ORIGINAL ARTICLES

The consent form as a possible cause of side effects

In a multicenter trial of aspirin or sulfinpyrazone in the treatment of unstable angina, we examined the possible importance to the outcome of mentioning potential side effects in the consent form. Inclusion, in two of the three centers, of a statement outlining possible gastrointestinal side effects resulted in a sixfold increase ($P < 0.001$) in the number of subjects in these centers withdrawing from the study because of subjective, minor gastrointestinal symptoms. Major gastrointestinal complications such as peptic ulcer or bleeding as diagnosed by study physicians were similar in the three centers. Furthermore, no patient discontinued therapy because of subjective, nongastrointestinal side effects. Post hoc analysis suggests that the inclusion of gastrointestinal side effects in the consent form may have increased the likelihood of patients attributing gastrointestinal symptoms to drug therapy, leading to subsequent withdrawl from the study. (CLIN PHARMACOL THER 1987;42:250-3.)

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Informed consent has become an essential part of clinical research. The Declaration of Helsinki concerning research involving human subjects stipulates that potential participants "must be adequately informed of the aim, methods, anticipated benefits, and potential hazards of the study." In the context of a clinical trial of a new therapeutic intervention, informing the patient of a possible side effect could influence the outcome of the study by increasing the likelihood that the patient will have a symptom through the "power of suggestion." The possible importance of including side effects in a consent form to the outcome of a study surfaced after the completion of a multicenter trial that examined the benefits of aspirin, sulfinpyrazone, both drugs, or placebo therapy for unstable angina pectoris.[1] In this study the inclusion of possible minor gastrointestinal side effects in the consent form of two of the three centers may have increased the number of patients withdrawing from the study because of gastrointestinal symptoms.

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METHODS

The study involved the administration of aspirin (325 mg q.i.d.), sulfinpyrazone (200 mg q.i.d.), both drugs, or matching placebo tablets to 555 patients admitted to the hospital with a diagnosis of unstable angina pectoris. The double blind was achieved by means of a "double-dummy" tablet administration as described previously.[1] After being randomized to one of the four treatment groups, each patient was followed up at 3-month intervals for 2 years or until the completion of the study. At each visit a brief medical history, physical examination, and ECG were performed. Possible side effects were elicited by a detailed questionnaire (Table I) and any volunteered symptoms were noted by a specially trained research nurse. Patients were also seen by a study physician on alternate visits (i.e., every 6 months) or on other occasions if new symptoms or medical problems possibly related to the study developed. The study nurse documented any side-effects reported by the patient but did not attempt to ascertain their clinical importance. Possible adverse reactions to

therapy were evaluated by the study physician. If the side effect was relatively minor (e.g., nausea, heartburn, or headache), the patient was encouraged to continue with the treatment, although many declined to do so. If a suspected major adverse drug reaction occurred (e.g., gastrointestinal hemorrhage, melena, or peptic ulcer), the physician discontinued therapy. In cases in which aspirin was believed to be the most likely cause of the offending symptoms, only the aspirin/placebo portion of the treatment was stopped, providing that the patient agreed to continue the sulfinpyrazone/placebo tablets. The study physicians confined their involvement to conditions that were possibly related to the aspirin or sulfinpyrazone therapy. Specific treatment of ischemic heart disease or other medical conditions was supervised by the patient's family physician or cardiologist. Details of the study protocol and characteristics of the 555 patients enrolled have been reported previously.[1]

The study was conducted in three centers, with centers A and B being comprised of four and three hospitals, respectively, and center C by a single institution. There were 313, 86, and 156 patients recruited from centers A, B, and C, respectively. All hospitals were university affiliated and each of the study physicians was a cardiologist with a full-time university faculty appointment. One research nurse was assigned to each of centers B and C with center A having two research nurses. At least one cardiologist supervised the conduct of the study at each hospital.

Informed consent was obtained from all patients before they were entered into the study. In centers A and B the consent form included the following statement: "side effects are not anticipated beyond occasional gastrointestinal irritation and, rarely, skin rash." A copy of the form containing this statement was given to the patient to take home and a letter outlining the same information was sent to the patient's family physician. The consent form in center C did not mention possible gastrointestinal symptoms but instead included the following statement: "sulfinpyrazone and aspirin are generally well tolerated by patients and have been used for many years to treat other conditions. There is no evidence that the drugs in this study will cause any harm to the heart or blood vessels. Occasionally a patient taking sulfinpyrazone or aspirin may develop a tendency to bleed but the risk of serious hemorrhage is extremely unlikely." These differences in the content of the consent forms were not planned prospectively but were the result of the individual hospital's review processes. The consent forms in the three centers were otherwise similar, describing the study design, confidentiality of the data, and freedom of withdrawal without prejudicing future care. Each consent form was approved by the ethics review committee of each institution.

Table I. Items included in the side-effect questionnaire used by the study nurse on each visit

Gastrointestinal bleeding	Weakness
Melena	Vomiting
Skin rash	Diarrhea
Itching	Constipation
Bruising	Vertigo
Peptic ulcer	Tinnitus
Indigestion	Abdominal discomfort
Nausea	Other

Differences in the proportions of patients in the three centers who had symptoms or discontinued therapy were assessed using a 2×3 χ^2 analysis.

RESULTS

Minor gastrointestinal symptoms were reported less frequently ($P < 0.001$) in center C compared with centers A and B (Table II). There were no significant differences among the three centers in the occurrence of major, drug-related adverse reactions as documented by the study physicians. These included frank gastrointestinal hemorrhage, melena, and peptic ulcer and were considered to be likely caused by the study medication, thus resulting in discontinuation of therapy. In contrast, the relatively minor gastrointestinal symptoms reported by the patients (e.g., nausea, indigestion, or heartburn) were not associated with clinical or laboratory abnormalities and generally could not be confirmed independently by the study nurse or physician. In centers A and B, 68% and 66% of patients who reported a minor gastrointestinal symptom did so on the first follow-up visit at 3 months whereas only 39% ($P < 0.02$) of gastrointestinal symptoms in center C occurred this early in the study. Of the 200 patients who reported minor gastrointestinal symptoms, only 56% were actually receiving aspirin.

Significantly ($P < 0.001$) more patients in centers A and B discontinued therapy because of minor gastrointestinal symptoms (Table II), with only five patients in center C stopping treatment for this reason. Four of these patients agreed to continue the sulfinpyrazone/placebo tablets. Of the 81 patients who stopped medication because of gastrointestinal symptoms, only 58% were receiving aspirin. The proportion of patients withdrawn from the study because of documented noncompliance or normal coronary arteriograms was sim-

Table II. All gastrointestinal side effects initiated by the patients (minor) or physicians (major) and reasons for premature discontinuation of study medication are listed; patients who stopped both drugs, aspirin, and sulfinpyrazone and aspirin only are listed separately; patients who had more than one gastrointestinal symptom were counted only once

		Center					
		A	*B*	*C*	*Total*	X^2	*P*<
No. of pts.		313	86	156	555		
Gastrointestinal side effects							
Minor		143	32	25	200	39.79	0.001
Major		8	1	6	15	1.58	NS
Withdrawals because of side effects							
Minor	ASA + S	44	12	1	57		
	ASA only	17	3	4	24		
	Total	61	15	5	81	22.81	0.001
Major	ASA + S	21	7	5	33		
	ASA only	6	0	6	12		
	Total	27	7	11	45	3.12	NS
Compliance		22	11	9	42	4.21	NS
Noncompliance or normal coronary arteriogram		18	1	4	23	4.94	NS

ASA + S, aspirin and sulfinpyrazone; ASA, aspirin only.

ilar in the three centers. No patient discontinued treatment because of a nongastrointestinal symptom.

DISCUSSION

The inclusion of possible gastrointestinal side effects in the consent forms used by two of the centers in this study appears to have resulted in a marked increase in both gastrointestinal symptoms and consequent patient-initiated cessation of therapy. More than six times as many patients discontinued aspirin/placebo treatment because of gastrointestinal symptoms in the centers in which gastrointestinal side effects were mentioned in the consent form. Because these data were obtained retrospectively and the analysis was post hoc, any conclusions must be preliminary. However, several aspects of the analysis tend to support a causal role for the consent form in the withdrawal of subjects from the study.

Withdrawals because of "major" side effects were similar in the three centers. These conditions included gastrointestinal hemorrhage, melena, and peptic ulcer, all of which could be confirmed objectively by physical examination or appropriate investigations. Thus study physicians in the three centers did not appear to differ with respect to the removal of patients for potentially serious conditions that could possibly be related to antiplatelet therapy. Also, not a single patient was withdrawn from therapy because of a subjective nongastrointestinal complaint, suggesting that the patients in centers A and B were not generally predisposed to stopping treatment because of any symptom, only those related to the gastrointestinal system. In addition, about two thirds of the patients who reported gastrointestinal symptoms in these centers did so on the first follow-up visit, raising the possibility of a temporal association between becoming aware of a drug-related gastrointestinal side effect and its occurrence.

The occurrence of minor gastrointestinal symptoms was not strongly associated with the administration of aspirin because only 56% of patients with gastrointestinal complaints were found to be actually taking aspirin when the medication code was broken. This observation suggests that other causes for the gastrointestinal symptoms, such as information provided in the consent forms of centers A and B, may have played a role. All study personnel were trained in a standard way with a common procedure manual including instructions for documenting side effects voiced by the patients. Study physicians in the different centers apparently exhibited a similar approach to the gastrointestinal symptoms documented by the nurses in that the number of major gastrointestinal events identified was proportionately similar in the three centers. Cardiovascular end points in the study also occurred in similar numbers in the different centers.

Previous investigators have also expressed concern about information provided in the consent form influencing the results of a clinical study. In one study[2] in

which an appetite suppressant was compared with placebo in the treatment of obesity, subjects who unmasked the double blind and correctly identified the active drug lost significantly more weight than did those taking medication who were unaware of their treatment status. The authors concluded that information on side effects in the consent form enabled patients to break the double blind and respond more favorably to the intervention. In another instance, Spohn and Fitzpatrick[3] offered eligible patients the opportunity of entering a study in which antipsychotic therapy might possibly be discontinued. These authors observed that individuals who agreed to participate and signed a consent form were substantially different with respect to important baseline characteristics from patients who refused to sign the consent form. Similarly, Gardner[4] noted that subjects who provided written, informed consent differed significantly in their responses to environmental noise when compared with individuals randomly allocated to a "no consent form" group.

In a recently published study, Dahan et al.[5] compared the effects of written, informed consent on the responses of patients with insomnia to a purported hypnotic agent that was actually placebo. Patients who received details of the study including information about possible side effects to a hypnotic drug reported less satisfactory sleep after the placebo than did a control group who were unaware of their participation in a clinical trial. Only four side effects were reported and all of these occurred in the informed consent group, although the difference from the control group was not statistically significant.

These findings support our own concerns that the consent form may alter the results of a study and suggest that both the content of information provided to a patient and the actual consent form process should be considered as possible sources of bias in the design of a clinical trial. Whenever possible it would seem preferable to focus the consent form on potentially harmful, drug-related adverse effects that can be verified objectively rather than common, relatively minor, "subjective" symptoms that the patient may already associate with the treatment.

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