Clinical Investigation

Effects of Nonsteroidal Antiinflammatory Drugs in Conventional Dosage on Glucose Homeostasis in Patients With Diabetes

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Larger-than-conventional doses of nonsteroidal antiinflammatory drugs (NSAIDs) are known to lower plasma glucose levels. This phenomenon has raised the questions whether or not NSAIDs in conventional dosage can be used for the treatment of hyperglycemia in patients who have non-insulin-dependent diabetes mellitus and whether or not NSAIDs added to preexistent hypoglycemic drug therapy taken orally may lead to unanticipated hypoglycemia. In this study we evaluated aspirin, sodium salicylate and ibuprofen given in conventional dosage to hyperglycemic patients with adult-onset (type II) diabetes. Half the patients were usually treated for hyperglycemia by means of diet only and half with diet plus hypoglycemic drugs given orally. Significant changes in plasma glucose levels were not seen after the administration of a combination drug containing aspirin and magnesium-aluminum hydroxide (Ascriptin, 650 mg three times a day; glucose change = 236±30 to 236±31 mg per dl) or sodium salicylate (600 mg three times a day; glucose change = 284±76 to 273±84 mg per dl). A statistically significant but small change was seen with the administration of ibuprofen (600 mg three times a day; glucose change = 196±60 to 179±47 mg per dl) but not when giving ibuprofen (300 mg three times a day; glucose change = 267±78 to 282±60 mg per dl). The results of this study indicate that conventional doses of NSAIDs should not be used for treating hyperglycemia and that, since the additive hypoglycemic effect of NSAIDs in conventional doses was minimal or negligible, they can be used safely for other purposes in diabetic patients taking hypoglycemic drugs orally.

The first observation that a nonsteroidal antiinflammatory drug could enhance carbohydrate tolerance in patients with diabetes mellitus was made by Ebstein in 1876.[1] He showed that sodium salicylate given orally would decrease the amount of glucose excreted in the urine of diabetic patients. Subsequently, other investigators reported that nonsteroidal antiinflammatory drugs could improve carbohydrate tolerance in diabetics.[2,3] In 1971 these drugs were discovered to inhibit prostaglandin synthesis.[4,5] At about the same time, certain prostaglandins, particularly prostaglandins of the E series, were found to inhibit glucose-induced insulin secretion in animals[6-8] and in humans.[9-11] The studies of Robertson and Chen[12] showed that intravenous infusions of sodium salicylate in patients with adult-onset diabetes could partially restore previously absent glucose-induced acute insulin responses and improve glucose disappearance rates after the intravenous administration of glucose.

Because of these investigative findings, questions have been raised by clinicians about the use of nonsteroidal antiinflammatory drugs as therapeutic agents

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in diabetic patients. One of these questions is whether or not nonsteroidal antiinflammatory drugs can be used to help regulate glycemia in patients with non-insulin-dependent diabetes mellitus. Another is whether or not adding a nonsteroidal antiinflammatory drug to an established therapeutic regimen of oral hypoglycemic agents in diabetic persons might lead to unanticipated hypoglycemia because of additive drug effects. These issues cannot be addressed from available data because previous studies for the most part have used higher-than-conventional doses of nonsteroidal antiinflammatory drugs for only brief periods. The studies described herein were designed to evaluate the effects on glucose homeostasis of conventional doses of several nonsteroidal antiinflammatory drugs used for extended periods in persons with non-insulin-dependent diabetes.

Patients, Materials and Methods

Patients

All patients studied had type II (adult-onset) diabetes mellitus and fasting hyperglycemia. Their usual therapy consisted of dietary measures only or dietary measures plus conventional hypoglycemic therapy taken orally. No one was treated with insulin. A total of 58 men and 19 women was studied; ages ranged from 38 to 78 (58±9; mean±standard deviation). All studies were done in the Outpatient Department of the Seattle Veterans Medical Center where careful attention was given weekly to monitoring compliance in drug treatment, symptoms and levels of circulating glucose.

Treatment Protocols

Group I. A total of 77 patients was randomly assigned to one of four drug subgroups: aspirin (Ascriptin [a combination drug in which each tablet contains aspirin, 325 mg, and magnesium-aluminum hydrochloride, 150 mg], 650 mg taken orally three times a day); sodium salicylate (600 mg taken orally three times a day); ibuprofen (300 mg taken orally three times a day), and a placebo taken by mouth three times a day. The drug subgroups to which the patients were assigned were unknown to them and to the investigator managing the patients. There was an initial two-week drug withdrawal period during which all drugs known to affect carbohydrate tolerance were withheld from the patients. This was followed by a 12-week period during which either a nonsteroidal antiinflammatory drug or a placebo was given to the patients. During the last eight weeks of this 12-week period, those patients who normally were treated with oral hypoglycemic agents were asked to resume taking these drugs in addition to their other regimen.

Group II. This study further evaluated the effects of ibuprofen, 600 mg taken orally three times a day, and a placebo. There was no initial drug withdrawal period; instead, subjects were allowed to continue with their usual pretrial oral hypoglycemic therapy, if any. A double-blind crossover design was used in which 24 of 48 persons began taking ibuprofen while the other half began taking a placebo. The duration of this drug trial was eight weeks and patients crossed over to the alternate regimen (ibuprofen or placebo) at the end of the fourth week.

Measurements

During these drug trials measurements were made of fasting plasma glucose and insulin levels. Glucose tolerance tests were done intravenously in some patients to determine glucose-induced acute insulin responses and glucose disappearance rates. All of these studies were carried out using conventional and standard techniques.[9] Statistical analyses were done using the Wilcoxon matched-pairs ranks test.

Results

Group I

Ascriptin, sodium salicylate, ibuprofen and placebo. The results from measuring fasting plasma glucose

TABLE 1.—*Fasting Plasma Glucose Levels in 50 Persons With Type II (Adult-Onset) Diabetes Before and During Treatment With a Nonsteroidal Antiinflammatory Drug (NSAID) Only for 4 Weeks, Then During Treatment With an NSAID Plus Usual Diabetic Drug Therapy (If Any) for 8 More Weeks**

Drug Group and Subgroups (Number of Persons)	*Fasting Plasma Glucose (mg/dl) Levels (mean ± SD)*			
	Pretrial	*After 2 Weeks Drug Withdrawal*	*After 4 Weeks NSAID Only*	*After 8 Weeks NSAID Plus Usual Therapy*
Ascriptin (11)	**193±62**	**236±30 (P<.01)‡**	**236±31**	**232±30**
Diet only (7)	**175±61**	**198±97**	**187±82**	**200±107**
Oral agent (4)†	**222±58**	**302±66**	**321±77**	**289±61**
Sodium salicylate (14)	205±51	284±76 (P<.005)‡	273±84	233±57
Diet only (7)	203±54	272±84 (P<.025)‡	225±59	210±62
Oral agent (7)	208±51	296±72 (P<.01)‡	321±80	256±44
Ibuprofen (14)	**203±57**	**267±78 (P<.005)‡**	**282±60**	**241±61**
Diet only (7)	**217±58**	**281±100 (P<.025)‡**	**272±70**	**265±70**
Oral agent (7)	**189±58**	**253±51 (P<.01)‡**	**293±51**	**217±43**
Placebo (11)	206±54	264±69 (P<.005)‡	273±74	258±69
Diet only (6)	193±53	228±36 (P<.025)‡	230±43	239±50
Oral agent (5)	222±56	308±78	324±74	280±87

SD = standard deviation

*Doses used were: Ascriptin (each tablet contains aspirin, 325 mg, and magnesium-aluminum hydroxide, 150 mg), 650 mg 3 times a day; sodium salicylate, 600 mg 3 times a day, and ibuprofen, 300 mg 3 times a day.
†The term "oral agent" refers to the use of any conventional hypoglycemic drug given orally.
‡*P* values as compared with pretrial values.

levels in the four groups of persons with diabetes are presented in Table 1. Of 77 patients, 50 completed the study. Fasting plasma glucose levels generally rose by the end of the two-week period during which all drugs known to affect glucose homeostasis were withdrawn from the patients. This occurred at a statistically significant level in each of the four groups. This observation was also made in five of the subgroups, in three of which the patients had not been receiving oral hypoglycemic agents before the pretrial fasting glucose level had been measured. There were no statistically significant falls in fasting plasma glucose levels in any of the subgroups after they had been treated four weeks with a nonsteroidal antiinflammatory drug or a placebo. Comparisons of the pretrial levels and the levels that occurred after the final eight weeks, during which a nonsteroidal antiinflammatory drug plus the usual hypoglycemic therapy was given orally, failed to show any significant differences. The only adverse drug effect occurred in one patient taking ibuprofen in whom a rash developed that disappeared when the drug was discontinued.

Group II

Ibuprofen-placebo crossover without a period of hypoglycemic drug withdrawal. Results of measurements from the persons participating in this study are given in Table 2. Of 48 patients, 37 completed the study. Significant decrements in plasma glucose levels occurred only in the persons receiving ibuprofen who were also receiving their usual oral hypoglycemic therapy. This occurred in both groups whether the placebo or ibuprofen was given for the first four weeks. In contrast, no glucose lowering was observed in the groups receiving ibuprofen who were normally treated with dietary measures only. Glucose decrements were also seen when data from both the patients who normally received oral hypoglycemic agents and the patients who normally were treated with management of diet only were pooled if ibuprofen had been given before the placebo. However, this effect of ibuprofen was not noted when the data from the groups receiving the placebo first were pooled. No significant changes occurred in fasting plasma insulin level in either of the two groups or the four subgroups. Because of the limited number of persons having intravenous glucose tolerance testing, the data from persons normally treated with diet only and diet plus hypoglycemic drugs taken orally were pooled. There was no significant alteration in glucose-induced acute insulin responses or in glucose disappearance rates in these subjects. There were no adverse drug effects.

Discussion

These studies were undertaken to assess whether or not conventional doses of commonly used nonsteroidal antiinflammatory drugs cause clinically significant falls in fasting plasma glucose levels when given to persons who have type II diabetes with fasting hyperglycemia. The usual treatment of diabetes before this study for about half of the patients consisted of dietary measures only; the other half were also taking hypoglycemic agents orally, usually either tolbutamide or chlorpropamide. The persons in group I received either aspirin, sodium salicylate, ibuprofen or placebo. For two weeks before the start of the 12-week drug ingestion period, all were asked to discontinue taking their oral hypoglycemic agents, if any. There was a uniform trend in all groups for fasting plasma glucose levels to rise during this two-week "washout" period. Interestingly, the tendency for hyperglycemia to develop was noted not only in the patients who had been using hypoglycemic agents but also in those who had been using dietary measures only. The meaning of these occurrences is not

TABLE 2.—*Fasting Plasma Glucose Level, Fasting Plasma Insulin Level, Acute Insulin Response and Glucose Removal Rate in a Randomized Double-Blind Crossover Study of Persons With Type II (Adult-Onset) Diabetes (N=37)**

	Diet Therapy Only (13)			*Diet Therapy Only (9)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	245±72	244±75	245±71	176±58	165±48	181±59
Fasting plasma insulin (μU/ml) ...	16±10	10±5	13±10	15±12	17±15	15±13
	Diet + Oral Agent (7)			*Diet + Oral Agent (8)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	261±15	268±53	223±64 ($P<.01$)†	218±57	194±45 ($P<.01$)†	200±54
Fasting plasma insulin (μU/ml) ...	22±14	14±9	12±6	24±21	19±12	18±11
	All Patients (20)			*All Patients (17)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Fasting plasma glucose (mg/dl) ...	251±58	252±68	237±68	196±60	179±47 ($P<.005$)†	190±56
Fasting plasma insulin (μU/ml) ...	18±12	12±7	12±8	19±17	18±14	17±12
	All Patients (4)			*All Patients (7)*		
	Pretrial	*Placebo*	*Ibuprofen*	*Pretrial*	*Ibuprofen*	*Placebo*
Acute insulin response (%)‡	95±15	91±19	80±13	90±35	106±28	80±14
Glucose removal rate (mg/dl a min)	.31±.26	.31±.16	.32±.21	.67±.34	.51±.11	.55±.14

*Some subjects received placebo for 4 weeks, then ibuprofen, 600 mg 3 times a day, for 4 weeks; the rest received ibuprofen for 4 weeks, then placebo for 4 weeks. Numbers in parentheses indicate the number of persons in each group and subgroup. Data are presented as mean ± standard deviation.

†Compared with pretrial values.

‡Percentage of basal fasting plasma insulin level.

clear but they suggest that some of the persons were less rigorous in their dietary measures during the washout period than they had been before the initial specimens for fasting plasma glucose levels were collected.

During the 12-week period when a nonsteroidal antiinflammatory drug or placebo was given, there was no evidence in any of the drug subgroups of a diminution of fasting plasma glucose levels. Even during the last eight weeks when about half the patients had resumed taking their usual diabetic therapy with oral hypoglycemic agents, there was no evidence that glucose levels were less than those at the beginning of the study before the drug withdrawal period. Consequently, it can be concluded that none of the three nonsteroidal antiinflammatory agents was adequate for treating hyperglycemia without the use of hypoglycemic agents. Moreover, a combination of oral hypoglycemic agents and nonsteroidal antiinflammatory drugs did not cause symptomatic or measurable hypoglycemia.

The persons in group II received a twice higher dose of ibuprofen and the placebo in a double-blind crossover manner. There was no withdrawal of hypoglycemic drugs before these studies; instead, the nonsteroidal antiinflammatory drug or placebo was simply added to a patient's usual therapeutic regimen for control of hyperglycemia. This trial was conducted because of the possibility in the first trial that deterioration of glucose homeostasis during withdrawal of oral hypoglycemic agents from group I might have masked slight glucose-lowering effects of nonsteroidal antiinflammatory drugs. In the subgroups of patients in group II who were usually treated with oral hypoglycemic agents, adding ibuprofen caused a further fall in circulating glucose levels whether it or the placebo was the first agent used during the trials. In contrast, this effect of ibuprofen did not occur in patients whose normal therapeutic regimen for diabetes consisted of dietary measures only. Consequently, it can be concluded only that adding ibuprofen to a therapeutic regimen of oral hypoglycemic agents may further lower circulating glucose levels. This did not occur to a great extent, however, and in no instance did any person have symptoms of hypoglycemia. The mechanism of this additive drug effect was not pursued in this study but possibilities include inhibition of cyclooxygenase as well as displacement by ibuprofen of albumin-bound oral hypoglycemic agents in circulation.

The data collected relating to glucose-induced insulin responses and glucose disappearance rates failed to show any significant effects of ibuprofen therapy. This is in contrast to prior observations of beneficial effects of nonsteroidal antiinflammatory drugs and ibuprofen specifically on acute insulin responses and glucose disappearance rates.[9-12] It should be recalled, however, that in the studies cited higher doses of a nonsteroidal antiinflammatory drug were usually used (for example, sodium salicylate infusions at 40 mg per minute given intravenously achieved serum salicylate concentrations of more than 25 mg per dl[9] compared with 600 mg by mouth three times a day in this study, which failed to cause detectable levels in serum) and normal persons instead of those with diabetes were used for the ibuprofen trials.

Conclusion

We can conclude from our studies that nonsteroidal antiinflammatory drugs may be used safely for control of symptoms of an inflammatory condition in combination with oral hypoglycemic agents. Nonsteroidal antiinflammatory drugs should not be considered as therapy for hyperglycemia. They are very useful tools, however, for research about diabetes in humans and for in vitro laboratory research. In this context, if the hypothesis is correct that the beneficial effects of larger-than-conventional doses of nonsteroidal antiinflammatory agents on glucose homeostasis in patients with diabetes are related to inhibition of cyclooxygenase activity and augmented insulin secretion,[13] then an evaluation of this class of agents for the treatment of hyperglycemia must await the development of future generations of drugs that are highly specific for pancreatic islet cyclooxygenase. Drugs such as these will need to affect pancreatic islets but not other tissues wherein inhibition of cyclooxygenase may lead to undesirable effects.

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