Indobufen interacts with the sulphonylurea, glipizide, but not with the β -adrenergic receptor antagonists, propranolol and atenolol

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1 This study assessed the possible interactions of the cyclooxygenase inhibitor indobufen with one sulphonylurea, glipizide, and with two β -adrenoceptor antagonists, one of which is extensively metabolised already in the first passage through the liver (propranolol) while the other essentially escapes biotransformation (atenolol). Indobufen was first given as a single 200 mg dose and then for a 5 day period in a dosage of 200 mg twice daily, to six healthy volunteers.

2 Glipizide (5 mg), propranolol (80 mg) and atenolol (100 mg) were given as single doses before and during indobufen medication. The drug concentrations were measured by selective and sensitive h.p.l.c. methods.

3 The findings suggest that the lipophilic acid indobufen can inhibit the metabolic inactivation of another lipophilic acid, glipizide, but does not interfere with the disposal of the two basic drugs, propranolol and atenolol. The increased glipizide concentrations following indobufen were associated with an enhanced blood glucose reduction. Hence, this interaction may be clinically relevant.

Keywords indobufen glipizide propranolol atenolol interactions

Introduction

The acidic lipophilic compound indobufen is a cyclooxygenase inhibitor, chemically related to indoprofen and other non-steroidal anti-inflammatory drugs (NSAID). As such, it could be of value also as an antiplatelet agent (Fucella *et al.*, 1979). In both cases, indobufen might be administered to elderly subjects on other medication, e.g. other acidic drugs such as sulphonylureas, or basic drugs such as β -adrenoceptor antagonists. The present study assessed the possible interactions of indobufen with one sulphonylurea, glipizide, and with two β -adrenoceptor antagonists, one of which (propranolol) is extensively metabolised while the other essentially escapes biotransformation (atenolol).

Methods

Subjects

A total of 18 healthy volunteers, 17 females and one male, age range 24–39 years, weight range 48–72 kg, were studied. Conventional clinical and laboratory examinations revealed no illness. With the exception of six women taking oral contraceptives regularly, all volunteers had been drug-free for at least 6 weeks, and all had refrained from ethanol for at least 2 days before the tests. All 18 subjects were exposed to indobufen medication. In addition, six of these subjects were exposed to glipizide, six others to propranolol, and the remaining six to atenolol

(see further below). The protocol had been approved by the Ethics Committee of the University of Lund.

Medication

On test days, the drugs were always given after an overnight fast, 30 min before a light standardized breakfast. During the rest of the test day, the subjects were free to eat their usual meals, but abstained from all ethanol intake during the whole test period.

On day 1, the subjects in group 1 were given 5 mg glipizide (Min(i)diab®, Farmitalia Carlo Erba, Milano, Italy), group 2 80 mg propranolol (Inderal®, ICI, Macclesfield, UK, and group 3 100 mg atenolol (Tenormin®, ICI, Macclesfield, UK). After this single dose, each subject was drug free for 1 week, and then on day 8 all subjects ingested a single dose of 200 mg indobufen. From day 10 to day 14, the subjects ingested 200 mg indobufen twice daily. Finally, on day 15, all subjects took a last 200 mg dose of indobufen together with either 5 mg glipizide (group 1), 80 mg propranolol (group 2) or 100 mg atenolol (group 3).

Blood sampling

On days 1, 8, 14 and 15, peripheral venous blood was sampled in Vacutainer® tubes immediately before and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 12 h after drug intake. Each sample was allowed to stand in room temperature for about 30 min, whereafter serum was obtained by centrifugation and then stored at -20°C until analyzed.

Urine sampling

On day 8, 14 and 15, i.e. on days when the subjects received indobufen, urine was collected during the 0–12 h interval.

Drug analyses

Serum concentrations of indobufen (Wåhlin-Boll *et al.*, 1981), glipizide (Wåhlin-Boll & Melander, 1979), propranolol (Pritchard *et al.*, 1979) and atenolol (Yee *et al.*, 1979) were determined by high-pressure liquid chromatography. Indobufen in urine was measured both as unconjugated and conjugated drug. The conversion of conjugated to unconjugated drug was carried out as follows: 1 ml HCl (1 M) was added to 0.5 ml urine in a test tube, which was placed in a boiling water bath for 1 h. Total indobufen was then determined by the methods referred to above for serum analyses. The

interassay variations were 6.2% (glipizide), 5.3% (atenolol), indobufen (2.7%) and 2.1% (propranolol).

Blood glucose concentrations were assessed by Glucometer (Ames) during days 1 and 15 in the group that received glipizide. The precision was 5–10%.

Calculations

Peak concentrations were defined as the highest values actually recorded, and the time to reach peak concentrations was obtained accordingly. The elimination half-lives were determined by regression analyses, and the areas under the concentration curves (AUC) were assessed by the trapezoidal rule. Absorption kinetics of glipizide was analyzed by the method of residuals.

The statistical significance of intraindividual differences were determined by Wilcoxon tests on intraindividual data pairs.

Results

Indobufen

The kinetic data (mean $\pm$ s.d.) concerning indobufen in serum and in urine are given in Table 1. As could be expected, the serum and urine concentrations of indobufen increased following repeated intake, even though the differences reached statistical significance only for urine values (Table 1). There was no change in serum indobufen kinetics when glipizide, propranolol or atenolol were added. Neither the urinary excretion of total nor that of conjugated indobufen was altered by administration of any of the other three drugs.

Glipizide kinetics and effects

The AUC of glipizide was significantly ($P < 0.05$) increased when the drug was added to indobufen (Table 2, Figure 1). The absorption rate of glipizide was calculated in four cases; in the remaining two cases there were too few observation points before $C_{\max}$ to ensure accurate measurements. There was no consistent difference in glipizide absorption rates with and without indobufen added. The numerical differences in peak concentration and in half-life did not reach statistical significance.

Five of the six subjects had lower postcibal blood glucose levels following glipizide when this drug was combined with indobufen than when glipizide was taken alone (Table 3). In the sixth subject, the absorption of glipizide was

Table 1 Kinetic parameters (mean $\pm$ s.d.) of indobufen after intake of 200 mg on days 8 and 14 and after intake of 200 mg indobufen together with 5 mg glipizide (group 1), 80 mg propranolol (group 2) or 100 mg atenolol (group 3) on day 15.

Group	$AUC_{0-12\text{ h}}$ ($\mu\text{mol l}^{-1}\text{ h}$)			C_{max} ($\mu\text{mol l}^{-1}$)			t_{max} (h)		
	Day 8	Day 14	Day 15	Day 8	Day 14	Day 15	Day 8	Day 14	Day 15
1	436 $\pm$ 83	563 $\pm$ 90	531 $\pm$ 82	96 $\pm$ 27	111 $\pm$ 23	94 $\pm$ 16	1.5 $\pm$ 1.2	1.3 $\pm$ 0.3	1.1 $\pm$ 0.3
2	455 $\pm$ 91	558 $\pm$ 114	540 $\pm$ 102	108 $\pm$ 22	120 $\pm$ 18	125 $\pm$ 23	0.9 $\pm$ 0.4	0.8 $\pm$ 0.3	0.8 $\pm$ 0.5
3	454 $\pm$ 90	688 $\pm$ 194	633 $\pm$ 202	95 $\pm$ 22	110 $\pm$ 31	111 $\pm$ 39	0.9 $\pm$ 0.2	1.8 $\pm$ 2.0	1.0 $\pm$ 0.3
Group	$t_{1/2}$ (h)			Unconjugated indobufen in urine (0–12 h) (mg)			Unconjugated + conjugated indobufen in urine (0–12 h) (mg)		
	Day 8	Day 14	Day 15	Day 8	Day 14	Day 15	Day 8	Day 14	Day 15
1	5.3 $\pm$ 0.9	6.2 $\pm$ 1.9	5.3 $\pm$ 0.8	3.0 $\pm$ 0.8	3.8 $\pm$ 1.1	3.1 $\pm$ 0.8	109 $\pm$ 18	162 $\pm$ 36	176 $\pm$ 14
2	4.9 $\pm$ 0.3	5.7 $\pm$ 1.4	5.6 $\pm$ 0.3	2.7 $\pm$ 1.0	4.2 $\pm$ 3.0	4.2 $\pm$ 1.8	122 $\pm$ 12	178 $\pm$ 27	178 $\pm$ 22
3	6.3 $\pm$ 1.6	6.4 $\pm$ 2.0	5.9 $\pm$ 1.2	2.3 $\pm$ 0.6	3.1 $\pm$ 0.6	3.2 $\pm$ 0.7	123 $\pm$ 18	206 $\pm$ 43	183 $\pm$ 17
				$P < 0.05$			$P < 0.05$		

AUC = area under the concentration curve, C_{max} = peak concentration, t_{max} = time to reach concentrations, $t_{1/2}$ = elimination half-life.

Table 2 Kinetic parameters of glipizide after intake of 5 mg on day 1 and after intake of 5 mg glipizide together with 200 mg indobufen on day 15 in six healthy volunteers.

Subject	$AUC_{0-\infty}$ (nmol l ⁻¹ h)		C_{max} (nmol l ⁻¹)		t_{max} (h)		$t_{1/2}$ (h)	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
1	4689	6109	718	1203	2.0	1.0	2.8	3.1
2	3770	6407	837	1327	1.0	1.0	2.2	4.2
3	4320	5387	671	851	4.0	3.0	2.6	2.8
4	7704	8335	1623	2038	1.0	1.0	3.7	3.2
5	5370	6677	1055	1026	1.5	4.0	2.9	3.1
6	5653	6367	1015	896	3.0	3.0	2.8	3.5
Mean ± s.d.	5251 ± 1383	6547 ± 980	987 ± 348	1224 ± 438	2.1 ± 1.2	2.2 ± 1.3	2.8 ± 0.5	3.3 ± 0.5

AUC = area under the serum concentration curve, C_{max} = peak concentrations, t_{max} = time to reach peak concentrations, $t_{1/2}$ = elimination half-life.

NS

$P < 0.05$

Figure 1 Serum concentrations (mean ± s.e. mean) of glipizide after intake of 5 mg alone (day 1, ▲) and after intake of 5 mg glipizide during medication with indobufen (day 15, ■).

delayed when combined with indobufen. The numerical difference in blood glucose was not statistically significant when the data of the sixth subject were included in the analysis.

Table 3 Area below fasting glucose level following intake of 5 mg glipizide on day 1, and after 5 mg glipizide together with 200 mg indobufen on day 15 in six healthy volunteers.

Subject	$\Delta AUC_{0-4 h}$ (nmol l ⁻¹ h)	
	Day 1	Day 15
1	-283	-326
2	-168	-314
3	-225	-329
4	-326	-378
5	-321	-259
6	-206	-367
	NS	
Mean ± s.d.	255 ± 65	327 ± 41

Propranolol and atenolol kinetics

The pharmacokinetics of propranolol and atenolol were unaffected by concomitant intake of indobufen (Table 4). The half-life for atenolol was shorter than usually reported and may be spurious because of the limited sampling time (0–12 h).

Discussion

The present findings suggest that the lipophilic acid indobufen interacts neither with the lipophilic base propranolol nor with the hydrophilic base atenolol. However, indobufen does seem to interact with another lipophilic acid, namely, glipizide: the AUC of the latter was significantly increased in the presence of indobufen, and the elimination half-life of glipizide was (insignificantly) prolonged.

As there was no evidence of absorption changes, it seems likely that the recorded interaction resulted from inhibition of glipizide inactivation by indobufen, favoured by the much higher concentrations of the latter. In addition, it is possible that displacement of glipizide by indobufen augmented the effect of glipizide; indeed, the combined interaction of displacement and metabolic inhibition is a likely explanation of NSAID-provoked hypoglycaemia during sulphonylurea treatment (Jackson & Bressler, 1981). Irrespective of the mechanism involved, indobufen can be added to the list of lipophilic acidic drugs that may augment the effect of sulphonylureas, whereas it does not seem to interfere with basic drugs, such as β -adrenoceptor blocking agents.

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Table 4 Kinetic parameters (mean $\pm$ s.d.) of propranolol and atenolol after intake of 80 mg propranolol (group 2) or 100 mg atenolol (group 3) on day 1 and after intake of 80 mg propranolol (group 3) or 100 mg atenolol (group 3) together with 200 mg indobufen on day 15.

Group	AUC (nmol l ⁻¹ h)		C _{max} (nmol l ⁻¹)		t _{max} (h)		t _{1/2} (h)	
	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
2	2004 $\pm$ 551	1827 $\pm$ 1000 NS	447 $\pm$ 104	474 $\pm$ 229 NS	1.6 $\pm$ 0.3	1.5 $\pm$ 0.5 NS	3.4 $\pm$ 0.5	2.5 $\pm$ 0.9 NS
3	9870 $\pm$ 3040	8940 $\pm$ 1810 NS	1870 $\pm$ 700	1770 $\pm$ 530 NS	1.6 $\pm$ 0.4	1.8 $\pm$ 0.7 NS	3.9 $\pm$ 1.6	4.3 $\pm$ 2.3 NS

AUC = area under the serum concentration curve, C_{max} = peak concentrations, t_{max} = time to reach peak concentration, t_{1/2} = elimination half-life.

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