J.C. VARADY & †D.S. ROBINS

Syntex Laboratories Inc.,
Stanford Industrial Park,
Palo Alto, CA 94304, USA

- 1 The influence of the nonsteroidal anti-inflammatory drug naproxen on glucose metabolism and on tolbutamide pharmacokinetics and pharmacodynamics has been studied in ten maturity-onset diabetics.
- 2 Comparison of both plasma glucose decay curves and insulin responses during an intravenous glucose tolerance test before and after eight 12 hourly doses of naproxen revealed that naproxen had no significant influence on fasting glucose levels or on rates of glucose elimination.
- 3 When the subjects were given a combination of naproxen and tolbutamide for 3 days naproxen had no influence on tolbutamide absorption, protein binding, disposition or pharmacological effect.
- 4 Treatment with tolbutamide in maturity-onset diabetics need not be modified if concurrent administration of naproxen is contemplated.

Introduction

Naproxen ((+)-6-methoxy- α -methyl-2-naphthalene acetic acid) is a nonsteroidal anti-inflammatory (NSAI) drug which can be of value in painful inflammatory conditions such as rheumatoid arthritis, osteoarthritis, ankylosing spondylitis and gout and in the alleviation of post-operative pain and dysmenorrhoea (Brogden, Heel, Speight & Avery, 1979). It belongs to a class of drugs which is frequently associated with adverse drug interactions—principally on the basis of changes in protein binding of a concurrently-administered drug and, for certain

members of the class, a tendency to inhibit the metabolism of other drugs. Phenylbutazone, for example, both displaces warfarin from plasma albumin binding sites (Aggeler, O'Reilly, Leong & Kowitz, 1967; Solomon & Schrogie, 1967) and, more importantly, inhibits S-warfarin metabolism to such an extent that augmented anticoagulation can occur (Lewis, Trager, Chan, Breckenridge, Orme, Rowland & Schary, 1974; Schary, Lewis & Rowland, 1975).

As a disturbance in the protein binding or metabolism of sulphonylureas could seriously compromise established diabetic control, we considered that it was important to study the combination of naproxen and a representative sulphonylurea, tolbutamide, in diabetic patients. This study, therefore, was designed to assess the influence of naproxen on the pharmacokinetics and pharmacodynamics of tolbutamide when

Present addresses:

*Department of Materia Medica, University of Glasgow, Stobhill General Hospital, Glasgow, G21 3UW, Scotland, and †International Clinical Studies, Syntex Research, 3401 Hillview Avenue, Palo Alto, CA 94304, USA

Figure 1 Dosing sequence and general plan for the naproxen-tolbutamide drug interaction study. 8a, 8p represent 08.00 h and 20.00 h each day. The break in the baseline after Day 5 and before Day 13 represents the washout period between the two parts of the study.

both drugs were administered orally to steady state. The protocol was also designed to include an assessment of the influence of naproxen on glucose metabolism, because in common with salicylates and other NSAIs, the anti-inflammatory activity of naproxen is probably mediated via inhibition of prostaglandin synthesis—a phenomenon which may also be implicated in modifying the regulation of insulin secretion in response to an acute glucose challenge (Chen & Robertson, 1978; Giugliano, Torella, Siniscalchi, Improta & D'Onofrio, 1978; Robertson & Chen, 1977; Robertson & Metz, 1979; Widström, 1976).

Methods

Ten patients with adult onset diabetes were selected for the study, aged 25–55 years and weighing 60–114 kg. There were six males and four females. An unequivocal diagnosis of diabetes mellitus was based on fasting blood sugars or glucose tolerance tests which adhered to the criteria laid down by the American Diabetes Association (Danowski, 1964). The study was approved by the Committee on Human Re-

search, University of California Medical Center, San Francisco and written, informed consent was obtained from each patient.

Each patient was assessed by clinical and laboratory examination, including complete haematological screening, SMA-12 profile and urinalysis. Previous exposure to oral hypoglycaemics or insulin were not grounds for exclusion, but as all antidiabetic agents (and any other medications, including over-the-counter preparations) were to be stopped one week before the start of the study it was essential that carbohydrate intolerance could be managed adequately for short periods by diet alone. Each patient was therefore instructed to follow an American Diabetes Association diet consisting of 25 calories $\text{kg}^{-1} \text{ day}^{-1}$.

Patients were excluded if there was any evidence of renal, cardiac, haematological, ophthalmological or hepatic disease, or if there was a diastolic blood pressure in excess of 100 mm Hg. Any allergy to sulphonamide derivatives, oral hypoglycaemics or non-steroidal anti-inflammatory drugs or a history of alcohol or drug abuse automatically excluded patients, as did pregnancy—or the likelihood of pregnancy.

Table 1 Characteristics of ten patients with non-insulin requiring diabetes mellitus

Number	Age (years)	Sex	Race	Height (in)	Weight (kg)	Sequence*	Other drug during study	Diagnosis of diabetes
1	54	M	C	70	87.4	AB	No	FBS = 167 mg%
2	25	F	C	64	94.1	BA	No	FBS = 141 mg%
3	52	F	C	68	82.0	AB	No	FBS = 286 mg%
4	53	M	C	75	114.0	BA	No	FBS = 356 mg%
5	51	F	C	62	75.0	AB	Hydralazine	FBS = 300 mg%
6	55	M	C	70	78.4	BA	No	FBS = 121 mg%
7	46	M	C	71	79.1	AB	No	Diabetic GTT
8	48	M	C	66	60.0	BA	No	FBS = 179 mg%
9	34	F	C	65	91.7	AB	No	Diabetic GTT
10	37	M	C	71	71.6	BA	No	FBS = 189 mg%

*The sequence of Part A followed by Part B was reversed in half of the volunteers.
FBS Fasting blood sugar, GTT glucose tolerance test.

The study was divided into two parts—A and B. In A, the influence of naproxen on glucose metabolism was assessed, and in B, the influence of naproxen on tolbutamide disposition and pharmacological effect was assessed. The sequence of the parts was reversed on a random basis in half the patients. Clinical details are reviewed in Table 1 and the general plan of the study is shown in Figure 1. As treatment schedules were relatively brief and simple and patients were seen each day throughout both parts of the study, compliance was assured as far as possible by daily tablet counts.

A. Influence of naproxen on glucose metabolism

On day 1, after an 8 h fast, an indwelling venous line was inserted into a forearm vein and after control blood samples were withdrawn (for blood glucose and immunoreactive insulin levels) 25 g glucose ($D_{50}W$) were administered intravenously within 3 min through a contralateral forearm vein. Blood samples were then withdrawn as follows: at 1, 5, 10, 20, 30, 40, 50 and 60 min (for glucose) and at 1, 5, 10, 30 and 60 min (for insulin). Plasma and serum were separated immediately after collection and stored at $-20^{\circ}C$ until required for analysis.

After the last sample patients were instructed to take naproxen, 0.375 g 12 hourly for eight doses, starting on the evening of Day 1 and ending at 08.00 h on Day 5. On Days 2–5, drug regimens were reviewed at 08.00 h and a blood sample was withdrawn for subsequent measurement of naproxen concentration and protein binding.

On Day 5, after an 8 h fast, glucose tolerance was again assessed exactly as on Day 1. The intravenous glucose was administered concurrently with the last dose of naproxen after blood samples had been taken for baseline glucose and immunoreactive insulin levels, and for the final determination of naproxen concentration and protein binding values.

After the glucose tolerance test, patients were allowed to resume their diet, but were asked to refrain from all antidiabetic medication until the start of Part B on Day 13.

B. Influence of naproxen on tolbutamide disposition and pharmacological effect

On Day 13, patients were instructed to start taking tolbutamide, 0.5 g orally twice daily for a total of 5 doses (Figure 1). Immediately before the first dose, a control blood sample for tolbutamide concentration and protein binding was taken. These values were determined before the first dose of tolbutamide on Day 14 and then on Day 15, after an 8 h fast, tolbutamide and glucose kinetics were assessed simultaneously together with insulin response. Thus blood samples were taken at frequent intervals over the

following time periods: for glucose and tolbutamide, 0–8 h, extended to 24 h for tolbutamide; for insulin, 0–1 h (seven samples). To permit the characterisation of a full 24 h tolbutamide profile, no further tolbutamide was given on Day 15. To permit analysis of an uninterrupted glucose profile on Day 15, patients remained fasting until 8 h after the dose of tolbutamide but they were monitored carefully—both biochemically and clinically—for evidence of hypoglycaemia.

On Day 16, patients were instructed to start taking naproxen, 0.375 g orally twice daily concurrently with tolbutamide, 0.5 g twice daily for a total of 7 doses. Trough concentrations and protein binding values were measured each morning thereafter on Days 16 to 19 and on Day 19, glucose and tolbutamide kinetics together with insulin response were assessed as before, after taking the final dose of tolbutamide and naproxen.

Within a few days of the end of the study, patients were given a final clinical, haematological and biochemical examination.

Analytical methods

Plasma glucose levels were determined by a specific assay based on the rate of oxygen consumption in a sample following exposure to glucose oxidase in a Beckman Glucose Analyser (Beckman Instruments, Inc., Fullerton, CA 92634, 1970).

Plasma insulin levels were determined by radioimmunoassay (Grodsky & Forsham, 1960).

Tolbutamide concentrations were determined by gas liquid chromatography (Matin & Rowland, 1973) with chlorpropamide as the internal standard. The coefficient of variation was 4.0%.

Naproxen concentrations were determined by gas liquid chromatography (Upton, Buskin, Guentert, Williams & Riegelman, 1980) using the methyl ester of 6-methoxy-2-naphthyl-acetic acid as internal standard.

Naproxen and tolbutamide protein binding determinations were carried out by equilibrium dialysis (Weder, Schildknecht & Kesselring, 1971) at $37^{\circ}C$ against Krebs-Ringer buffer for a period of 5 h for tolbutamide and 6 h for naproxen. Spectrapor 6 Dialysis Membrane was used, with a molecular cut-off of 2000 (VWR Scientific). For tolbutamide determinations, [^{14}C]-tolbutamide was used (New England Nuclear Boston, Mass.). For naproxen determinations, [3H]-naproxen was used (Syntex Laboratories, Palo Alto, California). The fraction of drug unbound in plasma, f_p , was determined by dividing the radioactivity in buffer by the radioactivity in plasma.

To exclude the possibility of erroneous results from labelled impurities, extraction of naproxen and thin-layer chromatography of selected buffer samples was

performed (Slattery, Levy, Jain & McMahon, 1979). In each instance the radioactivity migrated with unlabelled naproxen and recovery of radioactivity in association with naproxen was 90%, suggesting that radioactivity measured in buffer was attributable to labelled naproxen and not to labelled impurities. A similar approach applied to tolbutamide indicated that there was no significant contribution of labelled impurities to the value for radiolabelled tolbutamide in buffer.

Pharmacokinetic analysis

Each patient's plasma tolbutamide concentrations on Days 15 and 19 were analysed in terms of a one compartment steady state equation (Gibaldi & Perrier, 1975) thus:

$$C_x = \frac{k_a F X_0}{V_d (k_a - k_d)} \left[\left(\frac{1}{1 - e^{-k_d \tau}} \right) e^{-k_d (t-T)} - \left(\frac{1}{1 - e^{-k_a \tau}} \right) e^{-k_a (t-T)} \right]$$

where C_x is the drug concentration at any time t ,
 F is the fraction of the drug absorbed
 X_0 is the dose (0.5 g)
 k_a is the absorption rate constant
 k_d is the elimination rate constant
 T is the apparent lag time prior to the onset of absorption
 τ is the dosage interval (720 min)
 V_d is the volume of distribution

Clearance/ F could be calculated from the expression

$$\frac{\text{Clearance}}{F} = k_d \cdot \frac{V_d}{F}$$

and as it was assumed that tolbutamide absorption was essentially complete, Cl/F and V_d/F could be expressed directly as Cl and V_d . Thus the four parameters k_a , k_d , V_d and T were estimated by nonlinear least squares regression analysis of the concentration v time data (Holford, 1979).

Results

Unless otherwise stated, statistical results are based on the evaluation of the t -statistic for paired observations. Results are presented as the mean for each group, followed, in parenthesis, by the standard deviation of the difference between paired observations, s_Δ , and the associated two-tailed probability value. A P value of less than 0.05 indicates a statistically significant result.

Part A

(a) *Plasma glucose data* An example of the plasma glucose concentrations following a glucose tolerance test in one patient is shown in Figure 2, and this

Figure 2 Plasma glucose levels following 25 g glucose intravenously in one patient (No. 6) before (○) and after (●) naproxen had been administered orally to steady state. Glucose elimination rate constant before naproxen (---) was 0.0085 min^{-1} ; after naproxen (—) it was 0.0097 min^{-1} .

reflects the overall impression that naproxen administered to steady state had little effect on plasma glucose levels. Although there were slight differences between fasting blood glucose levels, pre- and post-dosing with naproxen (pre-dosing, mean = $152.2 \text{ mg}\%$; post-dosing, mean = $165.9 \text{ mg}\%$ ($s_\Delta = 16.3$, $P = 0.026$) corresponding glucose elimination rate constants were not significantly different: before naproxen, mean = 0.0081 min^{-1} ; after naproxen, mean = 0.0076 min^{-1} ($s_\Delta = 0.0030$, $P = 0.658$). Individual results are shown in Table 2.

Table 2 Glucose elimination rate constants in ten diabetic patients pre- and post-dosing of naproxen to steady state.

Patient	Elimination rate constant (min^{-1})	
	Pre-naproxen	Post-naproxen
1	0.0055	0.0055
2	0.0087	0.0102
3	0.0057	0.0037
4	0.0029	0.0050
5	0.0101	0.0114
6	0.0085	0.0097
7	0.0070	0.0059
8	0.0077	0.0053
9	0.0168	0.0094
10	0.0080	0.0105
Mean	0.0081	0.0076

$s_\Delta = 0.0030$, $P = 0.658$

(b) *Plasma immunoreactive insulin* There were no significant differences in fasting or peak plasma insulin concentrations before or after naproxen in response to intravenous glucose. Mean fasting level before naproxen was 22.4 mU/ml; after naproxen, it was 19.6 mU/ml ($s_{\Delta} = 5.0$, $P = 0.110$). Mean peak level before naproxen was 30.4 mU/ml; after naproxen it was 29.7 mU/ml ($s_{\Delta} = 4.9$, $P = 0.618$).

(c) *Naproxen concentrations* The naproxen trough concentrations measured on the second to the fifth days in Part A confirmed that steady state had been achieved by the fourth day and that with one exception, concentrations stabilised between 25 and 55 $\mu\text{g/ml}$. The single exception (patient 2) showed a decline in naproxen concentration on Day 5—probably the result of neglecting to take the evening dose on Day 4. However, as naproxen was administered under supervision on Day 5, there is no doubt that this subject (as well as the others) possessed significant concentrations of naproxen at the time of the second intravenous glucose tolerance test.

Part B

(a) *Tolbutamide pharmacokinetics* Final parameter estimates of tolbutamide absorption and disposition before and after administration of naproxen to steady state are shown in Table 3. A typical tolbutamide plasma concentration profile before and after naproxen is shown in Figure 3. In evaluating the significance of these results, Patient 1 was excluded because of difficulty in obtaining satisfactory fits to the data and the finding of a markedly prolonged half-life and reduced clearance in comparison with

Figure 3 Plasma tolbutamide concentrations in the 12 h period following a single oral 500 mg dose at steady state in one volunteer (No. 2) before (○) and after (●) naproxen had been administered orally to steady state. The broken (○---○) and continuous (●—●) lines represent the best least square fits to the data. Also shown in the lower part of the figure are simultaneously measured plasma glucose concentrations over the 8 h period following tolbutamide, pre (○) and post (●) dosing with naproxen. (x) are coincident points.

other subjects. Despite this, this patient's kinetics were unaffected by exposure to naproxen. For the remaining nine patients naproxen did not alter the absorption or disposition of tolbutamide: none of the paired values presented in Table 3 showed any significant differences.

Table 3 Absorption and disposition parameters for tolbutamide before (T) and during (T + N) naproxen dosing to steady state in ten diabetic patients.

Patient	$k_a (\text{min}^{-1})$		$k_d (\text{min}^{-1})$		$T_{lag} (\text{min})$		Half-life (min)		$V_d (l)$		Cl (ml/min)	
	T	T+N	T	T+N	T	T+N	T	T+N	T	T+N	T	T+N
1*	(0.0155)	(0.0706)	(0.00072)	(0.00035)	(11.3)	(105.0)	(964)	(1960)	(5.60)	(11.30)	(4.0)	(4.0)
2	0.0405	0.0778	0.0016	0.0013	59.0	52.8	437	548	8.78	12.30	13.9	15.5
3	0.0530	0.0313	0.0021	0.0019	43.5	35.6	334	373	9.95	8.21	20.6	15.2
4	0.0196	0.0069	0.0015	0.0023	39.3	58.2	459	301	11.70	7.83	17.6	18.0
5	0.0052	0.0089	0.0012	0.0012	35.8	40.8	585	555	6.15	6.17	7.3	7.7
6	0.0385	0.0144	0.0016	0.0014	55.0	54.0	429	482	10.70	11.50	17.3	16.5
7	0.1890	0.0464	0.0012	0.0015	59.3	50.2	572	470	8.40	8.27	10.2	12.2
8	0.0070	0.0204	0.0021	0.0022	109.0	216.0	337	318	6.64	7.31	13.7	15.9
9	0.0149	0.0753	0.0021	0.0015	81.7	50.8	335	471	10.40	13.60	21.5	20.0
10	0.0292	0.0068	0.0020	0.0021	51.8	18.3	350	323	8.04	8.88	15.9	19.0
Mean	0.0442	0.0320	0.0017	0.0017	59.4	64.1	426	427	8.97	9.33	15.3	15.6
s_{Δ}	0.0570		0.0004		41.67		95		2.27		2.6	
P	0.54		1.0		0.74		0.99		0.64		0.79	

* These parameter values are not included in the statistical analysis.

(b) *Plasma glucose data* In seven patients (2–8) plasma glucose concentrations were either identical or so similar that the differences were clinically unimportant after tolbutamide and after the concurrent administration of naproxen and tolbutamide. In three patients (1, 9 and 10) glucose levels were slightly to moderately lower during naproxen administration, but the differences were not substantial and again, were clinically unimportant. Moreover, at no time were there any symptoms of hypoglycaemia. Paired *t*-tests on fasting and nadir glucose levels after tolbutamide alone, and after tolbutamide and naproxen, showed no significant differences (Table 4).

Table 4 Fasting and nadir plasma glucose concentrations on the final days of dosing of tolbutamide alone (T) and of tolbutamide plus naproxen (N + T) in ten diabetic patients.

Patient	Plasma glucose (mg %)			
	Fasting		Nadir	
	T	T + N	T	T + N
1	109	77	61	61
2	155	157	75	71
3	224	236	110	112
4	158	160	90	92
5	99	130	66	63
6	120	113	78	72
7	73	88	67	68
8	98	97	72	72
9	116	95	71	71
10	160	152	89	53
Mean	131	131	78	74
s_{Δ}		18.0		11.4
<i>P</i>		0.9		0.25

(c) *Plasma immunoreactive insulin* There were no significant differences in fasting or peak plasma insulin concentrations after tolbutamide and after tolbutamide and naproxen. Mean fasting level after tolbutamide alone was 22.3 mU/ml; mean fasting level after tolbutamide plus naproxen was 21.4 mU/ml ($s_{\Delta} = 13.1$, $P = 0.82$) mean peak level after tolbutamide alone was 23.0 mU/ml; mean peak level after tolbutamide plus naproxen was 24.1 mU/ml ($s_{\Delta} = 12.7$, $P = 0.79$).

(d) *Naproxen concentrations* The naproxen trough concentrations measured on the second to the fourth days in Part B confirmed that steady state had been achieved by the last day of naproxen dosing, and that compliance during this phase was uniformly good.

(e) Protein binding determinations

1. Tolbutamide protein binding

Mean values for the fraction of tolbutamide unbound in plasma (f_p) in the 8 h following the last dose of tolbutamide or of tolbutamide and naproxen are shown in Table 5. In eight of the ten patients (2, 4–10), no significant changes in f_p occurred. In one

Table 5 Tolbutamide f_p values* in ten diabetic patients before and during naproxen dosing to steady state.

Volunteer	Tolbutamide	Tolbutamide plus naproxen	s_{Δ}	<i>P</i>
1	0.072	0.044	0.014	0.0016
2	0.060	0.057	0.011	0.51
3	0.065	0.078	0.011	0.018
4	0.081	0.075	0.011	0.27
5	0.055	0.057	0.004	0.14
6	0.064	0.062	0.004	0.29
7	0.058	0.054	0.007	0.17
8	0.054	0.059	0.017	0.46
9	0.054	0.053	0.004	0.57
10	0.061	0.058	0.008	0.30

* The values shown here represent the mean fraction of tolbutamide unbound in plasma in seven samples taken in the 8 h period after drug administration. A paired comparison of each of these samples was used to derive the individual *P* values.

patient (1) f_p values were significantly lower following naproxen, and in patient 3, this trend was reversed.

2. Naproxen protein binding

Values for naproxen binding during dosing to steady state indicated that there was no substantial or persistent change over the concentration range achieved in this study. The mean f_p value for all patients on Day 2 was 0.0344; on Day 4 it was 0.0342 ($s_{\Delta} = 0.0330$, $P = 0.98$).

Discussion

This study was designed to answer two questions, (a) what is the influence of naproxen on glucose metabolism and (b) what is the influence of naproxen on the pharmacological effect, pharmacokinetics and plasma protein binding of tolbutamide in diabetic patients when both drugs are administered orally to steady state? Single dose interaction studies with tolbutamide may fail to reveal an effect that is subsequently shown by longer term dosing, (Pond, Birkett & Wade, 1977) and steady state was therefore assured in the present study.

Taking an overall view, the first part of the study showed that naproxen had essentially no effect on glucose metabolism. This is surprising because naproxen, in common with salicylates and other NSAIs, is thought to exert its anti-inflammatory effect via inhibition of prostaglandin synthesis. Prostaglandins, notably prostaglandin E_2 , may be implicated in the regulation of glucose homeostasis (Metz, Fujimoto, & Robertson, 1979; Robertson, Gavereski, Porte & Bierman, 1974; Robertson & Chen, 1977; Robertson & Metz, 1979). Partial restoration of the acute insulin response in adult onset diabetics has

been achieved with sodium salicylate (Chen & Robertson, 1978) and a similar aspirin-induced improvement in glucose tolerance has been reported (Giugliano *et al.*, 1978; Micossi, Pontiroli, Baron, Tamayo, Lengel, Bevilacqua, Raggi, Norbiato & Foa, 1978). Current theory proposes that an endogenous substance, possibly produced in the pancreas (perhaps prostaglandin E, somatostatin, or a catecholamine), has a role in defective β cell function in diabetes. This substance may inhibit the production and/or secretion of insulin, and prostaglandin synthesis inhibitors, such as salicylates and NSAIs, may act as derepressors. The only significant change in the first part of the present study was a rise in fasting glucose levels, but this effect was not noted in the second part. Although a paired comparison (*t*-test) of pre- and post-naproxen glucose levels in Part A indicated a significant change ($P = 0.026$), the mean difference between these levels was only 13.7 mg%; this would not be clinically important. Moreover, as this effect was not observed in Part B it seems likely that it resulted from some failure to adhere strictly to dietary instructions. This, together with the lack of modification of the insulin response and the failure to influence the rate of glucose decay, strongly supports the view that naproxen did not alter glucose metabolism in these patients.

There is theoretical justification for assuming that naproxen might have a protein binding displacement action on tolbutamide because both drugs are extensively bound to plasma proteins but no *in vitro* data exists, as yet, to substantiate this. Naproxen causes a small but statistically significant increase in the free fraction of warfarin in serum (Slattery *et al.*, 1979) but this has no pharmacokinetic or pharmacodynamic consequences. Tolbutamide is somewhat less extensively bound than warfarin, but as initial (pre-naproxen) binding values in the present study were of the order of 94% (mean f_p 6.24 ± 0.86 (s.d.)%), it is possible that displacement could have led to transient increases in free tolbutamide tissue levels. The

administration of halofenate to healthy young men increased serum levels of tolbutamide and enhanced its hypoglycaemic effect in diabetic patients (Jain, Ryan & McMahon, 1975), but these authors were unable to demonstrate a redistributional phenomenon because their analysis was based solely on total and not on free drug concentrations. The f_p results in Table 4 indicate that any shifts in tolbutamide binding that occurred as a result of naproxen administration were negligible in the context of redistribution. It can be concluded that naproxen had no effect on tolbutamide binding in these patients.

Inhibition of tolbutamide metabolism by NSAIs—notably phenylbutazone and oxyphenbutazone—has been conclusively demonstrated by 3 to 4 fold increases in tolbutamide half-lives (Pond *et al.*, 1977) and it is possible that the prolonged tolbutamide half-lives noted after halofenate (Jain *et al.*, 1975) were also due to a similar mechanism. No such changes, however, were found after naproxen in the present study. Furthermore, the lack of effect on tolbutamide kinetics was substantiated by the finding that there were no differences in glucose and insulin profiles before and after the concurrent administration of naproxen.

These findings suggest that naproxen may be useful in maturity-onset diabetics because it does not disturb diabetic control in the short term. However, the present study was conducted over a relatively short period and if naproxen was to be given in association with tolbutamide over a longer period it would then be prudent to exercise the same degree of awareness that would be appropriate with any combination of drugs used in the treatment of a diabetic patient.

We are most grateful to the following colleagues for assistance with this study: Alison Fast (clinical study); Thomas Tozer and May Huang (tolbutamide assays); Svein Oie and Matthew Jones (protein binding determinations); Nicholas H.G. Holford (data analysis); Barbara Sullivan (Clinical Research Associate, Syntex Laboratories).

References

- AGGELER, P.M., O'REILLY, R.A., LEONG, L. & KOWITZ, P.E. (1967). Potentiation of anticoagulant effect of warfarin by phenylbutazone. *New Engl. J. Med.*, **276**, 496–501.
- BROGDEN, R.N., HEEL, R.C., SPEIGHT, T.M. & AVERY, G.S. (1979). Naproxen up to date: A review of its pharmacological properties and therapeutic efficacy and use in rheumatic diseases and pain states. *Drugs*, **18**, 241–277.
- CHEN, M. & ROBERTSON, R.P. (1978). Restoration of the acute insulin response by sodium salicylate. A glucose dose-related phenomenon. *Diabetes*, **27**, 750–756.
- DANOWSKI, T.S. (1964). *Diabetes mellitus: Diagnosis and treatment*. American Diabetes Association, Inc; New York.
- GIBALDI, M. & PERRIER, D. (1975). In *Pharmacokinetics*, p. 110, New York: Marcell Dekker Inc.
- GIUGLIANO, D., TORELLA, R., SINISCALCHI, N., IMPROTA, L. & D'ONOFRIO, F. (1978). The effect of acetylsalicylic acid on insulin response to glucose and arginine in normal man. *Diabetologia*, **14**, 359–362.
- GRODSKY, G.M. & FORSHAM, P.H. (1960). An immunochemical assay of total extractable insulin in man. *J. clin. Invest.*, **39**, 1070–1079.

- HOLFORD, N.H.G. (1979). Drugfun. In *Public Procedures: A Program Exchange for Prophet Users*, eds Perry, H.M. & Wood, J.J. Cambridge, Mass: Bolt, Beranek & Newman.
- JAIN, A.K., RYAN, J.R. & McMAHON, F.G. (1975). Potentiation of hypoglycaemic effect of sulphonylureas by halofenate. *New Engl. J. Med.*, **25**, 1283–1286.
- LEWIS, J.L., TRAGER, W.F., CHAN, K.K., BRECKENRIDGE, A., ORME, M., ROWLAND, M. & SCHARY, W.L. (1974). Warfarin: Stereochemical aspects of its metabolism and the interaction with phenylbutazone. *J. clin. Invest.*, **53**, 1607–1617.
- MATIN, S.B. & ROWLAND, M. (1973). Determination of tolbutamide and chlorpropamide in biological fluids. *J. Pharm. Pharmac.*, **25**, 186–187.
- METZ, S.A., FUJIMOTO, W. & ROBERTSON, R.P. (1979). Prostaglandin synthesis inhibitors partially reverse α -adrenergic inhibition of insulin (IRI) release. *4th International Prostaglandin Conference*, Washington, D.C., May 28–June 1.
- MICOSSI, P., PONTIROLI, A.E., BARON, S.H., TAMAYO, R.C., LENGEL, F., BEVILACQUA, M., RAGGI, U., NORBIATO, G. & FOA, P. (1978). Aspirin stimulates insulin and glucagon secretion and increases glucose tolerance in normal and diabetic subjects. *Diabetes*, **27**, 1196–1204.
- POND, S.M., BIRKETT, D.J. & WADE, D.N. (1977). Mechanism of inhibition of tolbutamide metabolism: Phenylbutazone, oxphenbutazone, sulphaphenazole. *Clin. Pharmac. Ther.*, **22**, 573–579.
- ROBERTSON, R.P., GAVERESKI, D.J., PORTE, D.J.R., & BIERMAN, E.L. (1974). Inhibition of *in vivo* insulin secretion by prostaglandin E_1 . *J. clin. Invest.*, **54**, 310–315.
- ROBERTSON, R.P. & CHEN, M. (1977). A role for prostaglandin E in defective insulin secretion and carbohydrate intolerance in diabetes mellitus. *J. clin. Invest.*, **60**, 747–753.
- ROBERTSON, R.P. & METZ, S.A. (1979). Prostaglandins, the glucoreceptor, and diabetes. *New Engl. J. Med.*, **26**, 1446–1447.
- SCHARY, W.L., LEWIS, R.J. & ROWLAND, M. (1975). Warfarin-phenylbutazone interaction in man: a long term multiple dose study. *Res. Comm. Chem. Path. Pharmac.*, **4**, 663–672.
- SLATTERY, J.T., LEVY, G., JAIN, A. & McMAHON, F.G. (1979). Effect of naproxen on the kinetics of elimination and anticoagulant activity of a single dose of warfarin. *Clin. Pharmac. Ther.*, **25**, 51–60.
- SOLOMON, H.M. & SCHROGIE, J.J. (1967). The effect of various drugs on the binding of warfarin- ^{14}C to human albumin. *Biochem. Pharmac.*, **16**, 1219–1226.
- UPTON, R.A., BUSKIN, J.M., GUENTERT, T., WILLIAMS, R.L. & RIEGELMAN, S. (1980). Convenient and sensitive high-performance liquid chromatography assay for ketoprofen, naproxen and other allied drugs in plasma and urine. *J. Chromatog.*, **190**, 119–128.
- WEDER, H.G., SCHILDKNECHT, J. & KESSELRING, P. (1971). A new equilibrium dialyzing system. *Am. Lab.*, **10**, 15–21.
- WIDSTRÖM, A. (1976). Influence of indomethacin on glucose-induced insulin response in normal man—Role of prostaglandins in the rapid insulin release? *Horm. Metab. Res.*, **9**, 172–175.

(Received May 30, 1980)